THE PHOTOCHEMISTRY OF SANTONIN IN APROTIC SOLVENT

PART I: PHOTOPRODUCTS
PART II: MECHANISM

Thesis by

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In Partial Fulfillment of the Requirements

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To My Parents

It is my opinion, therefore, that the sun is the sole cause of the phenomenon.

--Herodotus

ABSTRACT

Irradiation of santonin in aprotic solvents, e.g. benzene or dioxane, gives rise only to lumisantonin, but further irradiation of lumisantonin then leads to no fewer than four new photoproducts which will be designated mazdasantonin, H, B, and J. The further photoconversion of these compounds, although considerably less striking than that of lumisantonin, has also been studied in a qualitative way.

Studies of the singlet or triplet nature of these reactions provides evidence for triplet paths in the conversion of one isomer to another and in the subsequent dimerization of mazdasantonin. Thus, triplet states appear to play an important role in photochemistry even in simple isomerizations which quenching data show to be very fast and to have rates in the range of normal singlet reactions.

ACKNOWLEDGEMENT

I wish to express my deep appreciation for the guidance and counsel I have received from my thesis advisor, Dr. John H. Richards, whose enthusiasm has provided me with an example I shall long remember. I wish also to acknowledge the endless talks and discussions with Dr. Guy Moses, whose patience and insight were great assets in clarifying the problem. Lastly, I wish to thank for her aid in myriad things, great and small, my friend Sue.

TABLE OF CONTENTS

TABLE OF CONTENTS (continued) Page

PART I

THE PHOTOPRODUCTS

I. HISTORICAL

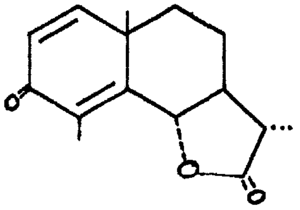
A. Santonin

Santonin (1) is a sesquiterpenoid lactone found widely distributed throughout nature in various species of Artemisia. It was first isolated in 1830 (1) and has been intensively investigated since that time. Most of the great organic chemists have worked with santonin at one time or another. The list is long and includes such notables as Cannizzaro, Woodward, Haworth, Barton, van Tamelen, and of course the noted Soviets, Goryaev and Sazonova. As late as 1951, the photochemistry of santonin, although voluminous, still was titled "Santonin Derivatives of Doubtful or Unknown Constitution." (2)

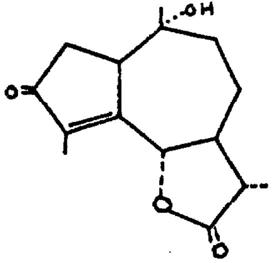
B. General Photochemistry

The first photoproduct isolated was called chromosantonin (1,3,4), melting point approximately 160°. However, for a given reaction, chromosantonin and santonin were found to yield the same substances. Moreover, the derivatives of chromosantonin were said to revert to those of santonin on recrystallization, so that chromosantonin appears to be merely an impure form of santonin.

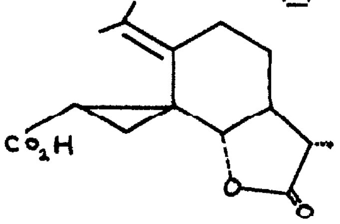
Other products have been discovered on irradiation in protic solvents, usually alcohol or acetic acid solutions. These products include photosantonic acid, isophotosantonic acid, photosantoninic acid, and a myriad of ethers, esters, and acids. The structures of all these compounds were completely unknown before the initial massive attack on the subject by Barton, de Mayo, and Shafiq, who elucidated the structure of isophotosantonic acid (5).



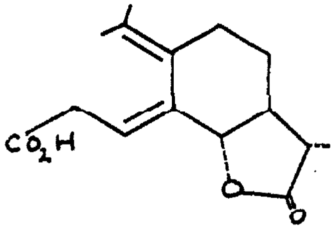
Santonin (1)



Isophotosantonic Acid (2)



(3)



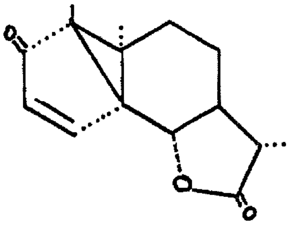
Photosantonic Acid (4a)

These workers succeeded in showing by chemical studies that isophotosantonic acid is a perhydroazulene of structure (2) and that the various derivatives of this compound could be characterized as methyl ethers, acetates, etc.

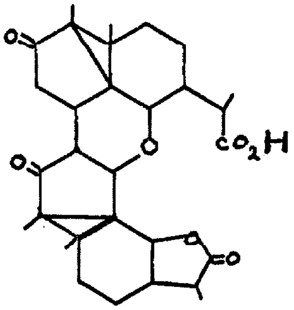
The same group studied the structure of photosantonic acid, but arrived at the erroneous structure (3), which was subsequently corrected by van Tamelen and coworkers (6). The Americans, using both classical chemical methods and the then novel technique of nuclear magnetic resonance, showed photosantonic acid to be (4a). Barton quickly published more evidence in favor of the new structure which may now be considered to be on extremely firm ground (7).

C. Lumisantonin as a Central Intermediate in Santonin Photochemistry

In 1957, a major step was taken when the existence of a photoisomer of santonin was demonstrated, the so-called lumisantonin (5) that was discovered by three groups (8). Lumisantonin was shown to be an intermediate on the pathway to other santonin photoproducts, specifically to photosantoninic acid (obtained on basic treatment), photosantonic acid and derivatives (obtained on irradiation), and to the perhydroazulenes (obtained on treatment with acid).



Lumisantonin (5)



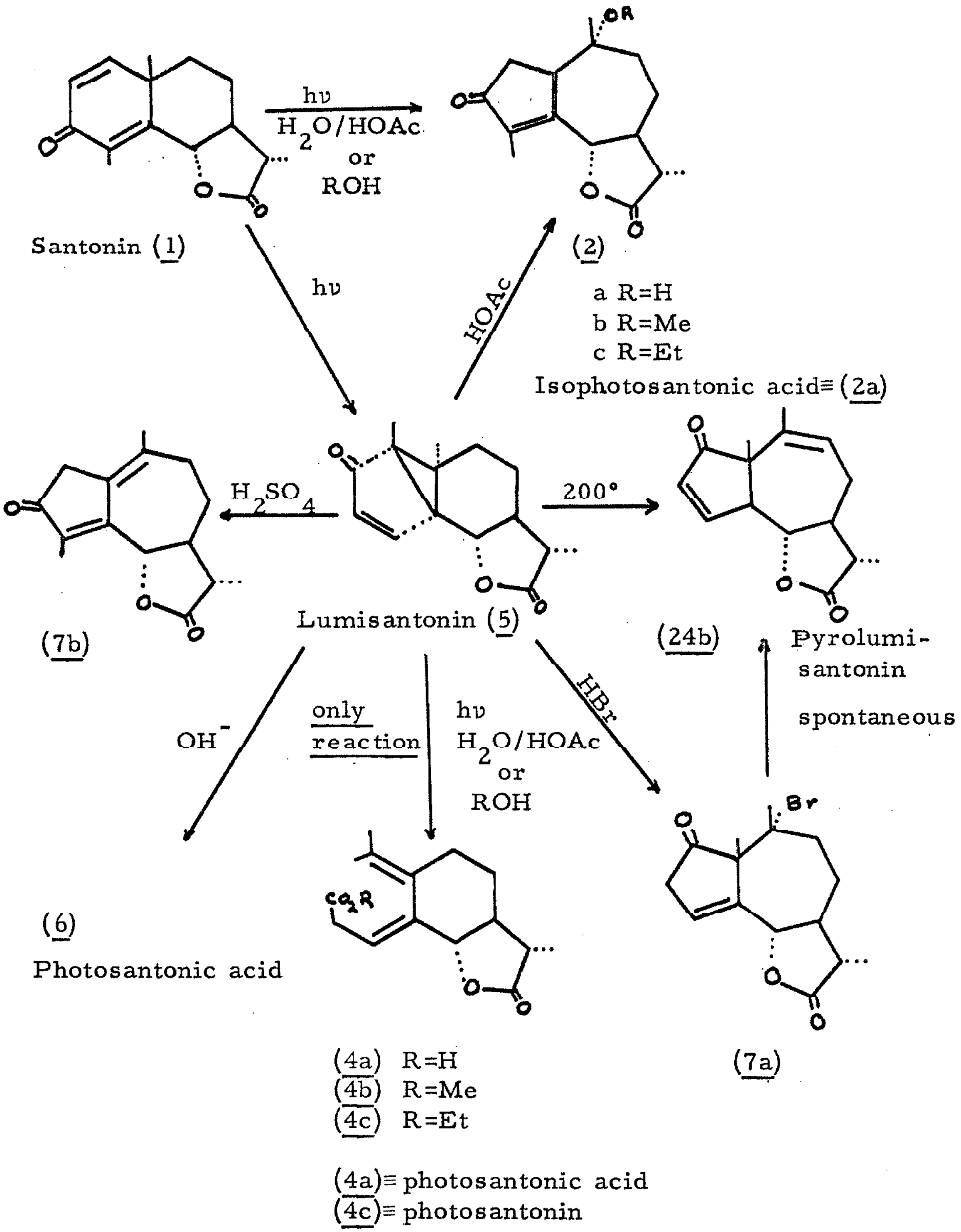
Photosantoninic Acid (6)

It was shown by Barton (8a) that although lumisantonin did yield isophotosantonic acid lactone on irradiation in refluxing aqueous acetic acid, it did not do so in the same solvent at 0°C. He suspected that this conversion was not a photoreaction at all, but merely an acid reaction and in agreement with this conclusion found that treatment of lumisantonin with refluxing acetic acid (in the dark) led to isophotosantonic acid.

Photoproducts are often labile under the experimental conditions and controls should always be run to ensure that the compound isolated is engendered in the photochemical act rather than as a consequence of secondary reactions. Barton's studies on the conversion of lumisantonin to isophotosantonic acid illustrate the need for caution when interpreting photochemical results.

The position of lumisantonin as a central intermediate to most of the known photoproducts of santonin was thus established and is summarized in Figure 1. Photosantoninic acid was subsequently characterized as a dimer of lumisantonin (6) (9).

The work by Hammond and coworkers in the early 1960's prompted the undertaking of the present investigation. They showed that triplet states (cf. Part II) played a much wider role in organic photochemistry than had previously been believed. Their basic work covered a large number of simple compounds, mostly olefins and dienes. The possibility of extending the work of the Hammond



For other work of a non-photochemical nature, see reference 2.

Fig. 1. Summary of Pertinent Santonin Photochemistry (1960).

school to more complex molecules, particularly dienones, opened exciting prospects. Santonin was chosen because it is a readily available dienone whose photochemistry had already received passing mechanistic study. It was felt that the work of Barton, Jeger, and van Tamelen outlined above would permit intensive study on the mechanism of santonin photoconversion without requiring exhaustive structural studies. That this was rather far from the truth was inevitable, but we were all naive in those days.

II. CONVERSION OF SANTONIN TO LUMISANTONIN

A. Results

When santonin is irradiated in carefully dried aprotic solvent (benzene or dioxane) using light of 2500-4500 Å, a number of products can be isolated. The photolysis will be discussed in terms of its various stages, and the products of each stage will be presented according to their position in the reaction sequence.

Lumisantonin is the first and only product obtained directly from photolysis of santonin. Monitoring of santonin irradiations in closed pyrex vessels (n.m.r. or v.p.c. analysis) showed only lumisantonin in the early stages of the reaction. Such data alone do not exclude the possibility that some small fraction of the product might be other materials, but the demonstration (Table I) that

Table I

Intermediacy of Lumisantonin*

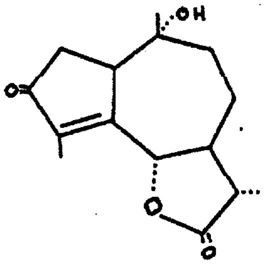
Run	S	LS	MS	H	J	B	E	Total
7	1	4½	59	8½	2½	2	24½	103
11	-	2½	58½	11½	3	4	9	88½

* Since the irradiation of lumisantonin was carried out at considerably lower concentration, the yield of the dimeric mixture E was markedly less.

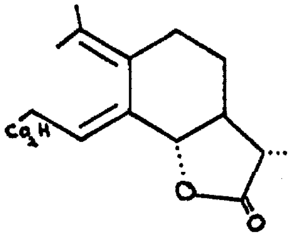
irradiation of lumisantonin leads to the same products in the same proportions makes any alternate route not involving lumisantonin quite unnecessary.

B. Discussion

The fact that only lumisantonin arises from santonin when irradiation is carried out in aprotic solvent is anomalous in view of the observations that irradiation of santonin in refluxing acetic acid (8a) or alcohol (8b) leads to two types of photoproducts: the perhydroazulene series exemplified by isophotosantonic acid lactone (2), and the hydronaphthalenes, e.g. photosantonic acid (4a).[*] However, in agreement with the results on santonin, two other cross-conjugated dienones, dehydrotestosterone acetate (8a) (11a) and 2-methyldehydrotestosterone acetate (8b) (11c) have very



Isophotosantonic acid lactone (2)



Photosantonic acid (4a)

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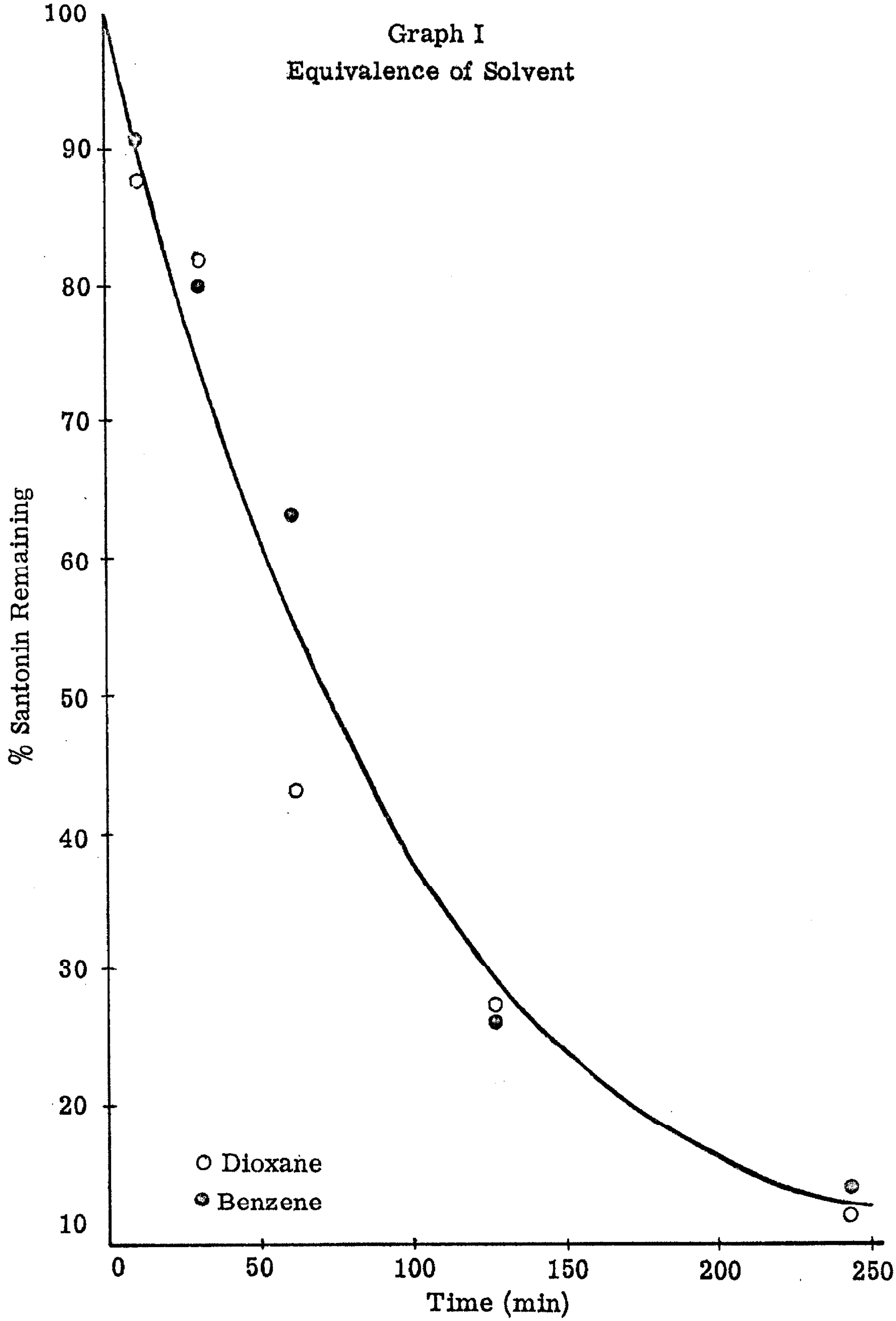
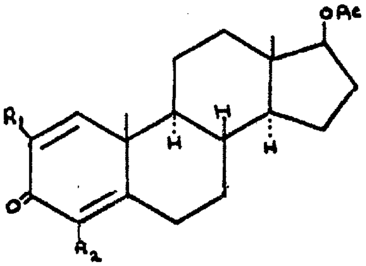
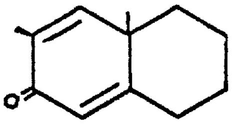
[*] An exactly analogous duality of paths is believed to exist for 4a β, 8 α-dimethyl-5, 6, 7, 8-tetrahydro-2(4aH)-naphthalenone (9b)·ref. 10.


Graph I
Equivalence of Solvent
100
90
80
70
60
50
40
30
20
10
% Santonin Remaining
0
50
100
150
200
250
Time (min)
○ Dioxane
● Benzene

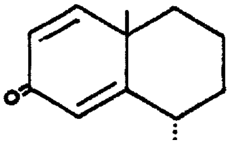


(8)
a R=H Dehydrotestosterone acetate
b R_1=Me, R_2=H
c R_1=H, R_2=Me

recently been reported to undergo a quantitative photoconversion to a lumiproduct in aprotic solvents. On the other hand, 3,4a-dimethyl-5,6,7,8-tetrahydro-2(4aH)-naphthalenone (9a) irradiation proceeds via at least two pathways even in aprotic solvents (12).



(9a)



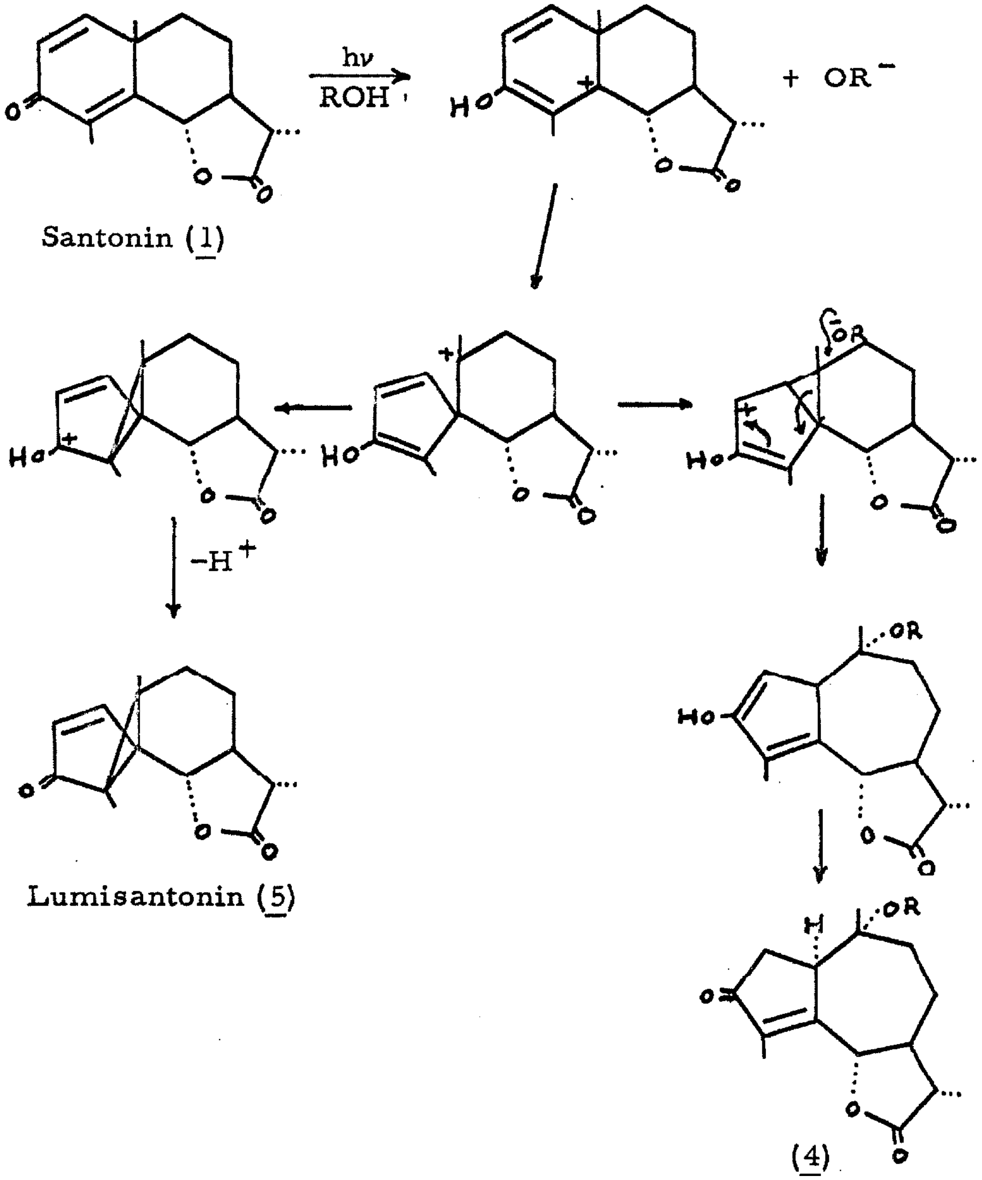
(9b)

Barton (8a) has shown that the perhydroazulenes do not arise from lumisantonin photochemically. Thus, the second mechanistic path in aprotic solvent must involve reaction of solvent with the excited state of santonin.

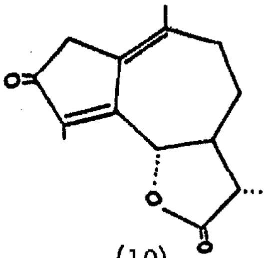
A plausible rationalization of the role played by protic solvent has been given by Kropp and Erman (13), and is shown in Figure 2. The lack of nucleophile and/or absence of protonated carbonyl under conditions of irradiation in aprotic solvent, suppresses internal alkylation at C-1.

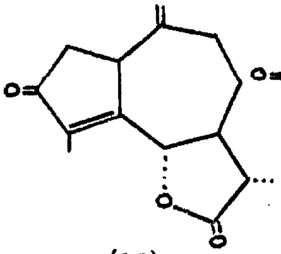
Figure 2

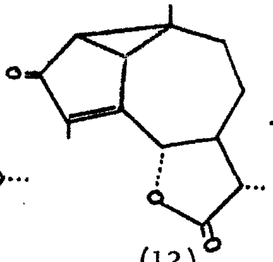
The Function of Solvent in Santonin Photochemistry

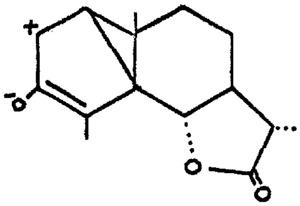


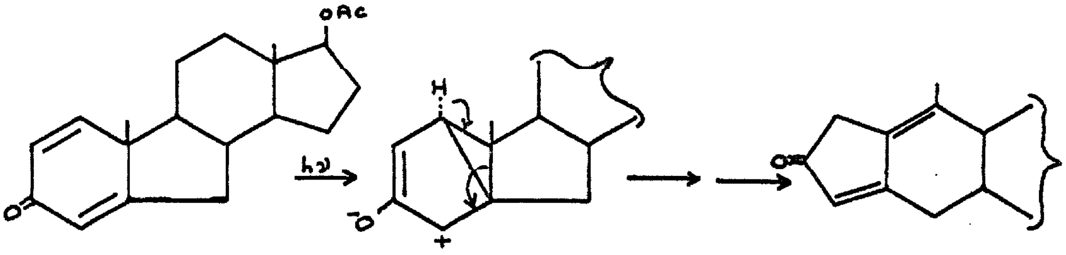
Without reactive solvent, the only perhydroazulenic products to be expected are (10)-(12) arising from (13). Their genesis, probably involving intermolecular hydrogen transfer, has pre-


(10)


(11)


(12)


(13)



(14a) (14b)

cedent in the formation of photoproduct (14b) from B-Nor-1-dehydrotestosterone acetate (14a) (11b, 16).

Compounds (10) (14, 15) and (11) (14) are known and stable. The oft-proposed cyclopropyl ketone (12) (7) may violate Bredt's rule, although Dreiding models appear no more strained for (12) than for lumisantonin. Nevertheless, analysis of many, many santonin photolyses in benzene or dioxane has never shown a trace of products with this 5:7 carbon skeleton. Apparently, photoconversion of dienones to perhydroazulenes of structure (2) is a less favorable pathway than formation of lumiproduct except in those photoconversions where solvent plays a critical role.

III. IRRADIATION OF LUMISANTONIN

A. Absence of Phenols

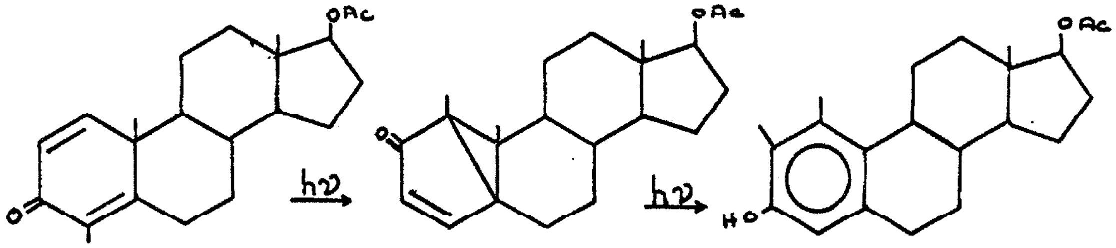
Irradiation of lumisantonin leads to several new products, but no phenols. This observation places santonin in a unique position among dienones, since, in all known photochemistry of other cross-conjugated ketones, the ultimate product is phenolic (18-21).

In view of the generality of phenol formation from photolysis of dienones, the non-conformity of santonin was very carefully tested by extraction of reaction mixtures with 10% sodium hydroxide solution prior to chromatography. No phenols were found, either by the author or by Dr. Paul Kropp, who checked this point independently (private communication).

The only differences between santonin and its more conventional brethren are the methyl substituent at C-4 and the lactone fused to the B ring. Both appear to be important in santonin photochemistry.

1. Substitution at C-4

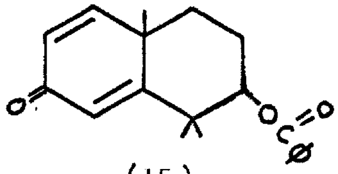
The effect of methyl substitution at C-4 has been studied by Jeger (18, 19) and by Kropp (22). The Swiss workers found that irradiation of dehydrotestosterone acetate (8a) in dioxane leads to a complex mixture containing at least five ketones and four phenols (18). By contrast, photolysis of the 4-methyl analogue (8c) leads only to a lumiproduct with a structure analogous to that of lumisantonin (8d). However, further irradiation of the steroid lumiproduct gives rise to phenol (8e) as the only secondary product (19). Thus, the 4-methyl substituent has an important role in cyclohexadienone photochemistry, but is not responsible for suppressing the pathway to phenols.



(8c) (8d) (8e)

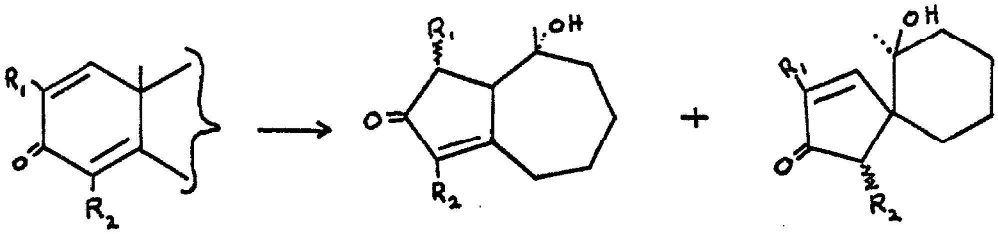
4-methyldehydrotestosterone acetate

There are two ways in which the 4-methyl group may direct the course of dienone photoconversions: electronic and steric. In order to obtain evidence bearing on this point, Kropp (22) has studied the photolysis of the dienone (15) in aqueous acetic or formic acid.



(15)

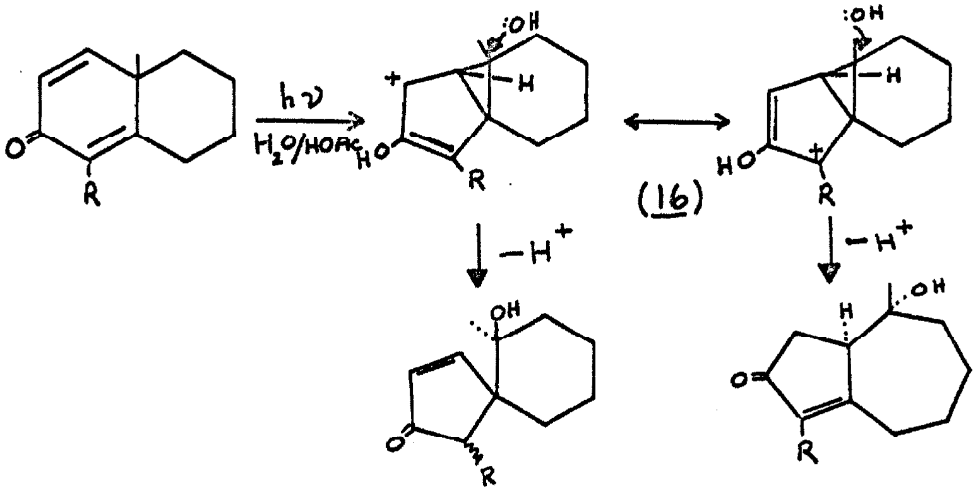
It should be recalled that under acidic conditions, there exists a reaction path for dienones other than the pathway which leads to product of lumisantonin type. For santonin and other 4-methyl dienones (9c), the alternate pathway produces perhydroazulenes (9d) analogous to isophotosantonic acid lactone (2). However, unsubstituted dienones such as (9b) yield spiro ketones of type (9e) and perhydroazulenes (9c) in roughly equal amounts (10, 13, 18b). Lastly, 2-methyl compounds (9a) lead by the alternate path only to spiroketones (11c, 23).



(9) (9d) (9e)

a R_1=Me, R_2=H
b R_1=R_2=H
c R_1=H, R_2=Me

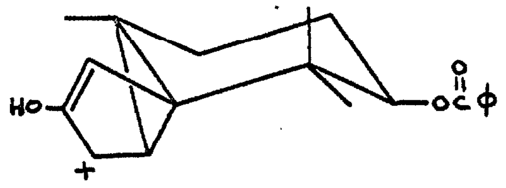
In the Kropp scheme for the role of solvent participation in dienone photolysis (p. 11), the key intermediate is the cyclopropyl ketone (16). The electronic effect of the methyl group would be expected to lead to the observed products by causing one or the other of the resonance forms (16) to predominate (Figure 3). However, the steric effect of the methyl group would also lead to the same products by hindering attack on the side bearing the methyl group.



(9e) (9d)

Figure 3

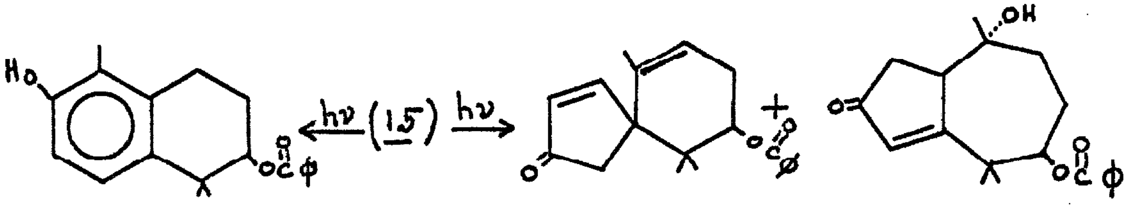
In the irradiation of (15), the key intermediate is (15a). There are no substituents directly on the chromophore so that electronic factors are eliminated (24), but one side of the molecule is hindered by the 6β methyl group. If the influence of the 4-methyl group were entirely steric, then the products from



(15a)

photolysis of (15) would be primarily of the perhydroazulene type in analogy to the irradiation of 4-methyl dienones.

In fact, a perhydroazulene derivative predominates. However, the other products differ from the compounds usually obtained in dienone photochemistry. The only important spiro compound is the dienone (17) and the phenol obtained via the major pathway is the *ortho* compound (18) rather than an analogue of the usual *meta* isomer such as (8e). These results show that purely steric factors, though significant, cannot alone account for the observed effect of the 4-methyl group.



(18) 23% (17) 5% 15%

2. Effect of the lactone function

Photochemical isomerizations of lumiproducts to phenols involve spiran intermediates (13). Such compounds have been isolated from the irradiation of prednisone acetate (19→ 19a) (8b) and dehydrotestosterone acetate (8a→ 8d) (6b).

Figure 4

Formation of Phenols from Lumiproduct (Reference 13)

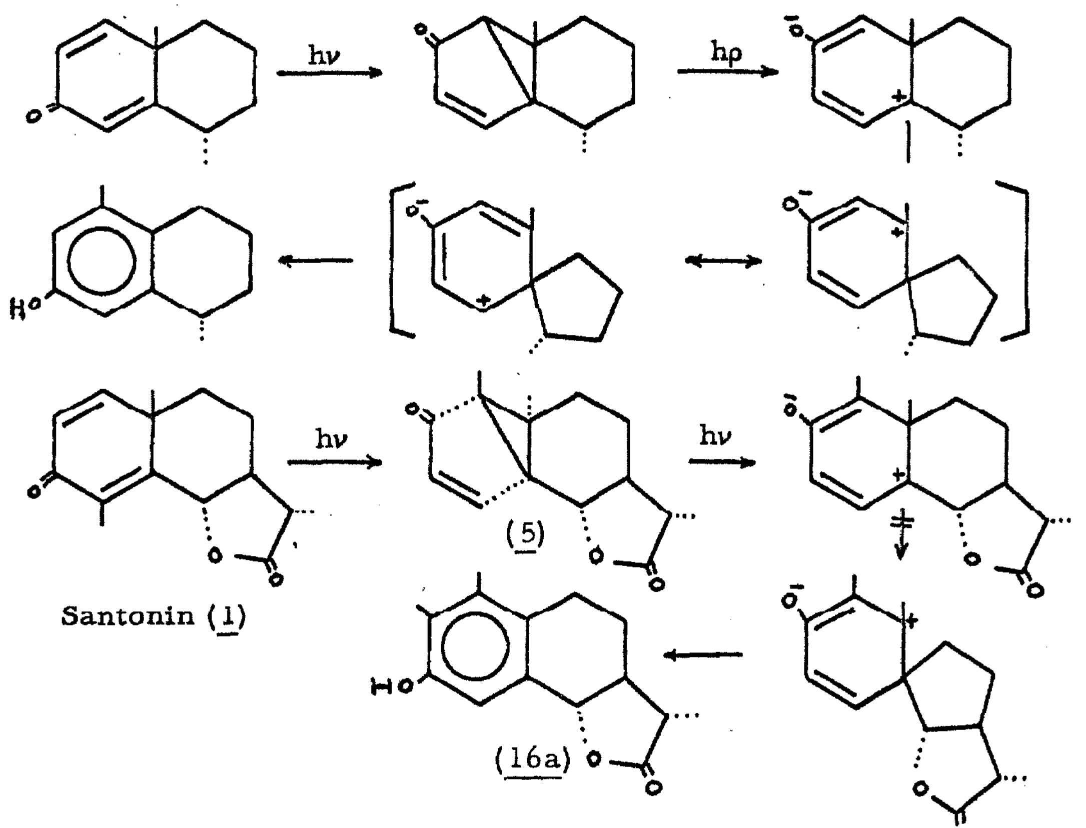
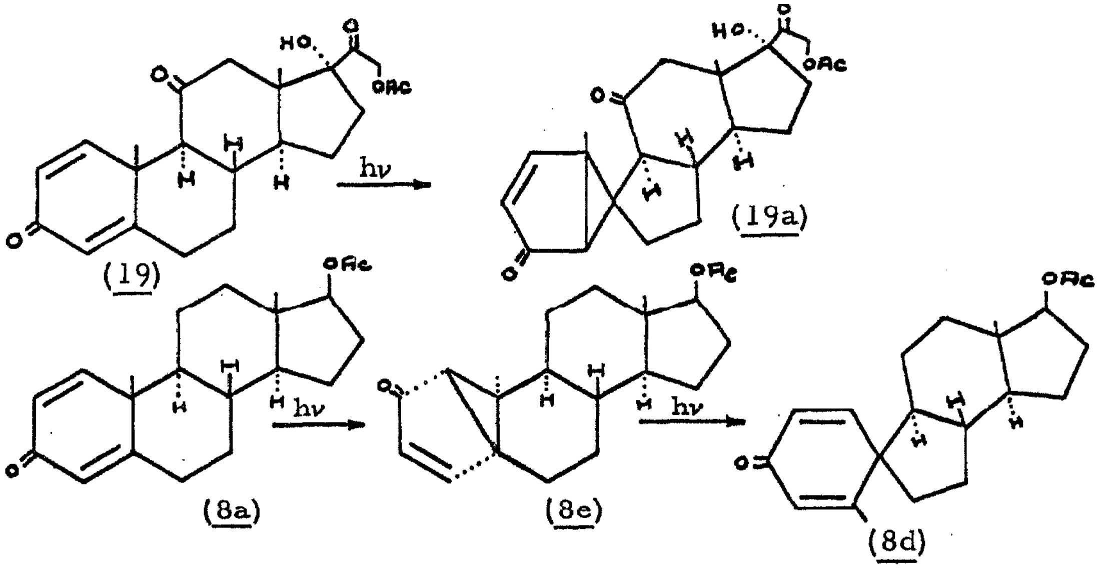
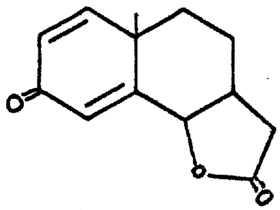


Figure 5

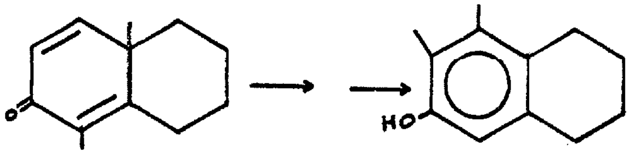
Isolation of Spiran Intermediates



However, in the requisite spiran intermediate from lumisantonin, enormous strain would be generated by the *trans*- fusion of two five-membered rings. Models show this fusion to be essentially impossible. On the other hand, a *cis*-fusion of two five-membered rings is considerably better. Preliminary experiments (with R. Essenberg) on the irradiation of 6-epi santonin led to the isolation of what may be phenolic products. This approach should be tested more completely, especially in view of the recent report that compound (20) does undergo the acid catalyzed dieneone-phenol rearrangement via a spiran intermediate, despite a 6α, 7α (*cis*-fused) γ-lactone (25).



(20)

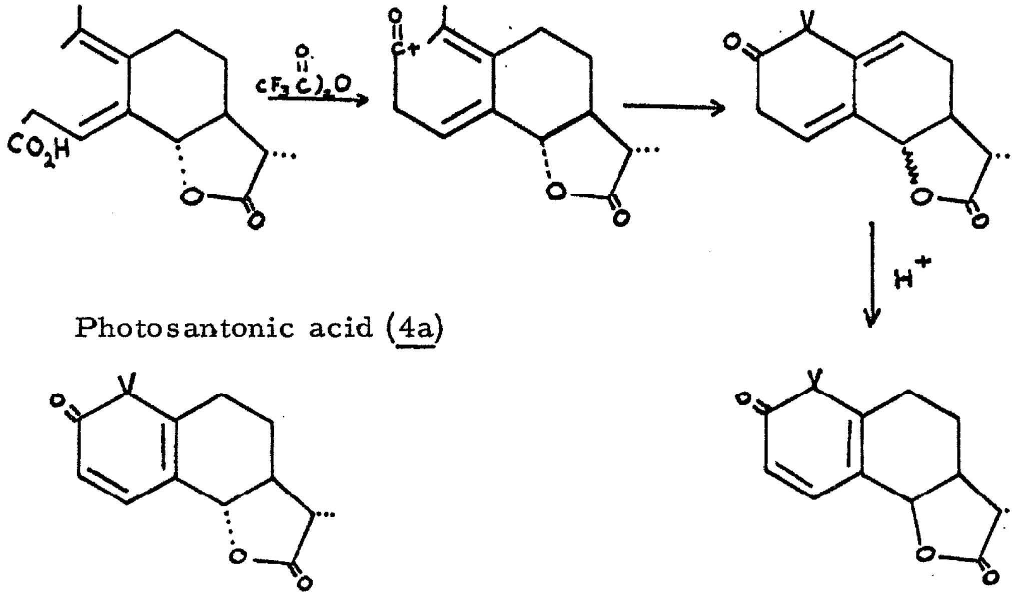


(21) (21a)

The crucial role of the lactone function of santonin in preventing phenol formation on photolysis has been confirmed by Kropp (26). Irradiation of compound (21) ("lactoneless" santonin) leads ultimately to *meta*-phenol (21a).

B. Mazdasantonin*

The major photoproduct of lumisantonin (approximately 80%) is mazdasantonin (23). It has previously been invoked as a transitory intermediate in the photoreaction of santonin to photosantonic acid (19).



Photosantonic acid (4a)

Mazdasantonin (23)

6-epi-mazdasantonin (22)

The 6-epi isomer of mazdasantonin is chemically accessible by a two-step reaction from photosantonic acid (6), and has also been isolated by Chapman (27), who characterized it as its dinitrophenylhydrazone.

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* After Ahura Mazda (also called Ormazd or Ormuzd), the "Good Spirit" and god of light in Zorastrianism. In the rapidly proliferating photochemical literature, the prefixes "photo" and "lumi" are sadly overworked. I therefore propose this addition to the mazda-literature.

He was able to demonstrate that his derivative was identical with the DNP of(22). However, a sample of Professor Chapman's DNP proved to be different from the DNP of mazdasantonin as synthesized in the present work.

This disparity was resolved by consideration of the genesis of(22). Acidic conditions are employed such as those normally used to epimerize various santonin derivatives (28) so that(22) would be expected to have the more stable cis-fusion. Exposure of mazdasantonin to the conditions of the van Tamelen synthesis of(22) yielded a new compound which was shown by n.m.r. to be the expected 6-epi-mazdasantonin (see below). The DNP of this material proved to be identical with that of Chapman's compound. Apparently, Dr. Chapman effected concomitant epimerization of the lactone ring when preparing the DNP of mazdasantonin. In the present work, all photoproducts were found to retain the trans-fusion.

The structure of mazdasantonin is indicated by the observation that irradiation in moist ether quickly and quantitatively converts mazdasantonin to photosantonic acid. This type of reaction for a 6,6-disubstituted homoannular dienone has ample precedent (29).

Physical evidence for the homoannular dienone is conclusive. In the uv, there is only one intense peak at 318 mμ (log ε=3.89)

(30). Rules predict 309 mμ for this system, which is rather close to the actual value (308 mμ) observed for the 6-epi-isomer (26). Thus the release of strain on going from the trans to the cis fusion is manifested in a 10 mμ bathochromic shift which reflects the greater planarity of the dienone system in the cis isomer.

Infrared analysis shows only three bands in the double bond and carbonyl region. One of these is the usual γ-lactone absorption at 1785 cm^{-1}. The second band, of approximately equal intensity at 1665 cm^{-1}, is due to a doubly conjugated ketone. There is, however, only one band (1630 cm^{-1}) attributable to a double bond in conjugation with the ketone, in agreement with the proposed structure of mazdasantonin where the second double bond is tetra-substituted and undetectable by infrared (31).

The n.m.r. of mazdasantonin provides final evidence. The methyl region of the spectrum is extremely simple, and consists only of a singlet (6 protons) ($\delta = 1.23$ ppm) and a doublet ($\delta = 1.27$ ppm, $J = 6$ cps) (3 protons). The doublet is obviously the lactonic methyl and the singlet is due to the gem-dimethyl group . In the olefinic region there is an AB quartet (2 protons) centered at $\delta = 6.67$ ppm ($J = 10$ cps), in which the two peaks at higher field are further split by long-range coupling with the proton on the oxygen-bearing carbon of the lactone function ($J \sim \frac{3}{4}$ cps) (32).

The n. m. r. spectrum of mazdasantonin is extremely concentration dependent and exhibits considerable shifts of the gem-dimethyl singlet as well as a general sharpening of all peaks on dilution. This constitutes a spectral indication of complex formation, which may be of great significance in the subsequent dimerization.

Chapman's compound, 6-epi-mazdasantonin, showed small but highly significant differences from mazdasantonin in the n. m. r. For example, in mazdasantonin the lactonic proton is a broad hash due to coupling with the adjacent proton and additional long-range coupling with the vinyl substituent (δ = 4.55 ppm). However, in 6-epi-mazdasantonin, the lactonic proton is shifted downfield and considerably sharpened into a broad doublet (δ = 4.92 ppm, J = 6 cps). The AB pattern is normalized in the 6-epi isomer in that the higher field peaks are no longer coupled; and the lactonic methyl doublet is somewhat shifted relative to the other methyl peak, but no peaks appear or disappear. These changes are exactly paralleled in the model compounds used for comparison, viz. santonin and its 6-epi isomer (28) (Table II).

The 6-epi-isomer of mazdasantonin has previously been obtained (24, 6), but only as a viscous oil. Mazdasantonin is likewise difficult to purify. If stored as an oil, it gradually oxidizes

Table II

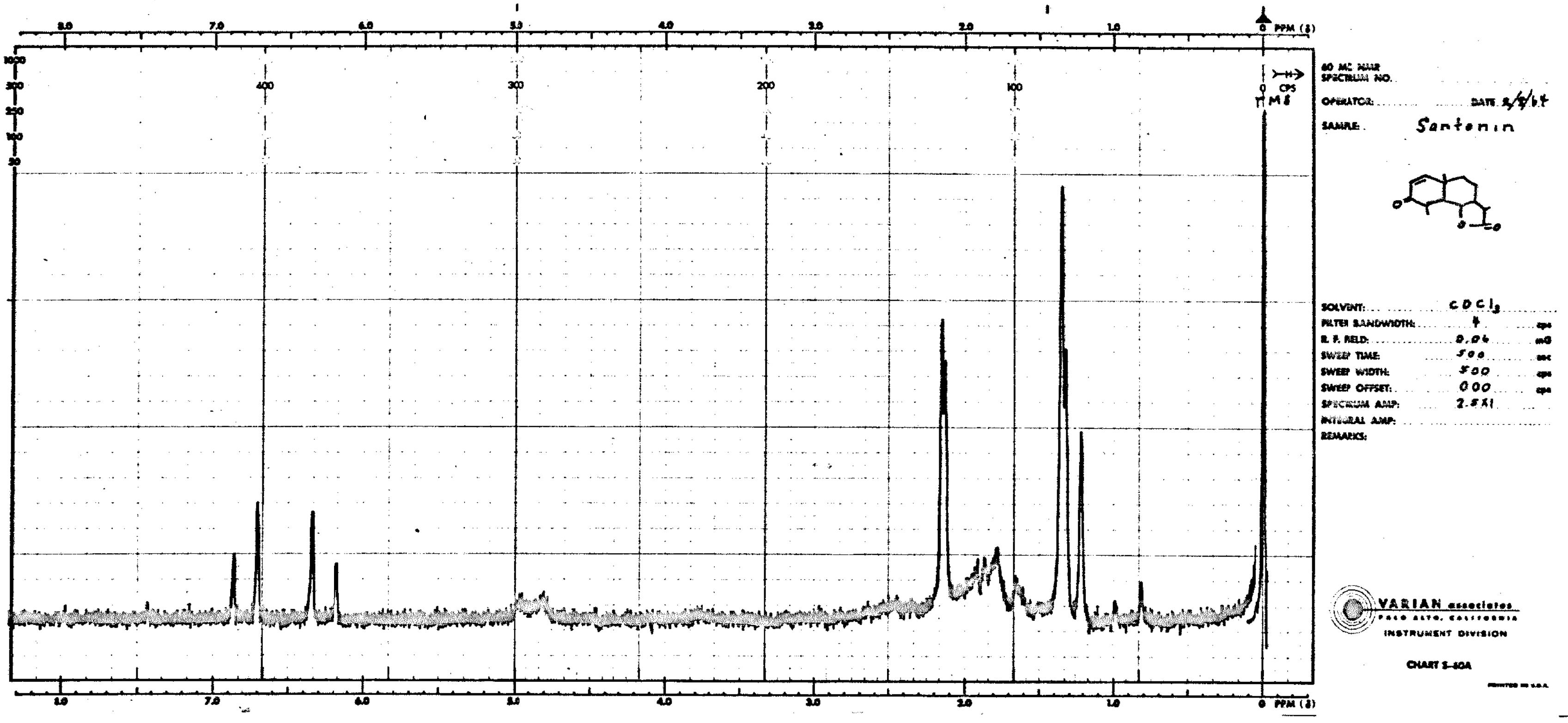
(Internal reference is TMS)

Solvent		lactonic proton	lactonic methyl	singlet Me
$CDCl_3$	Santonin	4.88	1.27	1.37
CCl_4	6-epi Santonin	5.48	1.37	1.30
$CDCl_3$	Mazdasantonin	4.55	1.27	1.23
CCl_4	6-epi Mazdasantonin	4.92	1.25	1.18

and forms numerous tarry products of apparently acidic nature. However, with some effort, mazdasantonin can be crystallized, yellow prisms being obtained by crystallization from acetone-hexane solution, m.p. 118.2-119.0°. In the crystalline state, mazdasantonin is stable for several weeks, provided it is kept in the dark (melting point decrease ~ 1° in two months.

