THE STRUCTURAL ELUCIDATION OF A PROPOSED INTERMEDIATE IN THE STEREOSELECTIVE SYNTHESIS OF dl-DESOXYPODOCARPIC ACID

Thesis by

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To the three beautiful women in my life-

my wife, Deborah;
my daughter, Lisa Brooke;
and my dog, Pogo.

ACKNOWLEDGMENTS

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ABSTRACT

The hydroxyketone C-3, an intermediate in the stereoselective total synthesis of dl-Desoxypodocarpic acid (ii), has been shown by both degradative and synthetic pathways to rearrange in the presence of base to diosphenol E-1 (5-isoabietic acid series). The exact spatial arrangements of the systems represented by formulas C-3 and E-1 have been investigated (as the p-bromobenzoates) by single-crystal X-ray diffraction analyses. The hydroxyketone F-1, the proposed intermediate in the rearrangement, has been synthesized. Its conversion to diosphenol E-1 has been studied, and a single-crystal analysis of the p-bromobenzoate derivative has been performed. The initially desired diosphenol C-6 has been prepared, and has been shown to be stable to the potassium t-butoxide rearrangement conditions. Oxidative cleavage of diosphenol E-1 and subsequent cyclization with the aid of polyphosphoric acid has been shown to lead to keto acid I-2 (benzobicyclo [3.3.1] nonane series) rather than keto acid H-2 (5-isoabietic acid series).

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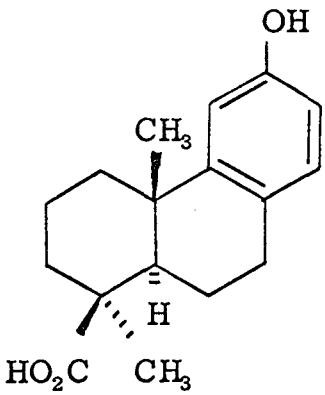
HISTORICAL INTRODUCTION

Podocarpic acid (i) was first isolated from Podocarpus cupressina var. imbricata by Oudemans[1a, 1b]. Campbell and Todd[2], in 1941, elegantly and conclusively proved the structure of Podocarpic acid as i.



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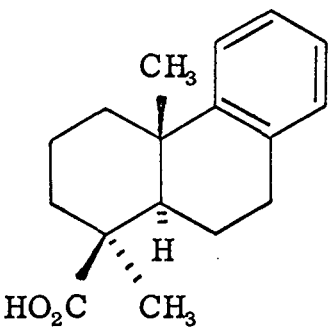

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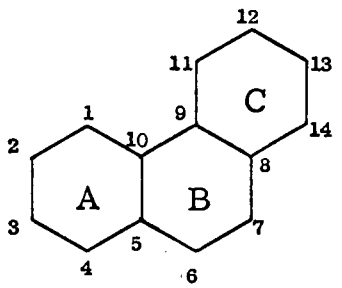
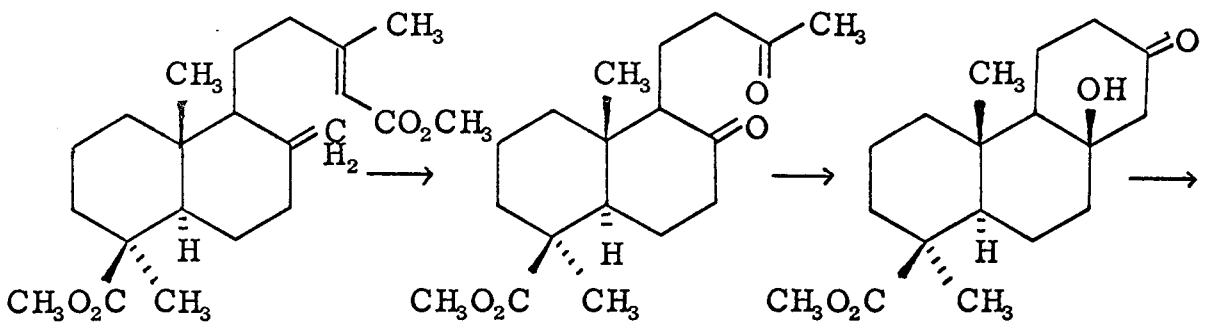


Synthetic efforts, directed toward the attainment of both podocarpic acid i and desoxypodocarpic acid ii and reported prior to 1967, are reviewed in a variety of publications[3, 4, 5, 6, 7]. In general, the syntheses involved two methods of attack: (a) ring B formation by attachment through the potential 9, 10 carbons of the intact A and C rings, or (b) manipulation of the preformed tricyclic ring system to introduce the correct stereochemistry at carbon atoms 4 and/or 5. These synthetic approaches lacked stereochemical control and high yields.