C. The Structure of H

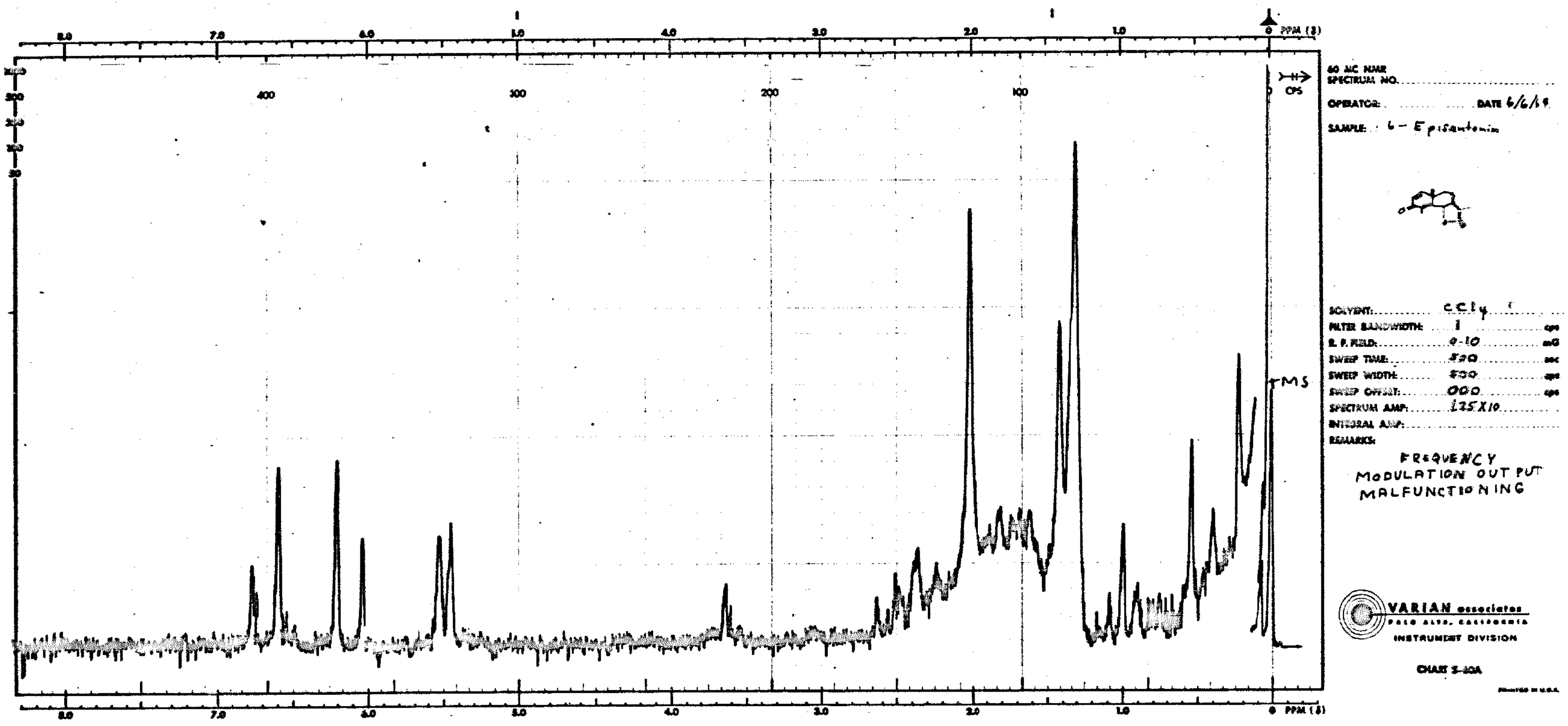
There are two types of perhydroazulene obtainable from lumisantonin. The first structure is exemplified by isophotosantonic acid lactone which is obtained when lumisantonin is treated with strong acid. In this case, the carbonyl group is at C-2. The



60 MC NMR
SPECTRUM NO.
OPERATOR: DATE 8/5/64
SAMPLE: Santonin

SOLVENT: CDCl3
FILTER BANDWIDTH: 4 cps
R. F. FIELD: 0.06 mG
SWEEP TIME: 500 sec
SWEEP WIDTH: 500 cps
SWEEP OFFSET: 000 cps
SPECTRUM AMP: 2.5X1
INTEGRAL AMP:
REMARKS:

Figure 7a. Santonin



60 MC NMR
SPECTRUM NO.
OPERATOR: DATE 6/6/69
SAMPLE: 6 – Episantonin

SOLVENT: CCl4
FILTER BANDWIDTH: 1 cps
R. F. FIELD: 0-10 mG
SWEEP TIME: 500 sec
SWEEP WIDTH: 500 cps
SWEEP OFFSET: 000 cps
SPECTRUM AMP: 125X10
INTEGRAL AMP:
REMARKS:
FREQUENCY
MODULATION OUTPUT
MALFUNCTIONING

Figure 7b. 6-Epi-santonin

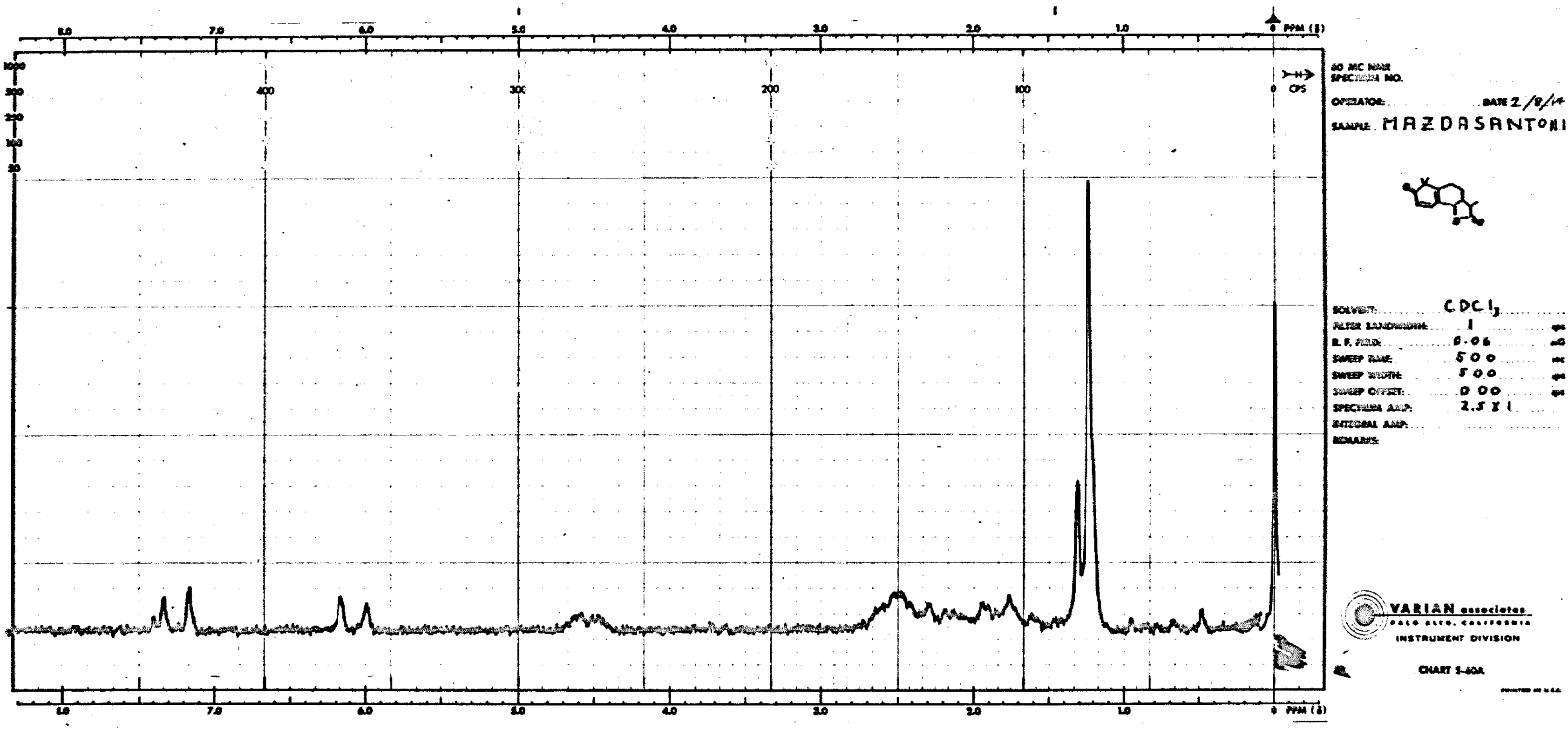


Figure 8a. Mazdasantonin

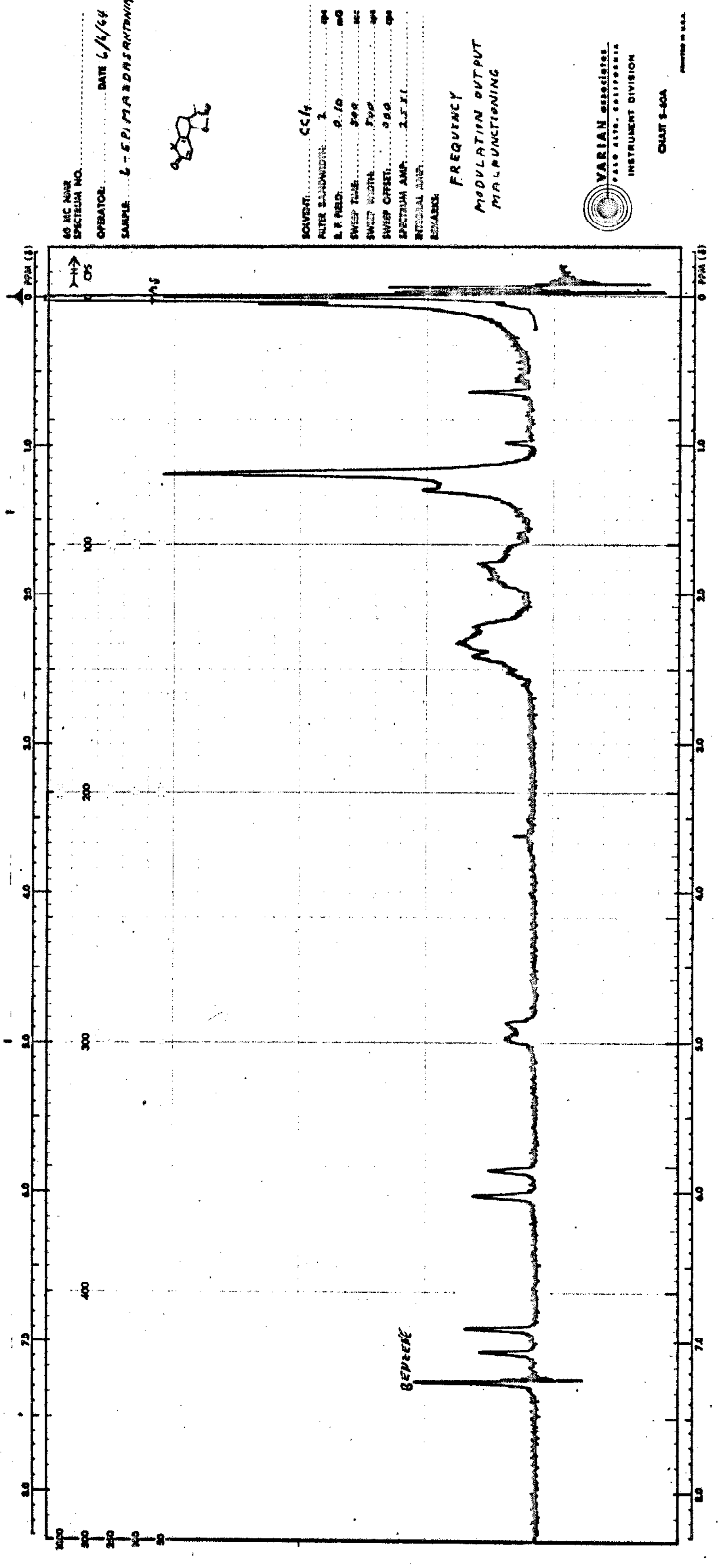


Figure 8b. 6-Epi-mazdasantonin

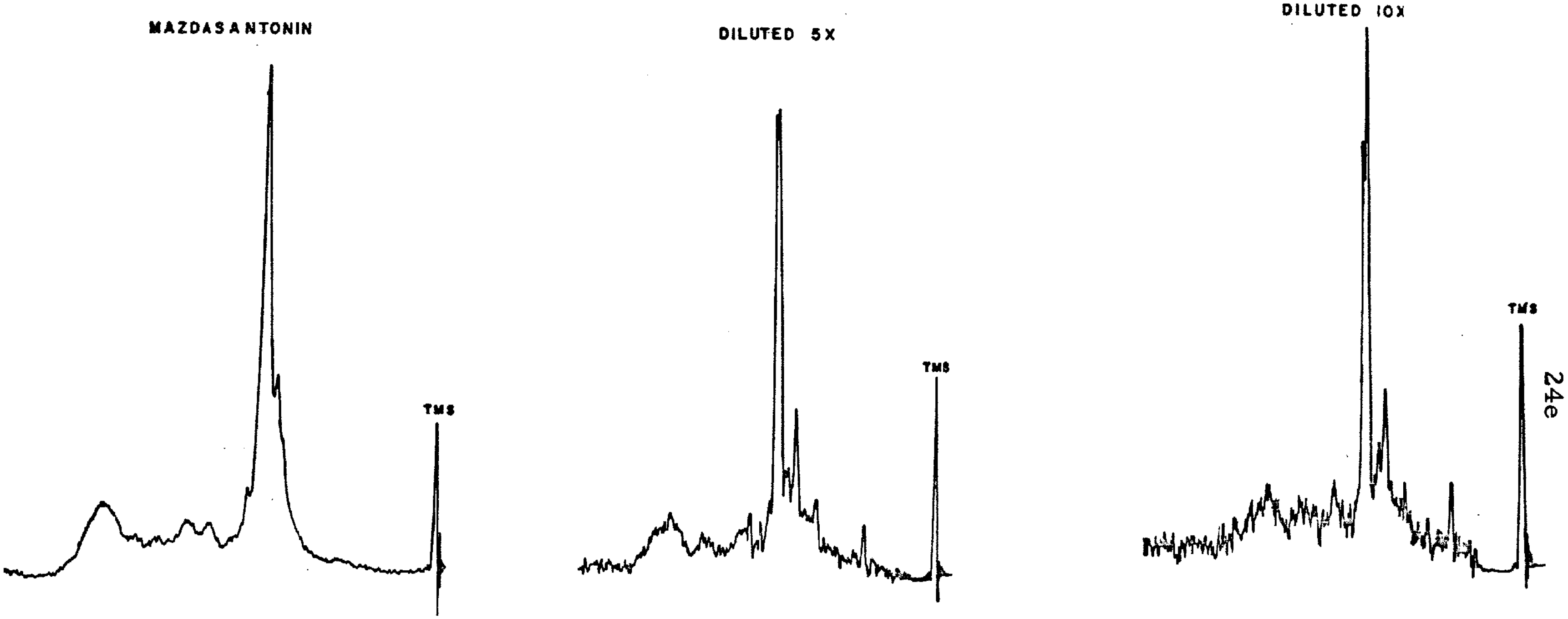
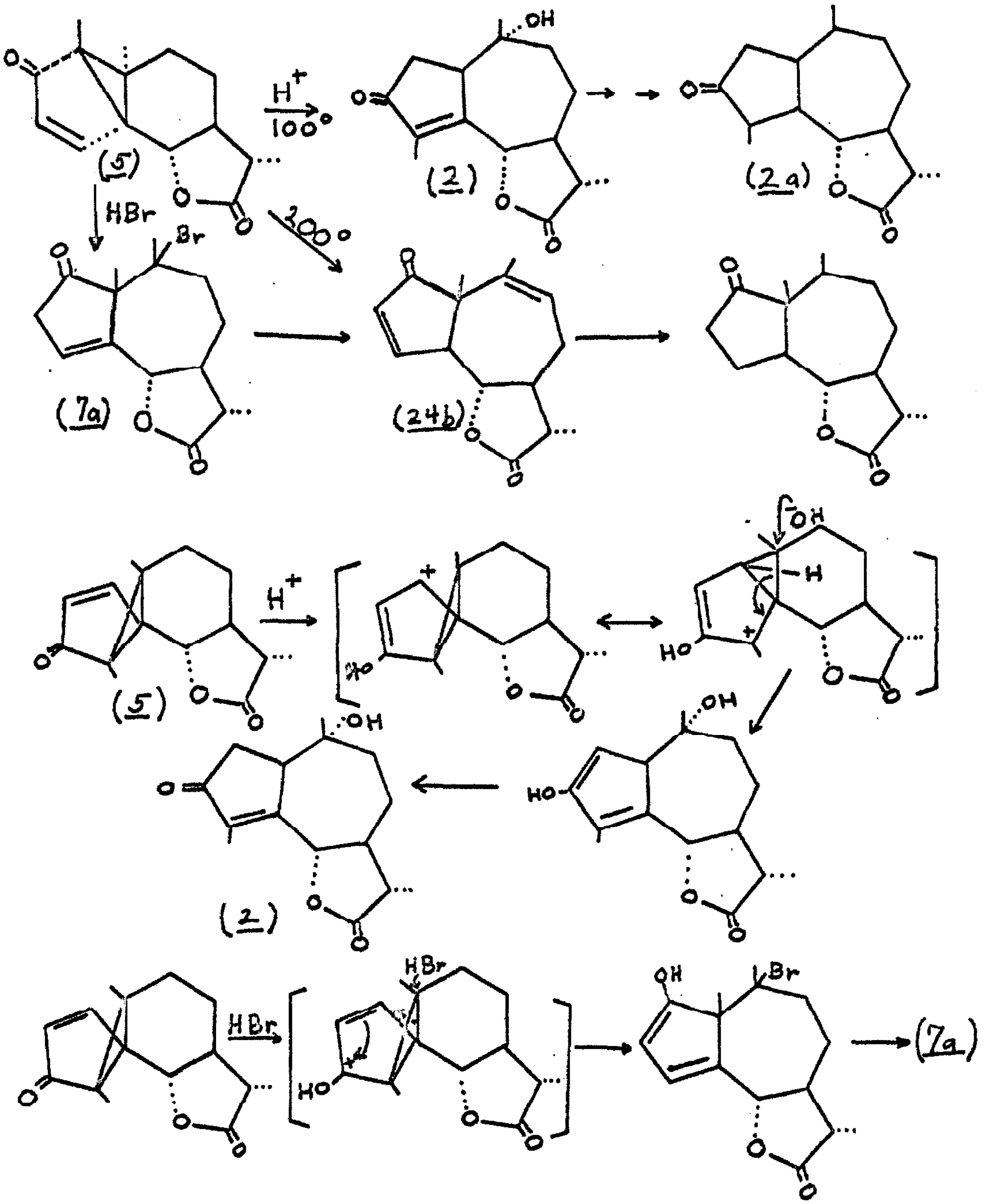


Figure 8c. Complexing of mazdasantonin.

structure has been proved both by chemical studies (5, 33b) and by X-ray determination (33a).

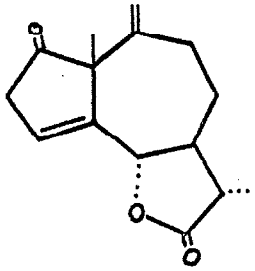


The alternate formulation places the carbonyl at C-1 as in (7a) or (24b). No complex rearrangements are involved in the genesis of this structure; rather the C_5-C_{10} bond of lumisantonin is broken by heat or attack of hydrogen halide (8a, c). Compound (24b) is the so-called pyrolumisantonin obtained by Jeger (8b) from the thermal decomposition of lumisantonin. It was also prepared by Barton (8a), who treated lumisantonin with HBr and isolated (24b) following elimination of hydrogen halide. The independent synthesis of (24b) by two groups involved extensive structural study, and the eventual formulation is well documented.

Irradiation of lumisantonin gives rise to only one terminal photoproduct. This compound is a colorless oil which has defied all attempts at crystallization, but which can be purified by sublimation. The *same material* is obtained when lumisantonin is pyrolyzed at 200°C for one hour (>90% yield). However, *H is not "pyrolumisantonin" (24b) obtained by Jeger from the latter reaction.*

Jeger purified his pyrolysis product by chromatography over "neutral" alumina. Since various brands of neutral alumina stocked in these laboratories were found to be basic to litmus, it seemed reasonable that H might be a thermodynamically less stable double bond isomer of pyrolumisantonin. The explanation that base-catalyzed rearrangement of H to pyrolumisantonin has occurred on chromatography was confirmed by passing H (in benzene solution) through neutral alumina, whereupon both the n.m.r. and infrared showed reaction, with development of a peak at 1715 cm^{-1} corresponding to pyrolumisantonin. As might be expected, acid-washed alumina did not effect this rearrangement. As proof that the conversion of H to pyrolumisantonin did not involve anything more drastic than double bond isomerization, the infrared spectra of perhydro H and tetrahydropyrolumisantonin were compared (KBr) and found to be superimposable.

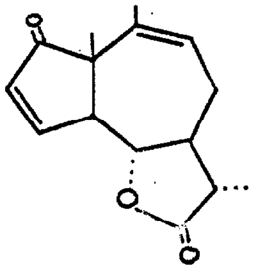
Thus the carbon skeleton of H was established; only the positions of the double bonds remained to be assigned. H exhibits a peak in its infrared spectrum at 1753 cm^{-1} characteristic of an unconjugated cyclopentenone (cf. structures (24c)(8a) and (8f)(7))



(24a)

KBr

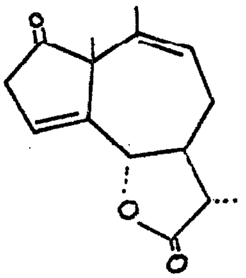
$\nu_{max} = 1753\ cm^{-1}$



(24b)

$CHCL_3$

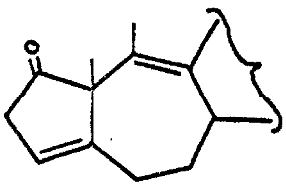
$\nu_{max} = 1715\ cm^{-1}$



(24c)

CCl_4

$\nu_{max} = 1752\ cm^{-1}$



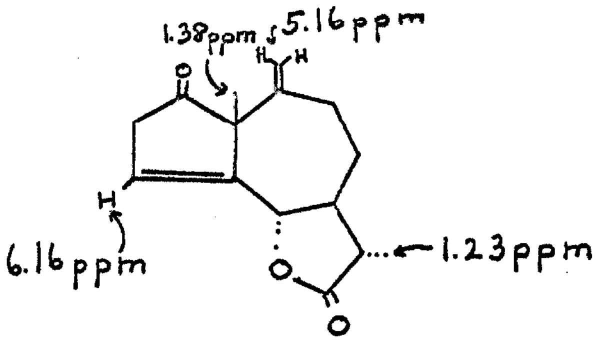
(8f)

KBr

$\nu_{max} = 1744\ cm^{-1}$

This result is consonant with the product (8f) obtained from the pyrolysis of lumi-4-methyl-dehydrotestosterone acetate (8e). The steroid product (8f) was reported to have the cyclopentenone unsaturation in the unconjugated position (7) in contrast to pyrolumisantonin (8b). Since the lumiproducts have the same functional groups and stereochemistry in the A and B rings, any difference in the course of pyrolysis would be remarkable.

Mechanistic considerations (Part II) indicate an exocyclic location for the cycloheptane unsaturation, despite thermodynamic preference for the endocyclic isomer. Examination of the n.m.r. spectrum confirms this expectation and also provides further support for the β assignment of the first double bond. In the methyl region there are only two methyl groups: a singlet corresponding to the quaternary methyl group (3 protons, $\delta = 1.38$ ppm) and the doublet of the lactonic substituent (3 protons, $\delta = 1.23$ ppm, $J = 6.5$ cps). In the double bond region of the spectrum, there is a clear doublet integrating to 2 protons ($\delta = 5.16$ ppm, $J = 5$ cps) obviously due to a methylene substituent. At much lower field ($\delta = 6.16$ ppm), there is a broad signal (one proton) attributable to the cyclopentenone proton. Thus H is formulated as(24a).



24a

The difference in chromatographic behavior of H and (8f) is no doubt due to the presence of the lactone ring in H. Thus (8f) survived chromatography without double bond shifts, at least in the cyclopentane ring, because there is less strain in the system without the lactone. However, the reported position of the second double bond in (8f) is probably not correct. The original paper in which structure (8f) is assigned (7) supplies no evidence for the location of the cycloheptane unsaturation; presumably, the endocyclic position was preferred by analogy with pyrolumisantonin. However, the double bond in ring B of the true lumisantonin pyrolysis product (24a) is certainly exocyclic, as shown by the foregoing evidence, and hence the cycloheptane unsaturation in the steroid pyrolysis product is very likely exocyclic also.

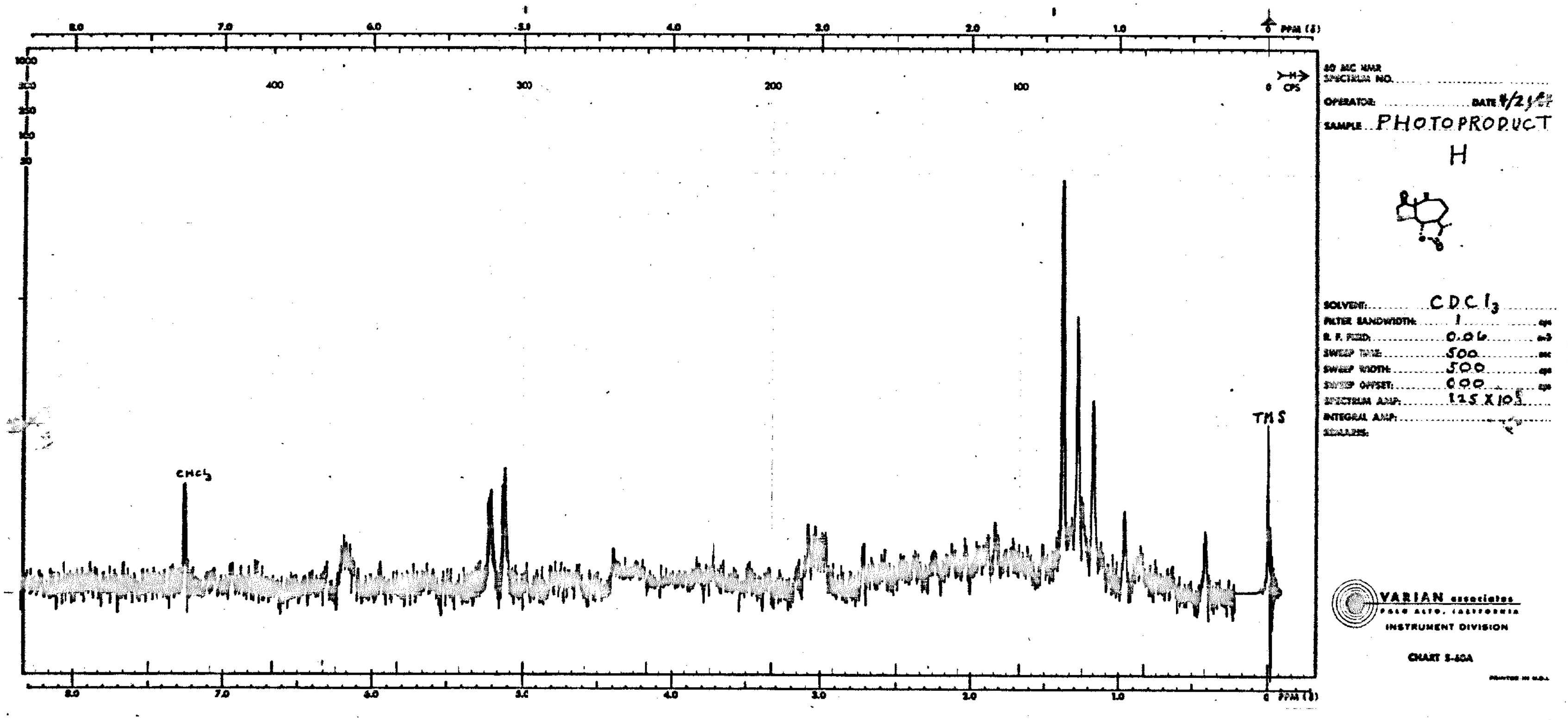


Figure 9. Photoproduct H

D. The Structure of B and J

Irradiation of lumisantonin leads to a complicated mixture. Mazdasantonin and its dimeric product, E, account for 80% of this mixture, the relative amounts of the two products varying with concentration and time of irradiation. Another 10% is H. The remaining material (10%) consists of two compounds, B and J, in roughly equal yield, plus traces of F and F', tertiary photoproducts arising from further reaction of B and J. Photoproducts B and J were isolated in approximately 3% yield after almost any time of irradiation except after very long photolyses (5 days) at which time neither was present.

Both B and J have spectra very similar to that of lumisantonin. The pertinent data are presented in Table 3.

Table 3

	Infrared	Ultraviolet
LS	$\nu_{max}^{KBr} = 1703\ cm^{-1}, 1576\ cm^{-1}$	$\lambda_{max}^{EtOH} = 239\ m\mu\ \log \epsilon = 3.70$ $= 338\ m\mu\ \log \epsilon = 2.41$
B	$\nu_{max}^{KBr} = 1695\ cm^{-1}$	$\lambda_{max}^{EtOH} = 244\ m\mu\ \log \epsilon = 3.67$ $= 338\ m\mu\ \log \epsilon = 2.02$
J	$\nu_{max}^{CCl_4} = 1700\ cm^{-1}$	$\lambda_{max}^{EtOH} = 237\ m\mu$

Hydrogenation of lumisantonin, B, or J over platinum oxide catalyst readily provided dihydrolumisantonin, and the perhydro products from B and J, respectively. These materials had especially instructive infrared spectra, particularly in the fingerprint region where almost all of the same peaks are present in the three compounds with only minor shifts in position and intensity. Moreover, any peak in dihydrolumisantonin, dihydro B, or dihydro J may be found in at least one of the remaining two compounds and the spectra above 1200 cm^{-1} are identical. Clearly, all three compounds are extremely similar, a conclusion that is supported in a negative way by the fact that neither lumisantonin, B, nor J forms a dinitrophenylhydrazone derivative, in contrast to santonin, mazdasantonin, 6-epi-santonin, 6-epi-mazdasantonin, and E.

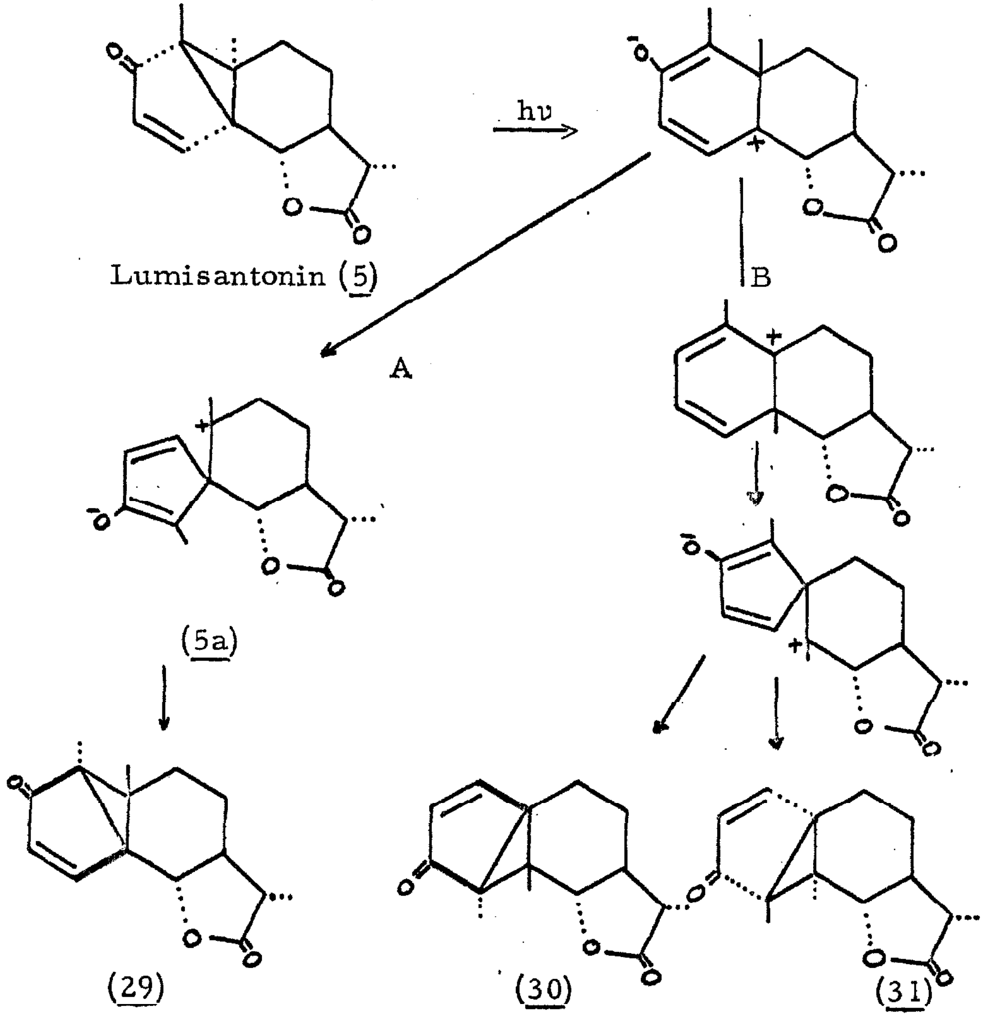
The n.m.r. leads again to the conclusion that lumisantonin, B, and J are very similar. There is an AB quartet, two singlets corresponding to quaternary methyl groups, and a doublet due to the lactonic methyl in each compound. The C-6 (lactonic) proton resonance is also the same for lumisantonin, B, and J, but quite unlike the corresponding patterns in the other isomers. This absorption is a clear doublet that is shifted to considerably higher field than in the precursor, santonin, or in the subsequent photoproduct, mazdasantonin.

The only structures that are reconcilable with these results are the alternate structure for lumisantonin (29), once believed to be the correct lumisantonin stereochemical formulation (8b), and the two stereoisomers of "upside-down" lumisantonin, (30) and (31). These are the only three possible structures for B and J.

The generation of these structures from lumisantonin can be easily rationalized, as shown in Figure 10.

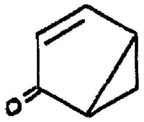
Figure 10

The Photolysis of Lumisantonin to B and J

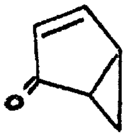


In the subsequent discussion, the two possible stereochemical arrangements which the photoproducts B and J may adopt will be referred to as the lumisantonin and alternate lumisantonin stereochemistries. A brief discussion of this nomenclature is in order.

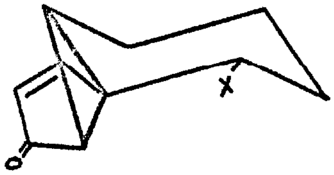
In the simplest cyclopropylenone (26), there is only one


(26)

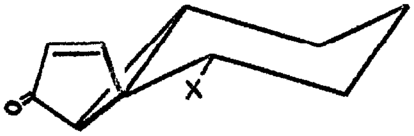

(26a)


(26b)

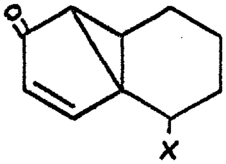
possible stereochemistry, that of the enantiomorphic pair (26a) and (26b). However, if a substituted second ring is present in the molecule, the two forms (27) are no longer mirror images. Rather,



(27a)



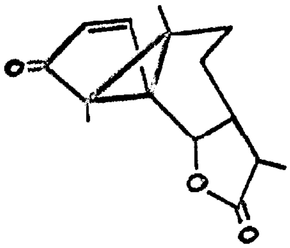
(27b)



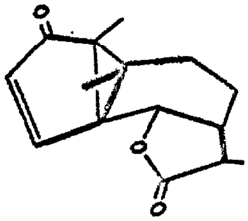
(28)

they are different compounds and may bear little or no resemblance to each other in physical or chemical properties, even though a two-dimensional representation (28) would be the same for both structures (27a) and (27b).

In the case of lumisantonin, the two possible stereochemical formulations are shown in (5) and (29).



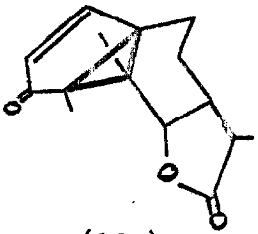
(5)



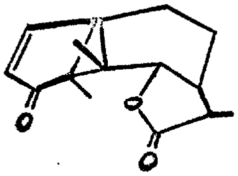
(29)

Structure (5) is the correct one for lumisantonin (34) and this disposition of the cyclopropylenone with respect to the B ring is hereafter designated the lumisantonin stereochemistry. Similarly, the disposition of the cyclopropylenone system relative to the B ring as in (29) will be referred to as the alternate lumisantonin stereochemistry.

In perfectly analogous fashion, the two "upside-down" lumisantonins (30) and (31) differ from each other only in their stereochemistries. The appropriate space pictures are drawn in (30a) and (31a). Note that (30) has the alternate lumisantonin stereochemistry whereas (31) has the usual lumisantonin stereochemistry.



(31a)

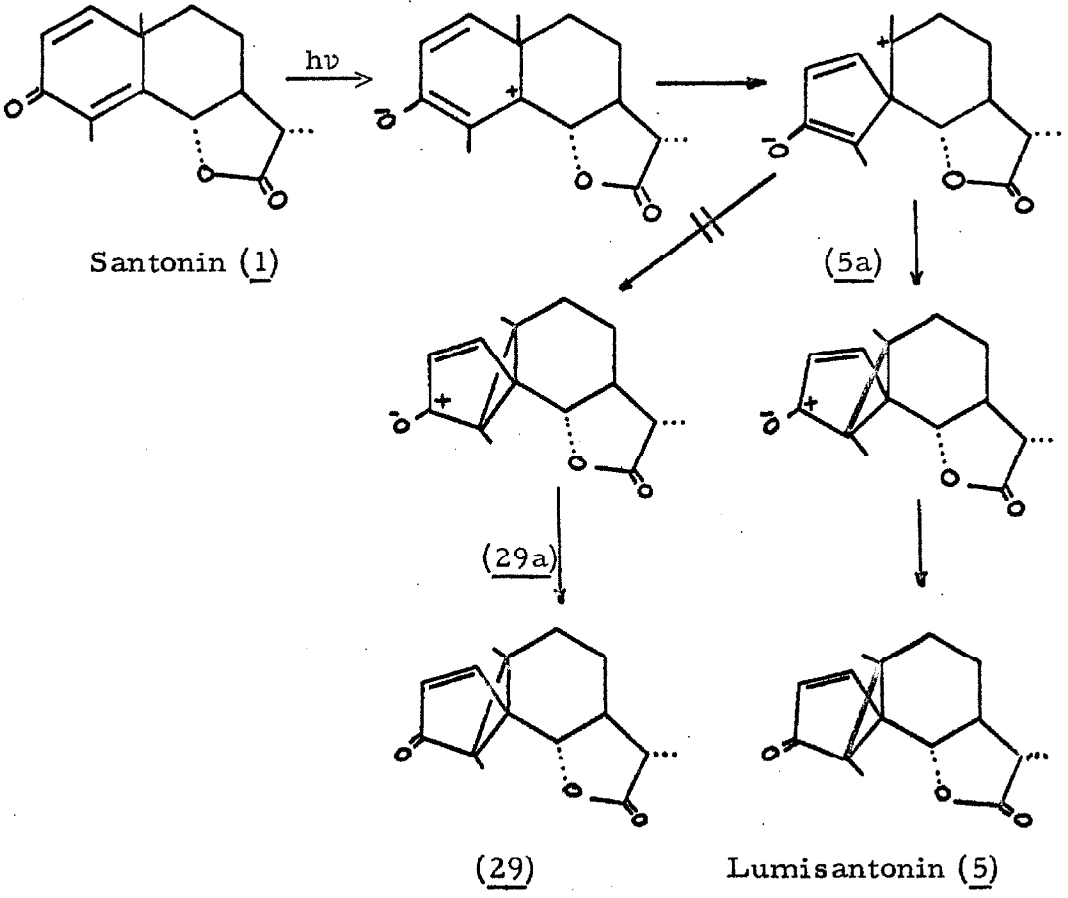


(30a)

Arguing on the basis of polar intermediates (cf. Part II) leads to the conclusion that the alternate lumisantonin (29) is not likely to be a product. If the formation of lumisantonin from santonin does proceed as in Figure 11 , then (29) could be formed from (5a), the same carbonium ion postulated for the conversion of lumisantonin to (29) (Fig. 10). As discussed previously, lumisantonin (5) is the only primary photoproduct formed by irradiation of santonin in aprotic media.

Figure 11

Formation of Lumisantonin from Santonin

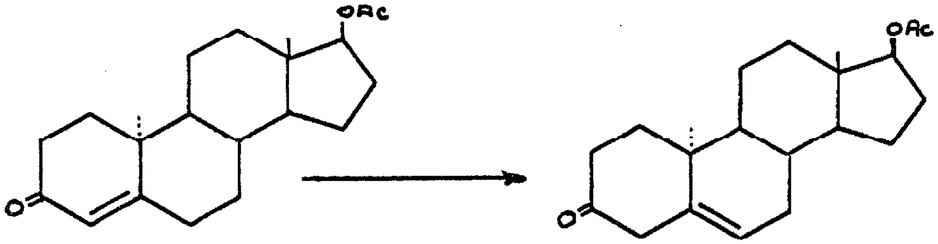


The fact that no (29) is produced on irradiation of santonin almost surely means that the formation of lumisantonin from santonin is a concerted process, i.e. (5a) does not occur as a free carbonium ion. Thus, irradiation of 10 α-testosterone acetate does not give any of the (stable) product analogous to lumisantonin (see below).

On the other hand, the formation of (29) from lumisantonin need not be concerted. Nonetheless, the process is still unlikely because in (29a), the methyl group at C-4 must be brought too close to the lactone function. The upside-down lumisantonins do not have any steric direction from C-9, so that equal amounts of the two upside-down lumisantonin stereoisomers would be expected if they were to be formed. The observation that B and J are isolated in approximately equal yield after almost any length of irradiation indicates that they may be the upside-down isomers.

The alternate lumisantonin stereochemistry appears to be disfavored although the reasons are not presently known. The photolyses of a number of enones and dienones are now known in which the primary lumiproducts have the lumisantonin stereochemistry, but no instances of the lumisantonin alternate stereochemistry have yet been reported. Indeed, photolysis of 10 α-testosterone acetate (32) leads only to double bond isomer (32a) (35).

In this case, inversion of the C-10 methyl group leads not to the alternate lumisantonin stereochemistry but to complete suppression of the reaction pathway to lumiproduct. By contrast, the normal 10β isomer photolyzes to the appropriate analogue of lumisantonin in quantitative yield (11a).



(32) (32a)

10α-testosterone acetate

The suggestion that B and J are the two upside-down lumisantonins is supported by various similarities between the compounds, including v.p.c. retention times, liquid-liquid chromatographic behavior and the complete infrared inactivity of the double bond in B and J (lumisantonin has a moderate absorption at 1576 cm^{-1}).

This expectation that B and J are the two upside-down lumisantonins was confirmed and the relative stereochemistries assigned by n.m.r. and photochemical results.

The resonance of the lactonic proton in various photoproducts has proved to be a very delicate probe in assessing electronic effects in the A ring. For example, the greater deshielding of the lactonic proton in the equatorial conformation has already allowed an unequivocal distinction between *cis* and *trans* lactonic epimers (p. 24). When compared with isomers such as santonin or mazdasantonin, in which the lactonic proton is involved in long-range coupling, photoproducts of the lumisantonin type all exhibit large shifts of the lactonic proton to higher field, and this shift is accompanied by a considerable sharpening of the doublet resonance because, in these substances, the long-range coupling is reduced. However, in the case of J, both the shift and the sharpening are much less marked than for lumisantonin and B, indicating an *orientation of the double bond parallel to the lactonic C-H bond*, Models show that only one of the three possible isomers has such a positioning, *upside-down lumisantonin with stereochemistry inverted* (*30*).

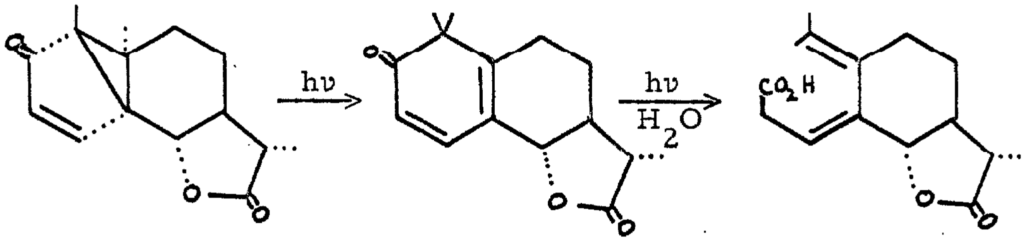
As previously discussed (p. 23), the formation of substances having the alternate lumisantonin stereochemistry is sterically disfavored. In the photolysis of 10α-testosterone acetate, the failure to isolate an appropriate lumisantonin-like product suggests that the alternate lumisantonin stereochemistry is inherently unstable. Such a stereochemistry has been assigned to photoproduct J on the basis of the n.m.r. spectrum, and the reader will therefore rejoice to learn that J is far less stable on storage than is B or lumisantonin, and in fact decomposes completely in the dark. If both B and J are upside-down lumisantonins, then the evidence demands that B have the lumisantonin stereochemistry (31).

The conclusion that neither B nor J is the alternate lumisantonin (29) is very strongly supported by analysis of the olefinic AB quartets of B, J, and lumisantonin (Table 4). The patterns for B and J are similar to each other, but clearly unlike the pattern for lumisantonin. Of particular significance is the fact that the coupling constants for the AB quartet of B and J are the same (10 c.p.s.), but markedly different from the coupling constant for the AB quartet of lumisantonin (5 c.p.s.).

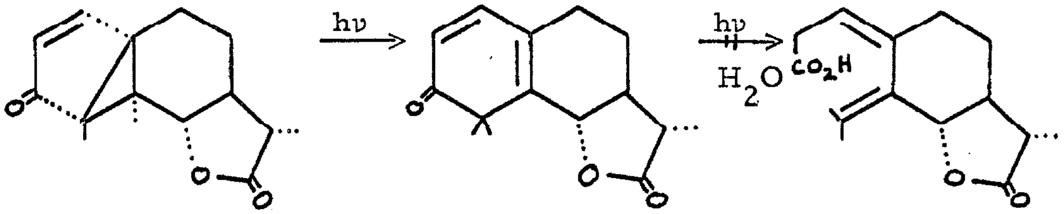
Table 4

	Solvent	Lactonic Proton	AB Pattern				Int Ref
			Center	δ_A	δ_B	J	
lumisantonin	$CDCl_3$	3.93	6.90	6.08	7.72	5	TMS
B	$CDCl_3$	3.95	6.80	6.17	7.43	10	TMS
J	CCl_4	4.15	6.80	6.20	7.40	10	Benzene

A final demonstration of B's structure is provided by its photochemistry. Irradiation (sealed, degassed n.m.r. tube) until the spectrum of the starting material is completely gone (3 days), yields the two tertiary products F and F' in 4: 1 ratio (v.p.c.). Infrared analysis reveals these compounds to be *analogous to, but different from* their lumisantonin analogues H and mazdasantonin. Specifically, the carbonyl absorption of F' (the minor compound) falls at 1685 cm^{-1} ($CHCl_3$), indicating disruption of conjugation by interaction between the *gem*-dimethyl group and the lactone. Moreover, irradiation in the presence of water *does not lead to acidic product.* Since interaction with a proton is sufficient to destroy conjugation in photosantonic acid, it is hardly startling that opposition by a methyl prevents isopropylidene formation.*



(5) LS (23) (4a)



(31) B (32c) F' (33)

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* Recall that photosantonic acid shows only end absorption above 200 mμ.

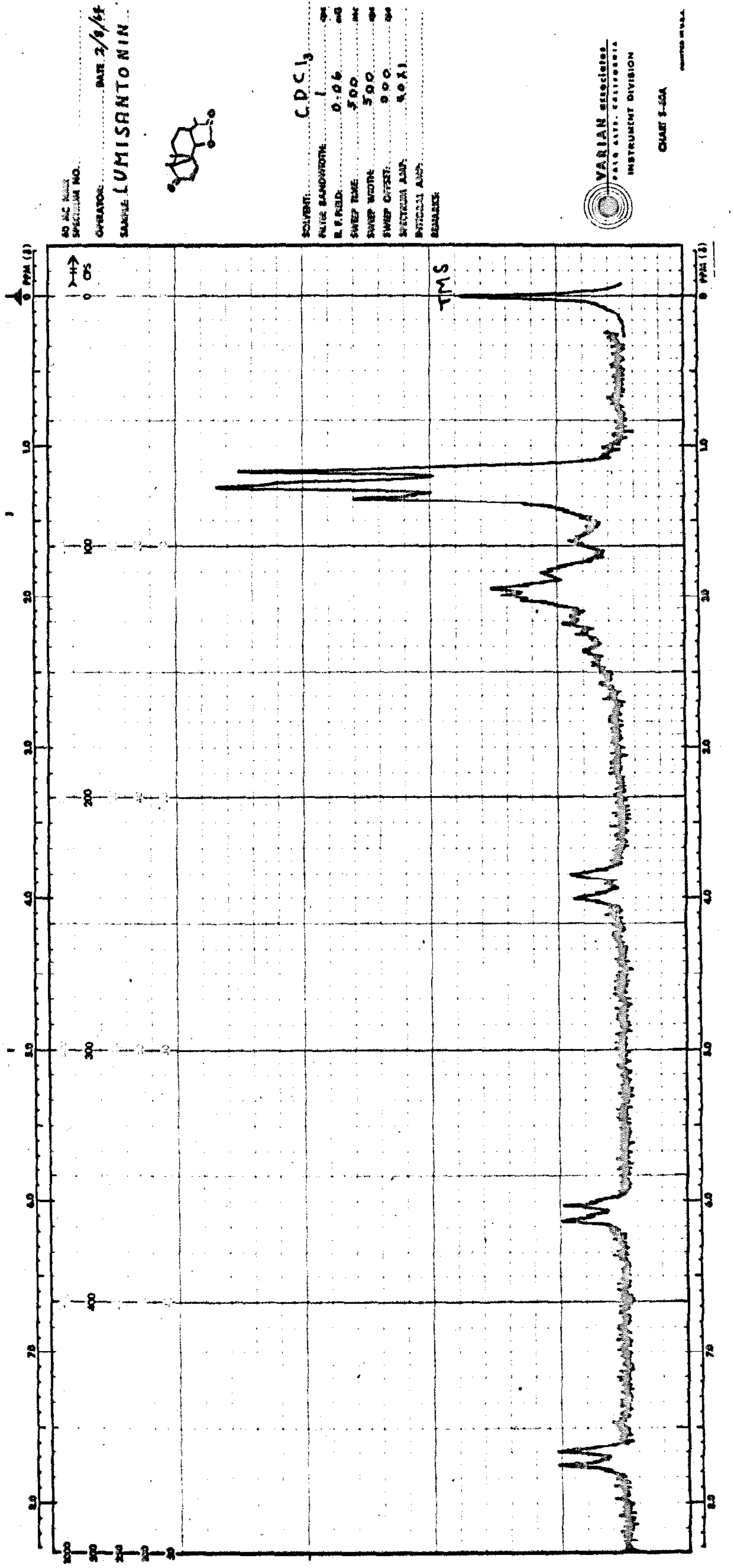


Figure 12a. Lumisantonin

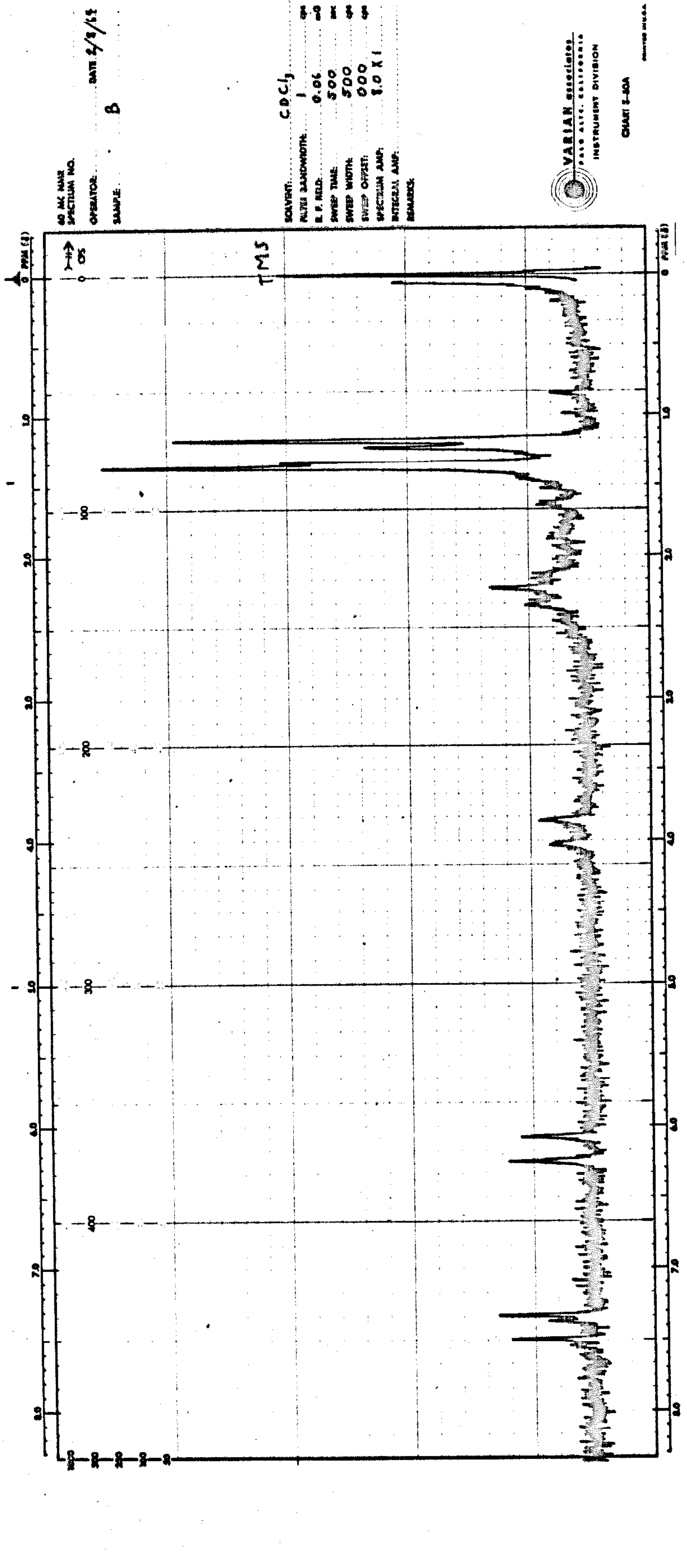
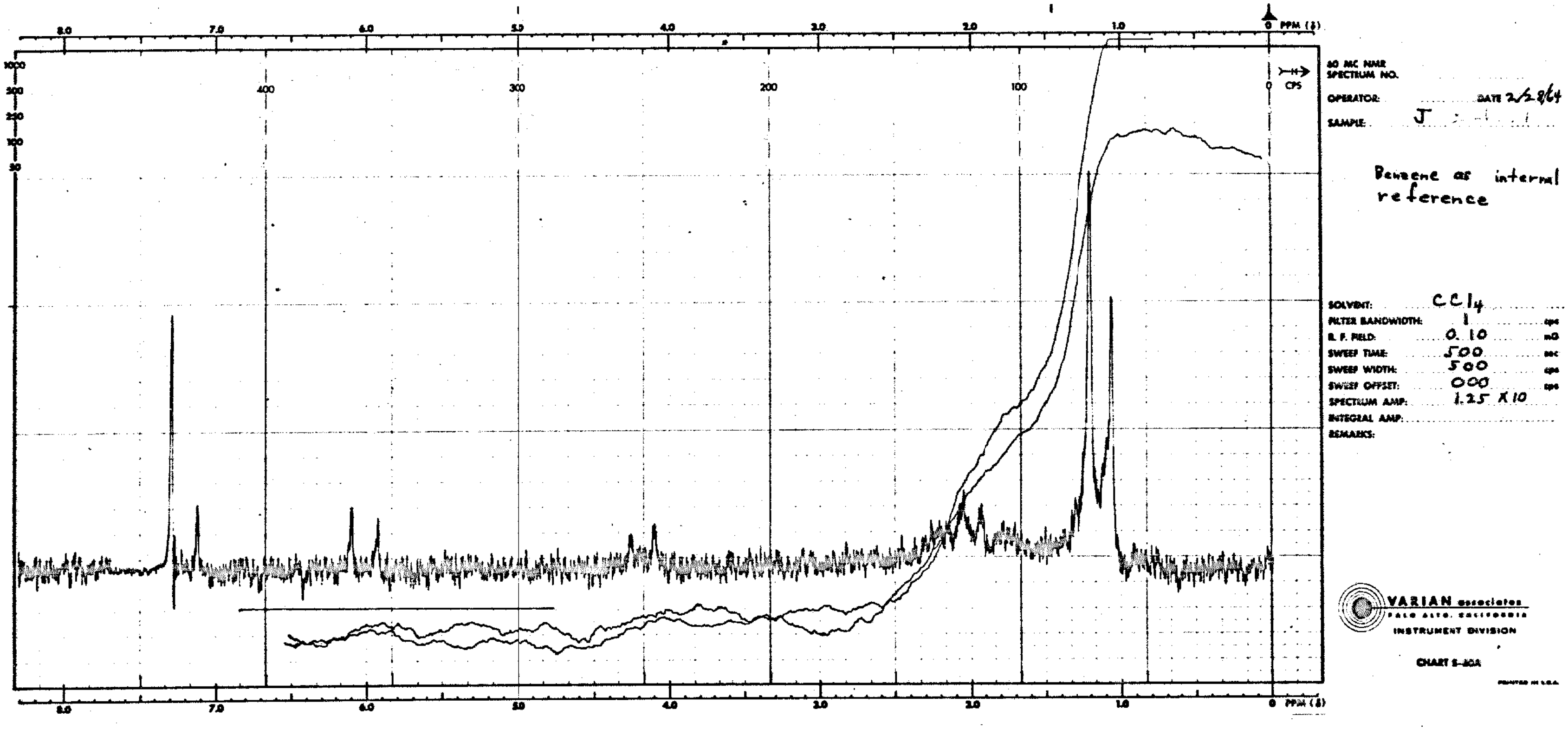


Figure 12b. Photoproduct B.



60 MC NMR
SPECTRUM NO.

OPERATOR: DATE 2/28/64

SAMPLE: J

Benzene as internal reference

SOLVENT: CCl4
FILTER BANDWIDTH: 1 cps
R. F. FIELD: 0.10 mG
SWEEP TIME: 500 sec
SWEEP WIDTH: 500 cps
SWEEP OFFSET: 000 cps
SPECTRUM AMP: 1.25 X 10
INTEGRAL AMP:
REMARKS:

Figure 12c. Photoproduct J.

Although only qualitative measurements were made, the photolysis of lumisantonin is certainly faster than the photoconversion of B by a factor of at least six. Inspection of models shows H to be neither more nor less strained than F, the upside-down isomer of H. On the other hand, F' (upside-down mazdasantonin) should be considerably destabilized by steric interaction of the gem-dimethyl group with the bulky lactone on the same end of the double bond. It may reasonably be argued that the decrease in quantum yield of B relative to lumisantonin arises primarily from suppression of the pathway to the dienone product. Thus, the observed ratio of naphthalenic and azulenic products of B photolysis is also in agreement with the proposed "upside-down" structures. From the foregoing evidence, structures (30) and (31) are assigned to J and B.*

The structural rearrangements of santonin in aprotic solvent are summarized in Figure 13. These results extend and complement the previous work in hydroxylic solvent shown in Figure 1.

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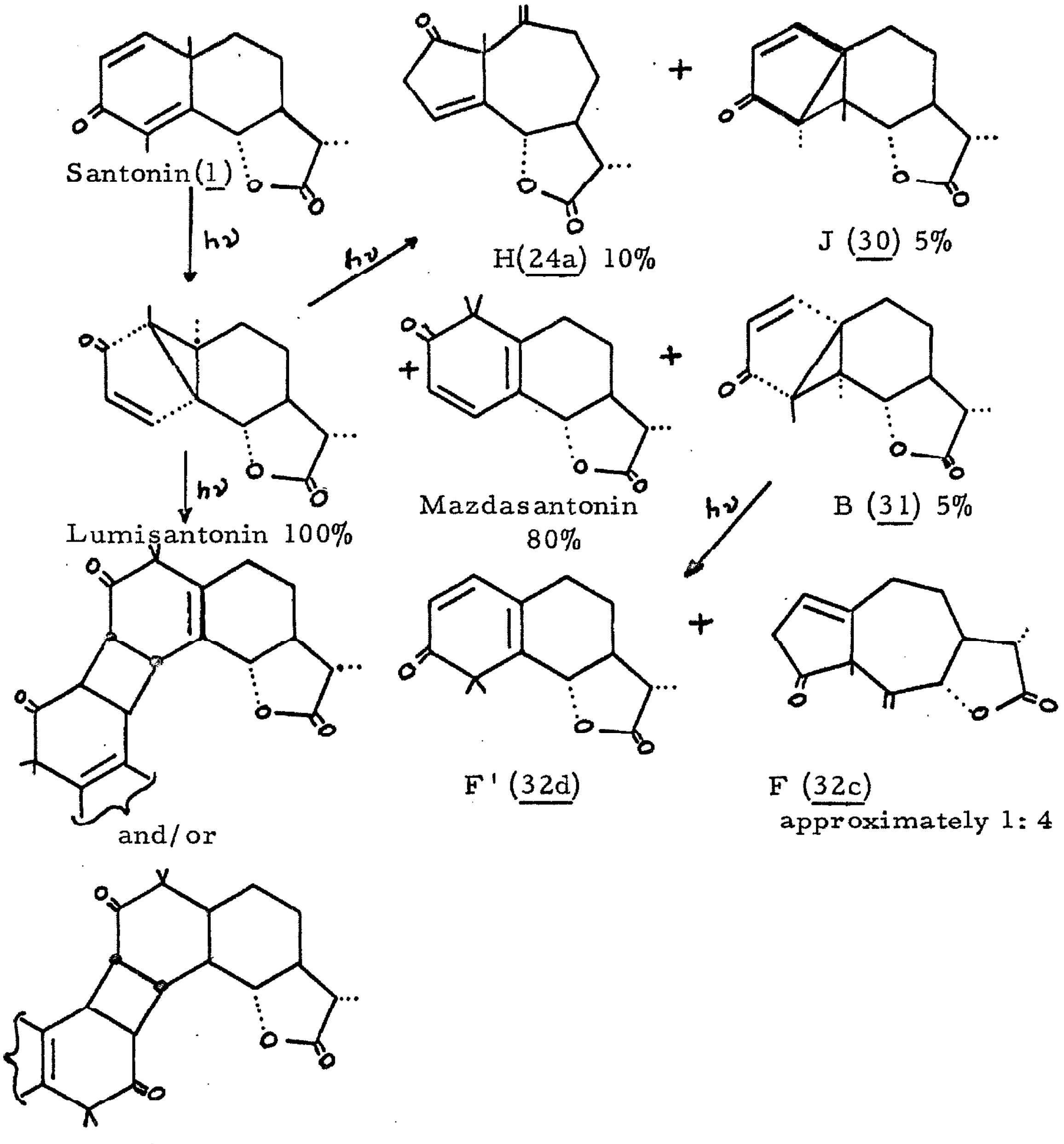
* The evidence presented seems rationalizable only as concluded. However, it must be pointed out that B has as yet failed to give a satisfactory analysis for carbon.

Figure 13

Santonin Photochemistry in Benzene (1964)



E. The Dimerization of Mazdasantonin

When mazdasantonin is irradiated in protic solvent, specifically in moist ether, it is quickly and quantitatively converted to photosantonic acid. Since mazdasantonin is a 6, 6 disubstituted homoannular dienone, ketene reactions are to be expected on irradiation in suitable solvents (29). However, in the absence of other reagents, e.g. in carefully dried benzene, mazdasantonin undergoes only one reaction, a very slow dimerization to a complicated mixture, E. This mixture cannot arise from reaction of mazdasantonin with impurities in the solvent, as the product was the same and equally intractable even when irradiation was carried out in specially purified, research grade (99.91% by freezing point curve) benzene (Phillips).

Several facts may be adduced in support of the dimeric nature of E. Firstly, E is much more polar and far less soluble in common organic solvents than is any other photoproduct of santonin. This enhanced polarity is manifested by the fact that E comes off partition chromatography with a retention time far longer than that of J, the last photoproduct eluted before it; and by the disheartening refusal of E to emerge from any v.p.c. column. These two facts are reconcilable only with some highly polar substance. In the absence of protic solvent, it is most difficult to see how any enhancement of polarity could arise other than that attendant on dimerization, with a concomitant doubling of oxygen functions. Moreover, partition chromatography work has shown that the formation of E suffers greatly as the concentration of mazdasantonin is decreased, as shown in Table 5. Since mazdasantonin is by far the major photoproduct from irradiation of santonin or lumisantonin in aprotic solvent, it is acceptable to examine variations in yield of E as the starting concentrations of santonin, lumisantonin, or mazdasantonin are varied. The trend is obviously to lower final yields of E as the concentration of mazdasantonin is reduced.

It should be emphasized in this connection that the n. m. r. spectrum of mazdasantonin clearly shows complexing in solution. The possible significance of mazdasantonin complexing in the genesis of E will shortly be discussed more fully (p. 128).

The formation of E from mazdasantonin was the only reaction quenched by azulene (or oxygen) of all those studied. This means that the formation of E from mazdasantonin involves an intermediate of different nature from that of the other reactions or that the lifetime of the reactive state must be considerably longer than that of santonin or lumisantonin. Since, as will be shown (Part II, Section 3), the triplet intermediate plays the active role in all cases, the author can only conclude that the formation of E requires a long-lived intermediate

Table 5

Effect of Concentration on the Final Yield of E

Run	Irrad. (hr)	S	LS	B	J	MS	H	E	Total	Concentration
9	3	29	31	$\frac{1}{2}$	$1\frac{1}{2}$	23	0	7	$94\frac{1}{2}$	1.09×10^{-2}
14	6	33	$38\frac{1}{2}$	0	3	$15\frac{1}{2}$	$\frac{1}{2}$	$9\frac{1}{2}$	99	7.43×10^{-2}
7	35	1	$4\frac{1}{2}$	2	$2\frac{1}{2}$	59	$8\frac{1}{2}$	$24\frac{1}{2}$	103	1.09×10^{-2}
11[a]	13	-	$2\frac{1}{2}$	4	3	$58\frac{1}{2}$	$11\frac{1}{2}$	9	$88\frac{1}{2}$	7.28×10^{-3}
12[b]	43	-	-	$1\frac{1}{4}$	$\frac{1}{4}$	$78\frac{1}{2}$	$\frac{3}{4}$	$6\frac{1}{2}$	87	3.54×10^{-3}

---

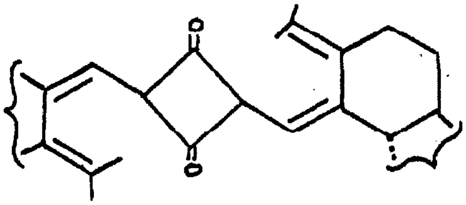
a. Starting from lumisantonin
b. Starting from 95% pure mazdasantonin

in contrast with all the unimolecular reactions in the santonin system. The fact that a long-lived intermediate is involved suggests that the formation of E might be a greater than first order reaction.

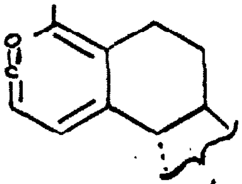
None of these considerations conclusively requires that the formation of E involve dimerization. However, a dimeric product satisfies all the suggestive evidence, and also obviates the nearly impossible task of devising some other photochemical reaction based on the known structure of mazdasantonin. Furthermore, dimerization would be expected to be disfavored because of steric interference between the lactone functions, in agreement with the observed inefficiency of the reaction.

Unfortunately, due to solubility and stability problems, it has not been possible to determine the molecular weight of E by isothermal distillation in benzene solution or by the Rast method. However, the evidence previously cited is so consistent with a dimeric structure that I shall consider possible dimeric products.

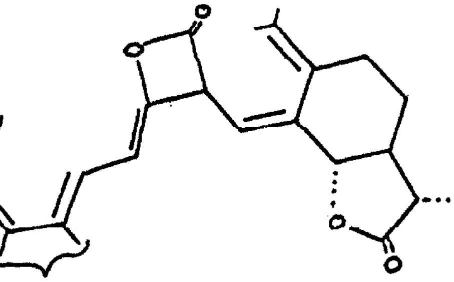
There are no fewer than six possible structures for the dimer, not including ring fusion and directional (head-to-head as opposed to head-to-tail) isomers. These are shown on page 51. The first 2 structures, (33) and (34), are the usual dimers expected from the ketene (34a) (36). The infrared spectrum of E eliminates both these structures $\nu_{max}^{CHCl_3} = 1720\ cm^{-1}$ (nothing in the region from 1800 to 2000 cm^{-1}). Neutral ketene dimers (36), by virtue of the β,γ-unsaturated butyrolactone structure, have a strong absorption in the region of 1875 cm^{-1}. Acid ketene dimers such as (33)



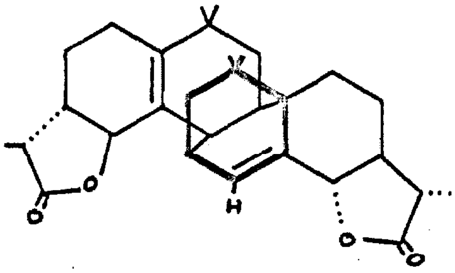
(33)



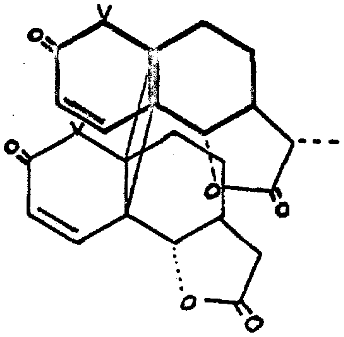
(34a)



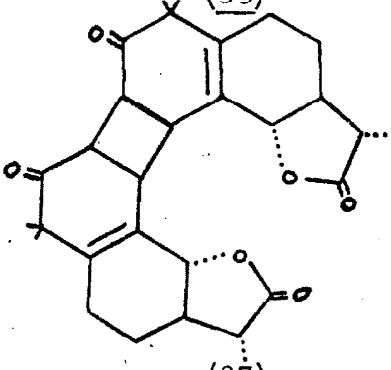
(34)



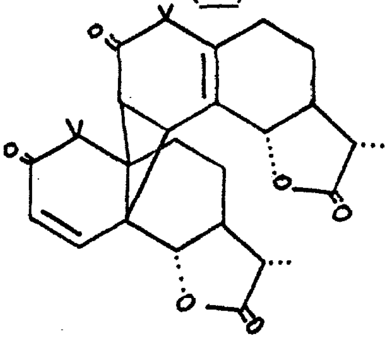
(35)



(36)



(37)

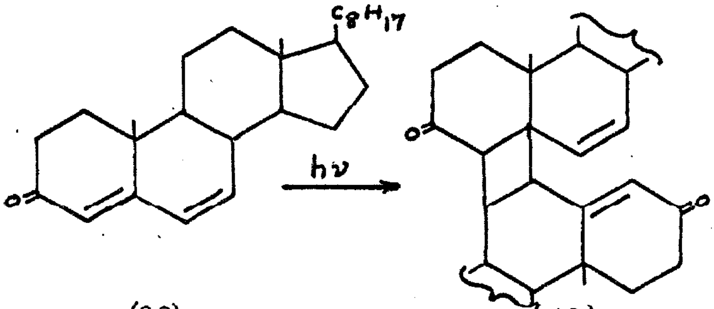


(38)

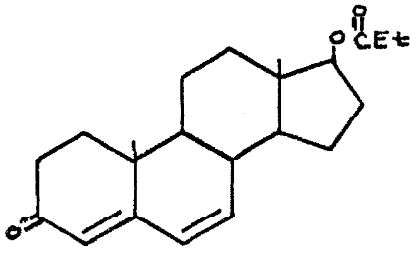
(shown as the dione; enolization of one carbonyl group of which accounts for the spectrum and the acidity) absorb at 1705 cm^{-1} in potassium bromide, and the carbonyl frequency would not be expected to be shifted more than 10 cm^{-1} to higher frequency in chloroform.

Another possible structure for the dimer of mazdasantonin is the Diels-Alder adduct (35), which, as will be shown below, is excluded by n.m.r.

There are three possible ways in which dimers can arise via cyclobutane formation by cycloaddition of two double bonds. These products are shown in (36)-(38). Structure (38) has precedent in the dimerization of $\Delta^{4,6}$-cholestadiene-3-one (39) (37), which leads to (40). Other examples of photochemical steroid dimerizations involving cross-coupling of dienones are to be found in the irradiation of $\Delta^{4,6}$-androstadien-3-on-17β-ol propionate (41) and various C-17 analogues, all of which lead to structures similar to (40) (38).

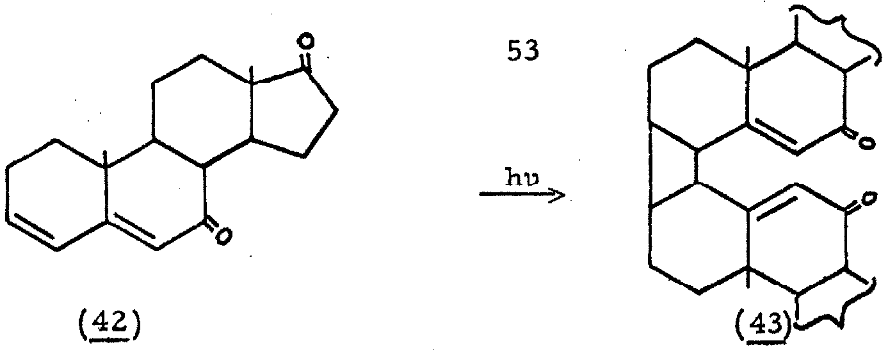


(39) (40)



(41)

A precedent for (36) is to be found in the photodimerization of $\Delta^{3,5}$-androstadiene-7,17-dione (42) to (43) (39).



(42) (43)

$\Delta^{3,5}$-androstadiene-7, 17-dione

The infrared spectrum of E provides evidence against conjugated enones such as (36) and (38) because there is no absorption in the region from 1600 to 1700 cm^{-1}. However, the peculiar constrictions of geometry may lead to shifts in the carbonyl frequency as exhibited for example by tetrahydromazdasantonin, which absorbs at 1724 cm^{-1}. The fact that tetrahydromazdasantonin has a carbonyl absorption in approximately the same position as E strongly suggests that at least one of the carbonyls is no longer conjugated. This can be accommodated by a reaction of the α, β double bond, which leads to structures such as (35), (37), and (38). The n. m. r. spectrum of E in deutero chloroform has a methyl region which is the same as for mazdasantonin itself, indicating that the partial structure (44) is retained. Suggestive evidence is most assuredly against the mixed structures (35) and (38), since the infrared spectrum of E shows only one type of carbonyl other than the lactone. Note this retention of the partial structure (44) again rules out dimers (33) and (34), which would be expected from an

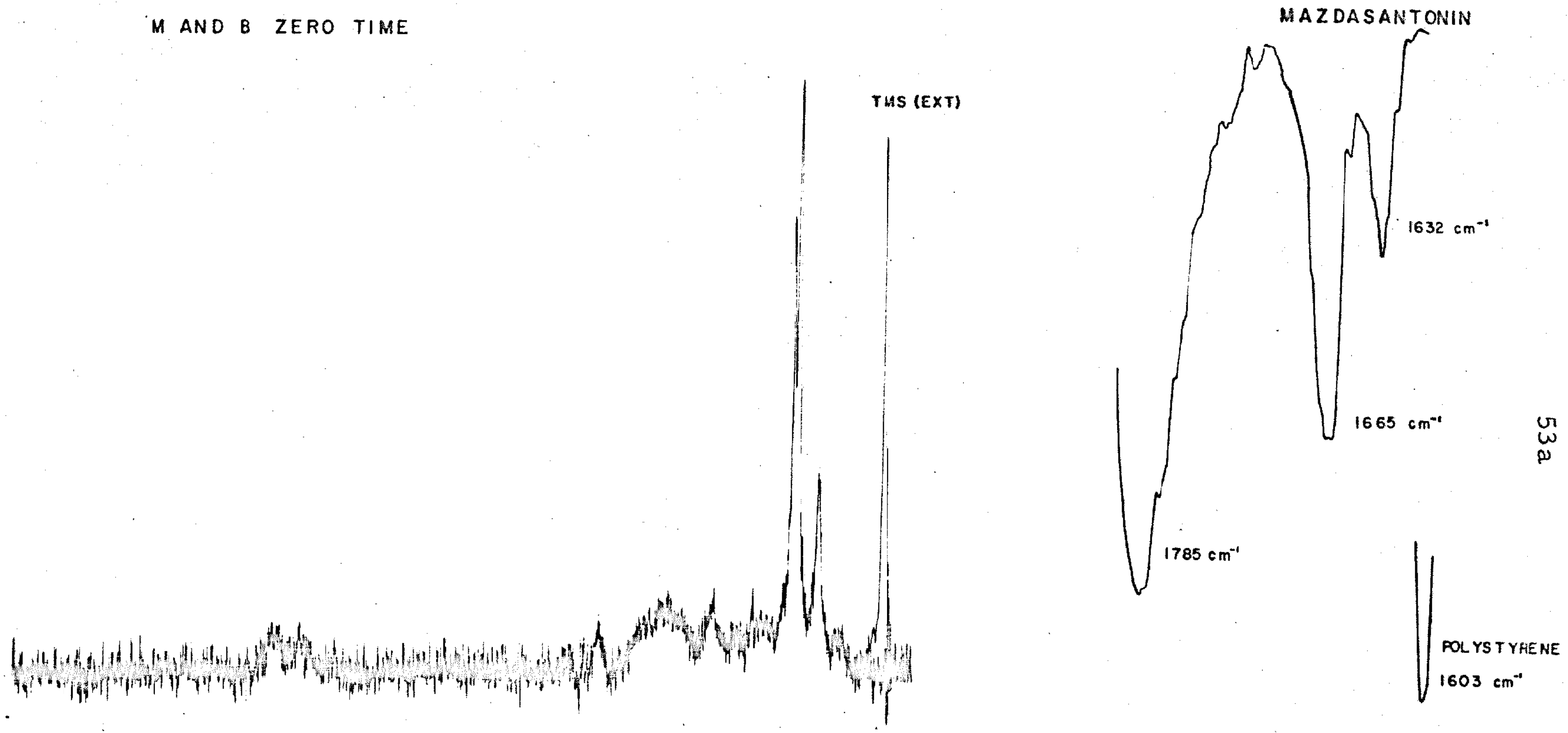


Figure 8d. The Methyl Region of E (First Part)

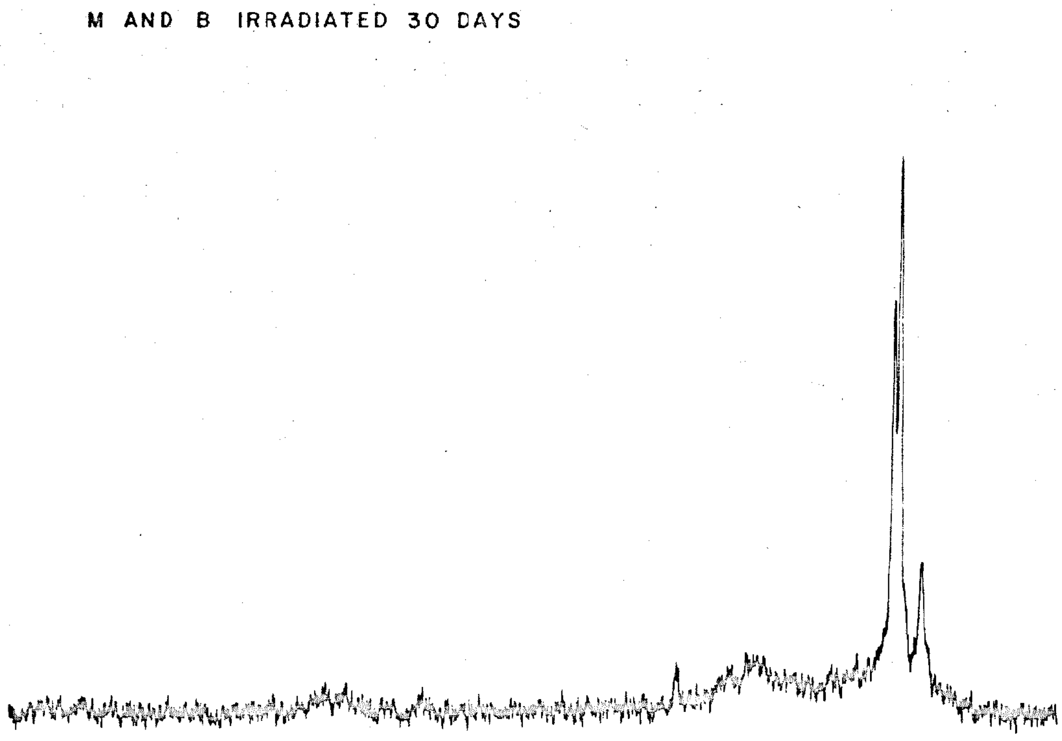
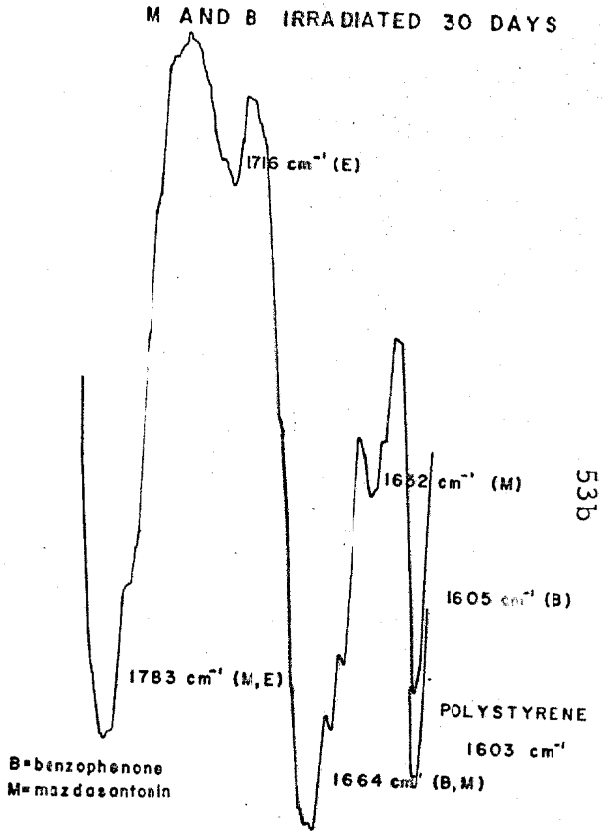


Figure 8d. The Methyl Region of E (Second Part)



intermediate ketene of structure (34a).

Spectral evidence has now been presented against all structures except (37). The conclusion that (37) is the correct formulation of E is further confirmed by the complete absence of olefinic protons as shown by n.m.r. Only (37) meets this requirement.

A structure of this type is the most common for dimers of α,β-unsaturated ketones (40). A recent literature example of cyclobutane formation across bonds of enones is the irradiation of cyclopentenone by Eaton (41),* in which he observed roughly equal yields of the head-to-head and head-to-tail dimers (47a) and (47b).

In the unpublished work of Hammond and coworkers (43a), the photochemical dimerization of cyclohexadiene has been studied. The major dimeric products (45) and (46) are good models for E in that, although there is no carbonyl, the double bonds in the rings adjacent to the cyclobutane fusion are disposed just as postulated in (37). The infrared and n.m.r. spectra of (45) and (46) agree well with values observed in the infrared of E itself and of its dinitrophenylhydrazone derivative.

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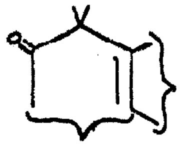
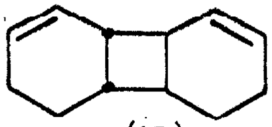
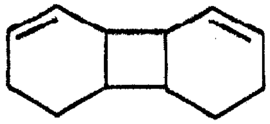
* See also the dimerization of testosterone acetate (42).



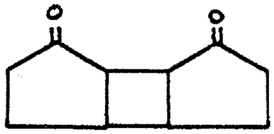
(44)



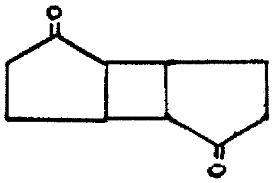
(45)



(46)



(47a)



(47b)

Table 6

Spectral Identification of E

	i.r. ($CHCl_3$)	n.m.r. ($CDCl_3$)
(45)	1006, 930, 865	2.35 ppm
(46)	1015, 975, 850	2.88
E-DNP	1003, 926, 843	----
E	1720, 1603	no resonance at 2.9 ppm strong resonance at 2.3 ppm

In addition to its methyl peaks, E exhibits a broad range of absorptions throughout the methyl and methylene regions. There is essentially no resonance at 2.88 ppm, but considerable absorption around 2.35 ppm, in accord with the trans-cis-trans structure, (45). Moreover, the dinitrophenylhydrazone derivative exhibits infrared bands at 843, 926, and 1003 cm^{-1}, which also agree with those reported for the trans-cis-trans dimer of the cyclohexadiene. The first two bands are not present in the dinitrophenylhydrazone derivatives of mazdasantonin, 6-epi-mazdasantonin, or 6-epi-santonin.

For these reasons the author considers that E has the general structural features of (37), and, further, he assigns the trans-cis-trans ring juncture because of the spectral similarity between E and (45).

The general structure (37) is the only one reasonable on steric grounds, since any dimerizations involving the second double bond of mazdasantonin require coupling of a tetrasubstituted double bond in preference to a disubstituted one. Unfortunately, the possibility of directional isomerism (head-to-head vs. head-to-tail) allows the mixture still to be disgustingly complex.*

The structural factors which determine whether a homogeneous photodimer is obtained are not presently understood. Whereas a variety of steroids dimerize nicely, the simpler hydronaphthalenic systems 9-methyl-$\Delta^{4,6}$-3-octalone (48) and 9-methyl-Δ^{4}-octalone (49) give only "uncharacterized, high-molecular weight products" (39,40). The resemblance between the products from (48)

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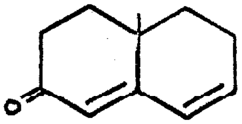
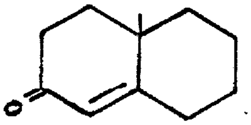
* No u.v. spectra of E were taken due to its impurity and instability. The crude mixture is yellow, presumably due to transannular interaction (43b,c).



(48)



(49)

and (49) and the product mixture E from mazdasantonin indicates that the same sort of dimers may be obtained in the two cases.

Since mazdasantonin appears to be the first homoannular dienone to be studied, and is hardly an ideal case, it would be interesting to investigate the dimerizations of other such compounds so as to determine whether reactions of heteroannular and homoannular dienones are indeed the same in kind.

PART II

MECHANISTIC CONSIDERATIONS

I. Photochemical Processes

At room temperature, essentially all molecules of a compound in solution are in the lowest vibrational level of the ground state. If the temperature is raised, some molecules are excited to higher vibrational levels and may undergo reaction (pyrolysis or thermolysis). However, the energy content of the molecule is so evenly distributed that, as soon as relatively few kilocalories per mole are added, the weakest bonds in the molecule break and the compound rearranges or decomposes.

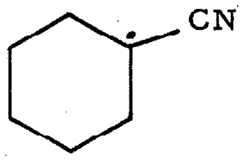
Consider now the difference in a photochemical reaction. If light is absorbed, an enormous amount of energy, which might be expected to shatter most organic molecules, is suddenly pumped into a specific portion of the system (the chromophore). (The 2537 Å line from the low-pressure mercury arcs commonly used corresponds to 113 kcal/mole. For comparison, the normal strengths of C-H and C-C bonds are about 100 kcal/mole and 80 kcal/mole, respectively.)

Fortunately, most molecules can dissipate energy so rapidly that molecular disintegration is not the only photolytic process. Otherwise, the abundant variety of photochemical products available from energy-rich systems (cf Part I of this thesis for some extraordinarily pleasing examples) would be denied us.

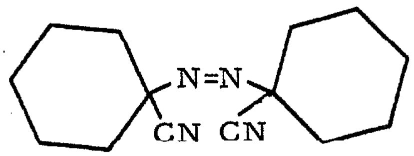
The periods of molecular vibrations are normally on the order of 10^{-10} to 10^{-12} seconds. Since the rates of electron promotions are about 1000 times faster, the ground state geometry does not have time to alter during excitation. This is the important Franck-Condon principle. Internal conversion (radiationless transition between states of like multiplicity, i.e. conversion of electronic energy into vibrational and kinetic energy) allows the molecule to pass quickly ($\sim 10^{-13}$ sec) (44) down through the densely packed energy levels to the first excited state (Path A). Generally, the energy gap between the first excited state and the ground state is larger than between the first and second excited states with succeeding gaps to states of higher energy becoming smaller as one progresses to states of higher energy. Since the oscillator strength, f, and hence the transition probability, is inversely related to the energy gap, the mean natural lifetime of the first excited state is far longer than that of any higher state (45). Even here, internal conversion to the ground state may be the fastest process, but it is obvious that if anything else is to happen, the first excited state is the only level likely to participate.

Thus we arrive at an enormous simplification: *For the vast majority of condensed phase photochemical reactions, only the first excited levels need be considered.**

A particularly dramatic illustration of the efficiency of collisional deactivation is provided by recent work of Hammond. The very rapid radical cage reactions of (50) have been shown to be the same whether decomposition of the precursor (51) is induced thermally (49) or photochemically (50). This in spite of the fact that the photochemically produced radicals, when first formed, have some 75 kcal/mole more energy than their counterparts of thermal origin.



(50)



(51)

A molecule in the first excited state has an energy content many kcal/mole greater than that of the ground state. In order to

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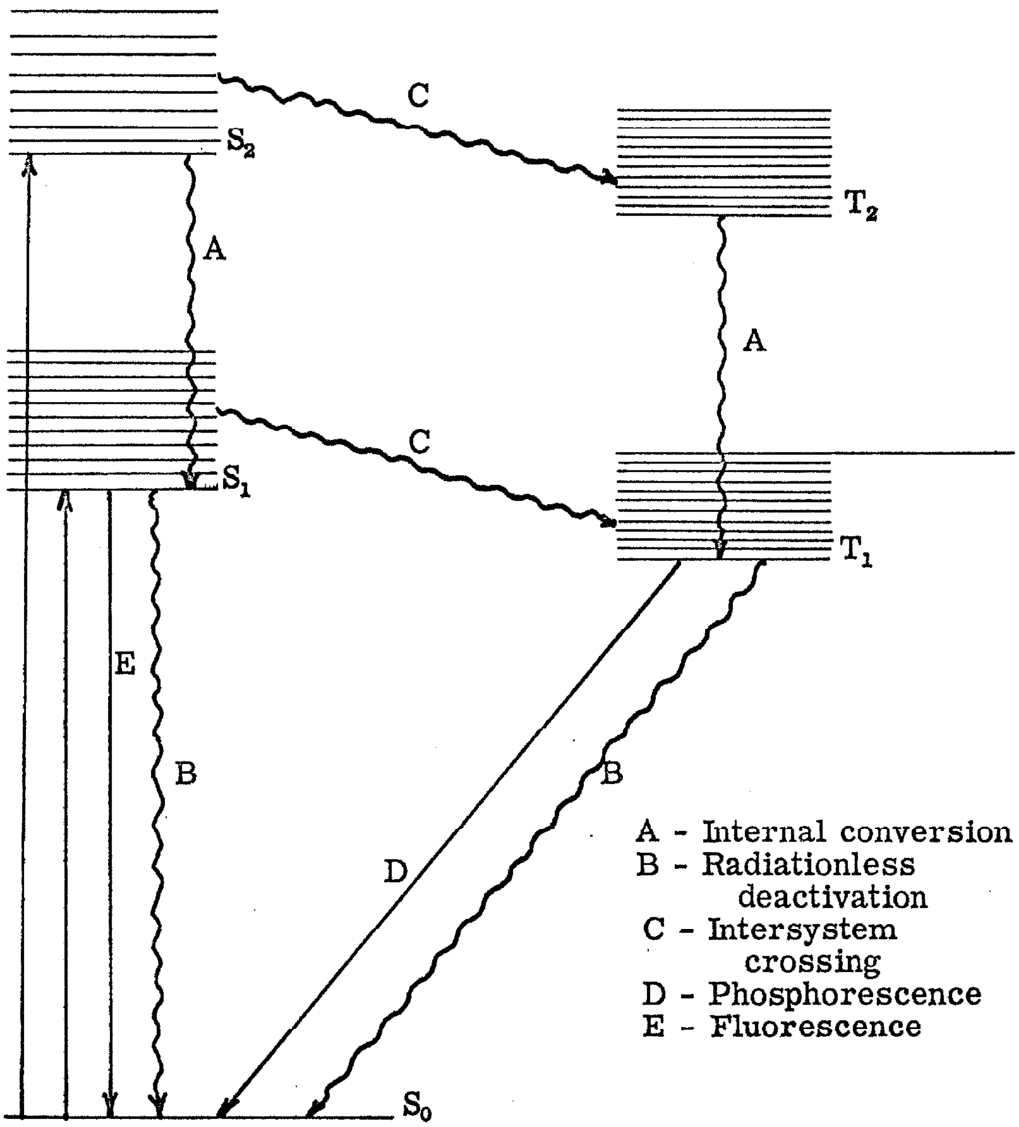
* Photochemical reactions involving states other than the lowest excited singlet are fairly common in the gas phase where collisional deactivation is not as efficient (46). Intersystem crossing (see text) from higher levels appears to be more frequent than formerly believed (47). An exceptional fluorescence from the second singlet state has been observed for azulene where the spacings between singlet states are uncommonly large (48).

return to thermal equilibrium with its surroundings, the compound must dissipate energy by one of the paths available. Often, the most facile transition is internal conversion (Fig. 15, Path A). However, if internal conversion is slow enough, it may be unable to compete with fluorescence (emission of light from the excited singlet (state with all spins paired)), Path B; intersystem crossing (radiationless singlet-triplet (state with two unpaired spins) transition), Path C; or photochemical reaction (not shown). Fluorescence is seldom observed in solution at room temperature, but is common in glassy solvents at low temperature. It is not clear why increasing the viscosity of the solvent is so effective in enhancing fluorescence. The explanation currently in vogue is that the solvent acts through its effect on the diffusion rates of adventitious quenchers present as impurities (176). The concentration of these impurities can be very low in order to account for the observed effects ($< 10^{-7}$M). Hence, the quenchers are usually not detectable even by the most sensitive techniques. An unfortunate consequence of this mechanism is that the concentrations of the offending impurities are very likely never reduced below effective levels, no matter how carefully the solvent is purified, because of the trace amounts involved.

Triplet energy levels are slightly lower than the corresponding singlet levels (Hund's rule) due to decreased electron repulsion. The energy gap between singlet and triplet state is usually small in comparison with the energy gap between the lowest excited state and the ground state. If energy gaps were the only determining factor in radiationless transitions, all excited molecules would ultimately arrive in the triplet state. This expectation is not realized in nature,

Figure 15

The Jablonski Diagram



because transitions, such as intersystem crossing, which involve a change in multiplicity, are forbidden; i.e. in the first quantum mechanical approximation, have zero probability. Experimentally, singlet-triplet transitions are very weak (53), but do occur because the apparent forbiddenness of the transition is alleviated by other factors. For instance, the space and orbital wavefunctions of real molecules are not totally independent, as assumed in the simplest LCAO-MO theory. If interaction (spin-orbit coupling) is included, the triplet state is no longer "pure" triplet; that is, there is a small admixture of singlet component. In this manner, the multiplicity restriction is avoided, since the apparent singlet-triplet transition occurs between the singlet components of the two states involved.

Another way in which the intensity of singlet-triplet (or triplet-singlet) transitions can be augmented is by substitution of heavy atoms in the molecule (51) or in the solvent (52). Addition of paramagnetic substances, particularly molecular oxygen, leads to a like result. For many years, it was believed that these effects resulted from the magnetic properties of oxygen, iodide, etc. (57a, 84b). Ultimately, this cherished notion was demolished (177). Current belief is based on charge transfer interactions in weak complexes, and the extra intensity of the singlet-triplet absorption is borrowed from the charge-transfer band.

Even though intersystem crossing can be rendered partially allowed, the rate of this process is normally much less than the rates of fluorescence and internal conversion. Consequently, when internal conversion is slowed by lowering the temperature, the major result is usually enhanced fluorescence rather than more efficient population of triplet levels by intersystem crossing from the first excited singlet.

A molecule which has arrived at the lowest excited triplet level may again dissipate energy through internal conversion, emission of light (<u>phosphorescence</u>, Path D), or reaction. However, the first two processes are multiplicity forbidden, so that triplet state lifetimes are many orders of magnitude longer than those of singlet states. Normal triplet lifetimes are of the order of 10^{-3} seconds, but may be longer. Triphenylene triplets, for example, attain the Methuselan age of 15 seconds. Consequently, the triplet state, although a dark horse at the time of the initial excitation, is easily the most capable candidate for photochemical reaction due to its long lifetime.

Under very favorable circumstances, intersystem crossing may be efficient. For benzophenone and its derivatives, internal conversion from the lowest excited singlet state is so slow in comparison with intersystem crossing that triplet benzophenone molecules are convenient reactive species. Some quantitative studies of the photochemical reduction of benzophenone with alcohols have shown the relatively difficult hydrogen abstraction process to be some thirty times faster than radiationless deactivation (54a). More facile energy transfer reactions(e.g. quenching)are several hundred times as fast as abstraction.* As a result, benzophenone functions very well in energy transfer reactions. Efficiencies of sensitization (see below) often reach 100%, showing that internal conversion is of negligible importance under the conditions employed.

If there are molecules present in solution which have energy levels suitably disposed in relation to the levels of the excited molecule, transfer of energy may occur with return of the excited molecule to its (singlet) ground state and concomitant excitation of the

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* For the benzhydrol/benzophenone system in benzene, quenching by naphthalene is 450 times as fast as abstraction (54b). In isopropanol, the corresponding numbers are $k_d/k_r \sim 0$ and $k_q/k_r = 2500$ (55).

acceptor molecule to its (triplet) excited state. Energy transfers which are exothermic by four or more kcal/mole appear to be diffusion controlled (56).

This process has different names, depending on the fate of the acceptor molecule.* If there exists some means by which the presence of excited acceptor triplets can be demonstrated (characteristic phosphorescence or reaction), the energy transfer process is called photosensitization. If the only apparent result is that the original triplet molecules can no longer be observed (because acceptor molecules undergo facile internal conversion), quenching is the appropriate designation.

II. Triplet Energy Transfer

In view of the short lifetimes of singlet states, it is not surprising that the relatively slow collisional mechanism does not appear to be the usual mode of singlet transfer. Normally, these transfers take place over long distances (occasionally as much as 200 Å, usually about 50 Å). The major experimental instances of singlet energy transfer are in the phenomena of induced fluorescence and fluorescence depolarization (57), and a reasonably successful

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* Cf., "Physics is not a function of its notation."--Polykarp Kusch.

theory has been developed based on dipole-dipole interactions (58a).

If the concentrations of two substances are in the same ratio in several solutions, the ratio of the light absorptions by the two substances remains constant. In the case of induced fluorescence, it is found that, as the total concentration increases, the fluorescence yield of the acceptor rises, whereas the fluorescence yield of the donor declines. The classic experiment of this type was performed by Bowen on the 1-chloroanthracene/perylene system (58b, c).

Singlet transfer also gives rise to another effect, the phenomenon of fluorescence depolarization, also called concentration depolarization. If the exciting light is polarized, then the fluorescence from the initially excited molecules will be polarized also, because only those molecules suitably oriented with respect to the incident light can be excited. However, energy transfer may occur to other molecules in solution which do not have the same orientation as the donor; and in sufficiently concentrated solution, several transfers will be made before fluorescence occurs. The experimental observation is, then, that the polarization of the fluorescence decreases as the concentration of the emitting substance is raised.

A theoretically predicted and experimentally confirmed requirement for long-range singlet transfer is that there be appreciable overlap between the fluorescence spectrum of the donor and the absorption spectrum of the acceptor. Compounds having low extinction coefficients are found to quench also, but by a different (collisional) mechanism which is like that operative in triplet energy transfer (59).

Since triplet lifetimes are orders of magnitude longer than those of singlets, collisional transfer seems intuitively sufficient for triplet transfer. All evidence to date indicates that this is the case, at least in solution (60).

For the reasons cited in Section I, triplet processes become more important with increasing viscosity. It was by use of glassy solvents to hinder collisional deactivation (internal conversion) that Lewis, Lipkin, and Magel (61) first showed the phosphorescent state to have an absorption spectrum different from that of the parent molecule. These experiments subsequently led to the identification of the metastable phosphorescent state as the triplet (62).

Nearly ten years before the beginning of the present work, the first well documented case of triplet energy transfer, the sensitized phosphorescence of naphthalene at liquid nitrogen temperature (77°K), was reported by Terenin (63). Triplet energy transfer is also well documented for fluid solution at ambient temperatures, from the flash photolysis studies of Porter (64).

Unfortunately, these results did not permit an immediate simplification of organic photochemical problems. The possible involvement of triplet intermediates was intriguing, but spectrographic methods could not always be applied to systems of chemical interest.

The first requirement for a systematic study of triplet intermediates in organic photochemistry was a method of efficiently exciting reactant molecules to their triplet states under ordinary laboratory conditions. In 1960, Bäckström and Sandros (65) reported benzophenone sensitized phosphorescence of biacetyl at room temperature. Independently, Hammond and coworkers (60) concluded that the reactive species in the photoreduction of benzophenone by alcohols is the triplet by demonstrating that the lifetime of the reactive species is too long to be that of the singlet.

By use of suitable sensitizer concentrations and selection of a wavelength at which the donor molecule absorbs all or almost all of the incident light, it was now possible to ensure that only triplet paths were available to an acceptor molecule in solution under ambient conditions. Of course, the results had to be interpreted carefully. Product analyses were necessary to show that direct excitation and a sensitized (triplet) process led to the same reaction of the acceptor molecule. If the triplet reaction were different from the reaction under direct irradiation, the ordinary photolysis might follow a singlet path; but failure to observe sensitization cannot be used as evidence against a triplet mechanism unless the triplet energies of both the donor and acceptor are known. If the sensitizer possesses insufficient energy to excite the acceptor to its triplet state, internal filtering would be the only reasonable expectation.*

A point which cannot be made too strongly is the fact that the observation of sensitization does not require a triplet path in the direct irradiation. It is astonishing how otherwise competent scientists cavalierly dismiss this consideration (67) or overlook it entirely (68).

The second requirement for elucidation of triplet mechanisms in organic photoreactions was a method of detecting triplet intermediates. The spectrographic methods mentioned above are not applicable here because reaction is an alternative to phosphorescence and the presence or absence of light emission under the reaction conditions says nothing about the photochemically active species.

Several compounds are now known to undergo intersystem crossing efficiently and to reach the triplet state in high

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* This simple view has been somewhat disturbed by the observation of "non-vertical sensitization" (66).

yield. When such a compound is added to a cis-trans mixture of an olefin and the resulting solution is irradiated, the composition of the mixture changes, provided that the sensitizer has sufficient energy in the triplet state to effect energy transfer to at least one of the olefins in the mixture. The cis/trans ratio at the photostationary state appears to depend mostly on the triplet energy of the photosensitizer used. Because of the simplicity of the method, the isomerization of olefins is the most widely employed triplet detector.

In the irradiations conducted in the present work, light of wavelength greater than 3300 Å was used.* Since dienes and simple olefins are essentially transparent above 3000 Å, the direct isomerization is so slow under the experimental conditions as to be negligible. Furthermore, the triplet energies of olefins and dienes are usually considerably lower than the triplet energies of most carbonyl compounds, so that olefins function as efficient quenchers for triplet states of ketones.

The most intensively studied olefins for the detection of triplet states in solution have been piperylene (69) and stilbene (70).

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* Light of 3000 Å wavelength has an energy content of 95 kcal/mole. The singlet states of simple dienes lie at ~ 124 kcal/mole (69), so that there can be no question of singlet excitation.

For the gas phase, the cis-trans isomerization of 2-butene has been recommended (71).

III. Triplet States in the Santonin Series

A. Historical

Due to the complexity of the reaction mixture, the mechanism of santonin photoconversion has been an unattractive subject for study. Most efforts have been directed toward elucidation of the products formed in various reactive media. Unfortunately, structural analysis, although basic to understanding any reaction, cannot give more than general indications of the mechanism. For example, as discussed in Section V-A, the products of the santonin photoconversion cannot be rationalized in any straightforward way from the polarity of the $n \rightarrow \pi^*$ excited state.

This work was begun shortly after the tools for detection of triplet states in organic photoreactions became readily available (60, 65, 69). A few triplet state organic reactions have long been known, the mechanisms having been established at great labor. The most common cases are photoöxidations and photoreductions. Some classic examples of the former are the photoöxidations of zinc chlorin (72) and polyacene aromatic hydrocarbons (73)*;

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* The linear polyacenes photoöxidize readily but the non-linear series is much more stable even with more rings. This result parallels the triplet energies (75).

and the sensitized photoöxidation of various dienes (74). Established cases of photoreductions involving triplets include zinc porphin (76), chlorophyll (77), and benzophenone (60). However, all these reactions were bound to favor longer-lived intermediates because they are second order. Moreover, the presence of heavy atoms (78) or oxygen (79) is known to facilitate singlet-triplet conversions so that these results were possibly exceptional. Known unimolecular reactions or carbonyl compounds (decomposition of ethyl pyruvate (80) and trans-annular ring closure of cyclodecanone (68)) had been shown to be accelerated by addition of sensitizers, but the assignment of a triplet mechanism to the direct irradiation was presumptive. No studies were available for cyclohexadienones.

Although various analytical techniques were employed in the course of this work, satisfactory workups and mass balances were obtainable only by liquid-liquid partition chromatography. The results are summarized in Table 18, from which particularly interesting comparisons will be extracted as needed.

B. Sensitization

Benzophenone was chosen for sensitization experiments because of its ready availability and high triplet energy. Initial qualitative studies were made using sealed tubes and n.m.r. or v.p.c. analysis. It was immediately apparent that addition of benzophenone made no difference in the rate of disappearance of santonin. (Graph II). Since benzophenone was absorbing 90% of the light at the wavelength employed (primarily 3660 Å), this result required that the intersystem crossing efficiencies of santonin and benzophenone (known to be unity*) (60, 65) be the same.

Further experiments confirmed this surprising result. Two tubes each 1.95 x 10^{-2}M in santonin (light absorption by santonin = 58% of the incident radiation) were prepared. One tube was brought to 4.31 x 10^{-2}M in benzophenone (partition of absorption: 91% to benzophenone, 9% to santonin; total = 100%). The two tubes were degassed and sealed on a vacuum line, then irradiated concurrently on an optical bench (see Experimental). The result is shown in Graph III . Although the analyses are not as accurate as could be wished (v.p.c. analysis), acceleration is obvious and the ratio of conversions at 4000 seconds (1.93) approximates the predicted value 100/58 = 1.72. Quantum yield determinations (with Mr. Gary Schnuelle) likewise led to a value of approximately unity for the photoconversion of santonin. Again in the quantum yield studies, addition of benzophenone made no difference in the rate of disappear-

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* The original report (60b) of completely efficient intersystem crossing was subsequently lowered to 0.94 from studies of piperylene isomerizations. However, when a correction was included for back reaction, the experimental efficiency for the intersystem returned to unity.

ance of santonin. The results of liquid-liquid partition chromatography collected in Table 7 show that only the usual photoproducts are formed in the sensitized runs, although the product proportions are profoundly affected.