An interesting synthetic approach to the podocarpic acid skeletal system recently reported by Carman, Deeth, Marty, Mori, and Matsui[8], is shown in Chart A. The scheme involves elaboration of ring C on the already preformed AB bicyclic system. Their ini-

tial reaction, which involved ozonolysis of dimethyl agathate (A-1),

Chart A



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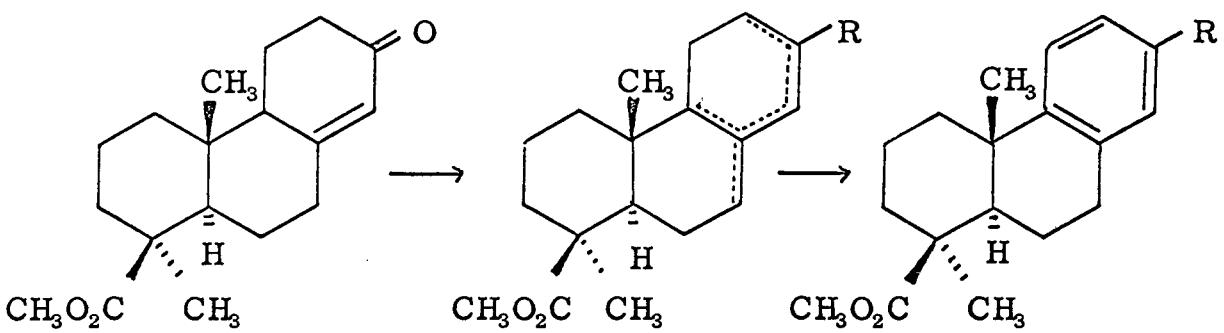
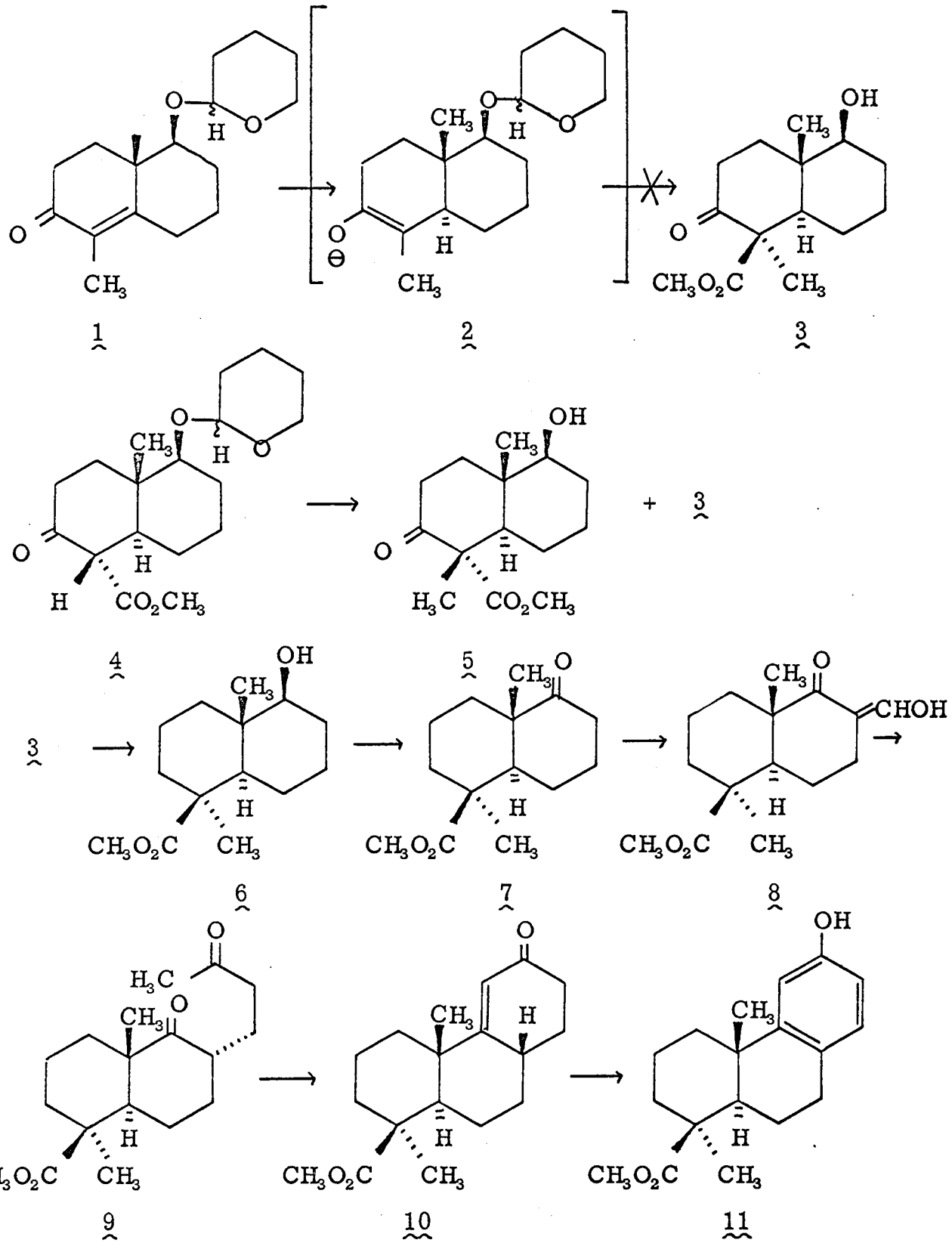