Table 7

Effect of Sensitization on the Photoproducts from Santonin

Run	S	LS	B	J	MS	H	E	Total	Remark
13*	42½	23½	1	1/10	18½	3½	8½	98	Sensitized
9	29	31	½	1½	23	0	7	94½	Under N_2
1**	38½	33	?	?	12	?	1½	92	Open to air

*Recovery of sensitizer was 97%.
** 6½% tar

The amount of lumisantonin isolated is greatly lowered due to the acceleration of further photoconversion. Thus the terminal products H and E are obtained in greater yield in the sensitized run than from an unsensitized photolysis carried to much higher percentage conversion. Similarly, very little B or J is observed in the sensitized run, also due to acceleration of further photoconversion of these compounds. Acceleration of mazdasantonin dimerization in the sensitized reaction is clear from Table 7 and Graph IIIc.

These results make it clear that the triplet is a possible although not necessarily unique path in these photoreactions.

During the sensitization studies, it was noted that sufficient Michler's ketone (4,4'-dimethylaminobenzophenone) to absorb all the light stopped the photolysis. In other words, Michler's ketone cannot sensitize santonin photoconversion due to its low triplet energy (61.0 kcal). This result made it possible to exclude the existence of a photoequilibrium between santonin and lumisantonin and to obtain a rough estimate of lumisantonin's triplet energy by irradiation of lumisantonin solutions in which Michler's ketone was acting as sensitizer and absorbing all the light ($\epsilon \sim 10^4$ at 3660 Å in benzene). Any santonin formed would have accumulated, but,in fact, none was detected. However, the disappearance of lumisantonin was accelerated relative to direct photolysis. Therefore, santonin and lumisantonin cannot have a common triplet state and the decline in the rate of santonin disappearance during the last stages of the photolysis can be entirely attributed to internal filtering by products rather than by an approach to a pseudoequilibrium.

$$\mathrm{S} \mathrel{\substack{\rightarrow \\ \not\leftarrow}} \mathrm{LS} \rightarrow \text{products}$$

Sensitization by Michler's ketone was also apparent for the disappearance of mazdasantonin. Therefore, the triplet energies of lumisantonin and mazdasantonin cannot be more than 64 kcal/mole.

C. Systematic Evaluation of Triplet Energies

1. Double bond isomerizations

Studies of diene reactions have shown that photostationary state compositions of stilbenes (66a) or piperylenes (69a) reflect the triplet energy of the photosensitizer. In the photosensitized dimerization of isoprene, a similar correlation has been made between triplet energy and the ratio cyclooctanes + cyclobutanes ÷ cyclohexanes (83). It was clear from the work with Michler's ketone that the triplet energy of santonin was too high to yield anything other than the value characteristic of sensitizers having triplet energies greater than 62 kcal/mole (66a, 69a, 83). However, the diene method seemed promising for lumisantonin and mazdasantonin.

Table 8

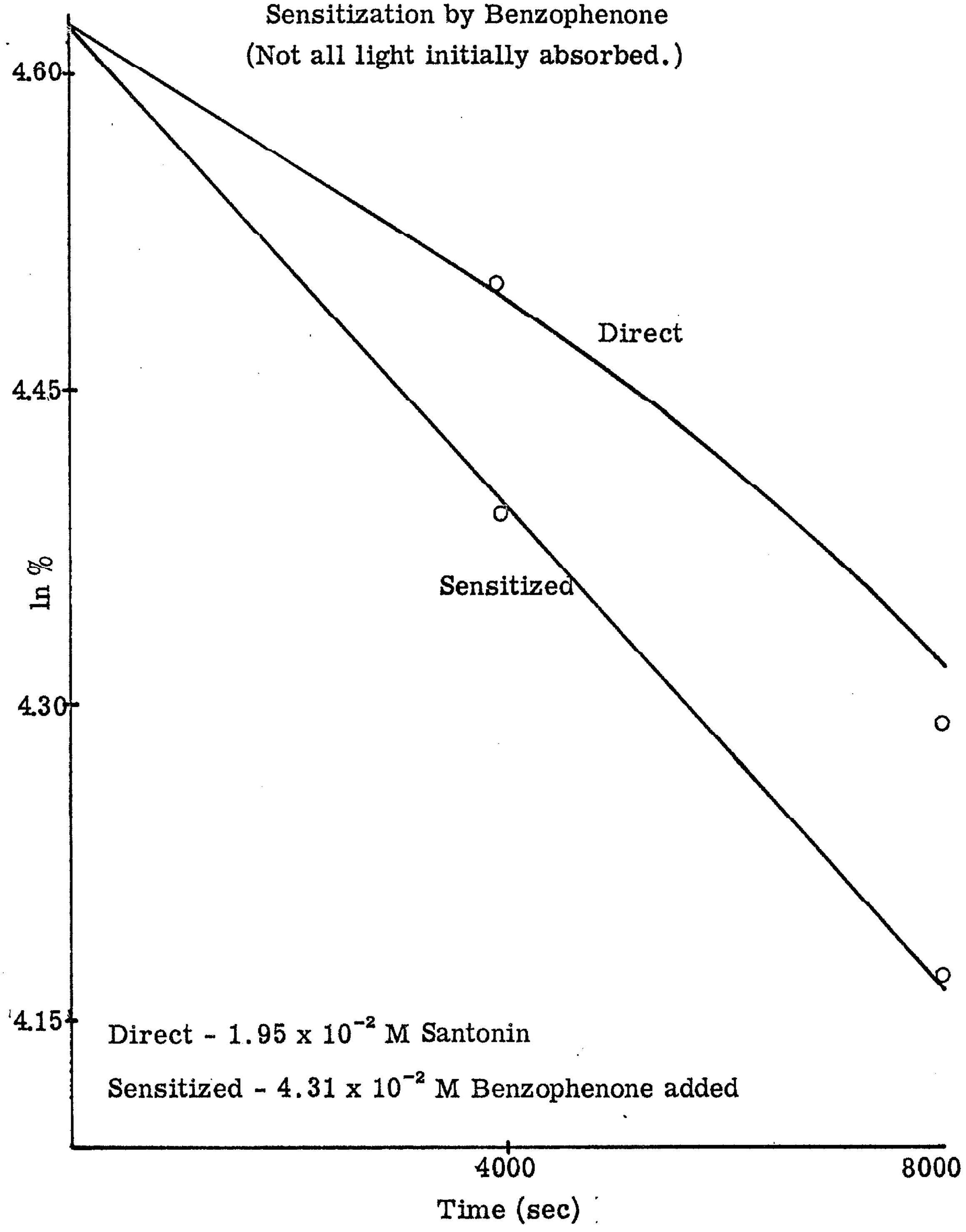
Triplet Energies of Selected Quenchers

	S_0-S_1	S_0-T_1
<u>cis</u>-piperylene) <u>trans</u>-piperylene)	~ 120	57.2[a], 56.9[b] 58.8[b]
<u>cis</u>-stilbene) <u>trans</u>-stilbene)	~ 92	~57[c] 50.8[c], 49.5[d]

a. From ethyl iodide method (84).
b. Oxygen method, R. E. Kellogg, cited in ref. 84a.
c. Oxygen method, cited in ref. 84b.
d. Ethyl iodide method, cited in ref. 84c.

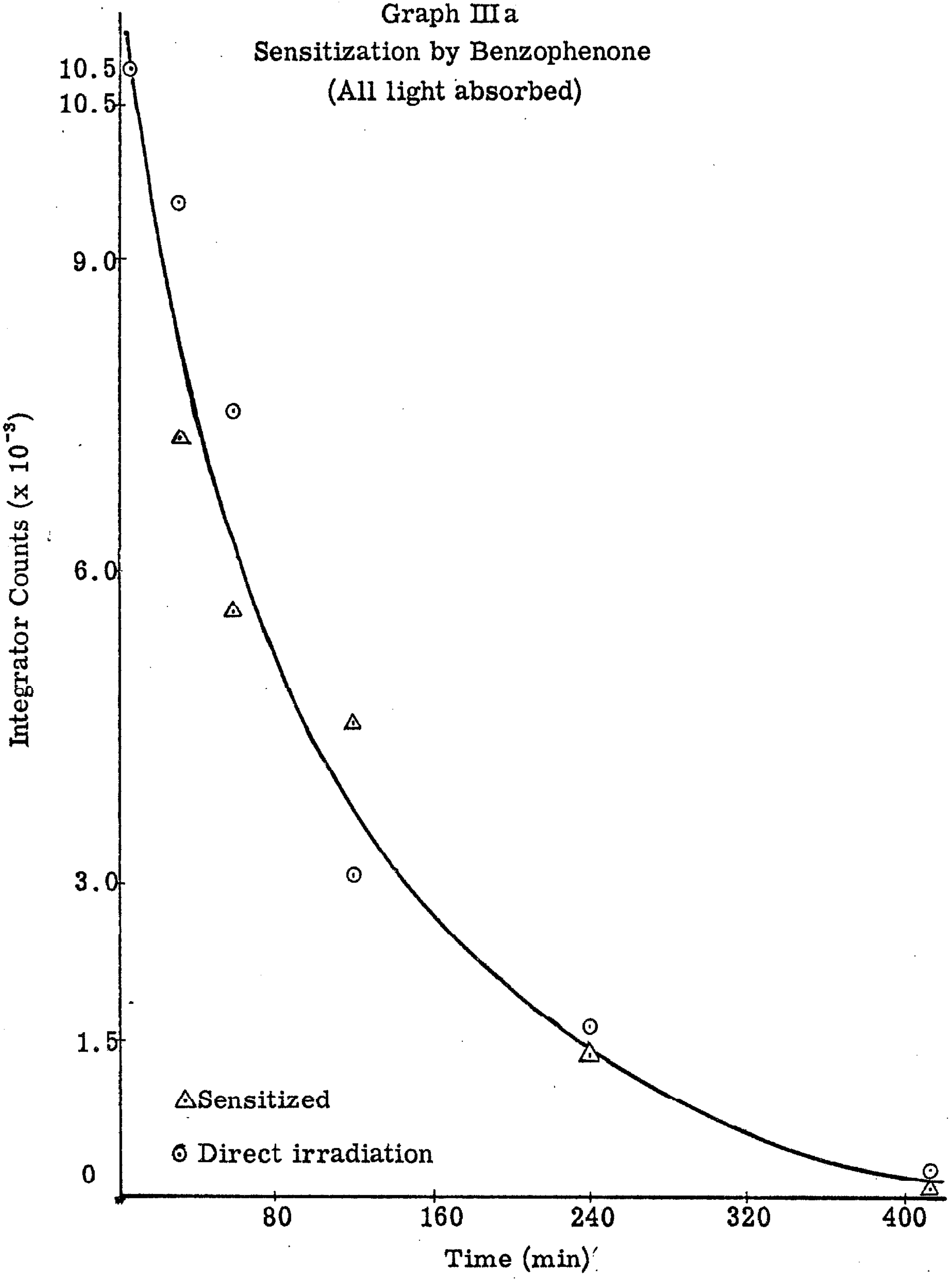
Graph II

Sensitization by Benzophenone
(Not all light initially absorbed.)

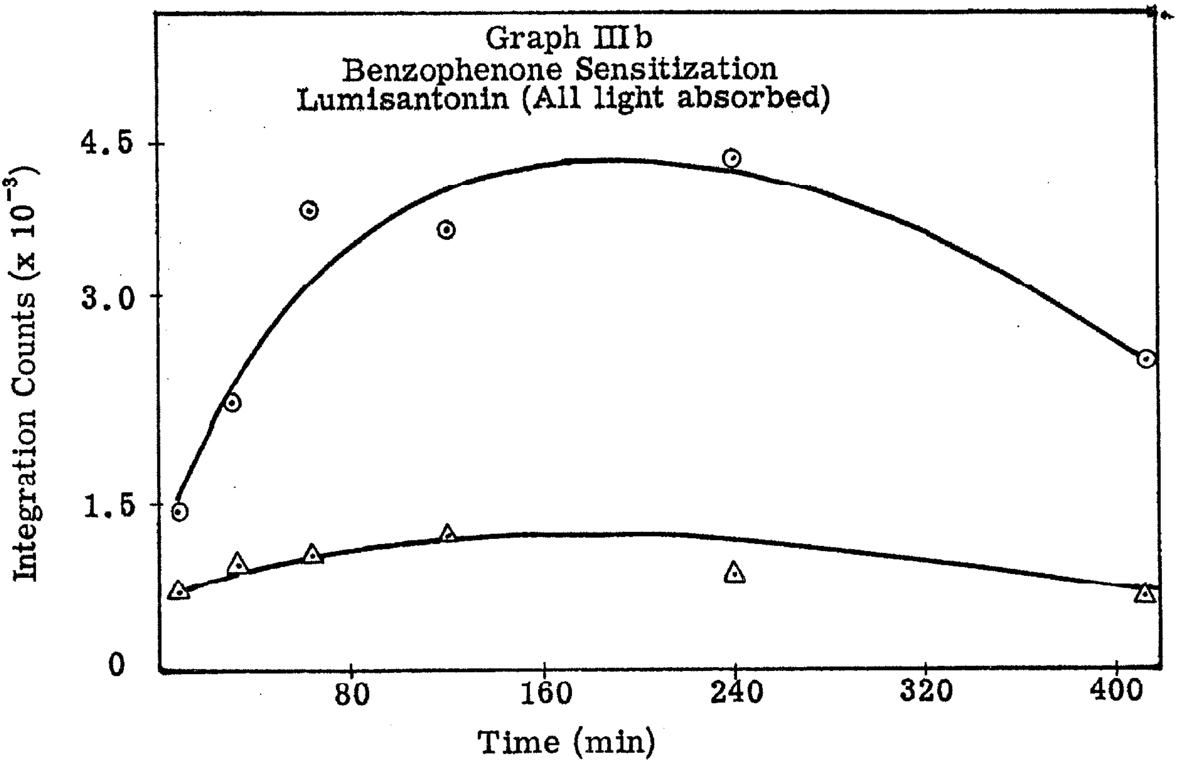


Direct - 1.95×10^{-2} M Santonin

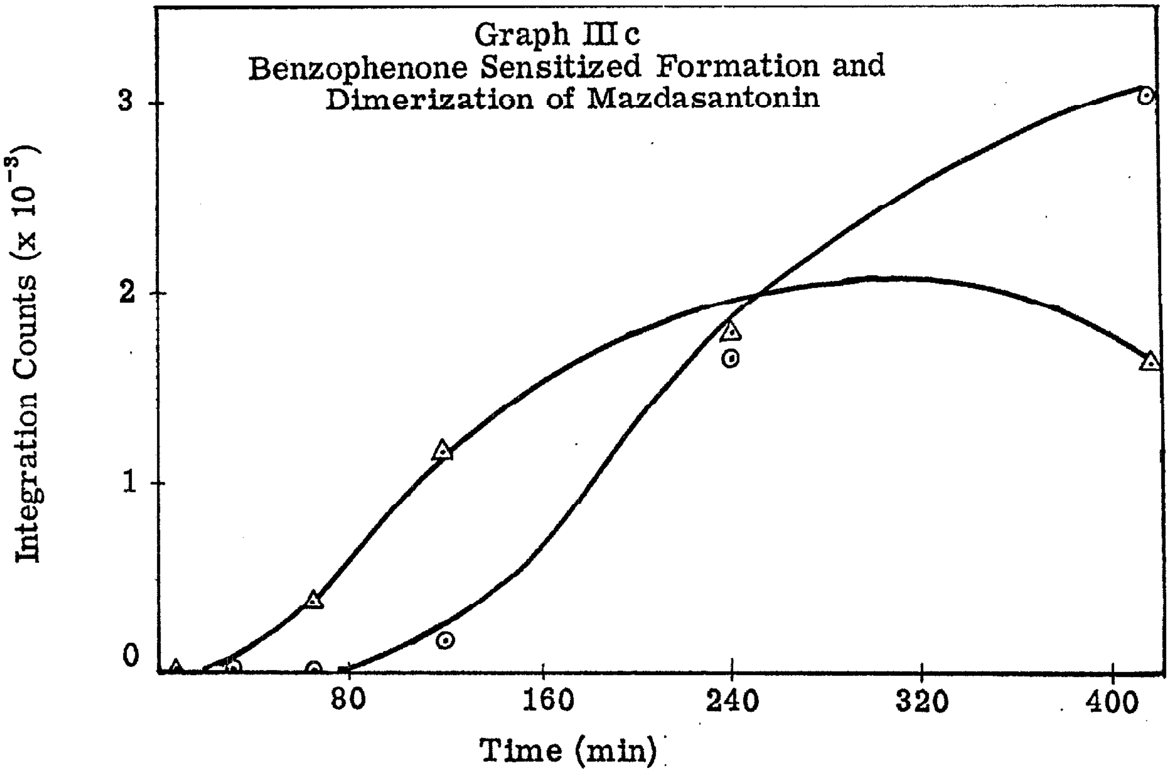
Sensitized - 4.31×10^{-2} M Benzophenone added



Graph IIIa
Sensitization by Benzophenone
(All light absorbed)



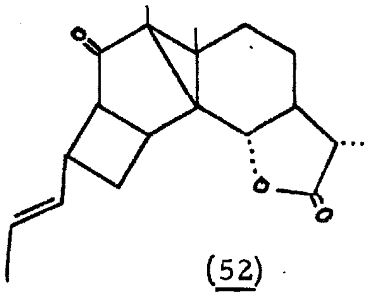
Graph IIIb
Benzophenone Sensitization
Lumisantonin (All light absorbed)



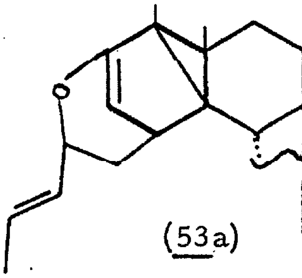
Graph IIIc
Benzophenone Sensitized Formation and
Dimerization of Mazdasantonin

Dilute solutions of lumisantonin in piperylene were prepared and irradiated for one week. Analysis by vapor phase chromatography showed that conversion of lumisantonin to mazdasantonin had occurred to a small extent. However, the primary reaction was addition of the piperylene to lumisantonin to give three products in the ratio 1: 2: 1.

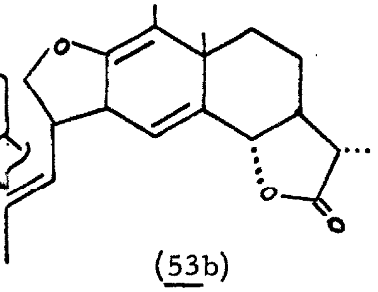
There are three types of possible products from addition of lumisantonin to piperylene. They are the cyclobutane (52) from photochemical cycloaddition, the pyran or furan (53) from dipolar addition, and the Diels-Alder adduct (54). Only one ring-juncture and double bond isomer has been shown for each type of compound; obviously variations are possible in each case.



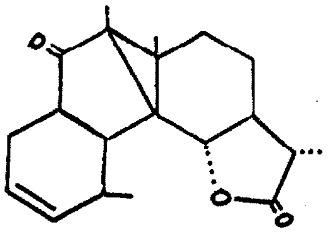
(52)



(53a)



(53b)



(54)

None of these addition compounds would be expected to have appreciable absorption at 3660 Å . Moreover, since the known cases of addition of water (27) or isoprene (see below) to mazdasantonin are rapid reactions, the fact that some mazdasantonin was still unreacted at the end of a week's irradiation indicates that mazdasantonin is inert to piperylene insofar as photoaddition is concerned. Thus, mazdasantonin was absorbing all the light, but was not reacting with piperylene (nor dimerizing because the concentration was too low). Therefore, the conditions for measuring the triplet energy of a sensitizer by the photostationary state olefin method were fulfilled.

The isomer composition of the piperylene was analyzed and found to be at a photostationary state characteristic of a sensitizer having a triplet energy of ~53 kcal/mole.* This result should not be stressed too strongly in view of the fact that low-energy sensitizers have not been too well studied.

The results given here are derived from the numerical values obtained by Turro (85). Note that these do not agree with the graph drawn by him (85a).

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* The data of Turro have recently been replotted (85b) and the photostationary state of the piperylenes in the presence of mazdasantonin could correspond to any one of three triplet energies: 53, 55, or 60 kcal/mole. However, the observation that mazdasantonin adds to isoprene (E_T=60 kcal/mole (84b)) suggests that the lower values are the more probable.

The attempt to check this result for mazdasantonin using the isoprene reaction (83) failed due to rapid addition of isoprene to mazdasantonin (the yellow color of mazdasantonin was completely discharged on irradiation after only a few hours).

2. Ethyl iodide absorption spectra

Ethyl iodide absorption spectra were taken for santonin and lumisantonin.* No new peaks were observed when the spectra in ethyl iodide were compared with the spectra of santonin and lumisantonin in benzene solution. Consequently, triplet energies could not be assigned by this method.

3. Graded sensitizers

In order to sensitize the photoconversion of santonin or lumisantonin efficiently, the sensitizer must provide sufficient energy to promote the acceptor to its lowest reactive state, presumably the lowest triplet state. As the energy of the sensitizer is reduced below that of the acceptor, transfer efficiency falls off sharply (56). Thus, one may determine the triplet energy of a reactant by using a series of sensitizers graded in energy which absorb most or all of the light. All donors having triplet energies

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* See 66b and references cited therein.

considerably above that of the acceptor will transfer equally efficiently. An approximate triplet energy is then assigned to the reactant by observing at what point in the series transfer efficiency, as measured by the rate of reaction, falls off. This method was applied to santonin and lumisantonin. The results are presented in Tables 9 and 10.

It is necessary from the reasoning behind the graded sensitizer method that the intersystem crossing efficiencies of the sensitizers in the series be equal. Otherwise, variations in reaction rate would reflect the variations in the intersystem crossing ratios of the sensitizers as well as their relative triplet energies. In the present studies, the intersystem crossing ratios of all sensitizers used are known to be approximately unity (84).

As expected, the higher energy sensitizers ($E_T > 67$ kcal/mole) were all equally efficient in sensitizing the photoconversion of santonin. The apparent rate of reaction was considerably less when thioxanthone was used as sensitizer, but still higher than for the conversion of the blank, showing that some generation of the santonin reactive state was occurring by transfer of energy from thioxanthone ($E_T = 65.5$ kcal/mole). The three lowest energy sensitizers ($E_T < 63$ kcal/mole) acted only as internal filters. On the basis of these results, the triplet energy of santonin is determined to be 67 ± 1 kcal/mole (in benzene).

Table 9**

Graded Sensitizers and Santonin

Sensitizer	E_T (kcal/mole)(86)	Remarks
Xanthone[a]	74.2	Perfectly efficient
Benzophenone[a]	68.5	Perfectly efficient
Triphenylene[b]	66.6	Efficient
Thioxanthone	65.5	Slightly faster than blank
Anthraquinone	62.4	No reaction
Michler's ketone	61.0	No reaction
Fluorenone	53.3	No reaction

** Irradiations were performed in benzene using a "merry-go-round" and a copper tetraamine filter solution which isolated the 404 and 436 mμ lines (see Experimental).

Table 10

Graded Sensitizers and Lumisantonin

Sensitizer	E_T (kcal/mole)(83)	Remarks
Benzophenone[a, c]	68.5	Perfectly efficient
Thioxanthone	65.5	Efficient
Michler's ketone	61.0	Relatively efficient[d]
α-Naphthyl phenyl ketone	57.5	No reaction
Fluorenone	53.3	No reaction

a. Using only a 3300 Å cutoff
b. Irradiated with 3130 Å line (see Experimental)
c. From quantum yield studies
d. The blank did not noticeably react.

The results are equally clear-cut in the case of lumisantonin. Sensitizers having triplet energies of 65 kcal/mole or more were efficient in promoting the photoconversion of lumisantonin, whereas sensitizers having triplet energies of less than 58 kcal/mole were ineffective. Michler's ketone (E_T = 61.0 kcal/mole) sensitized the photolysis of lumisantonin, but not as efficiently as the sensitizers having higher triplet energies. Thus, the triplet energy of lumisantonin is 63 ± 1 kcal/mole (in benzene).

4. Emission spectra

A final estimate for the triplet energies was obtained using a phosphoroscope to measure the emission spectrum of santonin and lumisantonin in various glasses at 77°K.

Santonin showed a very broad unstructured phosphorescence (Fig. 16) which was the same with or without the phosphoroscope (i.e. there was no fluorescence, as required for an intersystem crossing ratio of unity). The maximum in MCIP (methylcyclohexane: isopentane 5:1) falls at 4700 Å with the emission beginning at 4150 Å (Fig. 15). Lack of structure in the spectrum prevents definite assignment of the O-O band, but 67.5 kcal/mole (4240 Å) is a plausible figure.

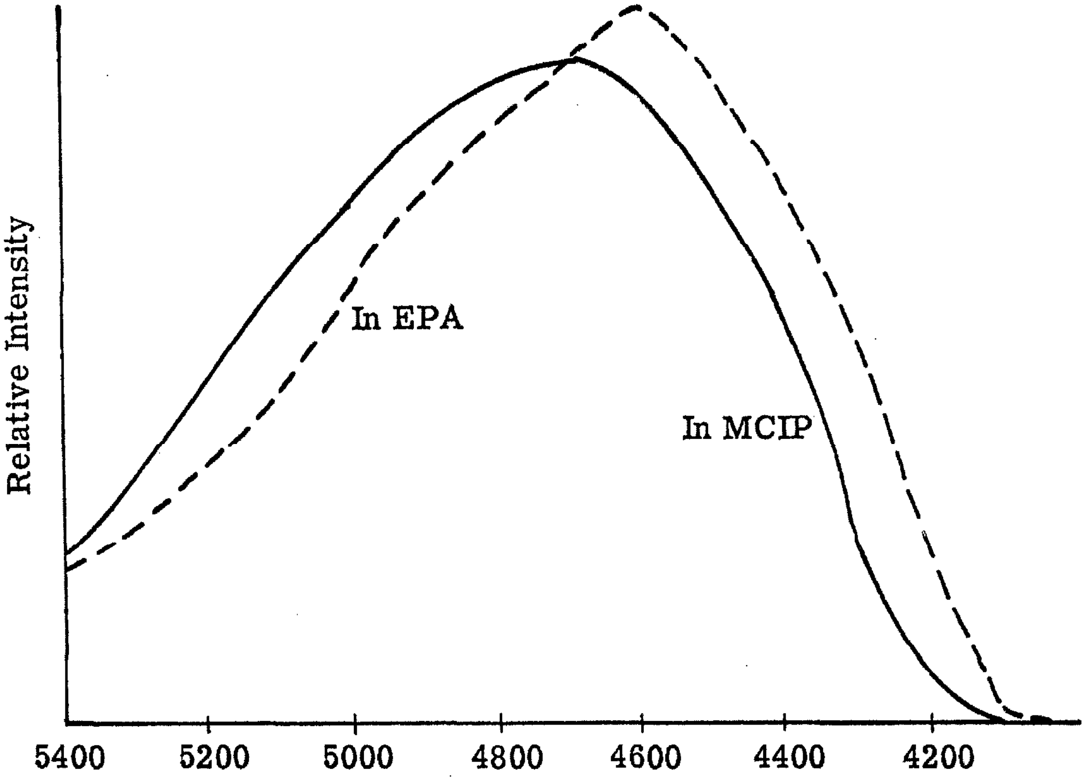
Lumisantonin did not emit in MCIP. However, in EPA (ether: isopentane: ethanol 5: 5: 2), a weak phosphorescence was recorded which showed a little more structure than that of santonin (Fig. 17). In this case, emission begins at ~4430 Å, placing the O-O band at approximately 64 kcal/mole, a value in agreement with that (63 ± 1 kcal/mole) obtained by the graded sensitizer method.

It should be recalled (Part II, Section I) that the likelihood of internal conversion to ground state is inversely related to the energy gap between the lowest excited state and the ground state. Mazdasantonin has been shown to have a much lower triplet energy that santonin (67-8 kcal/mole) or lumisantonin (63-4 kcal/mole). The value obtained from the piperylene photostationary state (53 kcal/mole) is plausible in view of the length of the conjugated system. (In general, the longer the conjugated system is, the lower are the energies of the electronic transitions.)

Since the triplet energy of mazdasantonin is so low, internal conversion is more likely than for santonin or for lumisantonin; thus, it is not surprising that mazdasantonin has no emission spectrum in either MCIP or EPA at 77°K.

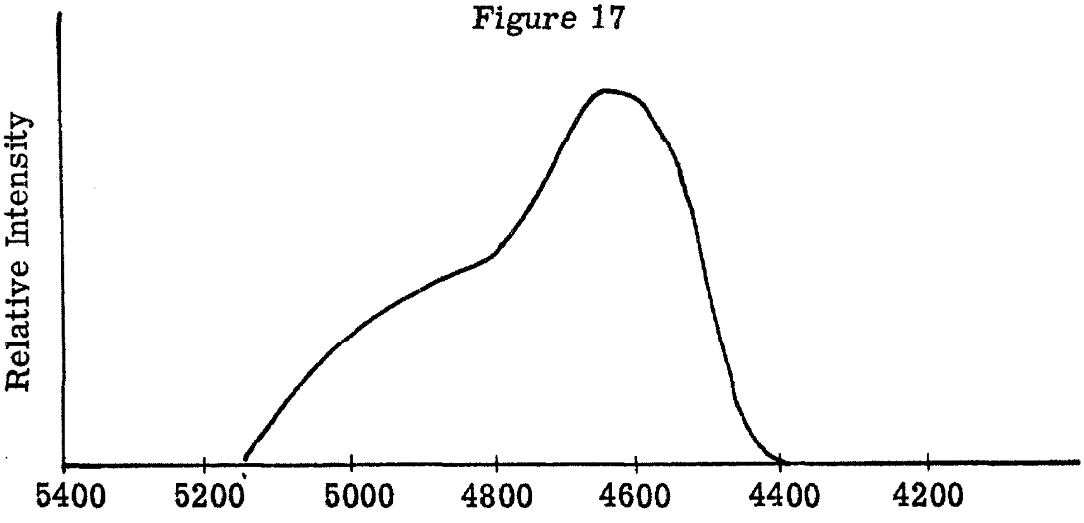
An alternate explanation for the lack of phosphorescence would be that the intersystem crossing ratio is very low. This factor certainly plays some role, since the quantum yield for reaction of mazdasantonin is raised on addition of a sensitizer. However, it is not presently possible to assess the relative importance of

Figure 16



Santonin Emission Spectrum

Figure 17



Lumisantonin in EPA

internal conversion and intersystem crossing inefficiency in preventing mazdasantonin phosphorescence.

D. Quenching

Normal quenching experiments were performed on santonin, lumisantonin, and mazdasantonin. It was found that conventional quenchers had no effect on the photoconversion of santonin to lumisantonin nor were they effective in preventing the further photolysis of lumisantonin to its photoproducts. Oxygen (10^{-3}M; Graphs IV and Table 11) and azulene (3×10^{-3}M) had no effect on the conversion of santonin or lumisantonin. Similarly, irradiation of a benzene solution equimolar in azulene and lumisantonin led to no difference in the rate of reaction of lumisantonin when compared with irradiation of a blank containing only lumisantonin in the same concentration (after correcting for internal filtering by azulene).

Dr. J. Saltiel kindly examined the effect of adding 0.005M stilbene before irradiation of a 0.1M solution of santonin in benzene. In this case, reaction was allowed to proceed long enough so that appreciable lumisantonin built up and underwent reaction, but the amount of quenching as measured by isomerization of the stilbenes proved immeasurably small. In fact, santonin and lumisantonin acted as internal filters for the slow direct photoisomerization of the stilbenes (66b).

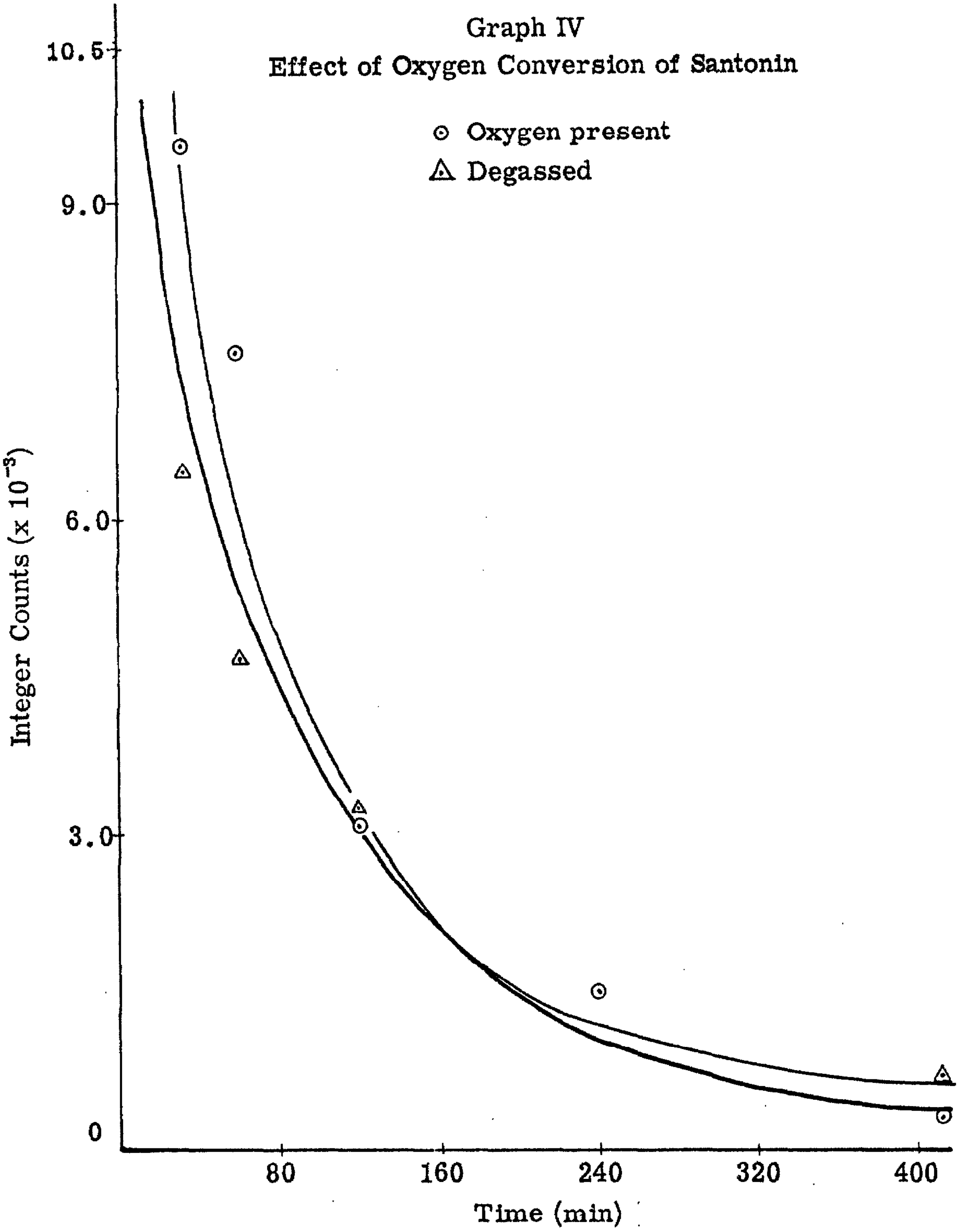

Graph IV
Effect of Oxygen Conversion of Santonin
⊙ Oxygen present
△ Degassed
Integer Counts (x 10^{-3})
10.5
9.0
6.0
3.0
0
80
160
240
320
400
Time (min)

Table 11

Effect of Oxygen

Run	S	LS	B	J	MS	H	E	Tar	Total	Atmosphere
1	38½	33	?	?	12	?	1½	6½	92	Air
14	33	38½	0	3	15½	½	9½	0	99	N_2
2	18	25	?	?	34	?	1½	8½	89	Air
4	15	23½	2½	1	37	½	4½	14½	101½	*
10	16½	24½	1½	1	35½	3	11	0	93	N_2
3	2½	4½	2½	4½	45	4	8½	30	102	Air
6	1	7	2½	1½	61½	6½	5½	½	89	Degassed

* Partly degassed

On the other hand, mazdasantonin photolysis could be quenched easily by oxygen or azulene (Graph V). In the former case, some reaction intervened to complicate matters, but the initial decline of mazdasantonin was still slower than under degassed conditions.

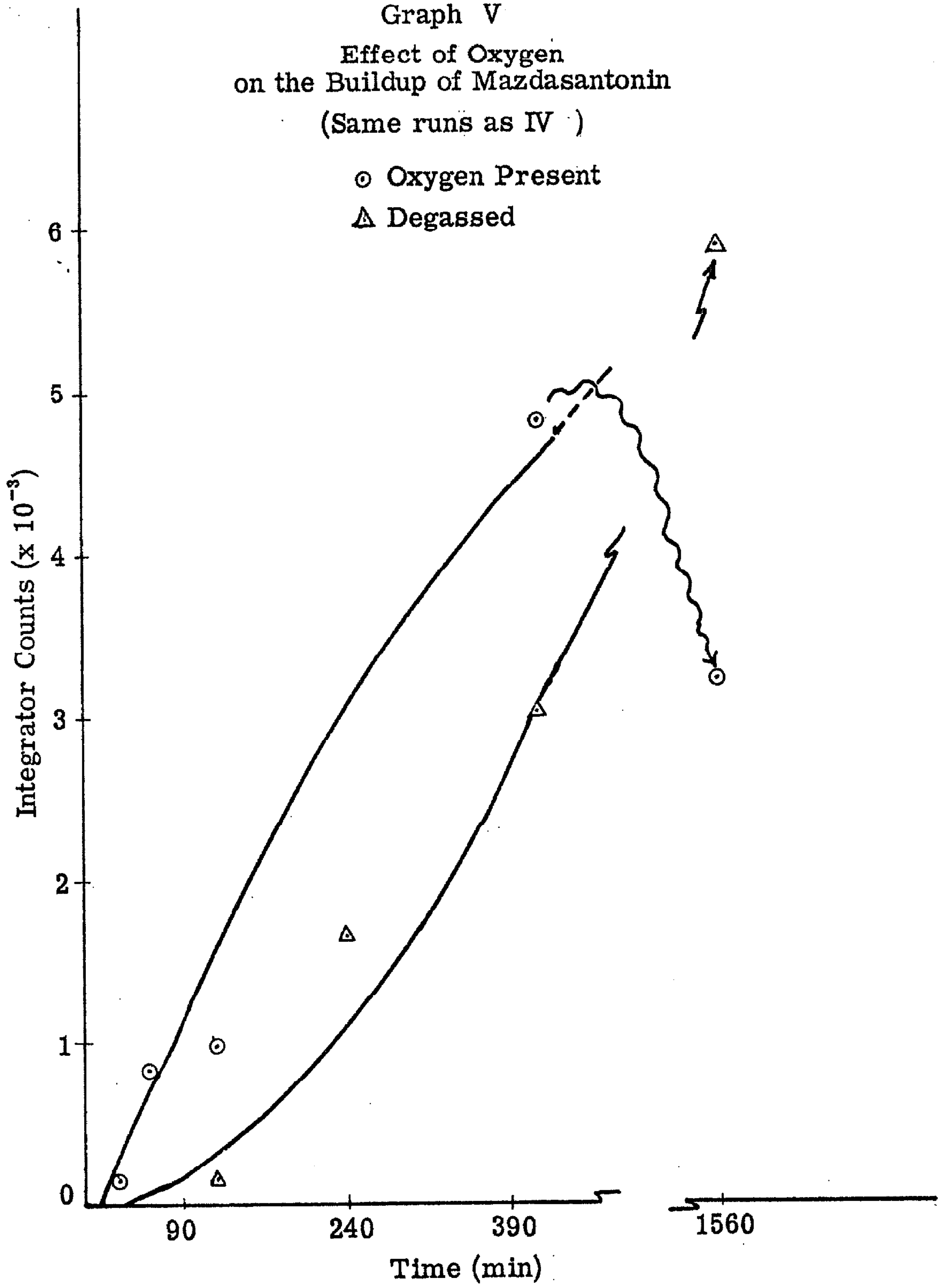
I have now presented both sensitization and quenching data for the dimerization of mazdasantonin. It is therefore demonstrated that *triplet intermediates are necessary for the dimerization of mazdasantonin*. This is not an unusual result, but it is nevertheless interesting because, in contrast to the apparent prevalence of triplet paths in the dimerizations of simple dienes, the scanty data available on aromatic systems (anthracene (95c, d) and β-methoxynaphthalene (95b)) indicate only singlet mechanisms to be operative. Consequently, it is particularly significant that a system as complicated as mazdasantonin dimerizes via a triplet intermediate.

A word of explanation is required for the fact that quenchers do slow the decline of santonin or lumisantonin in the last stages of the reaction. As the photolysis of santonin proceeds, the major constituent of the reaction mixture becomes, successively, santonin, lumisantonin, and finally mazdasantonin. Since each photoproduct has a much higher extinction than its precursor ($\epsilon^{3660\text{Å}}_{\text{benzene}}$ for santonin, lumisantonin, and mazdasantonin = 15, 104, and 323, respectively), the rates of photoconversion of santonin to lumisantonin and of lumisantonin to its photoproducts become slower and

Graph V

Effect of Oxygen on the Buildup of Mazdasantonin

(Same runs as IV)



slower as the reaction progresses because the successive photoproducts are ever more efficient internal filters.

Ponder now the photolysis of a solution of santonin or lumisantonin to which quencher has been added. In the early stages of the reaction, the usual kinetics are anticipated because quencher has no effect on the first photoreactions. In the later stages, mazdasantonin builds up to higher levels than usual due to blocking of the dimerization pathway. Therefore, internal filtering by mazdasantonin is more important when irradiation is carried out in the presence of quencher. If the concentrations of santonin or lumisantonin are plotted versus time, the decline of santonin or lumisantonin is predicted to be slower when quencher is added, but only after mazdasantonin has built up to an appreciable extent. Graphs IV show the expected pattern.

The failure of these conventional quenching experiments was a matter of serious concern. There were already a sufficient number of reactions reported in the literature in which sensitization constituted the sole evidence for the triplet nature of the intermediate. Clearly, such an assignment is not compelling, particularly if the effect of sensitizer is solely to accelerate an otherwise inefficient reaction. Acceleration alone is perfectly consistent with a singlet path in the direct reaction, operative in addition to an alternate, normally less favored, triplet path that leads to the same products.

Addition of sensitizer then merely superimposes the triplet pathway on the normally occurring singlet mechanism. Thus, sensitization alone cannot eliminate the singlet as the reactive intermediate under conditions of direct irradiation.

Some less conventional experiments using quencher (piperylene) as solvent were more successful. Unfortunately, the solubility of santonin in piperylene is so low that even a saturated solution (approximately 10^{-3}M) required flame detector v.p.c. for analysis. Nevertheless, the results were unambiguous.

Two sealed, degassed, samples were prepared: one was a piperylene solution 6.9×10^{-3}M in santonin and the other was a benzene solution 1.2×10^{-2}M in santonin. The two tubes were irradiated concurrently on an optical bench. After irradiation for four hours, reaction in the benzene solution was complete, but no conversion was detectable in the tube containing piperylene.

Apart from quenching, two possible explanations could be advanced to explain this result. First, the absorption of light by santonin in benzene at 3660 Å ($\epsilon = 15.0$) is about double the corresponding absorption in piperylene ($\epsilon = 6.4$). Thus, the predicted rate of reaction for irradiation of santonin in benzene solution is more than twice that of santonin in piperylene. However, even if only 10% of the original santonin had reacted by the time of analysis of the piperylene solution, this much conversion would assuredly have been detected. It is all the more significant, then, that no conversion was detectable in the piperylene solution although total conversion was apparent in the benzene solution.

Secondly, one must take account of the fact that no internal standard was used in this irradiation. It will be recalled from the previous section (p. 80) that lumisantonin reacts with piperylene to give higher molecular weight products that have rather long retention times on v.p.c. columns. If the reaction of lumisantonin with piperylene were very fast and perfectly efficient, then neither lumisantonin nor mazdasantonin would have been detected during the normal course of analysis. The apparent result would have been that no reaction had occurred because only santonin was detectable. However, mazdasantonin is formed from lumisantonin even in neat piperylene and is stable indefinitely under these conditions (p. 81). Of more importance, the quantum yield of lumisantonin disappearance is only 0.26 in benzene (see below); and a control run showed that addition of piperylene accelerated the reaction only slightly. Hence any appreciable conversion of santonin would have allowed lumisantonin to build up to a detectable amount.

Quenching is the only acceptable explanation of these results, but it was nonetheless apparent that quenching could not be 100% efficient since some mazdasantonin was formed when santonin or lumisantonin was irradiated in neat piperylene for extended periods of time. A rough estimate of quenching efficiency was obtained in the following way.

Identical, sealed, degassed tubes containing solutions 3.4×10^{-2}M in santonin (n-octyl phthalate as internal reference) were irradiated concurrently on the merry-go-round. The solvent in the first tube was pure benzene; in the second, benzene 2M in piperylene. By the time the reaction in pure benzene had converted 22% of the original santonin, only 10% conversion had occurred in the second tube. After correcting for the slight difference in absorption of santonin in the two solutions, quenching is found to be at least 70% efficient.

Unfortunately, no estimate of the rate of reaction or lifetime of the excited state of santonin can be made from this result. The processes available to an excited santonin molecule are reaction (equation 1) and deactivation (equation 2). If quencher is added, there is an additional process by which the excited state is deactivated to the ground state (equation 3).

	Rate	
$S^* \rightarrow LS$	k_r	(1)
$S^* \rightarrow S$	k_d	(2)
$S^* + Q \rightarrow S + Q^*$	$k_q[Q]$	(3)

The quantum yields in the presence and absence of quencher are given by equations 4 and 5, respectively.

$$\Phi^{q} = \frac{k_r}{k_d + k_r + k_q[Q]} \qquad (4)$$

$$\Phi^{o} = \frac{k_r}{k_d + k_r} \qquad (5)$$

Thus,

$$\frac{\Phi^{o}}{\Phi^{q}} - 1 = \frac{k_d + k_r + k_q\,[Q] - k_d - k_r}{k_d + k_r}$$

$$= \frac{k_q[Q]}{k_d + k_r} = k_{sv}\,[Q] \qquad (6)$$

Equation 6 is the Stern-Volmer equation, and the Stern-Volmer rate constant k_{sv} is equal to $k_q/(k_d + k_r)$. From equation 5, k_d may be expressed as

$$k_d = \frac{k_r}{\Phi^{o}} - k_r \qquad (7)$$

Substitution of 7 into 6 and rearrangement leads to

$$\frac{1}{k_r} = \tau = \frac{k_{sv}}{k_q\,\Phi^{o}} \qquad (8)$$

where τ is the mean lifetime of the excited state. The observed ratio of quantum yields in equation 6, Φ^{o}/Φ^{q}, is 3.28 for the experiment using 2M piperylene as quencher. This leads to a Stern-Volmer quenching constant (k_{sv}) of only 1.14. The quantum yield for the photoconversion of santonin in the absence of piperylene is unity (see below), so that equation 8 now reduces to

$$\frac{1}{k_r} = \tau = \frac{1.14}{k_q} \qquad (9)$$

Energy transfer reactions which are exothermic by more than 4 kcal/mole are normally diffusion controlled (56). The diffusion rate constant for piperylene in benzene is $\sim 10^{10}$ sec^{-1}, which would mean (equation 9) an excited state lifetime of $\sim 10^{-10}$ seconds.

This value explains the ineffectiveness of quenchers added in relatively high concentrations (5-10 x 10^{-2}M), but is abnormally small for the lifetime of a triplet species. Of course, some error arises from the inapplicability of the Stern-Volmer equation at such a high quenching efficiency. However, correction for this error lengthens the apparent lifetime and makes it more reasonable (87a). Nonetheless, the derived lifetime is abnormally short (10^{-9} sec) even if the most liberal correction is made for the inapplicability of the Stern-Volmer equation. Singlet state lifetimes are normally on the order of 10^{-8} to 10^{-9} seconds, and triplet state lifetimes are usually orders of magnitude longer because of the multiplicity restriction. However, these values refer to the lifetimes of excited states where decay to the ground state (by emission of light or internal conversion) is the only process under consideration. Rearrangement is a different case, and consequently there is no reason why the excited state could not be very short-lived even though the reactive intermediate is a triplet.

A possible factor, rendered likely by the fact that some conversion occurs even in neat quencher as solvent, is that the quenching rate is less than diffusion controlled due to an orientation effect, i.e. unless the excited molecule happens to be properly disposed relative to the quencher so that energy transfer can occur immediately, isomerization of the excited santonin takes place first. This explanation is supported by the recent observation that energy transfer is quite sensitive to orientation in the benzophenone/deuterophenanthrene system (87b); but such considerations cannot add more than a factor of three to the lifetime of the excited state, at the very most. Thus, the lifetime of the santonin triplet state is of the order of 10^{-9} seconds, i.e. in the range of normal singlet state lifetimes.

One might reasonably ask why it is that santonin does phosphoresce at low temperatures in glasses with a radiative lifetime of $> 10^{-4}$ seconds in spite of the abnormally short lifetime of the triplet state at room temperature in solution. The answer is that the rearrangement process that competes with phosphorescence involves drastic geometric changes, including inversion of the 10β methyl group, and these processes are effectively hindered at liquid nitrogen temperatures by the microscopic rigidity of the glass. In this way, the relatively less favored emission process becomes the fastest available means of deactivating the excited state at low temperature.

Similarly, when lumisantonin is irradiated in a glass at liquid nitrogen temperature, a blue color is generated (Section VB) which is stable indefinitely at 77°K, but cannot be detected at room temperature on flash photolysis of lumisantonin solutions. Here we have trapped an intermediate (not the triplet) in the photolysis of lumisantonin which cannot rearrange to mazdasantonin, B, or J at low temperature because methyl migration is prevented by the microscopic rigidity of the solvent. The influence of solvent viscosity on the lifetime of this intermediate is fantastic. As the temperature is raised from 77°K to 300°K, the lifetime falls from days or years to less than 10^{-5} seconds.

These piperylene experiments constitute a preliminary proof of triplet intermediates in the photolysis of santonin. There can be no question of singlet process in these studies because the exciting light is not sufficiently energetic to effect the lowest singlet-singlet transition of piperylene (cf Table 8).

But there is still an element of doubt because of the unusually high concentrations involved. To clarify this aspect of the problem, another experiment was run in which the solvent-quencher was methyl naphthalene (E_T = 60 kcal/mole) and the solution was 0.3M in cis-piperylene (analyzed to be < $\frac{1}{2}$% trans). After five hours irradiation, some conversion of santonin to lumisantonin had occurred and the piperylene had isomerized to the photostationary state, 70% trans, characteristic of a sensitizer of 60 kcal/mole. A blank run at the same time without added santonin still contained 87% of the cis-isomer. In this case, it is probable that the photolysis of santonin is quenched by the methyl naphthalene which transfers its energy and triplet character to piperylene, which then undergoes cis-trans isomerization. Whatever the mechanism of quenching in bulk quencher, the end result is the transfer of triplet energy from santonin to piperylene. The intermediacy of a triplet state in the photolysis of santonin is thus conclusively demonstrated.

The dimerization of mazdasantonin has already (p. 92) been shown to involve triplet intermediates. Only sensitization has been effected in the case of lumisantonin photoconversion, so that no conclusive assignment of a triplet pathway dare be made. However, a highly efficient triplet path is available when sensitizer is used (see below), and the apparent generality of triplet mechanisms in the santonin system adds support to the hypothesis that the photolysis of lumisantonin also proceeds via triplets in the direct irradiation.

It has already been emphasized that sensitization alone cannot be taken as proof of a triplet reaction path if no difference exists between the sensitized and unsensitized reactions. The same prudence should be exercised when dilute quenchers are found to be ineffective since, as shown here, the triplet reaction may be so fast that the reaction rate of photoconversion exceeds that of quenching.

In case the reader feels that such gross misunderstandings are never encountered in the scientific community, he should recall the study of the photoconversion of diphenylamine to carbazole, which was stated not to be a triplet reaction due to failure of butadiene to act as a quencher (88). This very reaction has now been shown to proceed via the triplet by flash photolysis studies (89).

Another lamentable example is the photolysis of 4,4-diphenylcyclohexadienone, where the authors solemnly intone against eliminating triplet mechanisms purely on the basis of negative quenching results, but assign a triplet mechanism solely on the basis of sensitization (67).

E. Quantum Yields of Santonin, Lumisantonin, and Mazdasantonin Photolyses

1. General

Quantum yields (with Mr. G. Schnuelle) were determined for the major reactions in the sequence and are presented in Table 12. The important point to be gleaned from these data has already been stated, <u>viz.</u>, benzophenone is within experimental error a 100% efficient sensitizer for both santonin and lumisantonin, and probably for mazdasantonin as well.

Table 12

Quantum Yields for the Major Reactions

		Santonin	Lumi-santonin	Mazda-santonin
Benzene	direct irradiation	0.94+0.04[a], 0.99[b]	0.263±.016[a]	< 0.01[d]
	benzophenone added	~ 1[c]	1.05±.06[c]	> 0.05[d]
In methylnaphthalene		0.93±.08[a]	0.482±.010[a]	

a. Analysis by Beckman DU
b. Analysis by flame v.p.c.
c. Analysis by conventional v.p.c.
d. Analysis by liquid-liquid partition chromatography (3×10^{-3}M)

2. Viscosity effects

There is a dramatic rise in the quantum yield of lumisantonin photolysis (0.26→0.48) on going from irradiation in benzene to irradiation in methylnaphthalene. Both solvents are aromatic and both are excellent solvents for lumisantonin. The most obvious difference between them is the higher viscosity of methylnaphthalene.

Solvents often exercise great influence on photochemical reactions, the more viscous solvents tending to favor triplet reactions. Ermolaev* (90) has discussed this matter in some detail and has concluded that the major effects arise because the T_1-S_0 (lowest triplet to ground state) radiationless transition is rendered less probable as molecular motions are hindered. Other, triplet state, reactions are able to compete more easily with internal conversion, and the net result is an increase in the phosphorescence yield and other triplet processes. Some recent cases in which this function of solvent is clearly operative are the studies by Stevens (91) and Porter (92) on the temperature dependence of triplet decay rates. For pyrene (91), the rate of triplet decay in liquid paraffin drops by a factor of two as the temperature is lowered from 0° to -25°C. Since phosphorescence lifetimes are not usually functions of temperature (84, 90), it is almost certain that disfavoring of the T_1-S_0

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* See also Porter (ref. 93).

radiationless transition is the important factor in the results of Stevens and Porter.

However, this explanation cannot account for the rise in quantum yield for the photoconversion of lumisantonin as solvent viscosity is increased. Sensitization by benzophenone in benzene raises the quantum yield for the photolysis of lumisantonin to unity, i.e. every molecule which arrives in the triplet state reacts. Therefore, if it is assumed that the direct photolysis proceeds via triplets also, the inefficient step in the photoconversion of lumisantonin must be intersystem crossing, rather than reaction from the lowest triplet. Hence, the higher quantum yield measured in methylnaphthalene requires that the rate of intersystem crossing be higher in the more viscous solvent.

At least one previous case (that of eosin dianion) has been reported in which the calculated rates of intersystem crossing are observed to be dependent on solvent. The higher rate is in the more viscous solvent; hence, triplet processes are more important in glycerol than in ethanol. Pertinent data are summarized in Table 13 (109).

Table 13

Effect of Solvent Viscosity on the Intersystem Crossing Rate of Eosin Dianion

	Glycerol	EtOH
$S_1 \rightarrow T_1$	4×10^7	1×10^7
mean intersystem crossing ratio (25°C)	0.044	0.023

A tantalizing coincidence is the fact that the intersystem crossing ratio for methylnaphthalene is the same as the quantum yield for lumisantonin photoconversion in methylnaphthalene (0.48) (84). The possibility that the solvent has been excited, undergone intersystem crossing, and then acted as a sensitizer is intriguing. This would predict the experimental quantum yield on very conventional grounds. Moreover, the triplet energy of methylnaphthalene ($21,000 \text{ cm}^{-1} = 60.1$ kcal/mole) (94) is high enough to allow energy transfer. The possibility of solvent sensitization is, however, ruled out by the experimental conditions. The absorption spectra of lumisantonin and methylnaphthalene are such that at 3660 Å (the exciting radiation), more than 99% of the incident light is absorbed by lumisantonin. Moreover, the singlet energy of methylnaphthalene is so high ($31,450 \text{ cm}^{-1}$) (94) that the energy in the exciting light ($27,300 \text{ cm}^{-1}$) is insufficient to effect the S_0-S_1 transition of methylnaphthalene even if transfer of singlet excitation from lumisantonin to methylnaphthalene were to be considered.

The present data are not very extensive, but since the observed solvent effect for the photolysis of lumisantonin in benzene and methylnaphthalene is definitely not due to sensitization by solvent, the viscosity dependence of the intersystem crossing ratio seems to be the only plausible explanation of the enhanced quantum yield for the photolysis in methyl naphthalene. The fact that a previous case is known is comforting, but hardly conclusive.

In Section V-B, a photochemical mechanism is developed based on electron ejection. Even if the electron ejection mechanism proves to be true, the effect of solvent viscosity on the absolute intersystem crossing rate must still be invoked to explain the higher quantum yield for the conversion of lumisantonin in methylnaphthalene. For a detailed explanation, see Part 8 of Section V-B.

F. A Non-Spectroscopic Triplet State of Santonin

The failure of methylnaphthalene to quench spectacularly the conversion of santonin is interesting since methylnaphthalene evidently accepts triplet energy from santonin. Clearly, return of energy to santonin from methylnaphthalene is an efficient process and competes well with internal conversion of methylnaphthalene triplets to the ground state, even though the spectroscopic triplet energies of santonin and methylnaphthalene are approximately 67 and 60 kcal/mole, respectively. Once again, energy transfer appears to be highly favored between two species where the donor lacks some 7 kcal/mole of the energy necessary to excite the acceptor to its spectroscopic state.

A similar result has been obtained for the photosensitized isomerization of the stilbenes (66b). In that case, the eventual explanation was that a triplet level existed for *trans*-stilbene at lower energy than any previously assigned from spectroscopic work. The existence of this non-spectroscopic state required that the reported triplet-singlet transition involve the first vibrational level of the triplet state rather than the zeroth level as previous assumed.* Experimental studies with graded sensitizers led to the result that the transfer efficiency fell as the available triplet energy of the sensitizer dropped below the spectroscopic level. At yet lower energies, transfer efficiency rose again, reaching a maximum at the non-spectroscopic level (resonant transfer).

In the work with graded sensitizers (p. 84), no efficient sensitization of santonin was observed after the available energy fell

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* For a complete discussion, see 66b and 83b and references cited therein.

below 65.5 kcal/mole. However, no sensitizers between 61 and 53 kcal/mole were tested, so that resonant transfer at 60 kcal/mole might have been overlooked.

If a second acceptor is put into solution, e.g. piperylene, in sufficient concentration to compete with santonin for methylnaphthalene triplets, transfer to both species would be expected. Eventually, piperylene would reach its photostationary state. However, some conversion of santonin would also be expected. If only santonin is present in the methylnaphthalene solution and the photoconversion of santonin is fast relative to the degradation of methylnaphthalene triplets, as is certainly true, then no quenching would be observed. Thus, the non-spectroscopic state can account for these data.

The possibility of a non-spectroscopic triplet state of santonin at approximately 60 kcal/mole also suggests an alternate explanation for the inefficiency of quenching by piperylene. The triplet energies of the two piperylenes lie between 57 and 58 kcal/mole (84). This is high enough to permit inefficient energy return from piperylene to the non-spectroscopic triplet state of santonin in the same manner as suggested above for the return of triplet energy from methylnaphthalene to santonin. As a consequence, piperylene could not be a perfectly efficient quencher for santonin. The failure of oxygen or azulene to quench santonin triplets is in accord with the general observation that non-spectroscopic triplets (sometimes called phantom triplets) are very difficult to quench with these substances (83b, 85b).

This hypothesis could be tested by quantum yield measurements for the photoconversions in methylnaphthalene, using shorter wavelengths where methylnaphthalene has much higher extinctions than does santonin. Under these conditions, the only way in which reaction could occur at an appreciable rate would be by transfer of triplet energy from methylnaphthalene to the non-spectroscopic state of santonin.

This postulation of a non-spectroscopic state should not be confounded with the superficially similar case of the sensitization of 4, 4-diphenylcyclohexadienone by naphthalene (67). Zimmerman reported that the addition of naphthalene raised the quantum yield for conversion of 4, 4-diphenylcyclohexadienone from 0.11 (called relative conversion, presumably proportional to quantum yield for his discussion) to 0.29 with naphthalene absorbing 30 ± 10% of the incident light. As discussed above (p. 94), this is precisely the sort of effect to be expected if sensitizer is imposing a normally inactive triplet path on a singlet process. Moreover, for the particular case of Zimmerman's, it is clear that the sensitization by naphthalene need not involve triplets at all. No measure is given of how much light was absorbed by the dienone alone, but if the absorption spectrum is similar to that of santonin, the absorption even at the maximum (325 mμ) was no more than 35% of the total illumination.

The effect of the naphthalene in the sensitized photolysis was that additional energy reached the dienone via singlet energy transfer from naphthalene, an accepted process in the naphthalene/4-methyl-4-dichloromethyl cyclohexadienone (95a), β-methoxynaphthalene/benzophenone (95b), and coumarin/benzophenone (95e) systems. The apparent sensitization of the 4,4-diphenylcyclohexadienone photoconversion by naphthalene is a simple case of singlet energy transfer rather than the "uphill sensitization" which so perplexed Zimmerman.

In the present work on the santonin system, care was taken to ensure that no appreciable light was absorbed by solvent, so that complications such as singlet transfer are avoided. The postulated non-spectroscopic state is consistent with the data and present photochemical theory, but must be more extensively tested before being considered as proved.

There is a second possible explanation of the inability of methylnaphthalene to quench the isomerization of santonin. If santonin and methylnaphthalene form a loose complex, normal spectroscopic techniques might not be able to detect it. Thus the spectrum of santonin in methylnaphthalene does not greatly differ from that in benzene. However, complexing could be considerably more important in the excited state. If the result were that santonin had a lower triplet energy in methylnaphthalene due in some way to its involvement in the complex, then the fact that the quantum yield for conversion of santonin in methylnaphthalene is still unity means only that the triplet energy of santonin in the complex is about 60 kcal/mole relative to the santonin ground state. This value is sufficiently low that triplet energy can be transferred back from piperylene triplets to the complex. By this sort of shuttle process, both santonin and piperylene are isomerized.

Two experiments are desirable to clarify this point. One would be to test for complexing in the usual way by examining the absorption spectra of solutions of santonin and methylnaphthalene in some inert solvent, e.g. benzene, at various concentrations, and seeing whether Beer's law is obeyed. The second experiment would consist of a series of phosphorescence spectra at low temperature, using the 3660 Å line of mercury (so as not to excite methylnaphthlene directly), and seeing whether methylnaphthalene can quench the phosphorescence of santonin. Until these experiments are performed, energy transfer from santonin to methylnaphthalene in the quenching experiments is not definite, but the important conclusion that santonin triplet states are involved is in no way affected.

"...the skeletal changes resulting in dienone photochemistry are strongly suggestive to the organic chemist of rearrangement of an electron deficient _Pi_ system (i.e. carbonium ions)."

---H. E. Zimmerman (ref. 104d)

"Oh, but this is marvellous!" said Madame Dubarry, shaking with laughter. "I have never met a man at once so serious and so diverting."

---A. Dumas

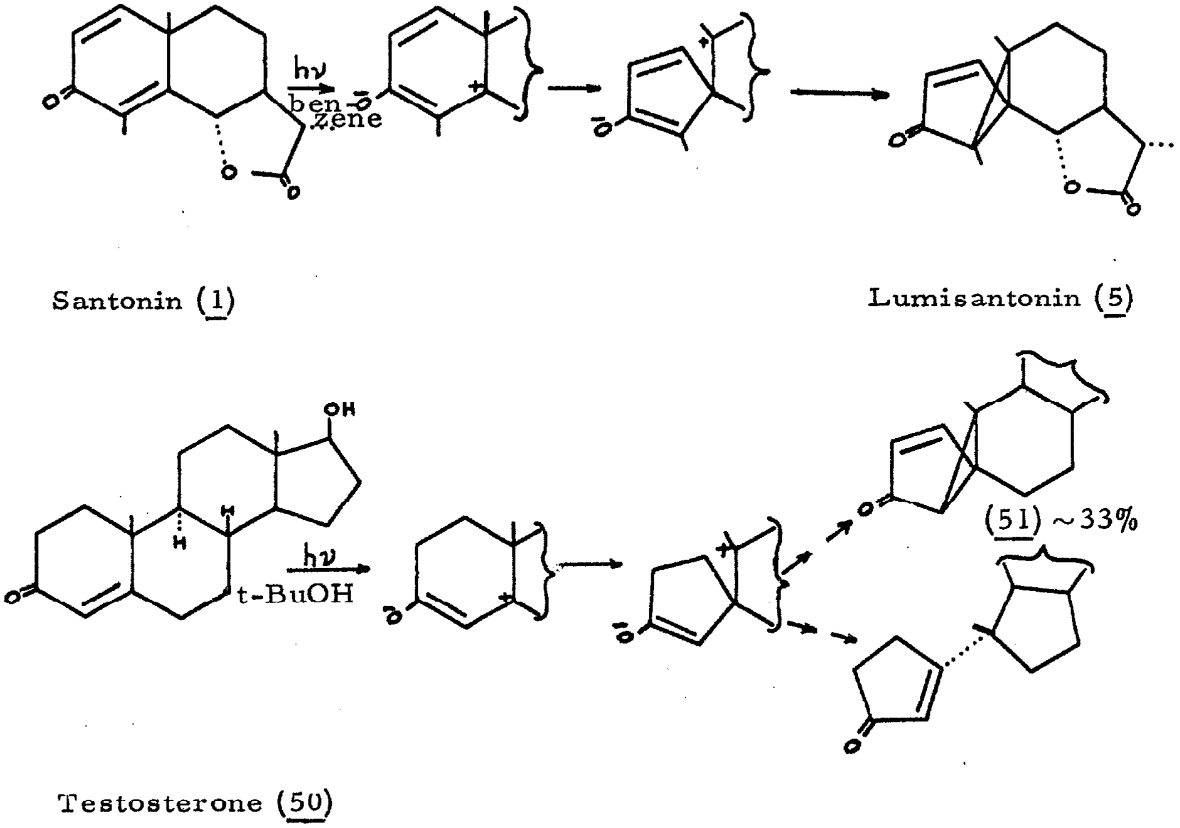
IV. The Mechanisms of Photoconversion in the Santonin Series

A. Polar States in Enone Photochemistry

1. Unimolecular rearrangements

All the known photochemical rearrangements of enones can be rationalized in terms of ionic intermediates (96), as shown in Figure 18 for santonin and testosterone.

Figure 18



Santonin (1)

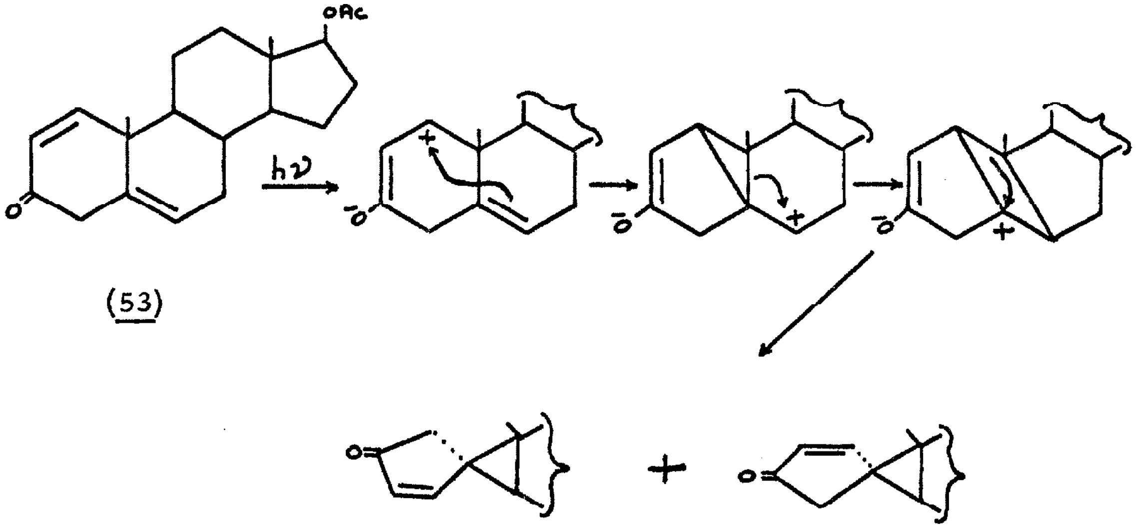
Lumisantonin (5)

(51) ~33%

Testosterone (50)

(52) ~67%

Rather elegant schemes are sometimes written, as in the photoconversion of 3-oxo-17β-acetoxy-$\Delta^{1,5}$-androstadiene (53) (42), for which a series of cyclopropylcarbinyl rearrangements are invoked (97), but the rationalizations are quite straightforward.



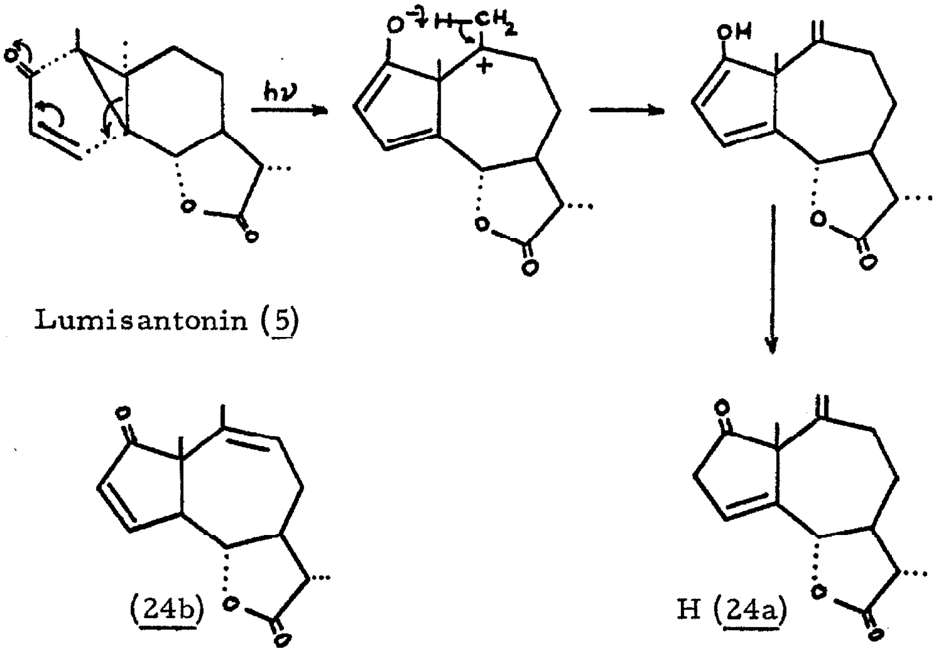
(53)

(54) 23%   (55) 6%

A rather pleasing application of the carbonium ion hypothesis is to the formation of H from lumisantonin. As discussed in Part I, the originally assigned structure of H (as pyrolumisantonin) was (24b), but the correct structure is (24a). It is therefore reassuring that the carbonium ion hypothesis based on purely intramolecular processes easily rationalizes the formation of (24a) from lumisantonin and even predicts the exocyclic location of the cycloheptane double bond (Fig. 19). Note that an endocyclic double bond in the B ring could be accommodated by invoking intermolecular proton transfer, but ionic intermediates cannot lead directly to the conjugated cyclopentenone system of (24b).

Figure 19

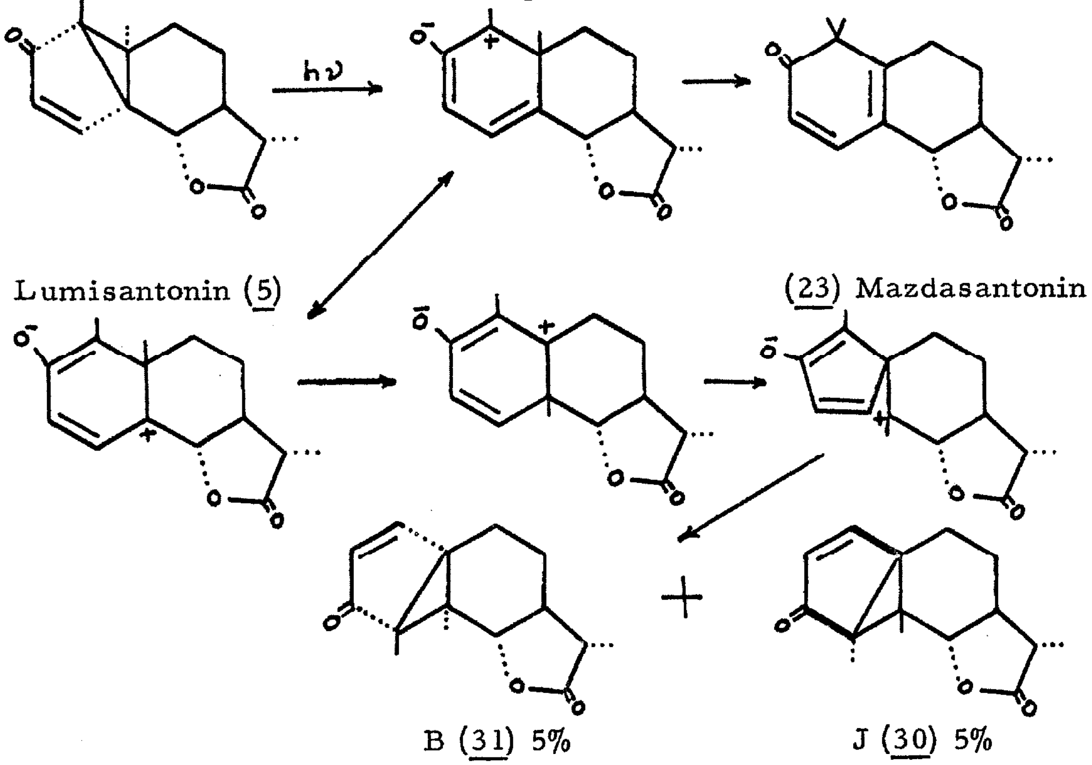
The Conversion of Lumisantonin to H



Although cases might eventually come to light which could not be rationalized on an ionic basis, at present none are known and cases do already exist in which an ionic mechanism is absolutely required. For example, the formation of B (31), J (30), and mazdasantonin (23), from lumisantonin all involve migrations of the 10α methyl group

This sort of process simply does not occur in radical reactions. Indeed, almost every known rearrangement of the carbon skeleton of radicals involves aryl group migrations,* and even these are relatively rare (98a, b), whereas methyl migrations are very well known in carbonium ion chemistry (99).

Figure 20



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[*] One well-established case of alkyl migration in a radical reaction is known (98c). However, it occurs only because all other processes in the system are severely hindered sterically. Even here, a relatively high reaction temperature is necessary. Other claimed instances of alkyl migration in radical reactions are not so well documented and may well be spurious (98d).

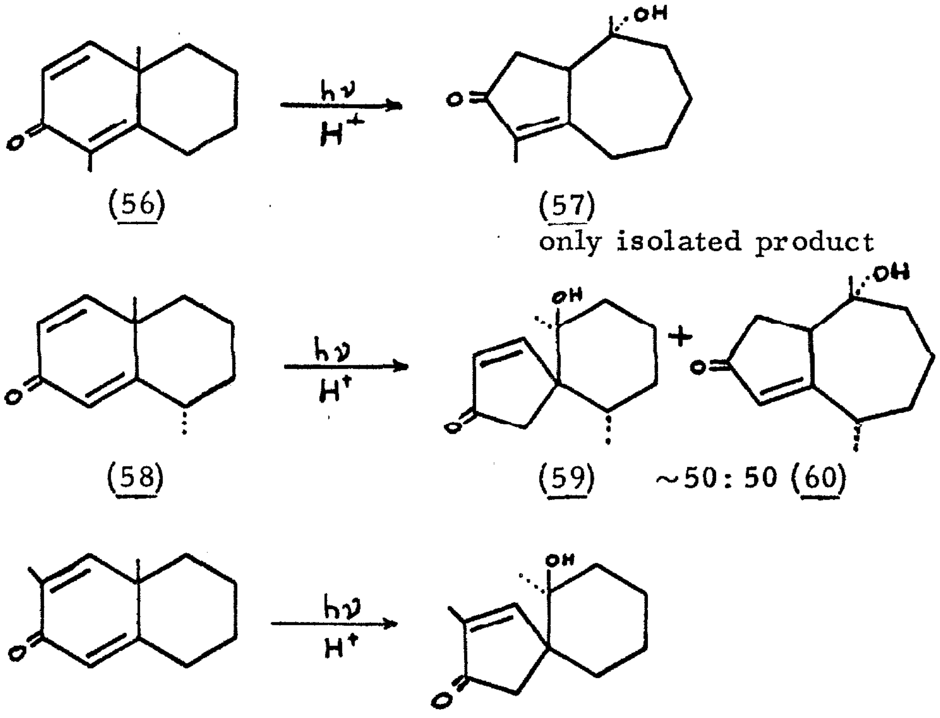
Note that the ions in the formation of (30) and (31) are the upside-down isomers of those in the formation of lumisantonin (5) from santonin (1) (Figure 18).

A particularly useful application of the carbonium ion concept is in the rationalization of substitution effects. Irradiation of santonin leads ultimately to the linear dienone mazdasantonin in aprotic media, but to a hydroazulene in water or alcohol (as well as to products derived from the ketene formed by a ring opening rearrangement of mazdasantonin). Recent studies have shown the course of the alternate path (i.e. not via lumisantonin-like product) in the irradiation of various simple (23) and steroid dienones (100) to be very sensitive to substituents on the chromophore. The products are shown in Figure 21.

A simple and perfectly acceptable explanation of the results presented in Figure 22 (26) is that the methyl group inductively stabilizes an adjacent positive charge.

Figure 21

Photolysis of Various Dienones



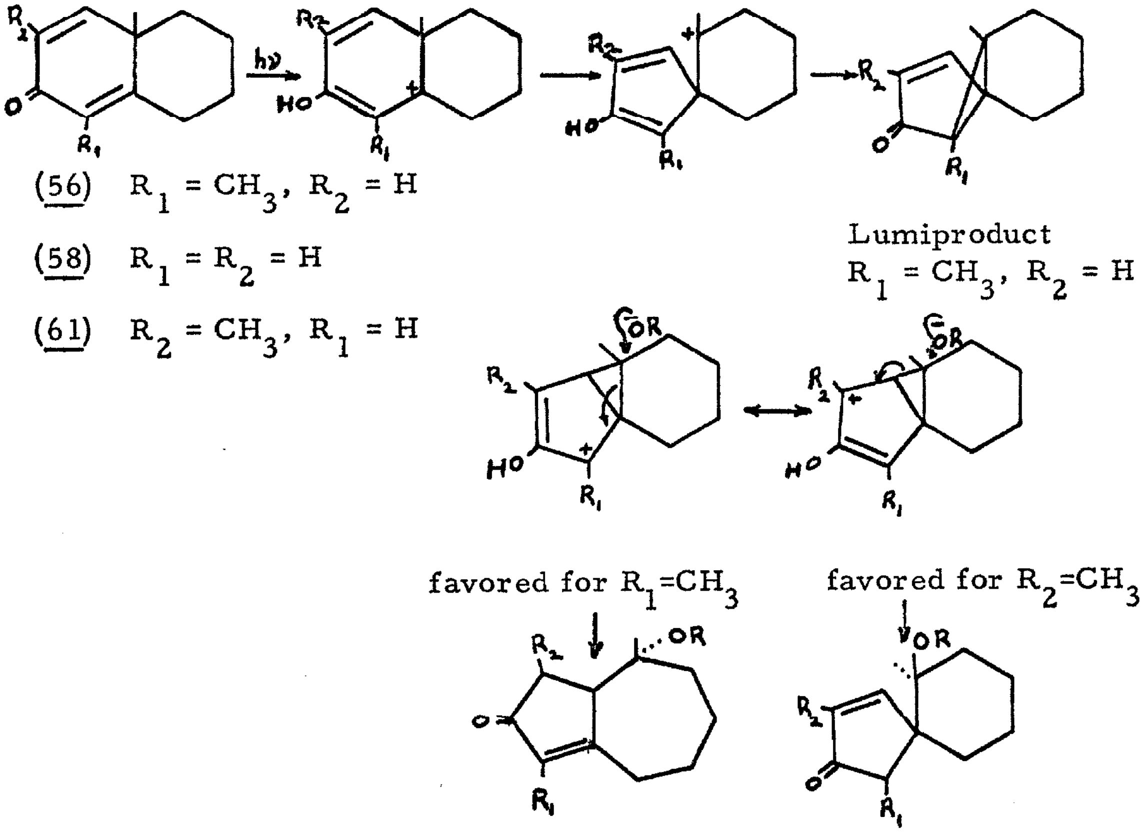
(56) (57)
only isolated product

(58) (59) ~50: 50 (60)

(61) (62)
48-51% + a trace of perhydroazulene

Figure 22

Methyl Substituent Effects on Dienone Photolysis



(<u>56</u>) $R_1 = CH_3$, $R_2 = H$

(<u>58</u>) $R_1 = R_2 = H$

(<u>61</u>) $R_2 = CH_3$, $R_1 = H$

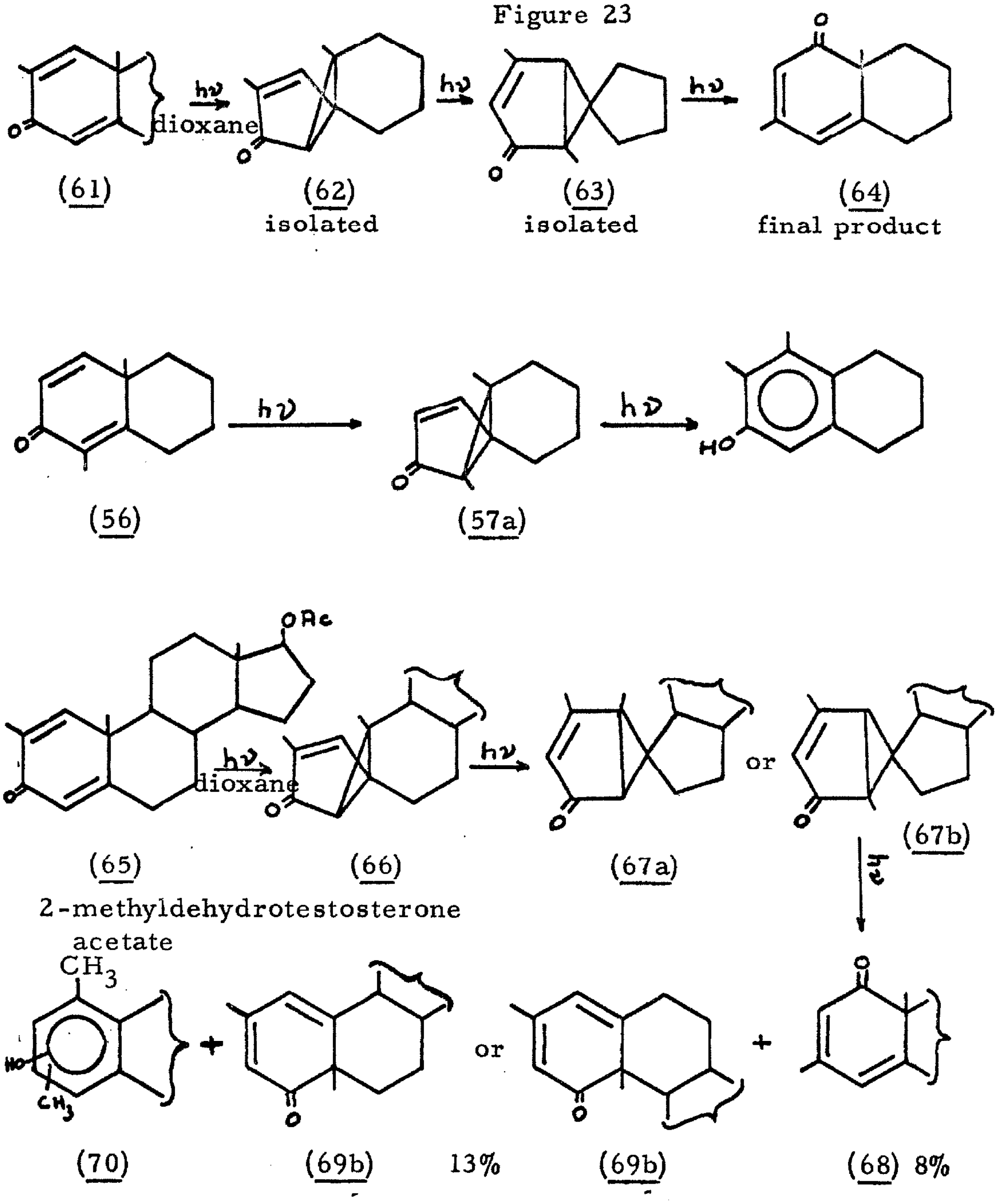
Lumiproduct
$R_1 = CH_3$, $R_2 = H$

favored for R_1=CH_3

favored for R_2=CH_3

The major reaction of cross-conjugated dienones is also influenced by substituents (Figure 23) (13, 18, 19, 23, 26, 100).

Figure 23



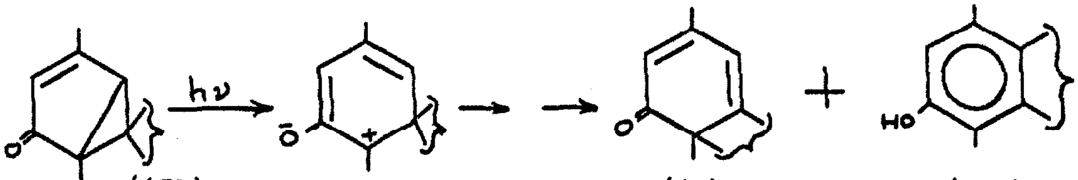
(61) (62) isolated (63) isolated (64) final product

(56) (57a)

(65) 2-methyldehydrotestosterone acetate (66) (67a) (67b)

(70) (69b) (69b) (68)

As usual, the ionic mechanism provides a simple rationalization.



(67b) (69) (70a)

The structure of the final products depends on the intermediate (67). If (67b) is chosen by analogy with Kropps' results (99), the predicted structure for the phenol is (70a). At present, this substance is unknown. It would be of interest to elucidate the structure of the phenol, as this would define the other products in the reaction sequence and establish the generality of the reaction for 2-methylcyclohexadienones.

2. The Zimmerman and Hoffmann Explanations

As will be discussed in Section V-A, conventional (i.e. other than that envisaged by Hoffmann(105) $n \rightarrow \pi^*$ transitions do not localize negative charge on oxygen but rather tend to render the carbonyl function considerably less polar than in the ground state.[*] Zimmerman (104) avoids the problem by assuming electron demotion takes place before rearrangement (although bond formation is permitted in

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[*] In the ground state of most carbonyl compounds, a formal charge of at least $-\frac{1}{2}$ is localized on oxygen (102). The extremely polar character of ketones has been recognized for a long time (103).

the excited state). Thus, ground state, vibrationally excited molecules are the actual species involved in the rearrangement.

Zimmerman's explanation is unattractive because reactions proceeding strictly via vibrationally excited molecules (pyrolyses) do not follow the same patterns as do photochemical reactions. A perfect example from the present work is the photolysis of lumisantonin. Whereas the isomer of H is very likely the exclusive pyrolysis product (yield of isolated product exceeds 80%), it accounts for only about 10% of the lumisantonin converted photochemically. Thus, the C_1-C_5 bond is weaker than the C_5-C_{10} bond in the excited state, but the order is reversed in the ground state. Clearly, the bond-breaking process (the product-determining photochemical step) occurs in the excited state.

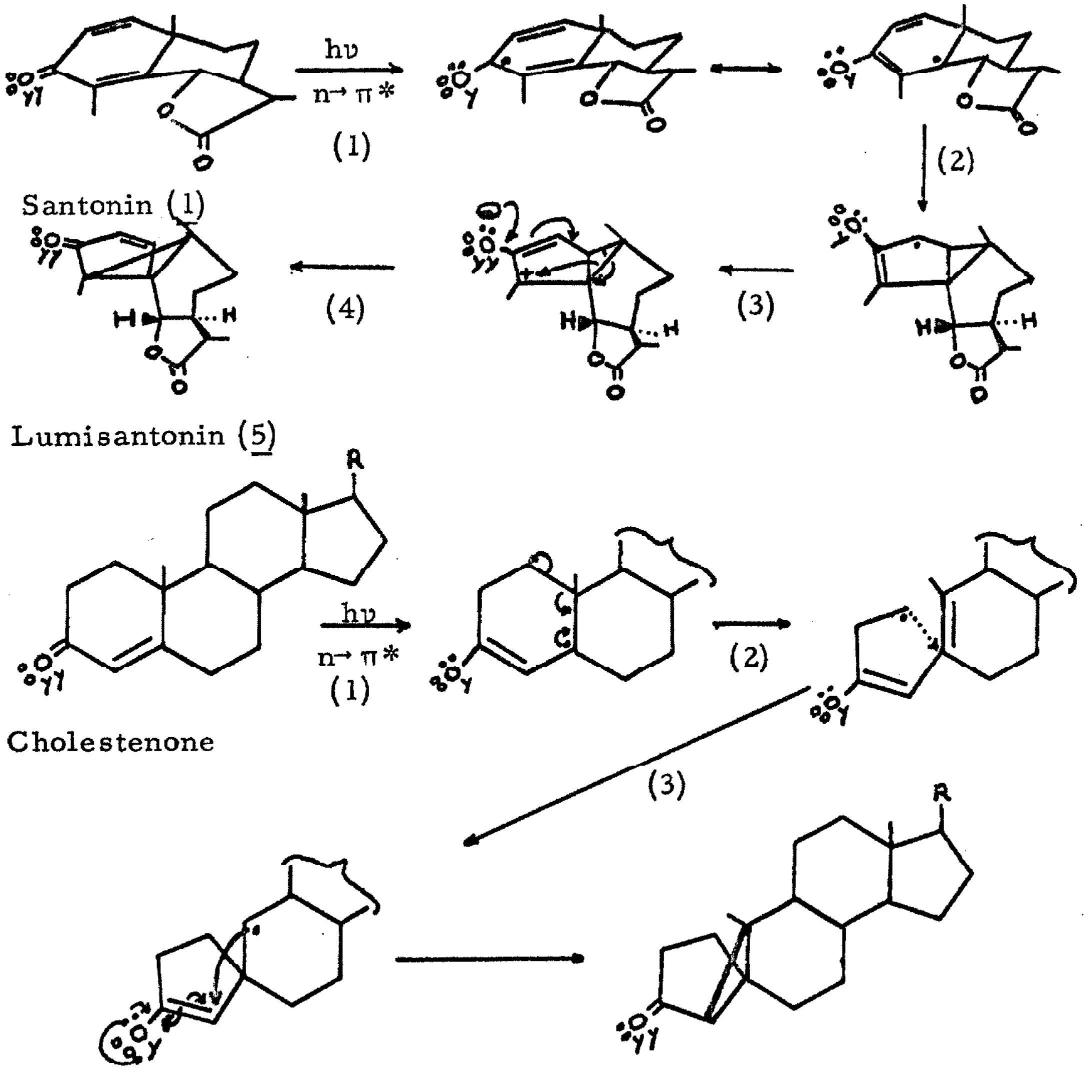
Another objection to Zimmerman's mechanism is its complexity. He undoubtedly takes into account the basic steps in dienone excitation (104), but does not account for the fact that cross-conjugated dienones and mono-unsaturated enones often follow exactly analogous photochemical paths. For example, the excited state ionic mechanism outlined on page 113 does not require participation of the second double bond in the formation of lumisantonin from santonin and predicts the same reaction for cross-conjugated dienones and for mono-unsaturated enones. Zimmerman's mechanism does involve the second double bond and consequently forces him into tortuous speculation,which results in two rather dissimilar mechanisms (104c) (both incorporating his principles, admittedly) to rationalize the photolyses of santonin and of cholestenone, substances which lead to exactly analogous photoproducts (Figure 24). Clearly, the simple carbonium ion hypothesis is preferable,if only for its simplicity in handling.

Hoffmann(105) has also examined the origin of the ionic states in dienone photochemistry and has shown that conventional $n \rightarrow \pi^*$ transitions can be used to rationalize generation of positive charge on the ring of a cyclohexadienone. By use of more refined calculations, he concluded that the original non-bonding electrons of the carbonyl are considerably delocalized in both the ground and excited states. Thus, very little charge is moved from oxygen into the ring upon excitation. More than enough positive character is acquired at what Hoffmann considers the proper positions in the ring to account for the observed rearrangements.

Unfortunately, Hoffmann's treatment does not provide an explanation for photoreductions, which proceed, formally at least, via hydrogen abstraction by a neutral center at oxygen. Hence, while solving one aspect of the problem, Hoffmann has created a new one. A concept which rationalizes both the ionic reactions and the

Figure 24

The Zimmerman Mechanisms (104c)



The numbers refer to the following processes:

(1) excitation (n→π*)
(2) bond alteration
(3) π*→n electron demotion
(4) further bond alteration

photoreductions is needed. Hopefully, the electron-ejection mechanism developed in later sections of this thesis will prove useful.

B. Mazdasantonin

1. Quantum yield

The low quantum yield for the dimerization of mazdasantonin is not surprising. The triplet energy of the intermediate is low (≤ 60 kcal/mole), a condition which favors the radiationless deactivation of the triplet state to the ground state. Furthermore, the triplet state has the electronic distribution characteristic of a $\pi \rightarrow \pi^*$ excitation; and transitions between such a state and the ground state are generally very fast (cf. Section IVa). Both these factors, the low triplet energy and the $\pi \rightarrow \pi^*$ character of the excited triplet state, tend to make radiationless deactivation more rapid than in systems such as santonin, which have high triplet energies and $n \rightarrow \pi^*$ lowest excited states. Consequently, alternate photochemical pathways for mazdasantonin have low quantum yields because they are less able to compete with radiationless deactivation.

Steric factors may also play a part. In order to dimerize, an excited molecule must attack a ground state mazdasantonin bristling with methyl groups and a lactone ring. Other bimolecular reactions, such as addition of water or isoprene, are rapid. These pathways differ from the dimerization of mazdasantonin in that the reactive species is the ketene in the first case and undetermined in the second. However, the fact that these reactions occur so efficiently shows that the reactive intermediate must have a lifetime of at least 10^{-9} seconds in these cases, and the reactive species in the addition of isoprene may very well be the triplet as in other cycloadditions of olefins in the presence of carbonyl compounds (82, 83). In any event, the observation of quenching of mazdasantonin triplets by dissolved oxygen (10^{-3}M) or azulene means that the lifetime of the mazdasantonin triplet state must be considerably longer than in cases where quenching is not possible, i.e. greater than 10^{-10} sec. An excited state lifetime of 10^{-9} sec is long enough to lead to dimerization in much better yield than that observed here (see, for example, the dimerization of anthracene (95c, d)). Therefore, it seems unlikely that the low quantum yield for the dimerization of mazdasantonin is entirely due to an unusually short lifetime of the excited state.

Two possible explanations arise. Either steric effects are very important, or the lifetime of the excited state in the dimerization is much shorter than the lifetime of the normal triplet monomer, i.e. some species other than the normal monomeric triplet state is the intermediate in the formation of E. The latter explanation is preferred and will be discussed more fully below.

2. Ionic character of the excited state

A large portion of this thesis is devoted to the question of ionic reactions in photochemistry. The dimerization of mazdasantonin cannot shed any light on this problem, since it does not definitely fall into this class. A perfectly plausible four-center or radical mechanism can be written for photochemical cycloaddition reactions and, furthermore, processes which are not ionic probably operate in cases such as cyclobutane formation from olefins (106).

Of course, an ionic mechanism might be anticipated for the dimerization of mazdasantonin in view of the generality of such mechanisms in other phases of the reaction sequence. Also, mazdasantonin is known not to undergo two reactions characteristic of radical-like states, photoreduction and oxetane formation (at least with piperylene). However, these negative results are explicable on grounds other than the nature of the excited state. Photoreduction would not be expected to compete successfully with the extremely fast ketene reaction available in hydroxylic solvents. Oxetanes are not formed unless steric conditions are favorable and the triplet energy of the olefin is above that of the carbonyl compound (81). For these reasons, the present evidence is not sufficient to define the importance of ionic contributors to the excited state of mazdasantonin.

3. The function of the complex in the dimerization of mazdasantonin

The n.m.r. spectra presented in Figure 8c demonstrate that mazdasantonin forms a complex with itself in benzene solution. It is now appropriate to consider how complexing affects the dimerization process.

The lifetime of the excited state of monomeric mazdasantonin is expected to be relatively short, but the experimental observation of quenching by dilute concentrations of oxygen or azulene requires that it be at least 10^{-9} sec, a time that would allow a normal dimerization process with a quantum yield of at least 0.03 under the conditions here (by extrapolation of the data of Bowen (95)). Although no precise quantum yield measurements for the dimerization of mazdasantonin were carried out, the present work showed that this quantum yield is certainly less than 0.01 at a concentration of 3×10^{-3}M. Thus, it is plausible that the dimerization of mazdasantonin does not involve attack of the monomeric triplet state on ground state molecules, but instead proceeds via the complex.

Consider now the situation of dimerization if preceded by association. The initial excitation gives rise not to the singlet of mazdasantonin but to the singlet of the complex. Such species are well known and are called excimers. Excimers exhibit characteristic fluorescence (107, 108b), sometimes decay to stable dimers (108a), and have very low quantum yields for most such processes because radiationless deactivation of excimers is much faster than internal conversion of monomer singlets to ground state (57, 109) due to the additional vibrational modes which are made available by complexing.

The data presented in Section III of Part II of this thesis show that the dimerization of mazdasantonin proceeds through triplet states. If excimers are necessary for the production of dimer, then the low quantum yield of the dimerization process is easily explained. The rate of intersystem crossing from the excited singlet state to the triplet state of the complex (and hence the rate of dimerization) is low compared to the rate of radiationless deactivation of the excimer because degradation is facilitated by the extra molecular motions made available by association. Hence, the inefficiency of the dimerization via the complex arises from the inability of intersystem crossing to compete with radiationless deactivation of the excited singlet state. Such an assertion is strongly supported by the fact that addition of sensitizer accelerates the reaction by a factor of at least five.

The intermediacy of excimer is entirely consistent with the observed association of mazdasantonin in solution and the low quantum yield of the dimerization. The only indication that complexing is not important in these dimerizations comes from the work of Rubin (38, 39). He was able to suppress completely the cycloaddition of two steroid dienones by addition of cyclopentene to the photolysis mixture, in which case the only isolated product was the steroid-cyclopentene adduct. Since association is by dipolar interaction which cyclopentene should not be able to prevent, it appears that complexing cannot be too important in Rubin's systems. It would be most interesting to see whether cyclopentene can similarly affect the dimerization of mazdasantonin.

Another possibility which would rationalise the sensitzer, quencher, and concentration data is that dimerization occurs <u>via</u> coupling of two monomeric triplet molecules. However, such a mechanism cannot be operative in the addition of enones to cyclopentene. Furthermore, the steady state concentration of triplets is very low, and for this reason cycloadditions are normally postulated to involve only one triplet per molecule of dimer formed, even in reactions where monomeric triplet states are involved, as in the photosensitized dimerization of coumarin (95e). In at least one case, the dimerization of isoprene, the triplet-triplet coupling mechanism has been explicitly eliminated (83b).

On the basis of these results, the dimerization of mazdasantonin is concluded to proceed in the following way. Mazdasantonin associates with itself in solution via dipolar interactions to form a complex which is excited to its singlet state (excimer) by ultraviolet light. The excimer has a low intersystem crossing efficiency, and most often decays to the ground state without reacting. The triplet complex, when formed, is sufficiently long-lived to enter into quenching processes, and decays to stable dimer with unknown probability, but with an efficiency which is at least five times that of intersystem crossing from the excimer. Thus, the origin of the low quantum yield for the formation of E is in the low intersystem crossing ratio of the mazdasantonin excimer, and sensitizers are very useful in promoting this reaction.

C. Summary

The usefulness of the polar state concept in rationalizing the photolyses of santonin and lumisantonin, and the apparent prevalence of ionic processes in the photochemistry of all but the simplest carbonyl compounds make it very tempting to view the excited state responsible for these occurrences as a dipolar intermediate in which the oxygen atom bears a negative charge and a positive charge is distributed throughout the rest of the molecule. As will be discussed in a moment, the conventional, pre-Hoffman $n \rightarrow \pi^*$ transition does not lead to such an excited state, and yet the ionic character of the reactions is not to be denied. This thesis will conclude with a consideration of this anomaly and two possible explanations will be advanced.

V. The Reactive State

A. $n \rightarrow \pi^*$ Excitation

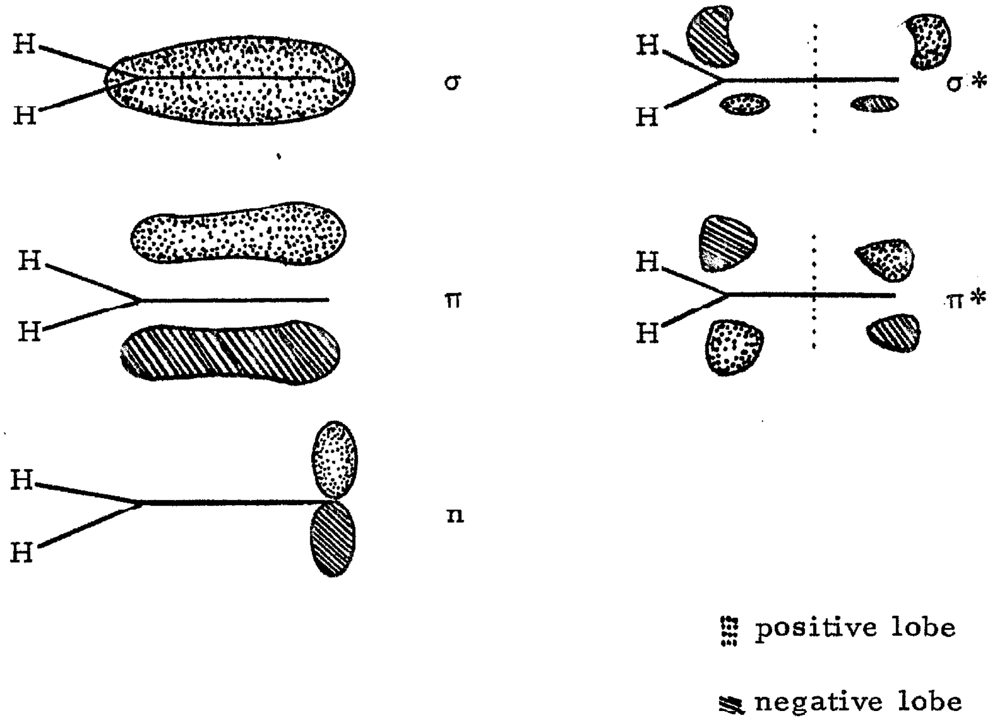
1. General

The various types of carbonyl orbitals are shown in Figure 25 for formaldehyde.

In any carbonyl compound, there is a possibility of excitation from a non-bonding (n) to an anti-bonding (π^*) orbital. This is the so-called $n \rightarrow \pi^*$ transition (after Kasha), and is the lowest energy transition in ordinary ketones, as is only reasonable since non-bonding electrons are held more loosely than bonding ones.

Figure 25

The Molecular Orbitals of the Carbonyl Function in Formaldehyde



The non-bonding (n) orbital is a 2p oxygen orbital in the plane of the carbonyl group (i.e. symmetric with respect to reflection in the molecular plane). The second pair of unshared electrons are in an approximately sp orbital on oxygen, are more tightly bound, and do not enter into ultraviolet transitions in the region above 2000 Å. The π orbitals are antisymmetric with respect to the molecular plane. To a first approximation, n→π* transitions are forbidden by symmetry considerations, and therefore have low extinctions.[*] However, distortions of the molecule in both the ground and excited states (vibronic effects) may alleviate or completely remove the forbidden character of an n→π* transition. For the two types of transitions which will be of interest to the present problem, representative extinctions in carbonyl systems are: forbidden n→π*, 10-100; allowed n→π*, 100-1000; forbidden or otherwise weak π→π*, 200-1000; allowed π→π*, 1000-100,000 (110a).

The σ and π orbitals are shown with the center of electron density shifted toward oxygen due to its greater electronegativity. Since σ* and π* orbitals are orthogonal to their bonding counterparts, the center of electron density is shifted toward carbon in the antibonding orbitals.

Once in the excited state, the molecule may react, deactivate to the ground state, or undergo intersystem crossing. Because singlet-triplet splittings (difference in energy) are much larger for π→π* transitions than for n→π* transitions (113c), the π→π* triplet may be the lowest energy triplet state in the molecule, even though the primary excitation is n→π* (Figure 26b). Thus, the π→π* triplet state may be the photochemically active triplet state in the photolyses of carbonyl compounds.