4 5 a, R = $CH(CH_3)_2$ 6 a, R = $CH(CH_3)_2$
b, R = H b, R = H

yielded a mixture of diketone esters consisting principally of the compound A-2. Hydroxyketone A-3 crystallized out of a solution of A-2 in methanolic sodium methoxide. Distillation of the alcohol A-3 at 0.1 mm gave principally the unsaturated ketone A-4, together with some of the 8(9) isomer. The crude ketoesters A-4, treated with isopropyl magnesium bromide, yielded the mixture of esters A-5a. Dehydrogenation over palladium on charcoal at 230-240° afforded methyl 4-epidehydroabietate (A-6a). Methyl desoxypodocarpate (A-6b) was obtained as a by-product from the dehydrogenation. This approach would also seem to be applicable to the direct synthesis of methyl desoxypodocarpate (A-6b).

The recently reported synthesis of podocarpic acid (i) by Spencer[9], which also incorporates the AB $\longrightarrow$ ABC approach, is described in Chart B. The approach had as its key step introduction of the axial carboxylate function by stereoelectronically controlled carbonation of enolate anion B-2, generated from α,β-unsaturated ketone B-1. The axial carbomethoxylation product B-3 was not detected in the product mixture. The major product (ca. 30% yield) was the hydroxyketone resulting from the reduction of the double bond of structure B-1. The saturated diol was isolated on occasion in yields up to 7%. The only monocarbomethoxylation product ever obtained was the epimeric 4-α ester. One of the key steps in the synthesis of methyl deisopropyldehydroabietate reported by Spencer[10] involved stereoselective β methylation of ketone B-4 to afford methyl-