There are various ways of differentiating between n→π* and π→π* transitions. For instance, if a carbonyl compound and a pure

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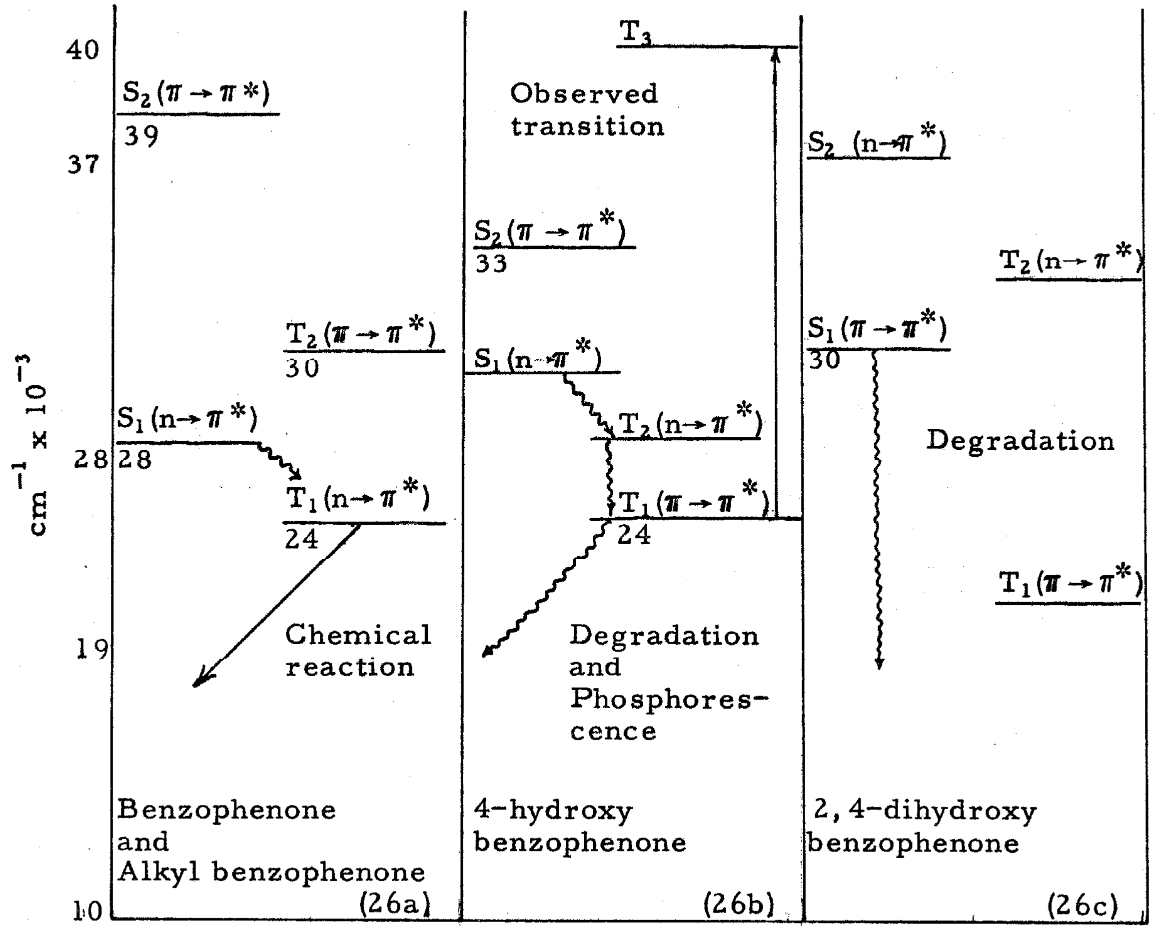
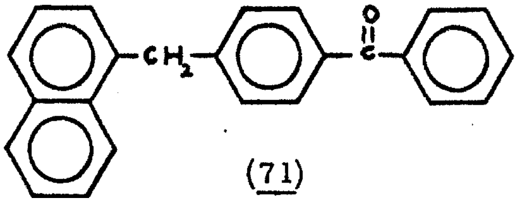
[*] I do not propose to get involved in a discussion of selection rules based on molecular symmetry. See references 57a, 110b, and 119b for a good discussion.

Figure 26

The Effects of Electron-Donating Substituents on n→π* and π→π* Levels (after Beckett and Porter (117))



hydrocarbon analogue have identical phosphorescence spectra, it is reasonable to conclude that the same (π→π*) state is involved in the emission of both. As an example, excitation of the carbonyl in (71) leads only to emission characteristic of naphthalene. Hence, the final phosphorescent state is a π→π* triplet state of naphthalene even though the initial transition is surely n→π* (111).



(71)

The carbonyl ground state is stabilized in hydroxylic solvents due to hydrogen bonding by interaction of the protons in the solvent and the unshared pair of electrons on oxygen. Hence, promotion of one of the unshared electrons requires more energy than if no solvent were present. As a result, n→π* absorptions of carbonyl compounds are found at shorter wavelengths in hydroxylic solvents than in hydrocarbons (blue shift or hypsochromic shift). On the other hand, π→π* transitions show a small solvent-dependent shift <u>in the opposite direction</u> (red or bathochromic shift). McConnell has tabulated a number of examples (112).

Spectral shifts may also arise as the result of substituents. Electron-donating groups (e.g. -OH or $-NH_2$) will interact with the carbonyl function to form a new set of molecular orbitals (Figure 27). Both the lowest unoccupied (π*) and the highest occupied (π) orbitals are destabilized, but the non-bonding orbital on oxygen (not shown) is essentially unaffected. Hence, a blue shift of the carbonyl absorption occurs if electron-donating groups are substituted because the energy gap between the non-bonding and lowest unoccupied orbitals is increased.

The highest occupied (π) orbital is destabilized more than the lowest unoccupied one (π*), and, as a result, the energy gap between them is somewhat smaller than in the unsubstituted compound. Hence, π→π* transitions are generally red-shifted by electron donating groups.*

Table 14

The Effect of Electron-Donating Groups on the n→π* Transition

Compound	λ_{max}(mμ)	ϵ_{max}	Solvent
Acetaldehyde	293.4	11.8	hexane
Acetic acid	204	41	alcohol
Ethyl acetate	204	60	water
Acetamide	214		water
Acetyl chloride	235	53	hexane

The predicted reversal of n→π* and π→π* triplet levels has been observed in substituted benzophenones. Michler's ketone (p,p'-dimethylaminobenzophenone) has an extremely high intensity long-

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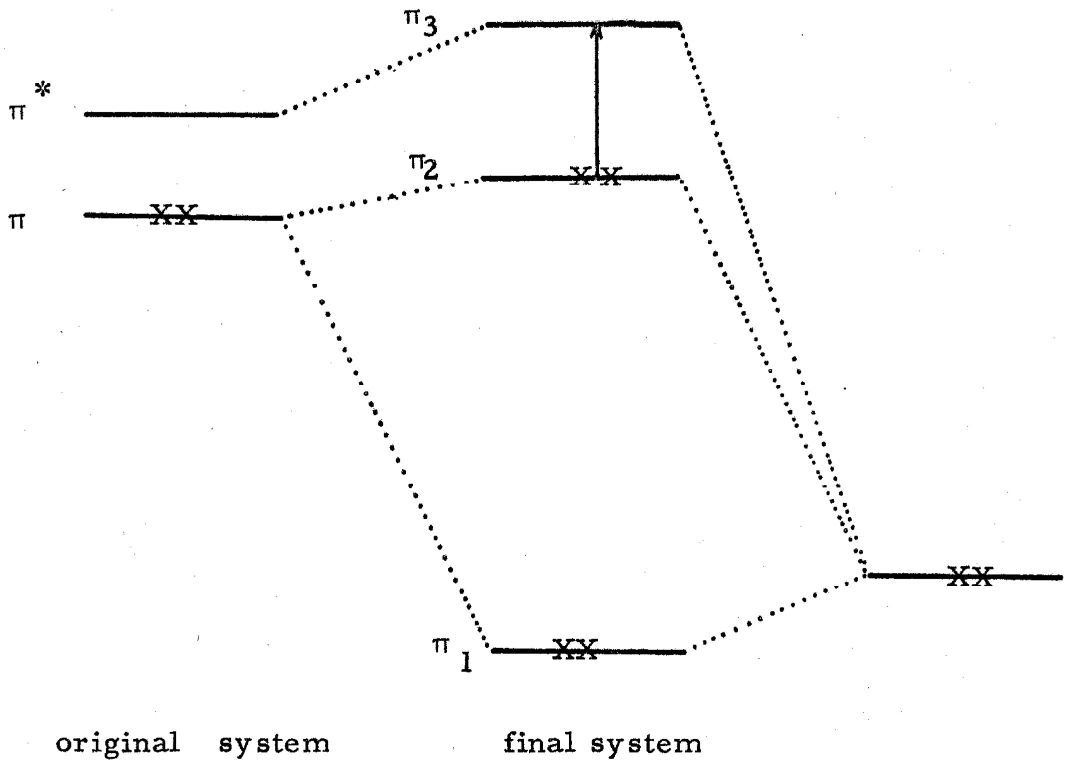
[*] Theoretical treatments have been made for both inductive (113a) and conjugative (113b) electron-donating substituents.

Acetone	279	14.8	Hexane

Figure 27

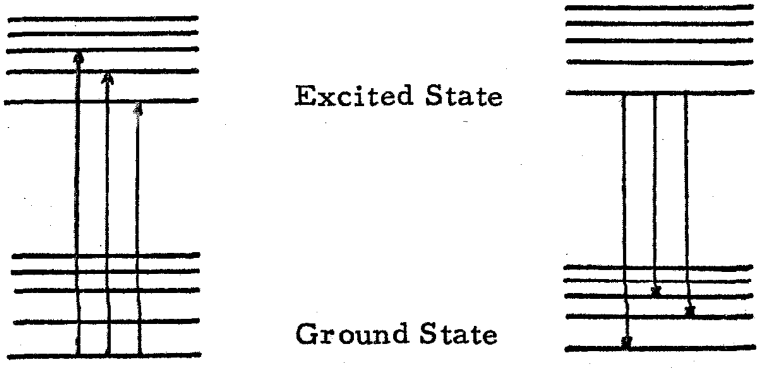


wavelength absorption ($\epsilon \sim 10^4$ at 3660 Å in benzene) and low triplet energy (61.0 kcal/mole (116), see below) and may have an electronic distribution characteristic of a π→π* transition in its triplet state. Another example is 4-hydroxybenzophenone (Figure 26b), which certainly undergoes efficient intersystem crossing, as shown by its strong phosphorescence, but does not photoreduce (117) because the 3° state is π→π* (Figure 26b). Indeed, electron-donating substituents may so profoundly perturb the energy level distribution that even the order of singlet n→π* and π→π* states may be reversed. An example is 2,4-dihydroxybenzophenone, which neither phosphoresces nor photoreduces (117), because the excited singlet is π→π*, has a high probability for transition to the ground state, and is degraded too fast for intersystem crossing to occur (Figure 26c).

Since the electron excited in an n→π* transition does not come from the bonding orbitals of the carbonyl group, the double bond is essentially intact in the excited state and the carbonyl stretching frequency is still a characteristic vibration of the functional group. Hence, absorptions of the n→π* type sometimes show characteristic vibrational patterns containing the carbonyl stretching frequency (~ 1700 cm^{-1}) which arise from transitions between the lowest vibrational level of the ground state and various vibrational levels of the excited state (Figure 28).

Figure 28

The Band Progressions in Absorption and Emission Spectra



On the other hand, an excitation of $\pi \rightarrow \pi^*$ type removes one of the bonding electrons from the carbonyl group and effectively breaks the second (π) bond. The stretching frequency of the carbonyl is therefore not expected in the vibrational structure of $\pi \rightarrow \pi^*$ absorptions, although it may occur adventitiously.

The emission spectrum arises from transitions between the lowest vibrational level of the excited state and various vibrational levels of the ground state. Therefore, the appearance of the carbonyl frequency in the band separations of an emission spectrum merely indicates double bond character in the carbonyl ground state, and says nothing about the $n \rightarrow \pi^*$ or $\pi \rightarrow \pi^*$ character of the excited state from which the emission arose. Attempts to define the nature of the excited state by arguing from the appearance of such progressions in the emission spectrum should be dismissed with scorn.*

Spin inversion is a relatively slow process on the spectroscopic time scale and seldom occurs in preference to radiationless deactivation. Hence, long-lived singlet states undergo intersystem crossing more efficiently than do short-lived singlet states.

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* See, for example, references 67 and 124. Dr. Leermakers has since assured me that he intends this argument to be only an empirical diagnostic test for an $n \rightarrow \pi^*$ excited state and concedes that it has no theoretical basis. He does not make this point in his paper, however.

Transitions in general become more probable between a pair of states as the energy gap between the states becomes smaller (cf. p. 59 and ref. 45). Due to the partial forbiddenness of the deactivation process, lifetimes of n→π* states are generally longer than those of π→π* states. Moreover, the singlet-triplet splittings of n→π* states are usually smaller than the splittings of π→π* states (113c). Thus, consideration either of lifetimes or singlet-triplet splittings predicts intersystem crossing to be more likely for n→π* states than for π→π* states, and triplet states are more important in the photochemistry of the former. Obviously, the mere intermediacy of the triplet is no proof that either the singlet or triplet excited state has an n→π* electronic distribution. Zimmerman (67) has attempted to use the fact that n→π* states have longer lifetimes than do π→π* states as a diagnostic tool; and he is basically right in doing so since, if two excited states were identical except for n→π* or π→π* character, the n→π* state would be the longer-lived. Unfortunately, this condition is never met in nature. Indeed, some of the longest-lived excited states occur in π→π* systems, e.g. triphenylene. However, a long lifetime is indicative of an n→π* state, and this criterion may prove to have some general application whe considerably more data are accumulated.

The photochemistry of n→π* and π→π* states should be considerably different, since only the former produces electron deficient oxygen. Hence, one may expect n→π* states but not π→π* states to be efficient in hydrogen abstraction reactions. A now classic example of this effect is the failure of naphthyl ketones, e.g. 1-naphthaldehyde (114) and 2-acetonaphthone (114, 115) to photoreduce with alcohols.*,**

Am empirical but useful diagnosis of n→π* character in triplet state emissions is provided by the triplet state energies. A number of dialkyl ketones in which emission must be n→π* have triplet energies on the order of 67-75 kcal/mole. A variety of alkyl phenyl ketones (e.g. acetophenone) and benzophenones which are photoreduced by alcohols and generally exhibit the characteristics of n→π* excitations (blue shifts, etc.) also have triplet energies in the same range (114, 118). By contrast, triplet energies for π→π* states are significantly lower: e.g. Michler's ketone, 61.0 kcal/mole (116), 1-naphthaldehyde, 57 kcal/mole (114), and 2-acetonaphthone, 59 kcal/mole (114). The generality of this observation is questionable, since the nature of the π system would certainly be expected to affect the energies of the π and π* orbitals profoundly,

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* The discussion of Sec. V-A is limited to neutral molecules. The electron ejection mechanism, which may involve π→π* states, produces a species perfectly equipped for hydrogen abstraction reactions.

** Actually, some reduction occurs, but the quantum yield is greatly lowered (J. R. Fox and G. S. Hammond, unpublished).

and thereby shift the triplet levels of both n→π* and π→π* states, However, it is encouraging that sensitizers so different as acetone and acetophenone have such similar triplet energies.

2. An Elementary Theoretical Comparison of the Two Transitions

A very simple Hückel treatment of the model cyclohexadienone molecule (119) leads to the set of molecular orbitals shown on the left side of Figure 29. Here the Coulombic integral for oxygen is taken to be $\alpha + 2\beta$, the commonly accepted value (119). For comparison, the published orbitals for the same molecule (67) are shown on the right side of the figure. An interesting bit of casuistry is evident in the generation of the second set of orbitals. Without specifying his value, Zimmerman picks the oxygen Coulomb exchange integral guided by the understanding that "the molecular orbital ordering... depend on oxygen Coulomb integral choice dictated by the necessity of n→π* excitation being lowest..." (120). Obviously, horse and cart have been reversed.

Charge distributions and bond orders using these orbitals are given in Table 15.

Before proceeding to a discussion of these calculations, it is pertinent to observe again that "the skeletal changes resulting in

Figure 29
Molecular Orbitals of Cyclohexadienone

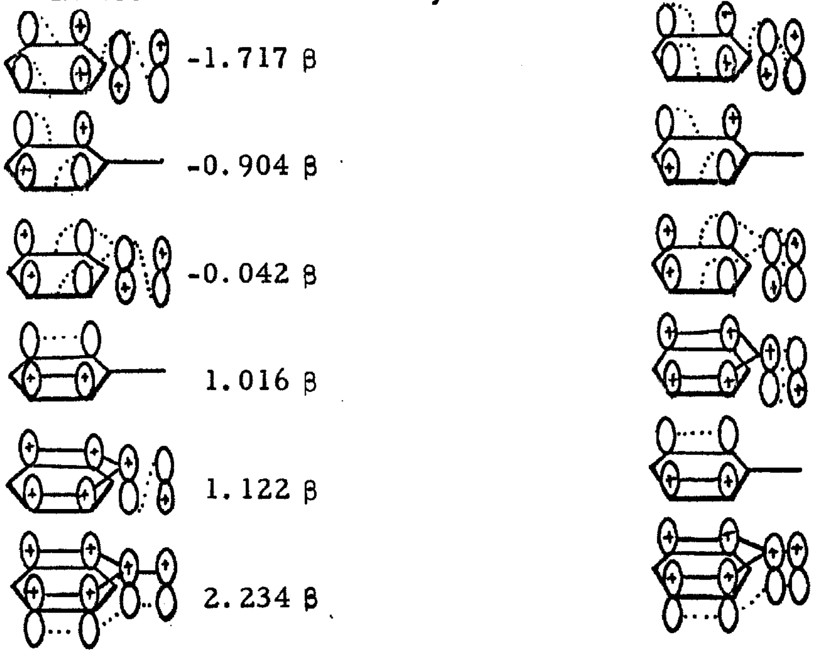

Figure 30
Molecular Orbitals of Cyclohexenone

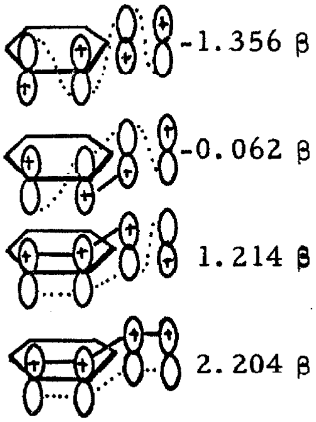

Table 15

Cyclohexadienone

	Ground State This work	Ref. 105
O_1-C_2	0.621	0.839
C_2-C_3	0.464	0.917
C_3-C_4	0.868	1.221
C_4-C_5	-0.230	-0.062

	$\pi \rightarrow \pi^*$ Excited State This work	Ref. 105
O_1-C_2	0.427	0.810
C_2-C_3	0.521	0.834
C_3-C_4	0.810	1.248
C_4-C_5	0.051	-0.036

	$\pi \rightarrow \pi^*$ State This work
O_1-C_2	0.428
C_2-C_3	0.521
C_3-C_4	0.561
C_4-C_5	0.321

Charge Densities

	Ground State This work	Ref. 105
O	-0.644	-1.191
C_2	0.251	0.833
C_3	0.034	-0.213
C_4	0.162	+0.085

	$\pi \rightarrow \pi^*$ Excited State This work	Ref. 105
O	0.218	-1.113
C_2	-0.022	0.646
C_3	0.024	-0.059
C_4	-0.119	-0.089

	$\pi \rightarrow \pi^*$ Excited State This work
O	-0.782
C_2	-0.022
C_3	0.256
C_4	0.148

Table 16

Cyclohexenone

Bond Orders

Ground	State	n→π*	π→π*
O_1-C_2	0.721	0.459	0.513
C_2-C_3	0.518	0.627	0.563
C_3-C_4	0.846	0.734	0.370

Charge Densities

Ground	State	n→π*	π→π*
O	-0.576	+0.250	-0.491
C_2	0.328	-0.059	-0.048
C_3	0.039	0.011	0.373
C_4	0.209	-0.197	0.168

dienone photochemistry are strongly suggestive to the organic chemist of rearrangement of an electron deficient Pi system (i.e. carbonium ions)." (104d). For the santonin system, the straightforward paths to lumisantonin and the secondary photoproducts have been shown in Figures 18 and 20 .

The difference in the calculated charge distributions for the n→ π* and π→π* excited states may readily be seen by comparison of the first two columns in Table 15 . Obviously, the n→π excitation does not result in an electron deficient Pi system.

One explanation of the anomaly is that pure n→π* and π→π* transitions do not really occur in nature. Rather, mixing of the two types of excitation better approximates the true state of affairs. This approach has been employed with apparent success to explain the enhanced intensity of the 3000 Å absorption in β , γ -unsaturated ketones having non-coplanar carbonyl and vinyl groups (121). An extension to the optical activity of the same class of compounds has also been reported (122). We have made a related suggestion for the photochemistry of dienones (123).

Some of the difficulty is no doubt a result of the assumptions underlying the calculations. Simple Hückel theory, is, after all, grossly qualitative, and a more sophisticated treatment might be expected to lead to rather different conclusions. The results of a recent calculation are also shown in Table 15 (105) for comparison. The conclusion that n→π* excitation may allow considerable negative charge to remain on oxygen is not inherently unreasonable, but Hoffman's calculation predicts little or no difference in the effective charge on oxygen in the ground and excited states. This does not accord with the usual conception of the oxygen atom in the n→π* excited state as an electron-deficient species (e.g. in hydrogen abstraction). However, the calculation does predict that the oxygen is less negative in the excited state, and in view of the approximate nature of the treatment, it is probably not overly profitable to cavil about the absolute values of the charges.

A far more serious objection may be raised in that Hoffmann seems to feel that ionic rearrangement will be favored by accumulation of positive charge at C-3, regardless of the charge at C-4. This is a most interesting point, since it would invalidate every ionic mechanism presented in this thesis. Admittedly, very little is known about processes in excited states, but it seems eminently reasonable that ionic rearrangements will be determined by charges and geometry in a fashion at least analogous to that so well established in ground state chemistry. In the absence of any other evidence to the contrary, this author will continue to reason on that assumption.

3. Application of Excited State Considerations to the Santonin System

a. Mazdasantonin

Mazdasantonin is clearly a case of π→π* excitation. The absorption spectrum shows only a single intense peak at 318 mμ with a molar extinction coefficient (ϵ = 7800) far outside the n→π* range. The triplet energy is very low (~53 kcal/mole) and, as might be expected, no emission is observed in EPA at 77°K, presumably due to the small energy gap between the ground and first excited states as well as to the tendency for π→π* states to have shorter lifetimes. The tendency to complex also undoubtedly plays a role in the reduction of the phosphorescence yield by facilitating the rapid deactivation of the excited singlet. Since, however, the photochemistry of mazdasantonin is rather uninteresting and the distribution of charge in the reactive species is not clearly ionic, the obvious π→π* character of the excited state has little general consequence.

b. Santonin and lumisantonin

The photoconversion of santonin to lumisantonin need not, and probably does not, involve open carbonium ions (p. 37). It is therefore unclear whether or not considerable charge is localized at any time during the photolysis of santonin. However, data are available on the nature of the photochemically active state of santonin and it is interesting to consider the nature of this state even though the results cannot be immediately generalized to other photoreactions of singly conjugated ketones.

The ultraviolet absorption spectrum of santonin is indicative of an $n \rightarrow \pi^*$ transition. The long wavelength maximum (325 mμ in ethanol) has a relatively low extinction (ϵ = 35). A red shift is apparent in non-polar solvents similar to that exhibited by benzophenone (Table 17). The triplet energy is high (68 kcal/mole) and in the proper range for $n \rightarrow \pi^*$ triplets. Even more significantly, the emission spectrum shows a blue shift from 67.5 kcal/mole (4240 Å) to 69 kcal/mole (4150 Å) on going from hydrocarbon (MCIP) to hydroxylic (EPA) solvent. Of course, the spectroscopic state need not be the photochemically interesting state, especially in view of the possibility that a non-spectroscopic state might exist at yet lower energy. But the data are consistent with the interpretation that santonin reacts via an $n \rightarrow \pi^*$ state. The failure of alcohols to photoreduce the santonin molecule is, then, due to the fact that the rate of unimolecular rearrangement is much faster than the rate of the bimolecular reduction.

Lumisantonin photochemistry, on the other hand, involves methyl migrations characteristic of carbonium ion reactions and therefore cannot be resolved on a radical mechanism such as are commonly invoked for n→ π* reactions, because alkyl groups do not migrate in radical reactions (p. 116).

The emission spectrum of lumisantonin lies at considerably longer wavelength than that of santonin. The spectroscopic triplet energy (64 kcal/mole) is in the lower, π→π* range. Unfortunately, lumisantonin shows no emission in MCIP. Hence, it is not presently known whether or not a blue shift occurs on going to a hydroxylic solvent.*

In an attempt to learn more about the nature of the excited state of lumisantonin, the absorption spectrum was measured in benzene and in ethanol (Table 17). The extinction (ε = 235) is in the range where n→π* and π→π* intensities overlap. There is a small blue shift, but very much less than generally observed in systems where n→π* transitions occur. Thus, the usual criteria do not lead to an unambiguous assignment, but it is certainly plausible that the lowest excited triplet state of lumisantonin has considerable π→π* character.

Table 17
Long Wavelength Maximum in the Absorption Spectrum

	Ethanol	Benzene
Benzophenone	325	343
Santonin	324	336
Lumisantonin	342	344

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* The blue shift of the emission spectrum is an indication of the nature of the excited state but must be interpreted with care.(cont'd.)

The postulated ionic rearrangement of lumisantonin requires that positive charge accumulate at C_4 in the excited state. Unfortunately, it is not possible to apply the simple LCAO method directly to lumisantonin, since the cyclopropane ring is not a pi system. However, it is well known that a cyclopropyl group conjugated with a carbonyl acts in the same fashion as a double bond in shifting the ultraviolet absorption maximum and the infrared carbonyl stretching frequency, although the magnitude of the effect is less for a cyclopropyl group than for a double bond (124b-d). From this fact it would appear that a proper evaluation of the cyclopropylenone (26) would show charge density at C_4 somewhere between those in cyclohexadienone (72) and cyclohexenone (73). As shown in Tables 15 and 16, both systems accumulate negative charge at C_4 in the $n \rightarrow \pi^*$ excited state and positive charge in the $\pi \rightarrow \pi^*$ state. Thus, it is reasonable that the cyclopropylenone (26) will likewise have appreciable positive charge at C_4 in the $\pi \rightarrow \pi^*$ but not in the $n \rightarrow \pi^*$ excited state. These results can be no more than indicative since the geometry of the excited state is undoubtedly different from that of the ground state by the time rearrangement occurs. However, the actual charge distribution should change on excitation qualitatively as indicated.

The recent assignment of the phosphorescent state of isopropyl pyruvate as an $n \rightarrow \pi^*$ triplet on the basis of a blue shift of $\frac{1}{2}$kcal/mole seems a bit over-eager (124a).

Of the various processes in the santonin system, only the photolysis of lumisantonin definitely requires ionic intermediates. It is therefore extremely interesting that the available evidence appears to favor a $\pi \rightarrow \pi$ triplet state for lumisantonin. Although these data are certainly not conclusive, the importance of the question warrants further examination of the hypothesis in lumisantonin and other systems.

B. The Electron Ejection Mechanism

1. Introduction

The generation of positive charge in the excited state of various molecules has now been briefly discussed on the basis of purely photochemical processes. There is another possible explanation drawn from radiochemistry which can account for the results here as well as or better than the usual considerations. Since most of those who will have occasion to read this thesis will not be acquainted with radiolytic theory and practice, it seems appropriate to preface the electron-ejection mechanism with the minimum amount of background material.

2. Radiolysis

Under radiolytic conditions, a good deal more ionization is to be expected than from the lower energy radiation employed in photochemistry. However, the rapidity of internal conversion from very high electronic states in solution makes it not inconceivable that similarities between photochemical and radiolytic processes might exist. Energy transfer, often highly efficient in photochemistry, does not appear to be significant in radiolysis (125a); yet there is no a priori reason to assume that other processes may not be common to both. This expectation is supported by the report that the emission spectra and quenching constants for various scintillators are the same in benzene for gamma or ultraviolet excitation (125b). It is therefore instructive to review briefly the importance of the electron-ejection mechanism in radiolysis.

In 1960, Weiss discussed the possibility that the "reducing species" in γ-irradiated water might be the solvated electron (polaron), H_2O^-, formed by electron ejection from an irradiated water molecule. Weiss advanced a theoretical basis for the stability of such a species.

At first, this idea was considered unlikely to be important in chemical reactions since any solvated electron would be expected to be extremely short-lived and probably could not enter into reactions at a rate fast enough to compete with that of diffusive recombination or dissociation of the electron-carrying water into hydroxyl ion and hydrogen atom. On the other hand, the use of low temperature and a glassy solvent would be expected to slow diffusion and possibly even trap electrons (and also "positive holes" which appear to migrate too (125)), so that it would be possible to study γ-irradiated glasses and look for solvated electrons.

This experiment was carried out by a number of workers who reported the visible (127, 128) and e.p.r. spectra (127-129) of the solvated electron formed by irradiation of ice at 77°K. The spectral result agrees with the earlier work of Linschitz (130), who studied the trapped electron in photoöxidations (see Section V-B-3).

Radiolytic studies have been extended to non-aqueous solvents, and electron ejection appears to be a general phenomenon (131-133a). However, hydrocarbons are not normally capable of solvating electrons (131, 133a). Consequently, foreign substances which act as traps (e.g. naphthalene) must be added in order to prevent instantaneous recombination of the electron with the solvent from which it came.

An extremely important step was taken when, on purely kinetic grounds, the "reducing species" in irradiated water under ambient conditions was shown to be the solvated electron (134a). Thus, recombination is slow enough so that ionic species arising via electron ejection may be considered as conventional candidates for reaction intermediates. Very recent evidence indicates that the lifetime of hydrated electrons is long enough for the species to be selective in its subsequent reaction, as shown by a correlation with Hammett parameters in the addition of hydrated electrons to aromatic hydrocarbons (134b).

Hamill (125) has presented a long study of benzene radiolysis from which he concludes that "... the significant primary indirect effects in irradiated organic solutions are consistently interpretable in terms of ionic processes." In other words, electron-ejection can lead to ionic processes. Precisely the same conclusion was reached by Libby in his study of the low temperature radiolysis of n-hexane (133b), in agreement with the theories of Williams (133c) for the radiolysis of alkanes in the liquid state.

Recently, the spectrum of the solvated electron in water has been observed at room temperature (135), and shows a considerable red shift when compared with the spectrum obtained at low temperature. This shift may indicate significant loss of energy by collisional deactivation in solution,* and will be important in the role of electron-ejection as a pathway to the triplet state (Section V-B-5).

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* At liquid nitrogen temperatures, λ_{max} = 5800 Å (128, 129) or 6000 Å (130, 133a). At room temperature, the maximum falls at 7000 Å (135). The difference is far too large to be attributed to experimental differences. Alternatively, the solvent may not be able to solvate the electron effectively at higher temperatures due to thermal agitation.

3. Electron Ejection in Photochemistry

The suggestion that excitation of a ketone may lead to electron ejection is consistent with the known fact that the n-electron involved in the long wavelength ($n \rightarrow \pi^*$) absorption is also the electron with the lowest ionization potential (136). If electron ejection does occur, whether from ketones or other heteroatomic functions, the products are a "free" electron and a cation radical. Reaction may occur directly via the cation radical, recombination may intervene, or bond-breaking may follow, in which case the products appear to arise from a heterolytic cleavage. The last pathway may be significant in the decomposition of leuconitriles (137).

A few photoreactions have been shown to proceed by electron ejection, but unimolecular examples are rare. Lewis (138) (who appears everywhere) postulated an electron-emission mechanism for the photoöxidation of N-heteroaromatics. This was eventually demonstrated by the proof of second-order decay of the intermediate from p-toluidine, diphenylamine, sodium phenolate, sodium thymolate, and sodium tyrosinate (139), and by the direct observation of trapped electrons (130).

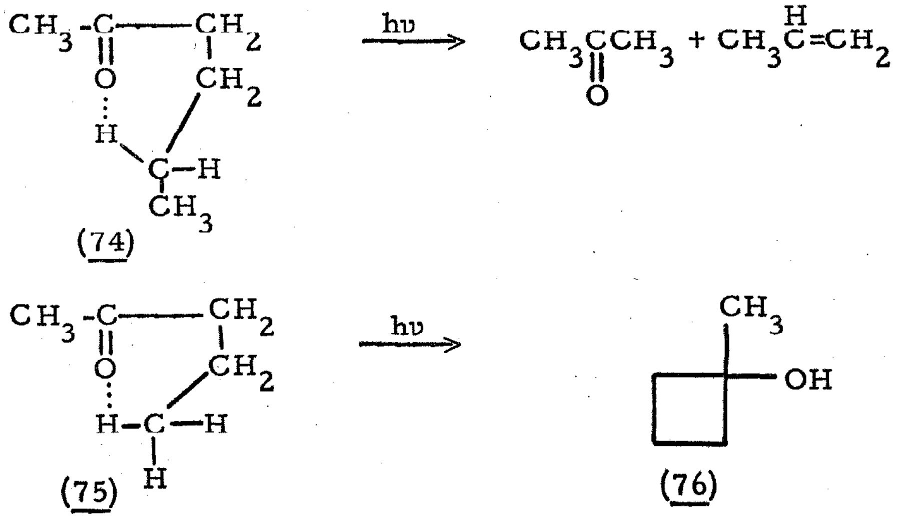
Other photochemical processes in which free electrons may play a part are the photobleaching of chlorophyll (130, 140), ionic photochromism (141), and the delayed fluorescence of acriflavine (142a). In the second case, a weak e.p.r. signal has been observed.

4. The Norrish Reaction

Should electron ejection prove to be a common phenomenon among organic compounds, the question arises as to whether the charged species (cation radical) would undergo normal photochemical reactions. In answer, a brief survey of the known Norrish reaction under photochemical and cation radical conditions is presented.

Irradiation of simple aliphatic ketones usually leads to bond cleavage, but if γ-hydrogen is available, rearrangement (Norrish type II cleavage) (Fig. 31) may intervene (143). Work with labelled compounds (144) has demonstrated that only the γ-hydrogen is involved, and the isolation of methyl cyclobutanol from the gas phase photolysis of 2-pentanone strongly supports the contention that cleavage involves hydrogen bridging (145).

Figure 31



(74)

(75)

(76)

In electron impact mass spectrometry of aldehydes and ketones, the first step is known to be the ionization of an oxygen non-bonding electron and the species produced is undeniably the cation radical. Therefore, it is extremely significant that the Norrish cleavage is a routine occurrence in mass spectrometry, both for field ionization (146) and electron impact instruments (147). In fact, the cation radicals undergo not only Norrish cleavage, but all the usual fragmentations of simple ketones. To quote Murad and Ingraham (146), "The results obtained...indicate that there is a remarkable similarity between the fragmentation pattern of the excited neutral species ($RCOCH_3*$) and the molecular ion ($RCOCH_3^+$)."

In view of the similarities between photochemical and mass spectrometric results, it is just frosting on the cake to mention that in radiolysis, where electron ejection is not unorthodox, the Norrish reaction is as important as in photochemistry (144b, 148).

5. Electron Ejection as a Method of Enhancing Triplet State Formation

There is some question as to the nature of the state which ejects the electron. Ottolenghi has shown that the dependence on pH of the yield of solvated electron in the irradiation of β-naphthol (150) quantitatively parallels the pH dependence of the fluorescence (149).

From these data, he concludes that the state responsible for ejection is the lowest excited singlet. This is not strictly true since the lowest excited singlet is also the species most likely to undergo intersystem crossing, and the same parallelism between the pH dependence of fluorescence and electron-ejection would be observed whether it were the singlet or triplet state which ejects the electron. Ottolenghi's kinetic data indicate that the ejecting state is relatively long-lived, since it undergoes an acid-base equilibrium before deactivating. Unfortunately, no lifetime measurements were made, so the nature of the excited state cannot be decided on the basis of Ottolenghi's work alone.

However, an educated guess can be made. If the electron is ejected, the rate of recombination will depend both on the viscosity and the electron affinity of the solvent. Under some conditions, the electron is trapped indefinitely (138). It seems reasonable that throughout a large part of the range of solvent viscosities and electron affinities, the rate of recombination is slow in comparison with the rate of spin inversion. If the emitting state was a singlet, the predicted ratio of triplet and singlet states on recombination is 3: 1 on a statistical basis. However, triplet states are somewhat lower in energy than singlets. Therefore, if the electron has lost some of its energy while free, the probability of return to the triplet is going to be greater than statistical, i.e. 3:1 is a minimum prediction for the triplet/singlet ratio following recombination. If, on the other hand, the excited state which ejects the electron is the triplet, then there is not sufficient energy for recombination to result in anything but the triplet.

Porter (151) has recently studied the thermoluminescence (light emitted following the recombination of the solvated electron with the parent radical) of naphthalene; and finds the phosphorescence/fluorescence ratio to be five times that normally observed. This result does not mean that recombination of the electron with the naphthalenic cation radical generates five times as many triplets as singlets; it merely reflects the fact that the increase in phosphorescent states comes at the expense of fluorescent states. On the basis of admittedly crude calculations, Porter estimates the observed ratio to correspond to statistical generation of triplet and singlet states by recombination. A similar result has been reported by Dolan (152). Therefore, the expectation that recombination of free electrons and cation radicals will statistically distribute the regenerated species among triplet and singlet states does appear to be borne out in some instances. Also, the observation of statistical recombination strongly suggests that in these cases the singlet state was the one which originally ejected the electron.

Other examples show that recombination may favor triplet formation on much more than a statistical basis. Linschitz (130) found that N-lithium carbazole (which has a strong fluorescence that assuredly would not have been missed) has a thermoluminescence consisting entirely of phosphorescence. In this case, only triplets were formed on recombination. The same conclusion applies to β -naphthol (150) since Ottolenghi reports that electron scavenging has no effect on the fluorescence yield. In these cases, either the triplet is the ejecting species, or the electron loses considerable energy while solvated.

Charge transfer studies provide a final illustration that electron ejection favors the formation of triplets. This is not precisely electron ejection, but it shows that removal of the electron from the chromophore results in a dramatic increase in the efficiency of intersystem crossing. Christodouleas and McGlynn used naphthalene and acenaphthene as donors with sym-trinitrobenzene as acceptor in their charge transfer studies and found that the ratio φ_p/φ_f of the donors was multiplied by factors of thirty and seventy-five, respectively (153).

Electron ejection may occur either from the triplet or the singlet. If the triplet is the ejecting species, then the major result of the process is the formation of the cation radical and any reactions peculiar to such a species. If the singlet is the ejecting species, the cation radical is again formed and may react; but if recombination occurs first, then the system is still affected by the ejection-recombination process in that the intersystem crossing efficiency is enormously augmented. Thus, electron ejection can be important either as a means of generating cation radicals or triplet states or both.

The one reported case (142a) in which recombination gives rise only to fluorescence is not an objection against the arguments presented here. The compound studied, acriflavine, did show some phosphorescence which was attributed to intersystem crossing from the regenerated singlet. However, Lim and Swenson did not consider the possibility that the delayed fluorescence which they observed might have arisen from interaction of triplet pairs to give one singlet and one ground state molecule from each pair (P-type delayed fluorescence) (142b). Such a mechanism is consistent with their report that the delayed fluorescence decayed more rapidly than did phosphorescence. Hence, it is not absolutely certain that recombination of electrons with acriflavine ions did in fact give rise only to the singlet. This case is pertinent to the present discussion as a further example of photochemically induced electron ejection, and possible should be classified as another instance where ejection occurs from the singlet.

6. Lumisantonin Photochromism

We now proceed to apply these arguments to lumisantonin. It should be realized that if reaction occurs while the electron is solvated, i.e. if the cation radical is the reactive species, then the whole question of the $n \rightarrow \pi^*$ or $\pi \rightarrow \pi^*$ character of the excited state becomes irrelevant. However, if recombination occurs before reaction, then electron ejection could be the method by which inter-system crossing predominates; in which case the nature of the excited state is vital because it determines the charge distribution. In either case, the rather knotty problem of explaining the enhanced quantum yield for lumisantonin isomerization in methyl naphthalene then reduces to noting that both the electron affinity and the viscosity of methyl naphthalene are higher than for benzene, so that the ejected electron is solvated longer.

When lumisantonin is irradiated in glassy solvent (EPA or ethanol) or a matrix (acetylene dicarboxylic acid dimethyl ester) at 77°K, a fearful blue color develops.* Hydrogen bonding cannot be involved since: 1) the ester cannot hydrogen bond and 2) slight warming of the glass (to 100°K) completely discharges the color,

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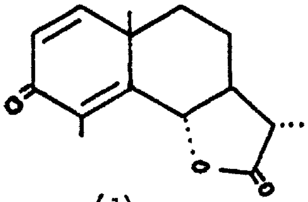
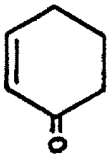
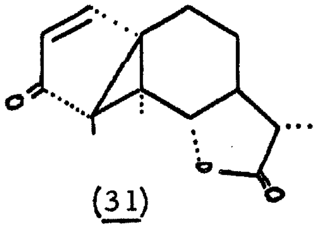
[*] I am indebted to Dr. A. A. Lamola, who first noticed this phenomenon while measuring the phosphorescent emission of lumisantonin.

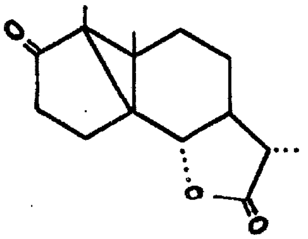
although intermolecular interactions would be expected to be essentially undisturbed. Phosphorescence is likewise not responsible for this phenomenon as the color persists indefinitely (and has been kept up to thirty-six hours) at liquid nitrogen temperatures.*

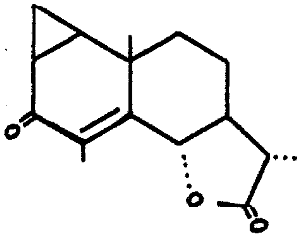
Evidently, an intermediate in the photolysis has been trapped. This is a great stroke of luck as lumisantonin has proved to be a most unusual case. Although the processes postulated are general, they do not normally give rise to trappable intermediates. None of the compounds shown below gave a blue color, or indeed any color, under the same conditions which gave rise to the photochromism of lumisantonin.


(1)


(73)


(31)


(5b)


(77)

Compounds (1), (50), (73), and (77) show that simple conjugation cannot be the only requisite for the observed coloration

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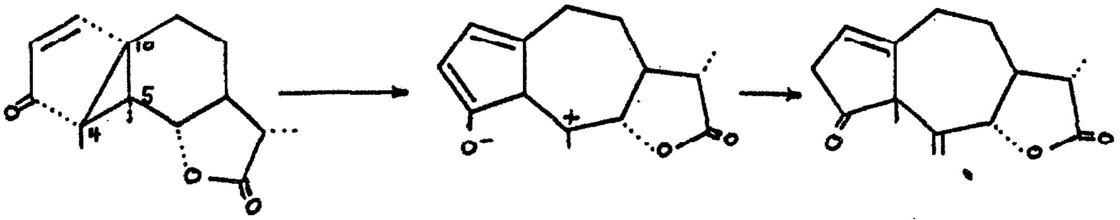
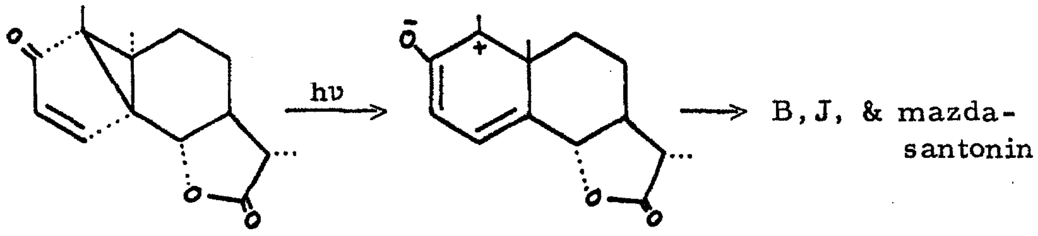
* Thermoluminescence is not visible to the naked eye.

whether the conjugation is from olefin, cyclopropyl, or a combination. Compound (<u>31</u>) (B) is of particular significance because the chromophore is precisely the same as for lumisantonin apart from the disposition relative to the lactone.

The difference in photochromic behavior of B and lumisantonin is no doubt related to the difference in photochemical behavior, where, as we have seen, different bonds break in the cyclopropane ring. Accurate quantum yields were not determined for the photoconversion of B, but the initial rates of conversion of lumisantonin and B were in the ratio of at least six to one as measured by n.m.r. No doubt the difference in photochemistry arises not from acceleration of the C_5-C_{10} bond breaking, but rather from suppression of the scission (C_4-C_{10}) analogous to that prevalent in lumisantonin.



(<u>31</u>) (<u>78</u>) (<u>32b</u>)



lumisantonin (<u>5</u>) (<u>80</u>)

In order for structure (78) to react further, proton loss to solvent will suffice, whereas structure (79) requires methyl migration. Microscopic rigidity of the solvent blocks the latter pathway and thus stabilizes (79). The assumption that solvent rigidity prevents rearrangement seems particularly reasonable when it is recalled that santonin, which has a quantum yield of unity for reaction in fluid solutions, does phosphoresce at 77°K. The generally observed increase in phosphorescence yield with solvent viscosity arises from hindrance to molecular vibrations just as postulated here (90,93).

Formation of (79) from lumisantonin does not appear to be reversible, probably both because of strain inherent in the lumisantonin structure and resonance stabilization of structure (79) which has three mesomeric forms. (79) is formulated as the cation radical. This is not the only possibility, however, as a diradical (either singlet or triplet) or a dipolar intermediate are also possible. However, since the species is very long-lived, it seems more reasonable that the colored intermediate have its electrons disposed in the lowest possible energetic arrangement, i.e. either as the cation radical or the dipolar intermediate. The latter is lower energy than the diradicals because it utilizes the electronegativity of oxygen. The cation radical is the only possible result if the electron is trapped. (The solvated electron is known to be blue, cf. Section V-B-2.)

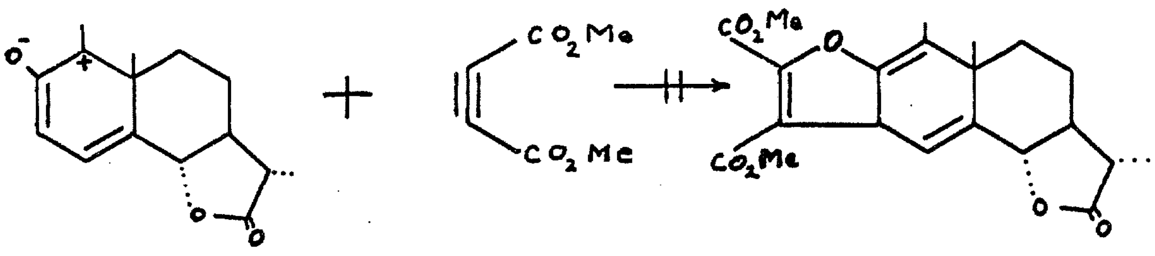
Repeated irradiation of the glass with only sufficient warming to discharge the color eventually leads to a distinct yellow tinge, indicating that mazdasantonin is being formed, i.e. that the usual mechanism is operative. This impression was strongly supported by workup of product mixtures from the irradiation of lumisantonin in acetylene dicarboxylate dimethyl ester as solvent at room temperature. Mazdasantonin was formed as usual, and no new products were detected.

Several observations favor the electron emission mechanism. These include the failure to observe color formation in acetone (an electron scavenger) (150) or MCIP glass (which cannot solvate electrons) (131), and the already discussed dependence of quantum yield on the electron affinity and viscosity of the solvent.

Furthermore, the only plausible alternative, the dipolar compound (80), was not trappable either at room temperature or at 77°K, even when the powerful dipolarophile (81) was used as solvent (154a). If the origin of the blue color is dependent on the prevention of migration of the methyl group by solvent, as postulated; then it seems reasonable that (81) should have a better chance to interact electrostatically with the charged centers at liquid nitrogen temperatures so as to make formation of (82) more likely in preference to further conversion to mazdasantonin. In fact, mazdasantonin is formed as usual in acetylenecarboxylic acid dimethyl ester as solvent.

Unfortunately, this negative result is not compelling because the degree of molecular reorganization concomitant on formation of (82) may very well be such that interaction of (81) with polarophile is also prevented by solvent rigidity. However, this result is certainly consistent with the electron ejection mechanism.

Irradiation of lumisantonin in the ester matrix leads to the blue color indicating that the normal intermediate is formed. The trapped species was not the usual purple, however. Rather, it was a paler, robin's egg blue. This observation indicates an important influence of the solvent, a role easily understandable on the basis of a solvated electron. Nonetheless, it does not militate particularly strongly against the dipolar intermediate (80).



(80) (81) (82)

7. Quenching and Quantum Yield Results Reinterpreted

An explanation of the quenching and quantum yield results based on the assumption of energy transfer has already been presented. In view of the possibility of electron ejection, these results must be rediscussed. The following scheme is applicable.

$$R_2C{=}O \xrightarrow[M]{h\nu} R_2C{=}O^+ + M^- \qquad (1)$$

$$R_2C{=}O^+ + M \longrightarrow R_2C{=}O + M^+ \qquad (2)$$

$$R_2C{=}O^+ + M \longrightarrow R_2C{=}O^T + M^+ \qquad (3)$$

$$R_2C{=}O^+ + M^- \longrightarrow R_2C{=}O^T + M \qquad (4)$$

$$R_2C{=}O^+ + M^- \longrightarrow R_2C{=}O + M \qquad (5)$$

$$R_2C{=}O^T \longrightarrow \text{reaction} \qquad (6)$$

$$R_2C{=}O^+ \longrightarrow \text{reaction} \qquad (7)$$

$$R_2C{=}O^T \longrightarrow R_2C{=}O + h\nu \qquad (8)$$

$$R_2C{=}O^T \longrightarrow R_2C{=}O \qquad (9)$$

$$M^+ + Q \longrightarrow M + Q^+ \qquad (10)$$

$$M^+ + M^- \longrightarrow 2M \qquad (11)$$

$$M^- + Q^+ \longrightarrow M + Q \qquad (12)$$

$$R_2C{=}O^+ + Q \longrightarrow R_2C{=}O + Q^+ \qquad (13)$$

Initial excitation of the carbonyl compound leads to ejection and formation of the cation radical. No preference for a singlet or triplet as the ejecting species is intended. The electron is solvated. The cation radical may abstract an electron from solvent (2 and 3), or recombine (4 and 5) to produce the excited triplet (3 and 4) or the ground state directly (2 and 5). Reaction may occur from the triplet (6) or from the cation radical (7). If some other system is present, it too may enter into the same sort of reactions (10 etc.).

Clearly, if the reactive species is the excited singlet, then electron ejection is not necessary, and indeed must be unimportant since (Sec. V-B-5) it favors the generation of triplets on recombination. If the reactive species is the triplet, then electron ejection can be vital as the means by which intersystem crossing is favored. Finally, if reaction occurs via the cation radical, then ejection may occur from either the singlet or triplet, but the $\pi \rightarrow \pi^*$ triplet is the most likely precursor of the cation radical. The triplet is preferred to the singlet because it is more polarizable (154b) and the $\pi \rightarrow \pi^*$ state is preferred to the $n \rightarrow \pi^*$ state because it tends to localize negative charge on oxygen. Thus cation radicals are most likely to be important in the photoconversions of species, which, like lumisantonin, appear to react via $\pi \rightarrow \pi^*$ triplet states.

Consider now the photolysis of santonin to lumisantonin. The following facts are known from this thesis: 1) the triplet is necessary for reaction; 2) the quantum yield is unity in both benzene and methylnaphthalene; 3) the reaction is very fast, irreversible, and very likely concerted in that it is stereospecific and probably does not involve free carbonium ions; 4) the triplet energy of santonin is 68 kcal/mole relative to the ground state of santonin; 5) the triplet energy of lumisantonin is 64 kcal/mole relative to the ground state of lumisantonin. Suggestive evidence has also been brought forward to show that the triplet is very likely necessary for the photochemical rearrangement of lumisantonin, and it has been demonstrated that the reaction of lumisantonin via the triplet (using sensitizers) is perfectly efficient.

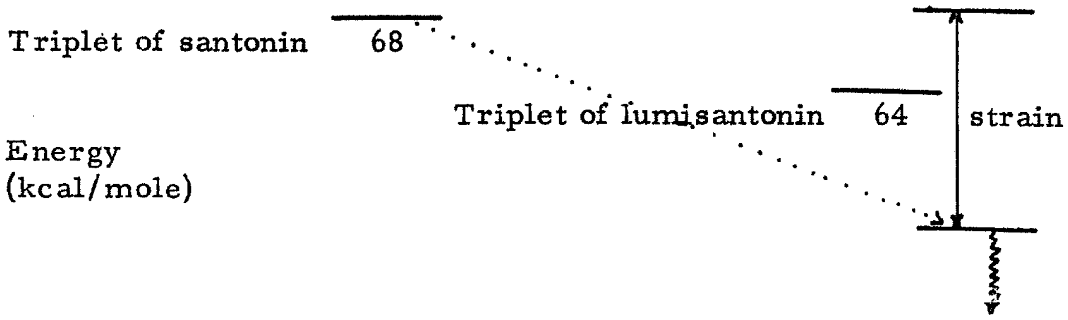
The fact that lumisantonin is isolable means that the photolysis of santonin cannot give rise to that energy-rich form which is an intermediate in the photochemical rearrangement of lumisantonin, unless the efficiency of further conversion of this excited state of lumisantonin is so low that its most frequent fate is simple deactivation to a lumisantonin molecule in the ground state. However, the lumisantonin triplet state reacts every time it is formed, i.e. it is never deactivated back to lumisantonin. This is required because the quantum yield is unity for the sensitized reactions. It therefore follows that the photochemical rearrangement of santonin to lumisantonin cannot proceed through the triplet state of lumisantonin.

There are two conceivable intermediates in the conversion of santonin to lumisantonin: the neutral triplet and the cation radical of santonin. Of these two, the neutral triplet is far more likely to be the photochemically active intermediate. The triplet of santonin has a great deal of $n \rightarrow \pi^*$ character, whereas the triplet state of lumisantonin is probably $\pi \rightarrow \pi^*$. Because of localization of negative charge on oxygen in $\pi \rightarrow \pi^*$ states, electron ejection has a greater probability of occurring from the excited state of lumisantonin than from that of santonin. Therefore, if the cation radical intermediate is to be postulated for the photochemical rearrangement of only one of the first two isomers in the reaction sequence (santonin or lumisantonin), the photolysis of lumisantonin is the reaction in which the cation radical should be encountered. Indeed, the cation radical cannot be the reactive species in the photochemical rearrangement of both santonin and lumisantonin. This statement is a consequence of the quantum yield of unity in the sensitized reaction ; for if the cation radical is the reactive species in the photochemistry of lumisantonin, the fact that every triplet of lumisantonin rearranges demands two things: that the cation radical of lumisantonin be accessible from the triplet state of lumisantonin and that every cation radical of lumisantonin rearrange. If the conversion of santonin to lumisantonin proceeded through the cation radical of santonin, then lumisantonin would be produced as its cation radical. This species, as has been shown, would have to react further and thus lumisantonin would not be isolable.

Assuming that the reactive species in santonin conversion is the neutral triplet state, one must still explain how the rearrangement of santonin fails to produce lumisantonin as the triplet. The lumisantonin molecule has considerable potential energy stored as strain in the cyclopropylenone system,as anyone who has ever tried to make the models will testify.

The difference in triplet energies of santonin and lumisantonin relative to the respective ground states is only 3-4 kcal/mole, and it is probable that distorting the santonin skeleton consumes so much of the 68 kcal/mole energy of the santonin triplet that there is then available significantly less energy than the 64 kcal/mole required for formation of the electronically excited triplet state of lumisantonin. Thus lumisantonin, when formed from santonin triplet, would be in a vibrationally excited ground state and would be deactivated by collision with solvent molecules.

Energetics of the Formation of Lumisantonin



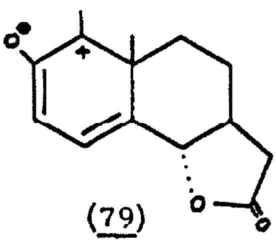
A further possibility which has not been seriously considered is that santonin isomerizes only after intersystem crossing from the electronically excited triplet state to a high vibrational level of the ground state. This pathway seems unlikely in view of the evidence that such processes do not appear to be vital to other rearrangements involving triplet states (85b), and is very likely excluded by the present evidence. Thus, the observed quantum yield for the conversion of santonin to lumisantonin is unity, and this requires that, if the vibrationally excited S_0 states of santonin are actually instrumental to the isomerization, the decay to the ground state of lumisantonin must be favored exclusively over the direct cascade to santonin; and such a partition of vibrational energy is inherently unreasonable.

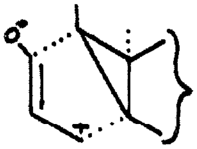
If the conversion of santonin to lumisantonin does proceed from the neutral triplet state of santonin to lumisantonin in a high vibrational level of the ground (S_0) state, then subsequent excitation of lumisantonin would be necessary for further conversion to the secondary photoproducts. The reactive species in the rearrangements of lumisantonin could be either the neutral triplet or the cation radical.

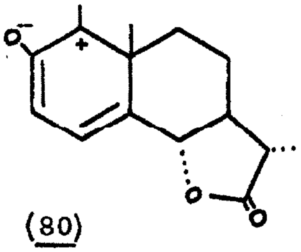
8. Generalization

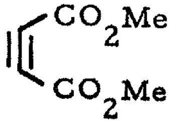
Generalization of electron ejection mechanisms to other photochemical processes is tempting, but any speculation advanced here should be viewed as no more than that until unambiguous experimental proof is forthcoming.

Lumisantonin is very likely an instance of a substance which undergoes ionic rearrangements via a $\pi \rightarrow \pi^*$ triplet, and therefore electron ejection is probably as favored in this case as possible. If electron ejection occurs, it may have two possible functions. One is to generate the cation radical; and if this cation radical is the intermediate in the photochemical rearrangement of lumisantonin, electron ejection would have to occur from the triplet state, since it is known that every triplet of lumisantonin rearranges. The general argument that solvent can raise the efficiency of a reaction which involves a cation radical by increasing the lifetime of the reactive species (through solvating the electron and thus hindering recombination) does not apply to a rearrangement of lumisantonin via the cation radical because the reaction is already perfectly efficient when the triplet state is reached, i.e. before generation of the cation radical. Therefore, the quantum yield for the photolysis of lumisantonin is higher in methylnaphthalene than in benzene. However, the solvent still can have an effect on the efficiency of the reaction even if the cation radical is the reactive species. Since intersystem crossing appears to be the inefficient step in lumisantonin photochemistry, the solvent could raise the final quantum yield for the rearrangement by increasing the absolute intersystem crossing rate from the lumisantonin singlet and thus making the production of lumisantonin triplet states more efficient. As Parker has shown for eosin-dianion (Table 13), the absolute rate of intersystem crossing does appear to be a function of solvent, with the more viscous solvents favoring the higher rates. Therefore, the role postulated for solvent if lumisantonin reacts via the cation radical has precedent. Moreover, if the cation radical mechanism is valid, the blue color formed on irradiation of lumisantonin at low temperature is probably due to the trapped cation radical (79) and the solvated electron.


(79)


(79a)


(80)



(81)

If the neutral triplet of lumisantonin is the photochemically active species rather than the cation radical, electron ejection could still play a part in the complete mechanism by augmenting the yield of triplets via an ejection-recombination process. Such a role would require that ejection occur from the singlet and is somewhat less attractive than the one just outlined, because ejection should be more likely from the triplet than from the singlet, which is less polarizable (154b). The rate of the recombination process would depend on the solvent in which ejection took place, and varying amounts of intersystem crossing would occur for solvents in which the rate constant of recombination is of the same order as the rate of spin inversion (10^7 sec^{-1}) (44). If the blue color arises from trapping an intermediate in the reaction of the neutral triplet, then the dipolar form (80) is probably the species which has been trapped.

The solvated electron and the cation radical derived directly from lumisantonin, (79a) (in which the geometry has not been altered), could also give rise to the blue color if this system were trapped by solvent when the electron is ejected, regardless of the chronology of the process, i.e. whether the electron is ejected before or after intersystem crossing. This possibility is discounted because B (31) does not show photochromism when subjected to the identical conditions under which solutions of lumisantonin turn blue.

Since B and lumisantonin are "upside-down" isomers of each other and have almost identical chromophores, it is unreasonable that solutions of B do not show coloration on irradiation if solvated electrons and cation radicals of the type (79a) are the fountainhead of the observed photochromism.

There is an additional reason for discounting the possibility that (79a) is the trapped species if lumisantonin reacts via the cation radical. The amount of reorganization involved in the collapse of (79a) to (79) is so small that it is unlikely that even a rigid solvent would be very effective in hindering this step. Moreover, the process is almost certainly exothermic, since the strain energy of the lumisantonin system is released; and, although bond-breaking might require some activation energy, it is probable that (79a) would proceed along the reaction coordinate as far as the much more stable isomer (79).

It should be possible to distinguish between the two possibilities (79) and (80) chemically. A dipolar intermediate such as (80) should be trappable by conventional dipolarophiles, and the fact that (81) does not affect the reaction even at low temperature militates against the intermediacy of (80), although not very strongly, because the changes in geometry necessitated by dipolar addition may be as severely hindered by solvent rigidity as is the methyl migration. A radical cation such as (79), as well as the solvated electron itself, should be detectable by e.p.r., but essays along this line have failed thus far.* Even this negative result is not conclusive by any means because the sensitivity of the instrument was unknown and the concentration of the colored material could not be estimated.

It will not be possible to decide definitely whether the blue intermediate in lumisantonin photochemistry is the cation radical (79) or the dipolar intermediate (80), unless an e.p.r. experiment works or a successful dipolarophile is found. However, the electron ejection mechanism itself can be tested by scavenging the solvated electrons with nitrous oxide (150, 155) and analyzing by mass spectrometry for evolved nitrogen. Preliminary experiments along these lines were inconclusive due to lack of proper equipment, but the approach should yield highly useful information. If electrons are detected by this means, then (79) is the preferred intermediate. If no electrons can be scavenged, then (80) is to be preferred, and probably should be considered as arising directly from the triplet following conventional intersystem crossing. In this case, the failure to observe coloration in certain solvents would have to be

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* I wish to thank Dr. A. Merkl, who labored valiantly, ultimately to overcome the difficulties inherent in e.p.r. spectroscopy at temperatures less than 77°K.

attributed to differences in microscopic rigidity between these solvents and ethanol at liquid nitrogen temperatures.

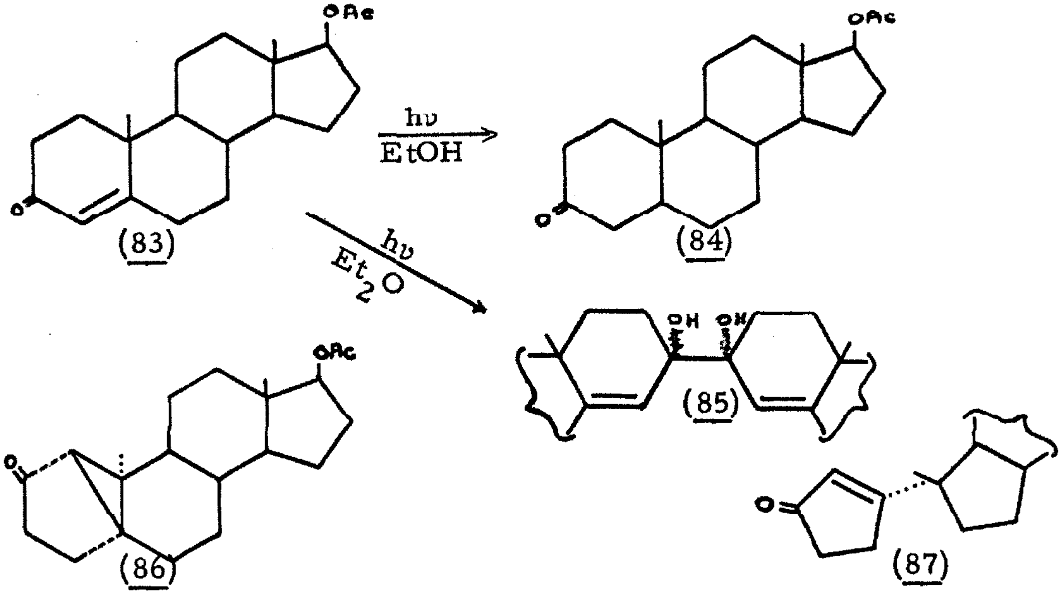
Of course, the trivial possibility remains that the blue color does not arise from a derivative of lumisantonin at all, but from some impurity present in solution. Although not impossible, this explanation is unlikely because the lumisantonin used had been carefully purified. Furthermore, trace impurities of lumisantonin would probably have been present also in at least some other members of the system; yet B, santonin, and mazdasantonin all failed to show photochromism.

My personal preference in this matter is that the color arises from the dipolar intermediate (80). If the solvated electron were necessary for photochromism, then all the compounds which do not turn blue when irradiated in a glass would be concluded to be non-ejectors. This would require that lumisantonin is unusual both in that it gives rise to a trappable intermediate and in that it ejects an electron. However, since the chromophore is precisely the same in B and in lumisantonin, it is reasonable that ejection should occur from both compounds or from neither. I suggest that B, though it might rearrange through a dipolar form analogous to (79), does not show photochromism because its photochemistry does not involve methyl migration as a major reaction pathway, and therefore the intermediate is not prevented from rearranging by solvent rigidity.

Even if the blue color could be shown definitely to be due to the dipolar intermediate, this would by no means rule out the electron ejection mechanism as an important process in photochemistry. The concept of the cation radical still could be of use in rationalizing other ionic rearrangements as in the systems below.

Heteroatomic Systems

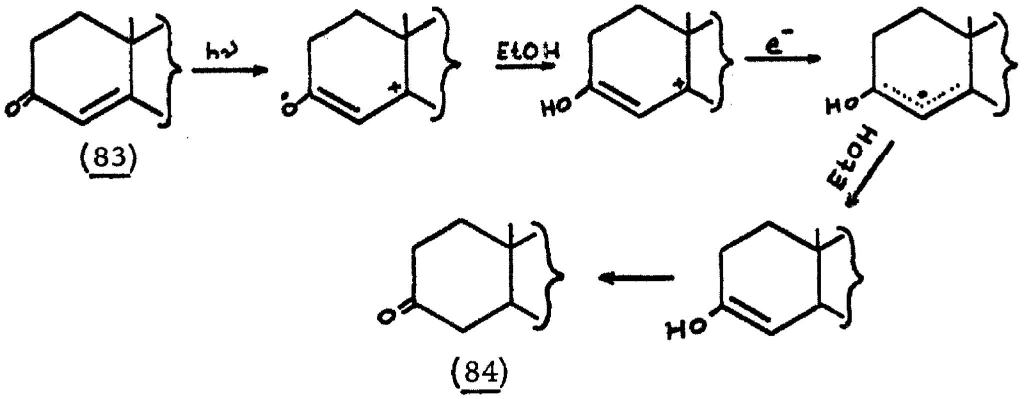
In his study of solvent effects on the photolysis of testosterone acetate (83), Jeger observed that in ethanol solution, the only product isolable was the reduced compound (84), whereas in ether a pinacol was formed (85). In the absence of readily abstractable hydrogen, photochemical rearrangement was observed, but the products obtained again depended on the solvent. Thus (86) was obtained in dioxane, but (87) was the major product in t-butanol (42, 96).



These solvent effects clearly implicate a change in the nature of the excited state from n→π* to π→π* when hydroxylic solvent is substituted for ether or dioxane. Thus (85) and (86) are the products of photochemical reduction and rearrangement, respectively, of the n→π* state, whereas (84) and (87) are the result of reaction of the π→π* state.

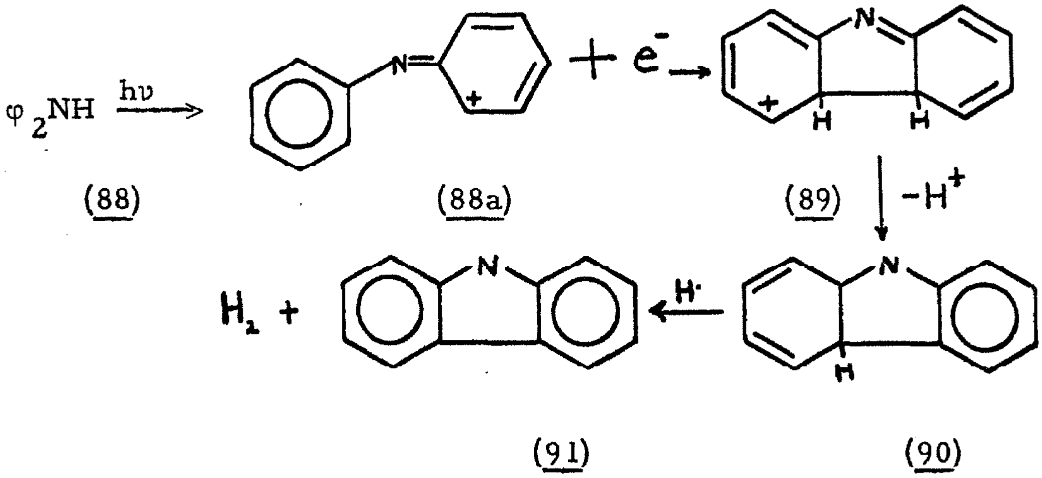
Pinacols such as (85) are believed to be the normal product of photoreduction of ketones which have lowest-lying n→π* triplet states (60). Porter has confirmed this belief by showing that substances which have nearly isoenergetic n→π* and π→π* triplet levels will photoreduce smoothly to pinacols in hydrocarbon solvent, but are inert to irradiation in alcohols. Thus, excellent yields of pinacols are obtained from photoreduction of p-dimethylaminobenzophenone and p-hydroxybenzophenone (the hydroxy compound is quantitatively reduced) in cyclohexane, but <u>both compounds are photochemically inert to isopropanol</u> (156). Since isopropanol is an excellent source of hydrogen for photoreduction (60), the inescapable conclusion is that the electronic state required for photoreduction is not lowest energy in isopropanol. Porter has shown elsewhere that the n→π* and π→π* triplet levels of p-hydroxybenzophenone have very nearly the same energy content with respect to the ground state (117), and it is plausible that solvent effects could make one or the other state the lowest-lying species.

Clearly, the photochemical species which leads to (<u>84</u>) is not the n→π* triplet. In alcohols, the π→π* triplet state of testosterone acetate (<u>83</u>) is apparently lower-lying than the n→π* triplet state. Therefore, the species active in the photoreduction of testosterone acetate to (<u>84</u>) could be either the π→π* triplet or a species derived from it, e.g. the cation radical. However, <u>the π→π* triplet is known to photoreduce only very slowly if at all</u> (114, 115, 156). Therefore, the possibility of a cation radical intermediate in the photoreduction of (<u>83</u>) to (<u>84</u>) seems most attractive.



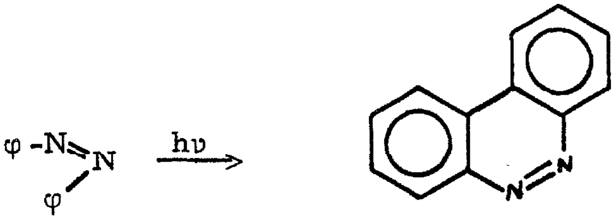
The results of Jeger on the photolysis of testosterone acetate are also pertinent to the santonin system. The product analogous to lumisantonin (86) is obtained under conditions where the n→π* triplet is presumably the reactive state. Furthermore, (87) rather than (86) is the major product in alcohols where π→π* states, and hence cation radicals are favored, thus demonstrating that a cation radical derived from an enone is not likely to rearrange to a lumisantonin-like product. These conclusions are exactly analogous to those presented here (pp. 147 and 170), viz., that the rearrangement of santonin involves its n→π* triplet state, but not the cation radical.

Other photochemical reactions are known which exhibit features that are anomalous when treated only on the basis of conventional considerations. An example is the cyclization of diphenylamine to carbazole which, although known to proceed via a triplet, is not quenched by added butadiene (88). This system contrasts with other photochemical cyclizations, e.g. stilbene (157), in that it proceeds smoothly in the absence of oxygen and all oxidizing agents. A cyclization via a cation radical would explain this feature. Proton loss from the intermediate (89) and hydrogen atom abstraction from (90) would both have driving force from the fact that each step gives rise to an aromatic system. In this way, external oxidizing agents would not be needed. On the other hand, there is no reason why a dihydrocarbazole formed by direct cyclization of neutral diphenylamine should spontaneously lose hydrogen. As is well known, the dihydrophenanthrene formed from direct irradiation of stilbene does not lose hydrogen but instead slowly reverts to cis-stilbene (85b, 157).



(88) (88a) (89) (91) (90)

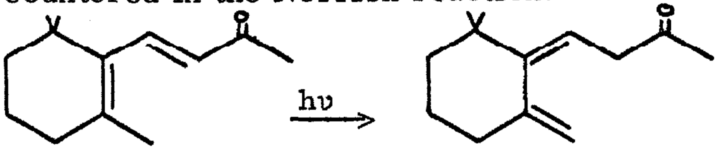
Another heteroatomic case in which analogous reasoning applies is the photocyclization of azobenzene to 9, 10-diazaphenanthrene. In non-polar solvents, or even in alcohols, azobenzene is photochemically inert (158, 159). However, cyclization proceeds smoothly on irradiation in ethanol with sulfuric acid added (160) or in glacial acetic acid containing a little Lewis acid (ferric chloride) (159). It may be that one of the unshared pairs of electrons on azobenzene must be tied up in order for cyclization to occur. However, electron ejection is also consistent with these results. *Reaction occurs only under conditions where* $\pi \rightarrow \pi^*$ *intermediates* are most favored. Hydrogen ion and ferric chloride could play conventional roles as electron scavenger (150) and electron trap, respectively, and favor reaction by preventing recombination of the radical cation and the electron. Since the cyclization has unfavorable entropy requirements, *it* would not be *surprising if the* cation radical were to require a very long lifetime in order for the cyclization to be efficient.



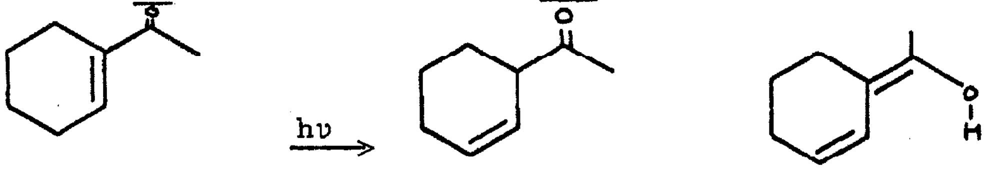
(92) (93)

Dienes

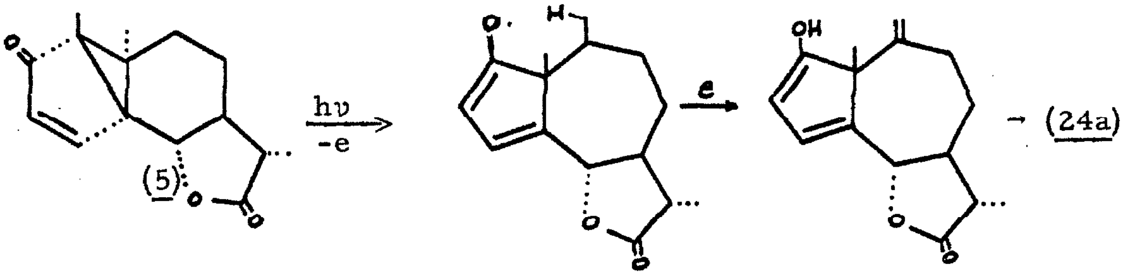
The rearrangements of ionone (94) (161) illustrate the sort of reaction to be found also in the formation of H (24a), the photoproduct from B-nortestosterone acetate (11b), and the photoproduct from 1-acetylcyclohexene (95) (162). Note that the formation of H (24a) formally proceeds through γ -hydrogen abstraction as encountered in the Norrish reaction.



(94) (94a)

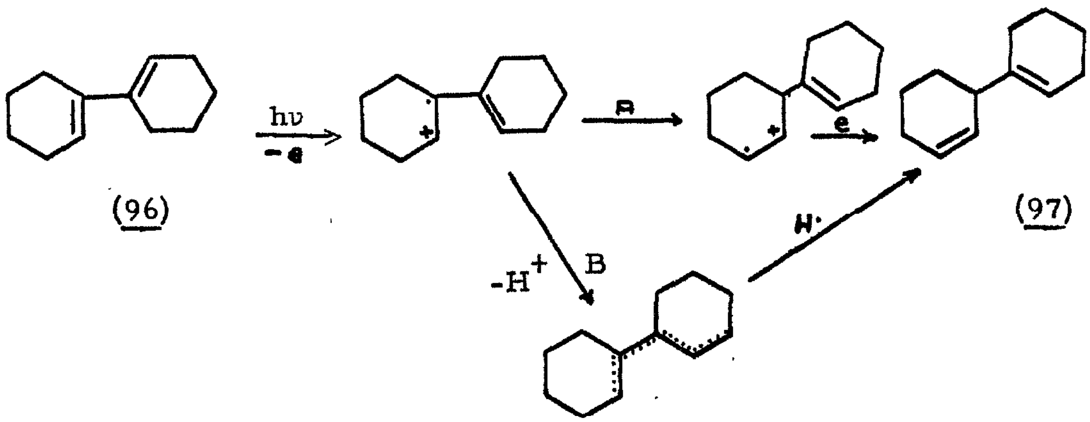


(95) (95a) (95b)



In these cases, an enolic intermediate can be written, as in (95b), although geometric considerations forced Jeger to draw "a concerted rearrangement with transient ionization" (11b). However, the observation that β -ionol undergoes precisely the same rearrangement (163) shows that the carbonyl function cannot be absolutely requisite to the reaction. Rather, the diene function is reacting on its own, although sensitization of the diene system by excited carbonyl may very likely be important in those instances where the reacting diene is conjugated with an aldehyde of ketone.

The electron ejection mechanism may be employed to understand these diene rearrangements. This is illustrated below for the rearrangement of bicyclohexenyl (164). Initial electron ejection is followed either by 1,3-hydrogen migration (Path A) or proton loss from the allylic position (Path B). In the latter case, there are three possible positions at which the hydrogen atom can be added to the radical system. Addition at A or B would result in conjugated systems which could still absorb light and undergo reaction. Only addition at C breaks up the diene system into two isolated double bonds which would not absorb light of the wavelength employed, and hence the product (97) would be expected to accumulate. This is in fact what is observed.



(96)

(97)

These considerations are not meant to imply that all rearrangements occur via radicals or even that electron ejection is important generally. However, success in interpreting certain known photochemical reactions and the lack of any equally consistent alternatives makes the electron ejection hypothesis worthy of serious consideration.

Sensitization and Quenching

Many of the carbonyl compounds most useful as sensitizers, e.g. benzophenone, are known to have $n \rightarrow \pi^*$ triplet states. Hence, electron ejection is not likely to be of universal importance in sensitization. However, it is interesting to note that in systems whose photochemistry depends on cation radicals, there exist two modes of preventing reaction in addition to quenching the singlet or triplet state which is the precursor of the cation radical.

Since hydrocarbon solvents, i.e. alkanes and alkenes, cannot solvate electrons, it is to be expected that the rate of recombination of the electron with the cation radical will be much faster in hydrocarbons than in hydroxylic solvents. Thus, the lifetime of the cation radical may be so much shorter in hydrocarbons that reactions characteristic of the cation radical are completely suppressed. This is particularly significant in view of the ever-increasing number of examples of photochemical reactions which are drastically altered by changing the solvent from, say, ethanol to cyclohexane. It may not be entirely fortuitous that hydroxylic solvents, which would ensure the longest lifetime for cation radicals, are also the solvents which favor reactions of heteroatomic systems via $\pi \rightarrow \pi^*$ states (Section V-A), the more likely precursors of cation radicals.

The cation radical could also be prevented from reacting if an electron were supplied to it very quickly by a second substance present in the solution. This second substance could be either a reducing agent or a compound which itself very easily loses an electron to form a cation radical. For example, ferrocene, which is known to form its cation radical very easily (165), appears to quench almost any triplet reaction (166). Unfortunately, this case is not clear-cut because the iron atom could also account for the observed quenching simply by paramagnetic enhancement of triplet-singlet interconversion.

Unless strongly solvated, the electron will return to the cation radical at very fast rates.* But reaction rates of cation

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* Solvation can make the rate of recombination much slower. For example, the half-life of the solvated electron in water at room temperature has recently been reported to be 5×10^{-5} seconds (167).

radicals must be faster than the rate of recombination with the electron in order for reaction to occur. Therefore, photolyses involving cation radicals will characteristically proceed very rapidly, and dilute quenchers will be relatively ineffective in deactivating the reactive states.* Such an explanation might be the reason for the peculiarly stubborn resistance to solvent quenching exhibited by certain triplets (109).

Summary of Santonin Photochemistry in Benzene

The results of Part I (photoproducts, structures, and yields) have been presented in Figure 13. The results of Part II will now be briefly reviewed.

The major point is that the reactions of santonin and mazdasantonin, and very likely lumisantonin also, require the triplet state at some vital point in the reaction sequence. The triplet state energies of the various compounds relative to their ground states have been determined and found to be 68 kcal/mole for santonin, 64 kcal/mole for lumisantonin, and approximately 53 kcal/mole for mazdasantonin.

The photoconversion of santonin proceeds through the $n \rightarrow \pi^*$ triplet. By rearrangement of the excited state, lumisantonin is

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* This statement assumes that the state which ejects the electron does not itself have a very long lifetime.

produced in a high vibrational level of the ground state. This species is then quickly deactivated by collisions with solvent molecules. Other reactions of enones and dienones to lumisantonin-like products probably proceed via the same mechanism.

It has been shown that the reactions of lumisantonin cannot be rationalized on the basis of conventional $n \rightarrow \pi^*$ excited states, and two possible explanations of this anomaly are presented. The first to be discussed is the suggestion that the $\pi \rightarrow \pi^*$ state could be the reactive species. This suggestion seems to rationalize the generation of positive charge at the appropriate positions for ionic rearrangements, and fits in with the fact that the triplet of lumisantonin is probably $\pi \rightarrow \pi^*$. The rearrangement of lumisantonin to its four photoproducts appears to involve primary bond-breaking of the cyclopropane ring in the excited state. This process forms a dipolar intermediate (trappable in glassy solvents at liquid nitrogen temperatures). The methyl migrations occur in this dipolar form which is a spectroscopic ground state, and it is therefore unnecessary to contrive a method of accumulating charge in the excited state to explain the ionic rearrangements of lumisantonin.

Consideration of lumisantonin photochemistry also led to a second suggestion for generating charge in excited states, which, although not applicable to the case of lumisantonin itself, may be of importance in other photochemical reactions. This hypothesis is that an electron is ejected from a $\pi \rightarrow \pi^*$ excited state, thus forming a cation radical which may abstract hydrogen from solvent or undergo ionic rearrangement. This hypothesis would rationalize several reactions which are not easily explicable on conventional grounds.

The dimerization of mazdasantonin involves its $\pi \rightarrow \pi^*$ triplet state. The reactive species is derived by excitation of a ground-state complex formed by association of mazdasantonin with itself.

EXPERIMENTAL

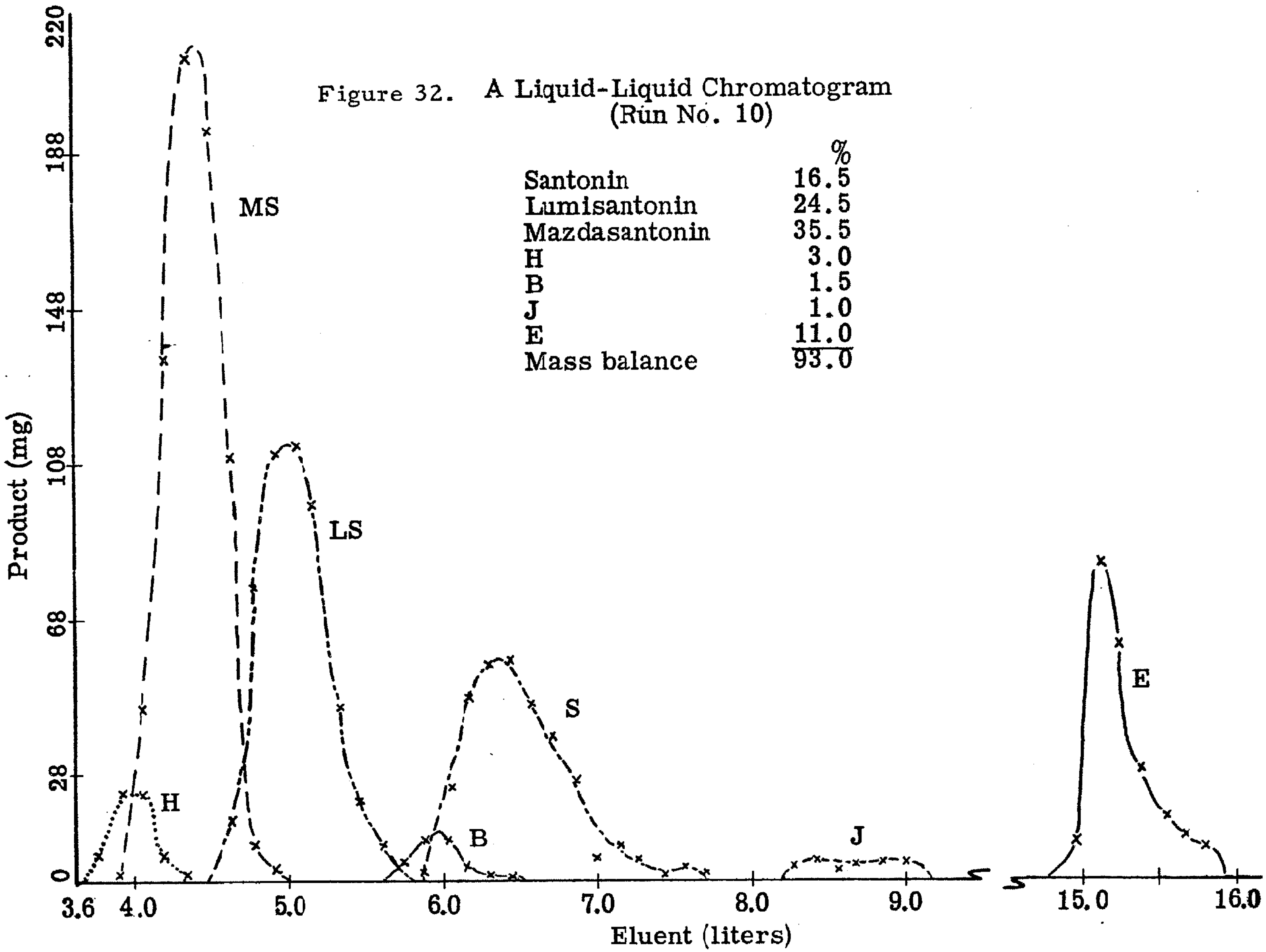


Figure 32. A Liquid-Liquid Chromatogram
(Run No. 10)

	%
Santonin	16.5
Lumisantonin	24.5
Mazdasantonin	35.5
H	3.0
B	1.5
J	1.0
E	11.0
Mass balance	93.0

Table 18. Summary of Liquid-Liquid Partition Chromatography

Run	Material	Duration of irradiation (hr)	S	LS	E	B	C	Tar	H	T	Total
1[a]	2g santonin	3¼	38½	33	1½	?	12	6½	?	?	92
2[a]	"	6	18	25	1½	?	34	8½	?	?	89
3[a]	"	32¼	2½	4½	8½	2½	48½	30	½	4½	102
4[b]	"	41	15	23½	4½	2½	37	16½	½	1	101½
5[b]	"	100	12	24	6½	0	51½	9½	?	½	105½
6[c]	"	225	1	7	5½	2½	66½	½	1½	1½	89
7[c]	"	3	29	31	7	½	23	½	0	1½	94½
8[c]	"	6	16½	24½	11	1½	35½	0	3	1	93
9[c]	"	35	1	4½	24½	2	64	0	3½	2½	103
10[c]	"	41	0	1	24½	1½	65	½	4½	0	100
11[c]	1.344g lumi "	13	0	2½	9	4	58½	0	11½	3	88½
12[c]	653 mg maz-dasantonin	43	0	0	6½	1¼	78½	0	¾	¼	87
13[c,d]	2g santonin	3	42½	23½	8½	1	18½	0	3½	1/10	98
14[c,e]	"	6	33	38½	9½	0	15½	0	½	3	99

a. open to air, in 110 ml benzene
b. some dissolved oxygen in solution in 100 ml benzene
c. under nitrogen, 750 ml benzene
d. 2.021g benzophenone added; recovery of sensitizer was 1.963g (97%)
e. in 110 ml "research grade" (99.91%) benzene (Phillips)

I. MATERIALS

A. Chemicals

Benzophenone was recrystallized from hexane, m.p. 48.0-48.5.

Benzhydrol was recrystallized from hexane, m.p. 66.5.

α-Methylnaphthalene (Columbia Chemical Co.) was passed through acid-washed alumina and distilled, the portion boiling at 59° (1 mm) being used for quantum yield and quenching studies. A 1 cm sample of this solution had an absorption at 366 mμ of 0.067 relative to benzene.

Santonin (Mutschler Chemical Co.) was recrystallized from ethanol, m.p. 172-173°.

B. Solvents

Benzene was dried one day each over two successive portions of calcium chloride, then refluxed at least four hours over calcium hydride, then distilled, b.p. 79°.

Hexane and heptane were treated as was benzene, b.p. 68° and 98°, respectively.

Nitromethane was dried over calcium sulfate, then distilled, b.p. 100°.

Ethyl iodide (Matheson, Coleman and Bell, reagent grade) was distilled before use.

Dimethylformamide was refluxed overnight over barium oxide and distilled before use.

Dimethyl sulfoxide (Baker, "Analyzed Reagent") was dried by distillation at reduced pressure from calcium hydride.

Dioxane was purified by the method of Hess and Frahm (168).

Methanol was distilled before use, b.p. 64°.

Ethyl acetate was distilled before use, b.p. 77°.

C. Sensitizers

Fluorenone and α-naphthyl phenyl ketone were obtained pure from Dr. J. Saltiel. Fluorenone had been recrystallized twice from n-heptane, m.p. 84.3-84.7°. α-Naphthyl phenyl ketone had been crystallized from benzene, m.p. 76.4-77.0°.

Michler's ketone (Eastman Kodak, Practical Grade) was recrystallized twice from ethanol, m.p. 173-5°.

Thioxanthone (Aldrich, Research Grade) was purified by Dr. A. A. Lamola. Chromatography on alumina with benzene as the solvent, followed by treatment with carbon black in methanol and recrystallization from methanol yielded white needles, m.p. 209.0°.

Triphenylene (Terra Chemical Co.) had a slight yellow tinge due to a trace of chrysene. Sublimation did not improve the color. Since the ultraviolet spectrum in the region of interest agreed with that published (110b), the material was used without further purification.

Anthraquinone was obtained pure from Dr. Helmut Werner, and used without further purification.

2. PROCEDURES

Ultraviolet spectra were taken on a Carey 11 instrument using 1 cm cells. For ethyl iodide work, 10 cm cells were employed.

Infrared spectra were taken on a Beckman IR 7. For spectra in potassium bromide micropellets, a Perkin-Elmer model 137 was used.

N. m. r. spectra were taken on a Varian A-60 in benzene, chloroform, carbon tetrachloride, or deuterochloroform. Chemical shifts are expressed relative to tetramethyl silane, normally as internal reference.

Melting points were determined on a Büchi melting point apparatus for the santonin compounds and are uncorrected. For sensitizers and other compounds, a Fisher-Johns or Thomas hot stage was used.

Flash spectroscopy was attempted on a 1.06 x 10^{-4}M solution of lumisantonin in benzene using 21 cm uranyl glass (pyrex window) cells and a flash photoelectric apparatus after Porter and Wright (169) (~ 10^{20} quanta/flash; flash duration ca. 15 μsec). No transients could be detected in the wavelength range 3650-6500 Å.

Mass spectra were obtained on a Consolidated Electrodynamics Corporation instrument. I am indebted to Dr. S. Manatt of the Jet Propulsion Laboratories for these data.

Liquid-liquid Chromatography:

Celite (Johns-Manville (535) was boiled batchwise in concentrated hydrochloric acid for one hour. After the first preparations, it was found equally effective and infinitely more convenient to leave the celite in warm (but not boiling) dilute hydrochloric acid overnight. The acid was then removed using a gargantuan sintered glass funnel and suction flask. There followed two washes with distilled water, after which the acid treatment was repeated. The acid was again removed by filtering off the celite, which was then washed three times with distilled water. The next wash was with a 1:1 mixture of methanol-ethyl acetate. Using the sintered glass funnel and suction flask, cleansing was completed with two water washes, another solvent wash, and finally five washes with distilled water; after which the celite was dried two days in an oven. The support thus prepared was stored in covered containers, but no special effort was made to keep it dry before use. In the particularly dry southern California climate, this procedure proved satisfactory, but precautions might be indicated elsewhere.

Phases were prepared by combining 500 ml nitromethane, one liter heptane (in later work the much less expensive and more readily available hexane was found to be satisfactory), and 200 ml benzene in a 3-liter erlenmeyer flask, and agitating on a shaking machine for at least four hours. The phases were separated in a 2-liter separatory funnel, and the lower phase volume brought back to 500 ml before the next equilibration by addition of fresh nitromethane. Due to slow decomposition of the lower phase on standing in glass containers, it was usually redistilled after each run.

Chromatography was performed at 30.0° (Brinkmann constant temperature bath) in a 2" x 1m thermal-jacketed column. To 320 g celite was added 150 ml lower phase, and the resulting mixture stirred until a consistent, essentially dry texture was obtained. The support was added in heaping tablespoon amounts to the column and tamped down. The charge (usually 2 g) was dissolved in 6 ml of lower phase and transferred to 20 g of celite. After washing with 2 successive 2 ml portions of lower phase, the charge was mixed and added as described for the support. Before chromatography was begun, the column, reservoir (2-liter), and equilibration chamber (2-liter) were equilibrated at 30.0° for at least an hour. The eventual flow rate was approximately 7 ml/min, and cuts of 140 ml were taken. Ultimate consumption of upper phase was 10-12 ℓ per run.

For testing solvent systems, etc., a ½" analytical column was employed. Scaling down was straightforward.

Analyses of all cuts containing ≥ 2 mg were performed by IR and/or v.p.c.

Vapor Phase Chromatography:

Conventional v.p.c. was performed on a Loenco model 15B gas chromatograph equipped with hot wire detector. The flame apparatus was a Perkin-Elmer model 810 dual column instrument. Columns were 6' stainless steel (absolutely necessary at the temperatures involved) coils prepared from $\frac{1}{4}$' (for the 15B) (conventional) or 1/8" tubing (for the model 810). Operating temperature was 220°, and packing 15% Silicone Hi-vac (Dow) by weight on Chromosorb W (Johns Manville) especially treated with hexamethyl disilazane to reduce tailing (supplied by Loe Engineering Co., Altadena, Calif.).

Piperylene analyses were obtained by v.p.c. at room temperature using a 20' x $\frac{1}{4}$" β, β-oxydipropionitrile column.

In the quantum yield and graded sensitizer studies, where v.p.c. was used for analysis, the internal reference was n-octylphthalate. Controls were made to ensure that the reference was stable to prolonged irradiation. It is transparent to light of 3660 Å. Peak areas were integrated directly by a Disc Integrator mounted on the recorder (Texas Instrument Servoriter). Planimetry was sometimes used as a check. Preparative v.p.c. was also attempted using a Wilkins "Autoprep" and a 12' column ($\frac{1}{4}$" o.d.) with 30% packing. Purification was unsatisfactory due to decomposition.

Thin layer chromatography on Silica gel plates using acetone-hexane mixtures was not applicable due to streaking. I am indebted to Dr. Ulrich Sheidegger of these laboratories who determined the value of this approach.

Conventional chromatography using alumina, silica gel, or cellulose, was not successful due to lack of separation. Considerable decomposition occurred, particularly if the column was not carefully wrapped, and the dimeric mixture (E) was more strongly held on alumina and silica gel than was water, i.e. could not be eluted.

Emission spectra were measured in EPA (ether:isopentane: alcohol 5:5:2) or MCIP (methylcyclohexane:isopentane 5:1) glasses at 77°K, using a photoelectric spectrophosphorimeter consisting of a Jarrell-Ash Ebert scanning monochromator (f/6), an EMI 9558 photomultiplier tube, a "rotating can" phosphoroscope, and appropriate recording electronics. A GE AH_4 source was employed along with appropriate Corning glass or interference filters to isolate the group of mercury lines near 3130 Å and 3660 Å.

Irradiations:

For preparative runs (2 g - 2.5 g), a quartz immersion reactor was employed, consisting of an inner well for the light source and sleeve filter with a water cooling system between the inner and outer jackets. Solutions were placed in an outer pyrex vessel protected by a drying tube and equipped with a fritted disc at the bottom, through which nitrogen was bubbled during the irradiation. Oxygen was removed by bubbling in nitrogen for one hour before turning on the lamp. The light source was a Hanovia 200 (654A) high-pressure mercury lamp. Various sleeve filters were used, the most common being pyrex (transmission ~ 10% at 3000 Å) and uranyl glass (cutoff at ~3300 Å). However, control runs showed the reaction to be independent of wavelength so far as products were concerned.

Nitrogen was CIT high-purity dry. Controls in which the gas was passed through activated copper powder, sulfuric acid, phosphorous pentoxide, and Ascarite before reaching the reactor gave identical results.

Kinetics and quantum yields were performed on various apparatuses. Irradiations of santonin in neat piperylene, acceleration by benzophenone (Graph II), and the quantum yield referred to in the table as being by flame v.p.c. were performed on an "optical bench," as described by Moore (170), equipped with a Westinghouse (SAH-800-C) 800-w short arc, medium pressure, mercury lamp. The light output was collected and collimated by mirrors so that parallel beams passed through four 15 mm pyrex tubes mounted in a Beckman DU holder. In order to compensate for differences in location of the tubes, the light source was blocked and the tubes systematically shaken, rotated, and changed in position every 1000 sec (total irradiation, 4000 or 8000 seconds). Corning 737 and O-52 filters were employed to isolate the group of lines at 3660 Å.

For other work, a "merry-go-round" was employed. This consisted of large rings held several centimeters apart by braces, the lower ring being several cm thick. At regular intervals, holes were cut into both rings so that up to 18 sealed tubes (13 mm o.d.) could be mounted. The whole device was immersed in a water bath and rotated. In the center of the wheel was a 450-w Hanovia (679A) lamp in an immersion reactor such as that described for the preparative runs, provided with a pyrex or uranyl glass filter. By means of this device, angular inequalities in light output were cancelled, as were also differences in shape of tube bottoms. For exact work, a specially modified merry-go-round was employed in which the two rings were replaced by a solid block, and each tube was exposed to light only through carefully matched windows. In this way, all tube inequalities were presumably avoided.

Samples were 4 ml for 15 mm tubes and 3 ml for 13 mm tubes. They were delivered by means of a spring-loaded reproducible syringe. This instrument was calibrated with water (by weight) when absolute volumes were required. The reproducibility was checked and found to be satisfactory.

Degassing of sealed tubes was performed on a vacuum line using three freeze-thaw cycles and dry ice/acetone or liquid nitrogen baths, depending on the solvent.

Filter solutions were used when suitable glass filters were unavailable. To obtain the 3130 Å line on the merry-go-round (for triphenylene studies), the immersion well was placed in a large quartz tube containing the filter solution: 690 g $NiSO_4 \cdot 6H_2O$ + 22 g $CoSO_4 \cdot 7H_2O$ diluted to 1 liter. For the isolation of the 4040 and 4358 Å lines, a stock solution of 200 g $CuSO_4 \cdot 5H_2O$ + 268 ml diluted to 800 ml was prepared. The stock was stable indefinitely, but the diluted solution could not be stored. Just before use, a four-fold dilution of the stock solution yielded the filter whose spectral characteristics are summarized in Table 19.

Table 19

λ (mμ)	A	T
370	>3	< 1%
380	1.88	1
390	0.935	12
400	0.525	30
404	0.425	38
436	0.297	51
440	0.344	45
450	0.516	30

This solution was used in conjunction with pyrex or uranyl glass filters for irradiations with low-energy sensitizers, so as to minimize the amount of absorption by santonin and lumisantonin.

Extinctions of santonin and pertinent sensitizers are listed in Table 20.

Table 20

Extinctions in Benzene

Compound	366 mμ	404 mμ	436 mμ
Santonin	15.0	0.13	~0
Lumisantonin	104	1.06	0.57
Mazdasantonin	323	----	----
Benzophenone	63	----	----
Thioxanthone	--	81	0.85
Anthraquinone	--	88	3.2
Michler's ketone	$\sim 10^4$	14	1.92
α-Naphthyl phenyl ketone	--	2.45	0.83
Fluorenone	--	113	42

Actinometry in the optical bench work was performed by Dr. D. Cowan (to whom I am deeply grateful) by the ferrioxalate method (66b, 171). Subsequent studies with Mr. Gary Schnuelle used the benzophenone/benzhydrol actinometer irradiated (172) concurrently with the same tubes.

Quantum Yields: For systems in which the initial absorbance was very high due to addition of sensitizer, v.p.c. was the only acceptable method of analysis. However, for direct irradiations, the Beckman DU was employed. Analysis at several wavelengths permitted a check on the accuracy of the method, which exhibited good precision. The major sources of error are undoubtedly the neglect of the absorptions of H and E in the calculations. Since the latter is not formed to any appreciable extent while conversion is small, and the former undoubtedly has a much smaller extinction than does mazdasantonin at the relatively long wavelengths employed, the approximation is probably valid. A second approximation which may be less acceptable was that B and J had absorption spectra very similar to that of lumisantonin. However, any errors introduced here would be small, since B and J are minor products and certainly have much lower extinctions than mazdasantonin.

Table 21

Extinction of S, LS, and MS

	Benzene				Methyl Naphthalene		
	Santonin	LS	MS		S	LS	MS
345	24.7	166	1220	345	27.4	173	1870
350	24.4	145	700	350	25.7	158	1190
355	20.4	139	459	355	21.6	153	764
360	18.3	145	367	360	20.0	156	542
366	15.0	104	323	366	15.1	114	428

The appropriate equations for quantum yield, assuming photoconversion to be unimolecular and dependent only on the amount of light absorbed, are for santonin (equation 1) and lumisantonin (equation 2).

$$Q_S^B = \frac{7\,S_0\,\ell n\;S_0/S - 6\,(S_0 - S)}{I\,t} \qquad \text{benzene} \qquad (1a)$$

$$Q_S^M = \frac{6.55\,(S - S_0) + (7.55\,S_0 + 19.8\,(MS) + 8.0\times 10^{18})\,\ell n\;S_0/S}{I\,t}$$

methyl naphthalene (1b)

$$Q_{LS}^B = \frac{-1.648\,(LS_0 - LS) + (2.516 \times 10^{22})\,\ell n\;LS_0/LS}{(104)\,(I\,t)} \qquad (2a)$$

$$Q_{LS}^M = \frac{2.104\,(LS - LS_0) + (2.821 \times 10^{20})\,\ell n\;LS_0/LS}{I\,t} \qquad (2b)$$

For methylnaphthalene, the solvent absorption has been included, but constitutes a small correction. For the irradiation of santonin in methylnaphthalene, mazdasantonin has been treated as a constant in deriving equation 1b, which is approximately true, since very little mazdasantonin is formed between samples (e.g. 0.09% at 1 hour); a maximum and minimum quantum yield are then calculated. Except for conversion of santonin amounting to more than 5%, the two values are close.

Hydrogenations were performed on a Pariser hydrogenation apparatus at 40 p.s.i. using a platinum oxide catalyst.

Dinitrophenylhydrazones were prepared by treatment of the ketone in ethanolic solution with Brady's reagent (dinitrophenylhydrazine in ethanol and sulfuric acid). The only exception was the DNP of mazdasantonin, which was prepared either by the above method or by the procedure of Shriner, Fuson and Curtin (173), as a check on the method used by Chapman. The same DNP was obtained in both cases.

3. PRODUCTS

6-Epi-santonin was prepared by treatment of 10 g santonin with 5% hydrochloric acid/dimethylformamide solution. Chromatography over 100 g alumina (grade III) with benzene as eluent isolated 4.3 g (43%) 6-epi-santonin. Recrystallization from ethyl acetate gave wart-like crystals, m.p. 105° (lit. 105° (28a); 103-4° (28b)). The infrared spectrum in chloroform exhibited major peaks in the carbonyl region at 1777, 1663, 1634, and 1613 cm^{-1} (lit. (chloroform): 1765, 1660, 1628, 1607 cm^{-1} (28a)); $[\alpha_D]^{CHCl_3} = -306°$ (lit. -332° (28a); -288° (28b)).

The dinitrophenylhydrazone was crystallized from chloroform/ethanol to give scarlet hexagons, m.p. 244-248.5° (dec.), (lit.

249-256° (28b)). The absorption maximum in chloroform fell at 394 mμ (log ε = 4.58), (lit. 393 mμ (log ε = 4.49)).

Mazdasantonin was obtained and purified from irradiations of liquid-liquid chromatography. After two crystallizations from acetone/hexane, the compound was isolated as yellow prisms, m.p. 118.2-119.0°. The ultraviolet spectrum consisted only of one intense peak at 318 mμ (log ε = 3.89). The infrared spectrum had three strong absorptions in the carbonyl region at 1781, 1661, and 1629 cm^{-1} in potassium bromide (1783, 1666, and 1632 cm^{-1} in chloroform).

Analysis: Calc.: C, 73.17; H, 7.14.
Found: C, 72.99, H, 7.32.