Chart B

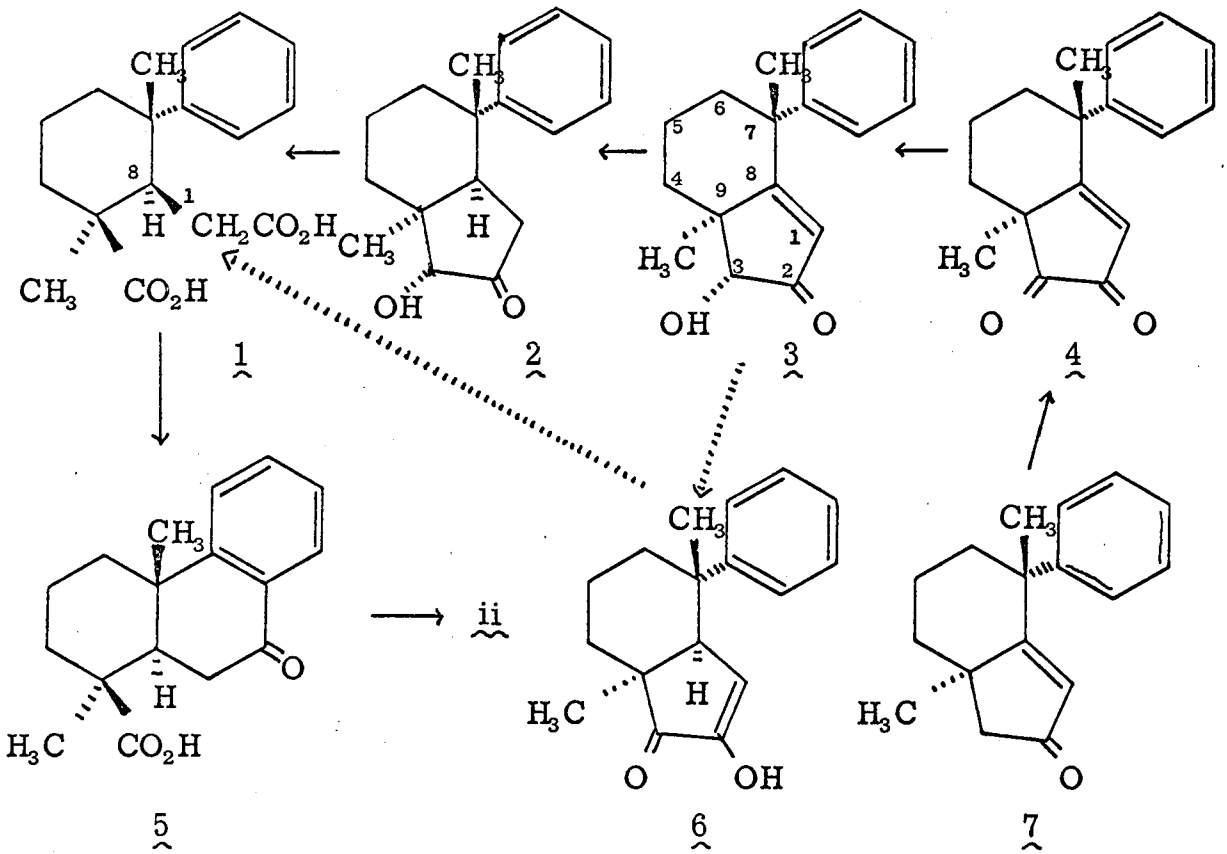


ated ketone B-5 after methanolysis. However, there was also formed approximately 10% of the α methylation epimer B-3. The yield of oily B-3 of reasonable purity isolated was roughly 5% from B-4. Reduction of ketone B-3 to desketo B-6 was effected by Raney Ni reduction of the thioketal derivative. Oxidation of alcohol B-6 afforded the desired ketone B-7. To facilitate annelation of ketone B-7, it was converted to its hydroxymethylene derivative B-8. Reaction with 1-diethylaminobutanone-3-methiodide afforded Michael adduct B-9, which was then cyclized to tricyclic ketone B-10. Conversion of ketone B-10 to methyl dl-podocarpate (B-11) was accomplished by treatment with N-bromosuccinimide.

The lack of stereochemical control and low yields reported in the synthetic pathways cited and discussed resulted in an investigation of approaches directed toward an efficient stereoselective synthesis of dl-Desoxypodocarpic acid (ii) in these laboratories. This investigation proved successful. The synthesis[7], as shown in Chart C, involved the selenium dioxide oxidation of ketone C-7 to diketone C-4. Diketone C-4 was reduced with sodium borohydride to hydroxyketone C-3. Catalytic reduction of the unsaturated hydroxyketone C-3 yielded the corresponding cis-fused hydroxyketone C-2. Hydroxyketone C-2 was converted to diacid C-1 by chromic acid--glacial acetic acid oxidative cleavage. Dehydrative cyclization of diacid C-1 to the tricyclic keto acid C-5 was effected with the aid of polyphosphoric acid. Hydrogenolysis of keto acid C-5 yielded Desoxypodo-