The dinitrophenylhydrazone was crystallized three times from chloroform/ethanol to give red-orange plates, m.p. 240.8-241.0° (dec.). On mixing this dinitrophenylhydrazone with a sample supplied by Dr. Chapman, the melting point was severely depressed, m.p. 219-223°. Numerous differences were also apparent in the infrared spectra of the two compounds, particularly in the fingerprint region. The major absorption of the ultraviolet spectrum (in chloroform) was at 403 mμ (log ε = 4.18).

Analysis: Calc.: C, 59.15; H, 5.16; N, 13.14.
Found: C, 58.76; H, 5.30; N, 13.06.

6-Epi-mazdasantonin was prepared from mazdasantonin (~ 10 mg) by treatment for two hours at room temperature with a mixture of one ml of concentrated hydrochloric acid and 2 ml of glacial acetic acid. The solution was diluted with water, neutralized with saturated sodium carbonate solution, extracted twice with chloroform, and dried over magnesium sulfate. This product was not crystallized. The ultraviolet spectrum in chloroform showed a shift of the single absorption to 307 mμ (lit. 308 mμ in ethanol (6)); and the carbonyl stretching frequency had been displaced from 1666 to 1670 cm^{-1} in chloroform.

The dinitrophenylhydrazone was crystallized from chloroform/ethanol to give scarlet plates, m.p. 225°; mixed m.p. with Chapman's compound, 225° (lit. 226° (6)). The infrared spectrum was superimposable on that of Chapman's dinitrophenylhydrazone.

H was prepared by two methods.

1) Pyrolysis: Lumisantonin (502 mg) was heated in a sealed, degassed ampoule at 200° (Wood's metal bath) for one hour. Liquid-liquid chromatography of the residual oil recovered 334 mg (67%) lumisantonin. The remainder, 172 mg (34%), was impure H.

2) Photolysis: Liquid-liquid chromatography of photolysis mixtures from santonin or lumisantonin irradiations (6-20 hours) gave isolated yields of H of 5-10%. The product was a colorless oil which did not crystallize from any of the solvents tested.

The infrared spectrum (taken from a film) showed the γ-lactone at 1783 cm^{-1} and the carbonyl at 1753 cm^{-1}. In chloroform, these absorptions were shifted slightly to 1781 and 1755 cm^{-1}. In the latter solvent, there was also a weak absorption at 1638 cm^{-1} (double bond).

When H was passed through alumina (Woelm neutral alumina, II), it was converted to pyrolumisantonin, which showed absorptions at 1779 and 1716 cm^{-1} in potassium bromide (lit. 1715 cm^{-1} (8b)). Catalytic hydrogenation of either H or pyrolumisantonin gave the same product. The infrared spectra of the two hydroproducts were totally superimposable, and showed major peaks at 1770 (γ-lactone) and 1735 cm^{-1} (cyclopentanone) in potassium bromide (lit. 1770, 1730 cm^{-1} (8b)).

B was isolated from irradiations of santonin or lumisantonin for 3-20 hours in yields of 1-3%, by liquid-liquid chromatography. B was recrystallized from acetone/hexane four times to give colorless prisms, m.p. 174.4-175.0°. The ultraviolet spectrum is quite similar to that of lumisantonin, but the long-wavelength maximum is less intense. The major absorptions in ethanol are at 244 mμ ($\log \epsilon = 3.67$) and 338 mμ ($\log \epsilon = 2.01$). The only important peaks in the carbonyl region are at 1791 (γ-lactone) and 1697 cm^{-1} (cyclopentenone) in potassium bromide.

Analysis: The analysis was performed on different samples by two analytical laboratories. The results are consistent, but do not correspond to an empirical formula of $C_{15}H_{18}O_3$.

Calculated: C, 73.17; H, 7.32.

Found: C, 69.13, 69.39, 68.83; H, 6.88, 7.31, 6.95.

These results demand an empirical formula of $C_{15}H_{18}O_4$. However, it is difficult to imagine how lumisantonin could have been oxidized under the experimental conditions. Furthermore, the starting material had been purified; thus, B is not likely to be a result of an impurity. Finally, the mass spectrum of B showed the parent peak at $m/e = 246 \pm 1$, which requires that B is an isomer of lumisantonin and rules out the empirical formula $C_{15}H_{18}O_4$. I have no explanation of the bad analysis.

B was reduced to its dihydroproduct by catalytic hydrogenation. This substance showed maxima in chloroform at 1776 and 1715 cm^{-1}.

J was prepared as was B, and was isolated in approximately equal yield. It was a colorless oil which was soon oxidized by air to a yellow-green goo. Its major ultraviolet maximum was at 237 mμ is ethanol; but this figure is somewhat uncertain due to the very real possibility of absorption by impurities. The shape of the ultraviolet spectrum was very like that of B and lumisantonin. The infrared spectrum showed peaks in the carbonyl region at 1803 (γ-lactone) and

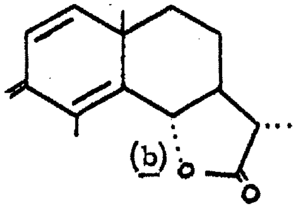
1700 cm^{-1} (cyclopentenone) in carbon tetrachloride. These peaks were shifted to 1777 and 1715 cm^{-1} in chloroform. Catalytic hydrogenation produced the dihydroproduct which absorbed in the infrared at 1773 and 1714 cm^{-1} (in chloroform).

Lumisantonin was prepared by irradiation of 15 g santonin for two hours in 750 ml ethanol. The lumiproduct was separated from unreacted santonin (8 g) and photosantonin by chromatographing twice on 200 g portions of alumina (II). The yield was 3.2 g (46% based on reacted santonin). A better light source for this preparation would have been a low-pressure (germicidal) lamp,which has its main output at 2537 Å . At this wavelength, the extinction coefficient of santonin is ten times that of lumisantonin. The high-pressure lamps employed have their major light output at 3660 Å, where the extinction coefficient of lumisantonin is seven times that of santonin. Considerable lumisantonin must certainly have been lost by further photolysis under the experimental conditions.

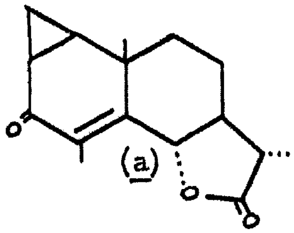
Three recrystallizations from acetone/hexane gave colorless prisms, m.p. 153-155°. The ultraviolet spectrum in ethanol showed two major absorptions at 237 mμ ($\log \epsilon = 3.70$) and 342 mμ ($\log \epsilon = 2.37$). The infrared spectrum showed three peaks in the carbonyl region at 1777, 1710, and 1575 cm^{-1}. Catalytic hydrogenation yielded a dihydroproduct with only two absorptions in the carbonyl region. These came at 1778 and 1716 cm^{-1} in chloroform (lit. 1775, 1710 cm^{-1} (8b)).

E has only two major peaks in the infrared region at 1778 and 1718 cm^{-1}. The hydroproduct shows a strong peak at 1781 and a very broad absorption, which possibly arises from two peaks at approximately 1720 and 1730 cm^{-1}.

The Wittig product from santonin was prepared by subjecting 10 g santonin to the Wittig process as modified by Corey (174). Only qualitative results were sought, and no product yields were determined. The only product isolable from chromatography on 200 g alumina (II) formed white needles when crystallized from hexane, m.p. 179.5-182 and 186-188°. This product is obviously not the expected triene, as it shows a carbonyl absorption in the infrared spectrum (1765, 1666, and 1637 cm^{-1} in potassium bromide) and gives a positive test for a carbonyl when treated with dinitrophenylhydrazine. The normal methylene vibration (885-895 cm^{-1}) is not present. The major absorption in the ultraviolet spectrum is at 244 mμ. This agrees with the cyclopropyl ketone (a) but not the triene (b), for which the calculated maxima are 245 and 229 mμ, respectively (110b). The formation of cyclopropyl rings from the Wittig reaction with hindered α,β-unsaturated ketones is well-established (175).



(b)



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16. Note that this product is formed by scission of the cyclopropane C-5 C-10 bond as in the formation of H.

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PROPOSITION 1

The complex process of mammalian metabolism has long been the subject of intensive study (1). Gradually, a cohesive picture has been emerging in which cholesterol (1) holds a central position. Cholesterol is the goal of several biogenetic pathways in mammals, and also serves as the precursor of other substances of physiological importance, including the bile acids and various hormones.

The major pathway of cholesterol metabolism in mammals leads to the bile acids. Of these, the two main primary ones are cholic acid (2) anc chenodeoxycholic acid (3). Other bile acids are also formed from catabolism of cholesterol, but the only further ones pertinent to this proposition are deoxycholic (4) and lithocholic acids (5).

The conversion of cholesterol to cholic acid involves three processes in addition to degradation of the side chain: hydroxylation of the nucleus, reduction of the Δ^5 double bond, and epimerization of the 3β hydroxy group. The sequence in which these transformations are carried out remains unknown, although it has recently been implied that hydroxylation precedes everything else, and that hydroxylation at C-7 precedes hydroxylation at C-12 (2).

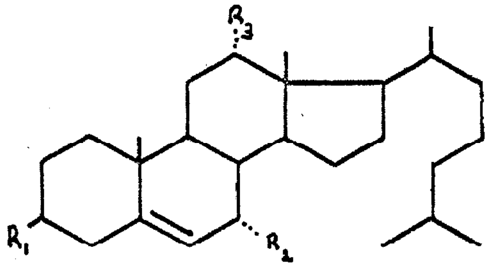
An examination of the literature indicates that a plausible sequence may be predicated on what is already known, and, further, that in all probability, at least two distinct pathways exist. The pertinent data are presented in the table. A + means that the substance indicated is metabolized to cholic acid; a - means that it is not; and a * denotes that this particular compound has been shown to be a metabolite of cholesterol.

Compound	±	Reference
cholest-5-ene-3-one (6)	-	3
3β-hydroxy-Δ^5-cholenic acid (7)	-	4
5β-cholestane-3β-ol (8)	-	5
epicholesterol (9)	-	5, 6
deoxycholic acid (4)	+	7
lithocholic acid (5)	-	3, 7
chenodeoxycholic acid (3)	-	3, 7
cholest-4-ene-3-one (10)	-	3, 5
7α-hydroxycholesterol (11)	+ *	8 9
5β-cholestane-3α, 7α-diol (12)	+	10
5β-cholestane-3α, 7α, 12α triol (13)	+ *	11 12
3α, 7α, 12α-trihydroxycoprostanic acid (14)	+ *	13 14
12α-hydroxycholesterol (15)	+	15

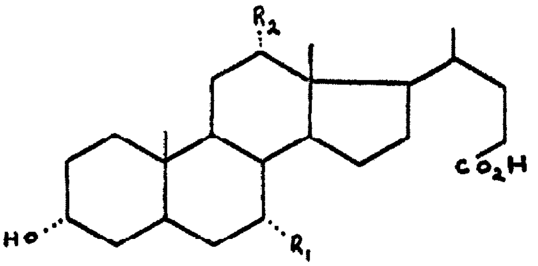
In view of the well established anchimeric assistance to solvolysis in cholest-5-ene systems (16), it is reasonable to anticipate some role for the double bond in the epimerization of the 3β hydroxyl group. Such a view is strengthened by the observation that the cholic-

Figure 1

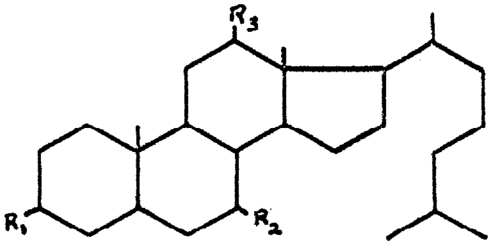
Pertinent Compounds



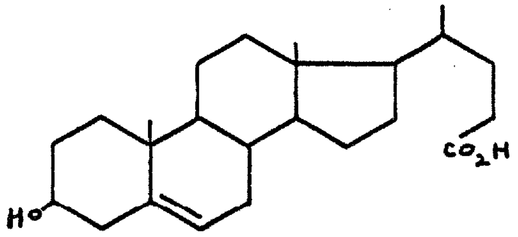
--cholesterol (<u>1</u>)
$R_1 = \beta$ - OH ; $R_2 = R_3 = H$
--epicholesterol (<u>9</u>)
$R_1 = \alpha$ - OH; $R_2 = R_3 = H$
--7α -hydroxycholesterol (<u>11</u>)
R_1-β - OH; R_2 = OH; $R_3 = H$
--12α - hydroxycholesterol
R_1 = B - OH; R_2 = H; R_3 = OH
--7α, 12α -dihydroxycholesterol (<u>17</u>)
R_1 = B - OH; $R_2 = R_3$ = OH



--cholic acid (<u>2</u>)
$R_1 = R_2$ = OH
--chenodeoxycholic acid (<u>3</u>)
R_1 = OH; R_2 = H
--deoxycholic acid (<u>4</u>)
R_1 = H; R_2 = OH
--lithocholic acid (<u>5</u>)
$R_1 = R_2 = H$



--5β-cholestane-3β-ol (<u>8</u>)
$R_1 = \beta$-OH; $R_2 = R_3 = H$
--5β - cholestane-3α, 7α-diol (<u>12</u>)
$R_1 = R_2 = \alpha$ - OH; R_3 = H
--5β - cholestane-3α, 7α, 12α-triol (<u>13</u>)
$R_1 = R_2 = R_3 = \alpha$-OH



--3β-hydroxy-Δ^5-cholenic acid (<u>7</u>)

deoxycholic interconversion in rat liver proceeds through an olefinic intermediate (17). This suggests that epimerization may proceed via removal of the 3β hydroxy with anchimeric assistance from the double bond rather than by oxidation to a ketone followed by reduction to the 3α-ol. This expectation is further supported by the fact that cholest-5-ene (10) and 5β-cholestane-3β-ol (8) do not metabolize to cholic acid. Consequently, the double bond is instrumental to the epimerization step, and therefore epimerization must occur before reduction.

A second conclusion is that degradation of the side chain must come near the end of the sequence. The acid formed by direct degradation of the side chain, 3β-hydroxy-Δ^5-cholenic acid (7), does not metabolize to cholic acid, thus demonstrating that at least some nuclear transformations must precede degradation of the side chain. Moreover, lithocholic (5) and chenodeoxycholic (3) are not convertible to cholic acid in any system studied, but the 5β-cholestanes (12)-(14) are. It is tempting to presume that all processes in the nucleus are complete before degradation of the side chain begins. This is not, however, required by the data, since one bile acid, deoxycholic (4), can be converted to cholic acid either by the rat or rabbit (7).

One further conclusion can be drawn from the data in the table. Since 3α-cholesterol (9) is not converted to cholic acid, it follows that epimerization cannot be the first step.

The following facts are clear: 1) some transformation of the nucleus must precede degradation of the side chain; 2) hydroxylation must precede epimerization; and 3) epimerization must precede reduction. Thus, the first step in the metabolic conversion of cholesterol to cholic acid must be hydroxylation.

There are only two positions for hydroxylation. Both 7α-hydroxy-cholesterol (11) and 12α-hydroxy-cholesterol (15) are metabolized to cholic acid, but only the C-7 isomer has as yet been shown to be a metabolite of cholesterol. In view of the difficulties inherent in isolation of metabolic products, the possibility of an initial hydroxylation at C-12 cannot be excluded. There are, therefore, two possible pathways from cholesterol to cholic acid, one beginning from 7α-hydroxylation and the other involving a primary hydroxylation at C-12. If both positions were hydroxylated before any further processes occurred, then the two paths would be indistinguishable. However, the fact that deoxycholic acid (4) can be hydroxylated to cholic acid suggests that the metabolic pathway via 12α-hydroxy cholesterol could involve degradation of the side chain before the 7α-hydroxyl group is added. On the other hand, chenodeoxycholic acid (3) is not converted to cholic acid, so that the pathway starting from 7α hydroxylation must complete all nuclear transformations before degradation of the side chain; i.e. proceed via 5β-cholestane-3α, 7α, 12α-triol (13), one of the compounds known to be metabolites of cholesterol.

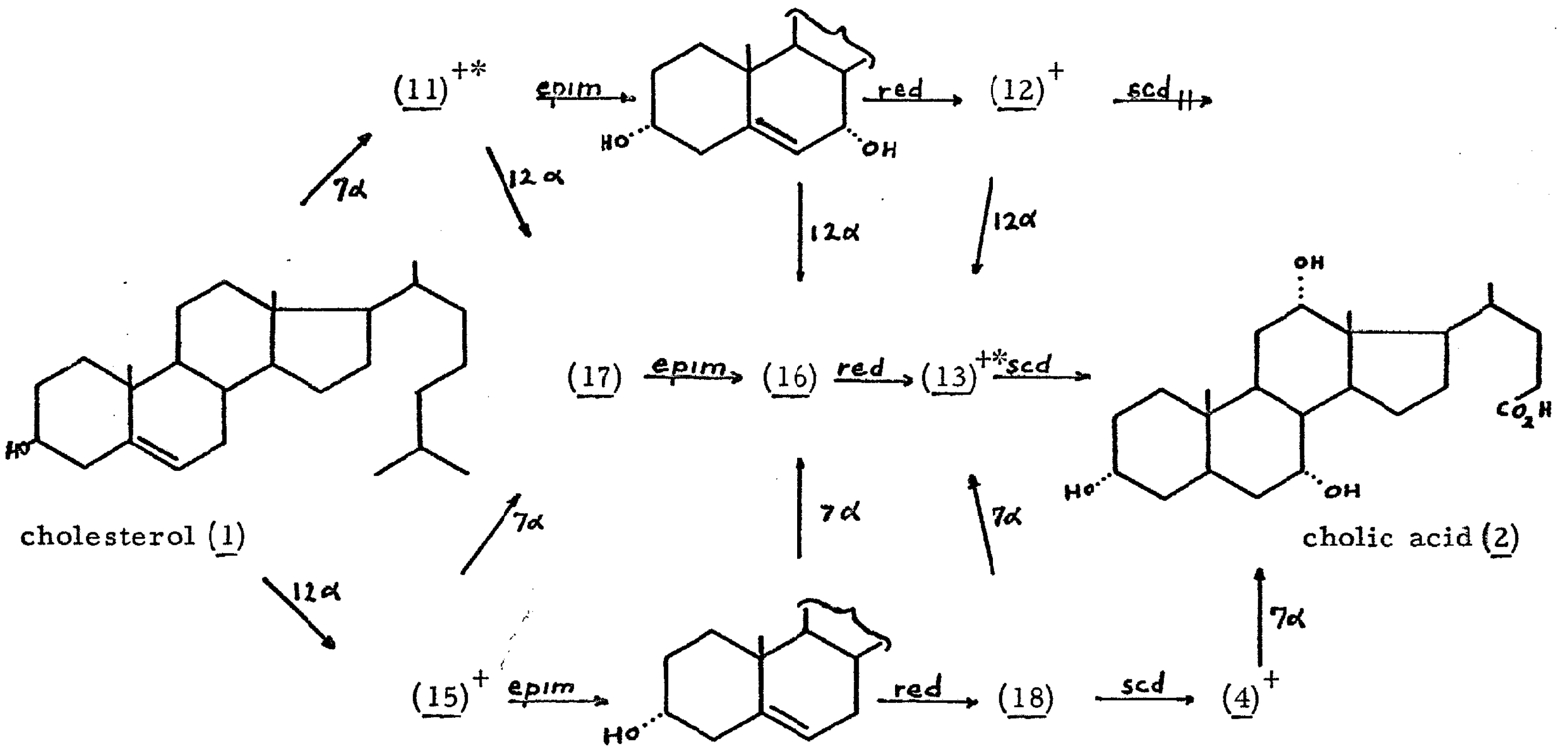
The possible pathways are summarized in Figure 2. The superscripts have the same meanings as in the Table. Of particular significance is the fact that the metabolism of 12α-hydroxycholesterol to cholic acid is known to be able to proceed via deoxycholic acid (15).

The known chemistry is sufficient to define two possible pathways as very likely operative, A and B. The possibility of a deviant path from 12α-hydroxy cholesterol to cholic acid via 5β-cholestane-3α, 12α-diol followed by 7α hydroxylation before side chain degradation cannot be decided from the present data.

As is evident from the figure, all remaining possibilities must proceed through the same intermediate, cholest-5-ene, 3α, -7α 12α-triol (16). It is therefore proposed that the metabolism of this compound both in intact rats and in liver mitochondria be investigated.

If cholic acid is a metabolite of (16), then the most likely formation would be the path in which hydroxylation is complete before the other nuclear transformations, by analogy with paths A and B, where hydroxylation does not intervene between epimerization and reduction. On the other hand, should cholic acid not be a

Figure 2. Summary of Reaction Paths



Code:
epim = epimerization of the 3β hydroxyl group
red = reduction of the Δ^5 double bond
scd = side chain degradation
7(12)α= α-hydroxylation at C-7 (12)

metabolite of (16), then the entire middle path is eliminated. In that case, 5β-cholestane-3α, 7α, 12α-triol could arise from the metabolism of 12α-hydroxy cholesterol only by 7α hydroxylation of 5β-cholestane-3α, 12α-diol, and isolation of the triol would then prove the existence of the deviant path from 12α-hydroxy cholesterol.

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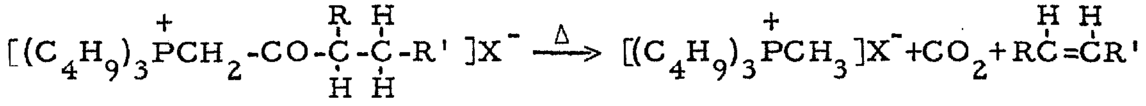
PROPOSITION 2

Summary: A mechanism is proposed for the reaction:

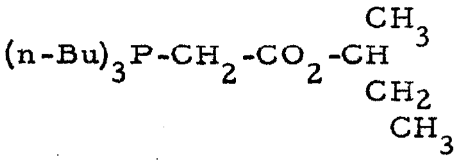
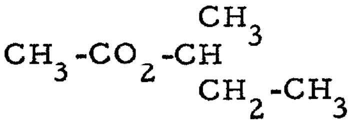
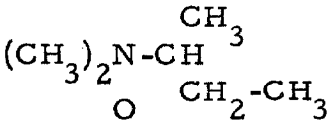
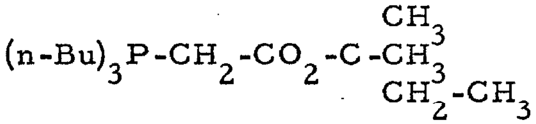
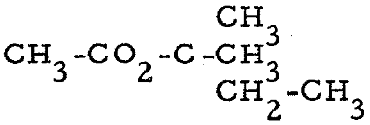


$$[(C_4H_9)_3\overset{+}{P}CH_2\text{-}CO\text{-}\underset{H}{\overset{R}{C}}\text{-}\underset{H}{\overset{H}{C}}\text{-}R']X^- \xrightarrow{\Delta} [(C_4H_9)_3\overset{+}{P}CH_3]X^- + CO_2 + R\overset{H}{C}=\overset{H}{C}R'$$

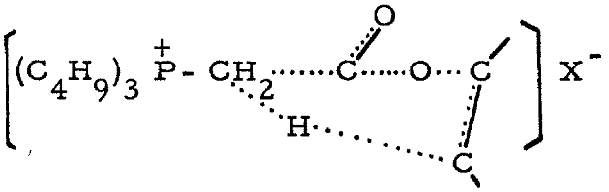
Denney (1) has recently investigated a "new" ester pyrolysis (first reported without product analysis by Michaelis (2)), which appears to proceed in some manner other than that followed by acetates and amine oxides. For one thing, carbon dioxide and the phosphonium salt were formed rather than the usual acid. Moreover, a striking difference in reaction conditions was observed, with convenient rates being obtained at temperatures as much as 250°C below those required for the pyrolysis of the corresponding acetates. Further (although the authors did not specifically make this point), the olefin product distribution appears to be controlled thermodynamically rather than kinetically. Their data are compared with those from the usual acetate and amine oxide procedures in Table 1.

It seems very likely that a change of mechanism has occurred in going from acetates to phosphonium salts. Denney *et al.* suggest a concerted process in which the transition state is to be considered as the cyclic structure I

Table 1

Pyrolysis of	Temp.	Distribution	Ref.
 $(n\text{-}Bu)_3P\text{-}CH_2\text{-}CO_2\text{-}CH(CH_3)CH_2CH_3$	170°	1-butene (33%) *cis*-2-butene (19%) *trans*-2-butene(48%)	1
 $CH_3\text{-}CO_2\text{-}CH(CH_3)\text{-}CH_2\text{-}CH_3$	450°	1-butene (57%) *cis*-2-butene (15%) *trans*-2-butene(28%)	3, 4, 5
 $(CH_3)_2\underset{O}{N}\text{-}CH(CH_3)\text{-}CH_2\text{-}CH_3$	150°	1-butene (67%) *cis*-2-butene (12%) *trans*-2-butene(21%)	6
 $(n\text{-}Bu)_3P\text{-}CH_2\text{-}CO_2\text{-}C(CH_3)(CH_3)\text{-}CH_2\text{-}CH_3$	140°	2-Me-1-butene(32%) 2-Me-2-butene(68%)	1
 $CH_3\text{-}CO_2\text{-}C(CH_3)(CH_3)\text{-}CH_2\text{-}CH_3$	400°	2-Me-1-butene(76%) 2-Me-2-butene(24%)	3, 7

- -

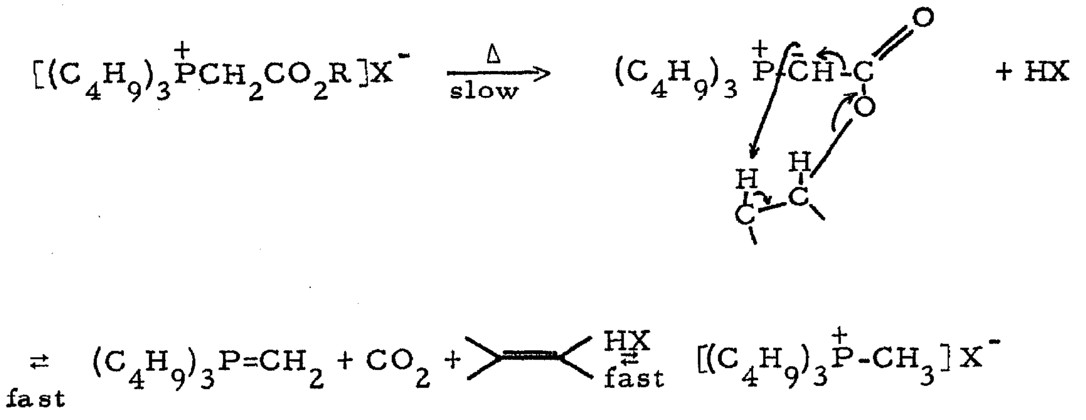


I

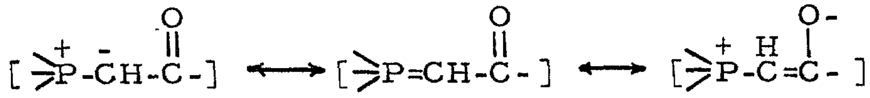
It is not specifically indicated whether the hydrogen being transferred is a proton or a hydride. If it is a proton, we are envisaging the shift of a positively charged particle to a center flanked on either side by electron-withdrawing groups. This center should be quite positive and the acidity of the methylene protons (vide infra) supports this view. Clearly, a proton transfer cannot be the interpretation of choice.

On the other hand, suppose the transferred protium is a hydride. In this case, we would expect those substituents on phosphorous which render the methylene moiety more positive to enhance the yields. It has been shown in ultraviolet spectral studies of various phenyl (8) and aryl (9) derivatives of group IV and V elements, as well as in studies of aryl phosphoric and phosphinic acids (10), that benzenoid rings have essentially no resonance interaction with tetracovalent phosphorous. Hence, any influence by phosphorous substituents on the charge distribution around the methylene must be attributed to inductive effects; and electron-withdrawing substituents should lead to the best yields. In fact, however, "the best yields and mildest reaction conditions were found with salts, $(C_4H_9)_3\overset{+}{P}-CH_2CO_2R'X$" (1).

These difficulties may be resolved by the following mechanism:



The particular type of ylide proposed is known to be much more easily prepared than most others, requiring only acqueous sodium hydroxide as the base rather than the usual phenyl- or butyllithium (13). This unusual stability is attributed to resonance with the carbonyl function as well as with the d-orbitals of phosphorous.



$$[\,{>}\overset{+}{P}\text{-}\overset{-}{C}H\text{-}\overset{\overset{O}{\|}}{C}\text{-}] \longleftrightarrow [\,{>}P{=}CH\text{-}\overset{\overset{O}{\|}}{C}\text{-}\,] \longleftrightarrow [\,{>}\overset{+}{P}\text{-}\overset{H}{C}{=}\overset{\overset{O-}{|}}{C}\text{-}\,]$$

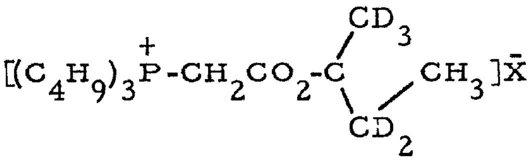
This stability is lost when the connection with the carbonyl is severed. The resulting ylide $(C_4H_9)_3P{=}CH_2$, which is notoriously unstable in the presence of acid or even hydroxylic solvents (11, 12), would immediately add HX to give phosphonium salt, the observed product. The work of Jaffé and Rao <u>et al</u>. predicts that substituents on phosphorous which increase the amount of negative charge on carbon (by decreasing the formal charge on phosphorous and thus weighting resonance structure A) will give the better yields. This

$$[\geqslant\overset{+}{P}\text{-}\overset{-}{C}H\text{-}] \longleftrightarrow [\geqslant P{=}CH\text{-}]$$

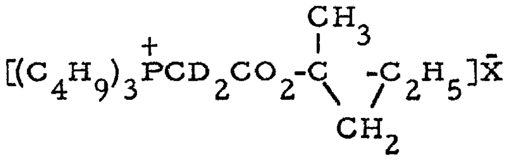
A B

prediction is observed to hold in the present case, and has recently been borne out by the work of Johnson and LaCount (14), who found that in the reaction of fluorenylides with various carbonyl functions, the tri-n-butyl compound was far superior to its triphenyl analogue.

The two mechanisms differ in the very basic respect of which C-H bond is being broken in the rate-determining step and a simple experiment should suffice to decide between them. If the compounds



and



were to be pyrolyzed, the mechanism of Denney predicts a kinetic isotope effect for the first but not the second salt, whereas the mechanism proposed here reverses that order.

This reaction is of particular synthetic interest since it will, should be prove generally applicable, provide a means of extending ester pyrolysis far beyond the boundaries presently set upon it by temperature requirements (15).

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PROPOSITION 3

Recently, Majer, Capey, and Robb (1) reported the application of Golay columns and v.p.c. to separate benzene and cyclohexane from their perdeutero analogues. The results obtained are most impressive and illustrate again the enormous potential of Golay columns as analytical tools. However, the first application by Majer *et al.*, analysis of the products from the reactions of cyclohexane and benzene with methyl radicals or carbene, gave results *directly contrary to all published experience.* These results are presented in Table 1.

Table 1. Isotope Effects after Majer, Capey, and Robb (1)

	k_H/k_D
Methylene insertion in cyclohexane	0.7
Hydrogen abstraction from cyclohexane by methyl radical	0.37
Mercury photosensitized decomposition of cyclohexane	2.7
Reaction of methyl radicals with benzene	0.73

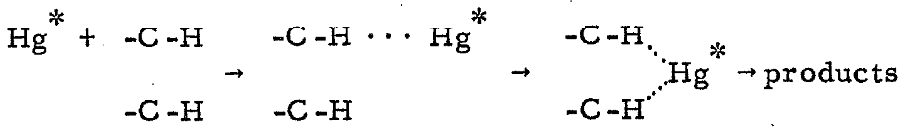
The mercury photosensitized decomposition of cyclohexane is the only entry which shows a normal isotope effect in the proper range for this type of reaction (2a). However, a word of comment is necessary because the postulated mechanism is wrong. The reaction is interpreted as proceeding via energy transfer followed by fragmentation of excited cyclohexane.

$$C_6H_{12} + Hg(^3P_1) \rightarrow C_6H_{12}^* + Hg(^1S_0)$$

$$C_6H_{12}^* \rightarrow C_6H_{11} + H$$

Since all the electrons of cyclohexane are committed to bonding orbitals, the only possible excitation is $\sigma \rightarrow \sigma^*$. In cyclohexane, this transition requires at least 156 kcal/mole (2b), and even the $\sigma \rightarrow \sigma^*$ triplet energy is probably much higher than the 112.7 kcal/mole available from excited mercury (2a). If, on the other hand, the excited cyclohexane is considered to be in an upper vibrational level of the ground state, then almost all the excitation energy would have to be concentrated in a single vibrational mode in order to break the C-H bond (D secondary C-H ~ 96 kcal/mole) (3). Since loss of vibrational energy is a very fast process even in the gas phase, this mode of decomposition is statistically unlikely.

In their discussion of mercury photosensitization(2), Gunning and Strausz conclude that the mode of energy transfer from excited mercury atoms to paraffins involves interaction between mercury and the C-H bond directly. Thus,



$$Hg^* + \begin{matrix}-C-H\\-C-H\end{matrix} \rightarrow \begin{matrix}-C-H \cdots Hg^*\\-C-H\end{matrix} \rightarrow \begin{matrix}-C-H\\-C-H\end{matrix}\!\!\vdots Hg^* \rightarrow \text{products}$$

The isotope effect arises not from bond-breaking, but rather from the difference in quenching efficiencies of the deutero and protio compounds. The rate-determining step is presumed to be the formation of the linear complex, and the isotope effect is attributed to the disappearance of the C-H bond's stretching and bending modes in the transition state. Gunning and Strausz have calculated the quenching cross-sections for a number of protio and deutero compounds and predict larger values for the undeuterated compounds in agreement with experiment (4).

Thus, even in the case where they have obtained a reasonable result, Majer _et al_. grossly misunderstood its origin.

The results from methyl or methylene attack on cyclohexane or benzene are not so reasonable. These conflict with all previous studies and therefore constitute extremely interesting experiments.

The explanation advanced for the observed inverse isotope effects in the reactions of cyclohexane with methyl radical or methylene is as follows:

> "In the methylene reaction and hydrogen abstraction by methyl radicals, an inverse isotope effect is indicated. In these two reactions, however, a secondary C-H bond is broken and a primary C-H bond is formed. Thus both these reactions are exothermic and if the exothermicity of the reaction for the C-D bond interchange is greater than that for the C-H bond interchange, then perdeuterocyclohexane would be expected to disappear more rapidly from the reaction system."

This statement is suitably vague, but appears to be wrong, regardless of interpretation. On the surface, it appears to state simply that the reaction course is determined entirely by the energy content of the reactants and products, despite the fact that hydrogen abstraction by methyl radical or carbene is certainly not an equilibrium process. This contention is obviously not true, as any kinetically controlled reaction (Birch reduction, acetate pyrolysis, etc.) will illustrate.

A considerably more subtle interpretation of this statement is that if the transition state looks considerably like products, then the energy gain in the bond-breaking, bond-making process lowers the activation energy and helps the reaction along. However, this condition will be more nearly satisfied as the reaction becomes less exothermic rather than more so (5).

The rationalization given for these results is clearly unacceptable. The question now arises whether the results themselves are. As already mentioned, the observed isotope effect for the mercury sensitized decomposition of cyclohexane is normal. We now turn to the remaining cases.

The isotope effect in hydrogen abstraction arises from the fact that in the transition state for the reaction, the C-H bond is being broken. As the bond is progressively stretched, the difference in zero-point energy between the initial C-H and C-D bonds becomes less and less, eventually reaching zero when the bond is completely broken. This case in which bond-breaking is completed and bond-making is essentially uninitiated in the transition state results in the maximum isotope effect, since the difference in the activation energies now includes the total zero-point energy difference from the ground state, 1.3 kcal/mole. If some bond-making also occurs before the transition state is reached, then the zero-point energy difference exists again in the products and the change in this quantity on going from the ground state to the transition state is less than the maximum. This simple explanation predicts an isotope effect ranging from zero to some maximum value (~8 at 25°C if the pre-exponential factors are the same) for a hydrogen abstraction reaction, but the k_H/k_D ratio should always be greater than or equal to unity (a positive isotope effect).

Representative isotope effects are collected in Table 2 for hydrogen atom abstraction by methyl radical from various substrates. Note that they are generally high, and always positive in contrast to the second entry in Table 1.

Table 2

Substrate[a]	Temperature	k_H/k_D	Reference
Ethane	150°C	6.3	6
$C\underline{H}_3NH_2$	"	7.2	7
$C\underline{H}_3OH$	"	6.8	8
$CH_3\underline{C}H_2CH_2CH_3$	400°C	5.1	9

[a] The hydrogen abstracted is underlined

The reaction of methyl radicals with benzene is a slightly different case. For the abstraction reaction, the above considerations apply and a positive isotope effect is anticipated. However, the major reaction of methyl radical with benzene is not abstraction but addition (10) to form a substituted cyclohexadienyl radical (referred to as a "complex" in reference 1). This species is very reactive and then undergoes a variety of reactions; but the isotope effect, if there is one, is determined in the slow addition process. In this case, whether the substrate is deuterated or protiated should be of relatively little consequence, since no C-H bonds are broken or even significantly stretched in the transition state.

Protium has a slightly larger amplitude of vibration than deuterium due to its lower mass, and would thus be sterically more likely to hinder an approaching reagent. On the other hand, the electron repelling character of protium is slightly greater than that of deuterium (11), so that the ring would be slightly more attractive to an electrophilic reagent in the undeuterated case. Both these effects are minuscule, and moreover oppose each other; hence one would not expect any significant isotope effect for this type of reaction.*

The only anticipated isotope effect for the reaction of methyl radical with the two benzenes would be that arising from the abstraction process, and thus the overall isotope effect would be predicted to be positive in contrast to the fourth entry in Table 1.

The nature of the insertion reaction by methylene is not clearly understood at present, despite considerable thought (13). However, insofar as the reaction involves the breaking of a C-H bond, the usual considerations apply and C-H should react more easily than C-D due to the zero-point energy argument. This expectation is borne out in the reported cases. The insertion of methylene into secondary C-H bonds has a reported k_H/k_D ratio of 1.3 (14), and the corresponding ratios for insertion into allylic and vinylic bonds are 1.96 and 1.55, respectively (25°C) (15), in contrast to the first entry in Table 1.

The results of Majer, Capey, and Robb are thus truly extraordinary in that they cannot be explained by the generally accepted

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* An experiment to test the inductive influence of protium vs. deuterium in aromatic substitution reactions showed no isotope effect (12).

rationalization of the kinetic isotope effect, and, further, that they conflict with all published experience. In view of the enormous potential importance of such iconoclastic data, the author proposes that a thorough reinvestigation of these results be made, employing established analytical techniques, both mass spectrographic (7) and capillary v.p.c. (16). Needless to say, I am considerably encouraged in my skepticism by the charming naiveté of the authors.

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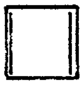
PROPOSITION 4

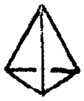
Cyclobutadiene (1) is one of the oldest puzzles in organic chemistry. During the last century, various workers throughout the world have attempted the synthesis of this elusive hydrocarbon, but it has withstood the assault of even the most redoubtable practitioners of the chemical art (1). As other fortresses fall, e.g. cubane (2), the continued inaccessibility of cyclobutadiene becomes ever more intriguing.

Planar cyclobutadiene has been discussed many times since the simplest LCAO treatment (3) led to a triplet ground state showing orbital degeneracy. It was concluded that this electronic distribution should lead to rearrangement in non-linear molecules (4). Subsequently, Moffit (5) did a more refined calculation for the system and decided that the two pairs of degenerate orbitals predicted by the simple LCAO method were in fact split into four levels, all very close in energy, but non-degenerate. Still, such an arrangement approximates that from the simple LCAO method sufficiently well that distortions would be expected to be favored which could produce new sets of levels where the filled orbitals are at lower energy and the unfilled orbitals at higher energy (4) than in the planar arrangement.

A planar distortion would most likely lead to acetylene. Lipscomb (6) has been very nearly alone in considering the possibility that a non-planar distortion might also stabilize cyclobutadiene relative to the planar form. Such a distortion would give rise to the tetrahedral, closed-shell hydrocarbon (2), hereafter referred to as tetrahedrane.



(1)

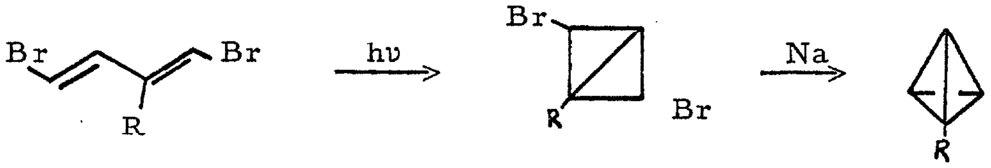


(2)

Lipscomb had two main reasons for considering this possibility. One was the fact that cyclobutadiene can be isolated as a silver complex (7). Lipscomb felt that considerable stabilization might be effected by distortion to a tetrahedral structure in the silver complex where individual silver ions are possibly coordinated with only one of the double bonds in each ring. This view does not appear to have been borne out (8a), and there is no present indication that the ring is non-planar in the metal complexes of cyclobutadiene or its derivatives (8).

Lipscomb's second reason for suggesting the desirability of the non-planar distortion was the existence of the known B_4Cl_4, in which the electronic configuration was essentially the same as that postulated for cyclobutadiene, and which assumed a stable tetrahedral structure. The fact that B_4Cl_4 existed and was stable whereas B_4H_4 was unknown has been attributed (9) to interaction of the lone pairs on chlorine with the unfilled orbitals in the tetrahedral structure. Thus, the unfilled orbitals cannot be very high energy and are probably weakly bonding. Since the corresponding orbitals in tetrahedrane would already be filled, Lipscomb suggested that substitution by electron-withdrawing groups might significantly stabilize the tetrahedral structure.

The recent work on highly strained small ring hydrocarbons suggests a simple two step synthesis to tetrahedrane and its substituted analogues. Photochemical ring closure of the appropriately substituted 1,3-butadiene (4) would lead to the bicyclobutane (5) (10), which could then be coupled internally by reaction with sodium (11). In this fashion, the possibility of an immediate planar distortion to acetylene is circumvented, if indeed this has been a major reason for the failure of past attempts to synthesize the planar molecule.



(4) (5) (2)

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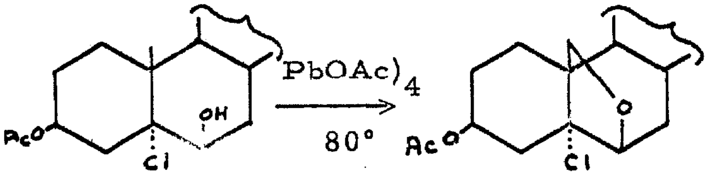
PROPOSITION 5

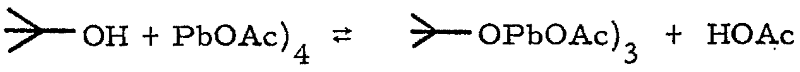
The search for new steroids of physiological importance has been one of the most lucrative and intensively studied fields of chemistry in recent years. One approach which has produced enormous dividends is the activation of methyl groups in the steroid nucleus by photochemical or radical means. Due to the enormous commercial potential of the new compounds, very little work has been carried out with a view to elucidating what mechanistic paths are operative. In some techniques, notably the photolysis of ketones or nitrite esters (the Barton reaction), plausible mechanisms are obvious on the basis of known photochemistry. However, other methods continue to lie half-obscured in the murky realm of "shazam" chemistry.

One technique in which the mechanism has not been entirely clarified is the oxidation of alcohols by lead tetraacetate. Several types of results are obtained, but those products which clearly arise from fragmentation of alkoxy radicals will not be considered here (1). The reaction path which forms the subject of this Proposition is the oxidation of monofunctional alcohols to cyclic ethers (Eq. 1) (2).



(1)

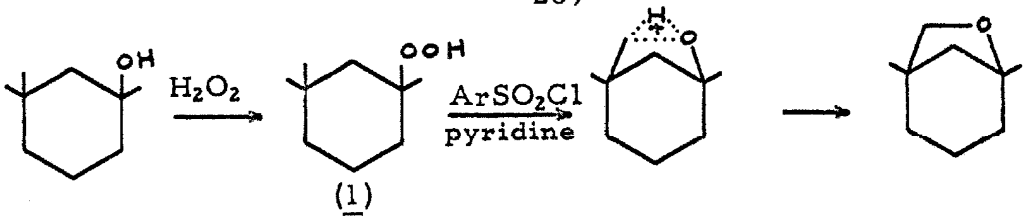
The first step is known to be a nucleophilic displacement of acetate ion by hydroxyl (3) to give an alkoxytriacyl lead compound (<u>2</u>) (Eq. 2).



$$\text{≻—OH} + \text{PbOAc)}_4 \rightleftarrows \text{≻—OPbOAc)}_3 + \text{HOAc} \qquad (2)$$

(<u>2</u>)

There are three possibilities for the next step, the first being a heterolytic cleavage to positive oxygen which then attacks the neighboring methyl group. This type of reaction has precedent in systems where the carbon-bearing positive oxygen is fully substituted. For example, the compound (<u>1</u>) is postulated to form a cyclic ether in just this way (Eq. 3) (4). However, this possibility



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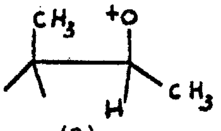

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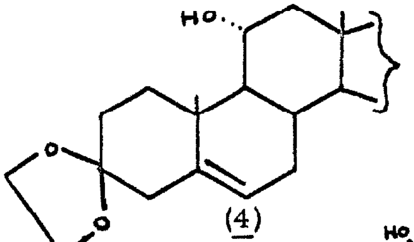
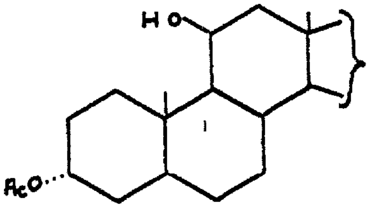
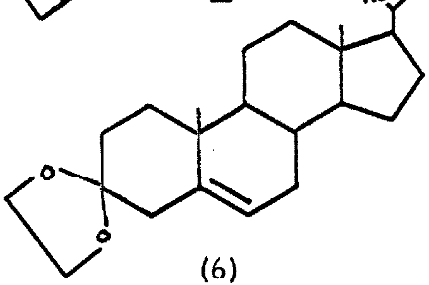


(4)



(5)



(6)

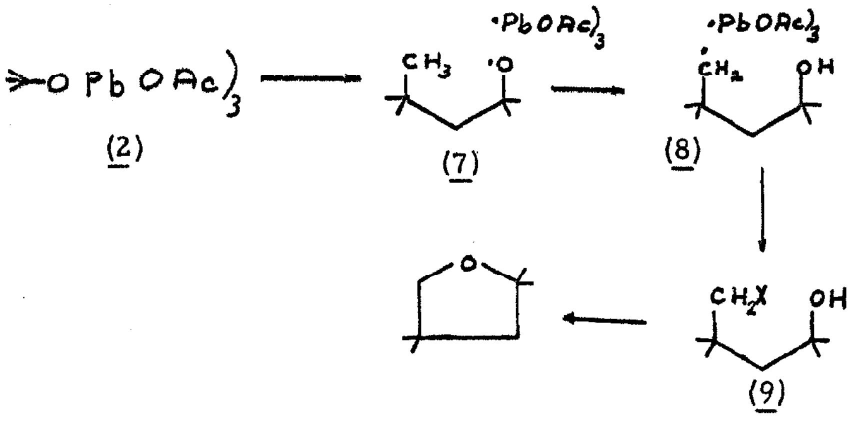
may be discarded in the present cases because intermediates analogous to (3) should immediately lose a proton to yield carbonyl compounds (5).

Appreciable charge does not appear to be generated in the later steps of the reaction. Solvent effects are quite unambiguous about this fact, the reaction becoming progressively less favored in more polar solvents. Moreover, consideration of the various processes requires surprisingly high energy intermediates in very efficient reactions if heterocyclic cleavage of the intermediate (2) is postulated (1, 6).

All evidence indicates that the competing fragmentation reactions involve alkoxy radicals (1, 6). However, the intermediacy of radicals (rather than a concerted mechanism) is not required for the cyclization reaction.

When monofunctional alcohols are oxidized with lead tetraacetate, the usual product is a tetrahydrofuran or pyran (7). When these products cannot be formed, unsaturated aldehydes or other fragmentation products characteristic of alkoxy radicals are formed (8). The choice of reaction pathway turns out to be a sensitive function of stereochemistry. Evidently, the possible paths are very highly competitive. Thus, compound (4) undergoes the cyclization reaction in excellent yield (9), but the closely related substance (5) is simply oxidized to the ketone (10). Similarly, the yield for the cyclic ether from (6) (C-20 R) is doubled in the hydroxy epimer (C-20 S) (4). Even more subtle examples of steric control of products have been reported (11).

The two remaining mechanisms rationalize the data presented so far. In one, the initially formed alkoxy lead is decomposed homolytically by heat or light (12) to give rise to an alkoxy radical which may abstract hydrogen from the neighboring methyl group. These intramolecular hydrogen abstractions are extremely rapid (13) and are followed in the postulated mechanism by coupling of the new radical pair to form the transient (9a). Subsequently, a nucleophilic displacement by hydroxyl produces the observed products (Eq. 4).

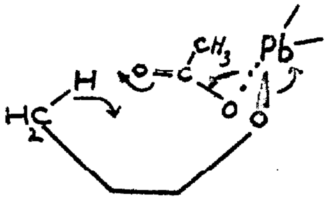


(4)

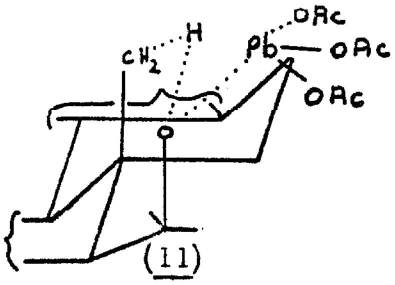
a X = PbOAc)$_3$
b X = I

The plausibility of this route is somewhat reinforced by the already-mentioned fact that other reactions of radicals seem to be intermediates to the products obtained when cyclization does not occur. Moreover, Heusler *et al.* have shown in an elegant series of papers (11a) that the course of the reaction in the presence of added iodine strongly suggests an intermediate (9b), possibly formed by scavenging of radicals (8).

The other possible mechanism involves a concerted collapse of the intermediate (2). This possibility is quite in line with the stringent stereochemical requirements of the system. The actual geometry of the transition state (10) would be essentially planar except for the lead atom which is positioned out of the ring. In this fashion a six-membered ring is postulated for the rearrangement and the unfavorable eight-membered ring (counting lead as two), which appears to be involved at first glance, is avoided. The hypothetical transition state is geometrically possible due to the size of the lead atom and the long lead-oxygen and lead-carbon bonds (14). This formulation is rather dissimilar from that (11)



(10)

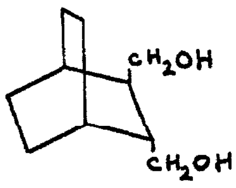


(11)

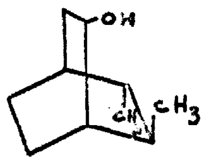
postulated by Jeger (6) in that (11) does not involve a role for the departing acetate group. It seems plausible to invoke such a role in view of the predilection of acetate to play such a part, but it is not feasible to decide between (10) and (11) without considerably more detailed knowledge of the reaction (e.g. entropy of activation).

It is possible to distinguish between these two possibilities by carrying out the reaction in bicyclic systems where the geometry is fixed, and varying the likelihood of alkoxy fragmentation (β - scission). Walling has shown that the rate of fragmentation depends on the group to which the alkoxy radical is attached, and follows the order methyl < chloromethyl < ethyl < benzyl < isopropyl < t-butyl (15). In the systems (13)-(16), the geometry is essentially the same insofar as the hydroxyl and methyl groups are concerned, but the benzo compounds (14) and (16) (which lead to benzyl radicals if scission occurs) should tremendously favor fragmentation and henc suppress the cyclization reaction if alkoxy radicals are the reactive species. On the other hand, a concerted mechanism should be relatively insensitive to such considerations and should lead to ethers in all four cases or else in none.

The simple substance (12) undergoes cyclization (16), which shows that the products are geometrically possible. On the other hand, one of the proposed substances (14) has been subjected to oxidation and found to undergo β -scission (16). It remains to complete the series.



(12)



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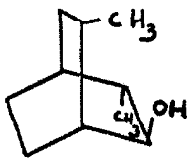

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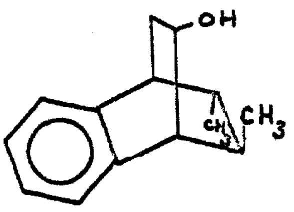

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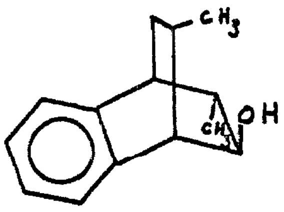

(16)

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