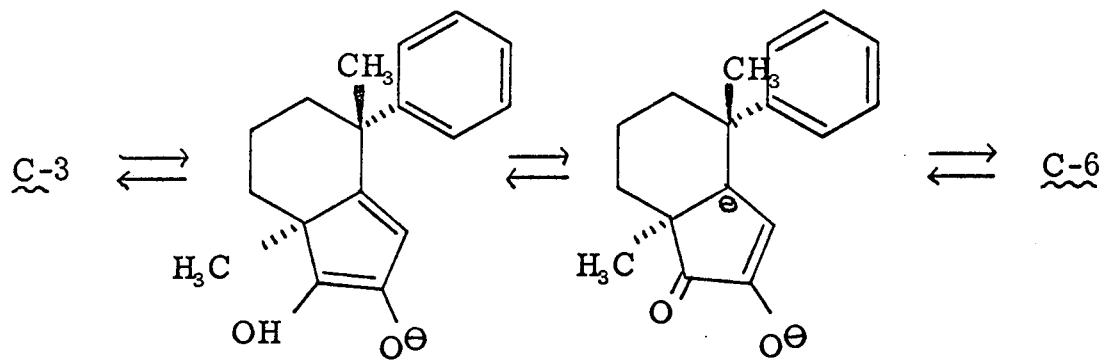
carpic acid (ii).

Chart C



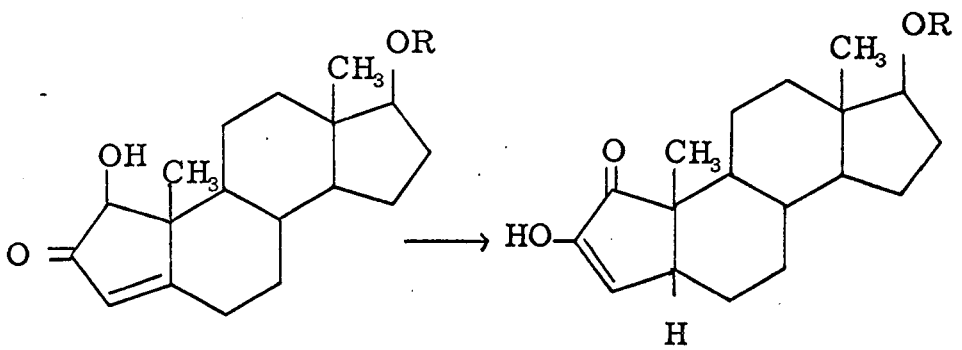
An alternative route through the diosphenol C-6 and subsequent cleavage to diacid C-1 would serve as a more efficient scheme for the synthesis of dl-Desoxypodocarpic acid (ii). A mechanistic pathway which would result in the desired transformation is indicated on the following page. Examination of the mechanism of the transformation indicates that reversible basic abstraction of the C-3 methinyl hydrogen of hydroxyketone C-3 would produce the enolate species I.

This anion could either revert to the hydroxyketone C-3 by the addition of a proton or be further transformed to the enolic diketone carbanion II. Even if the equilibrium resided far towards the enolate species I, protonation of the tertiary carbanion would displace the equilibrium and result in overall reduction of the C-8 center and oxidation of the C-3 center.



I II

A recent report by Yoshida and Kubota[11], noting the successful execution of a similar rearrangement in the androstane series, lends support to the proposed rearrangement. Their transformation, as indicated below, was effected with the aid of an excess of sodium hydroxide.



73% yield when R = H
70% yield when R = COC_2H_5

The rearrangement hypothesis was tested by treatment of the hydroxy indenone C-3 with two equivalents of potassium t-butoxide in t-butyl alcohol. Upon mixture of these components, the solution developed a blood red color which remained until the reaction mixture was quenched with hydrochloric acid. A product, different from the starting hydroxyketone, was obtained in a yield of 49% when the reaction components were stirred in a nitrogen atmosphere at room temperature for one hour.

The assignment of the structure of the product as diosphenol C-6 is aided by the interpretation of the spectral data. Its infrared spectrum exhibited absorption bands at 3500 and 3350 (shoulder) cm^{-1} (enolic-OH), and 1700 and 1650 cm^{-1} (enolic dione). A maximum was exhibited at 262 mμ (ϵ 9,038) in the ultraviolet. The nuclear magnetic resonance spectrum exhibited signals at δ 1.32 (s, 3, C-9 CH_3), 1.48 (s, 3, C-7 CH_3), 2.85 (d, 1, J = 3 hz, C-8 H), 5.65[12] (d, 1, J = 3 Hz, C-1 vinyl H), and 6.22 (broad s, 1, -OH).

The rearrangement product melted at 162-164°. The compound exhibited a purple color[13] upon the addition of ferric chloride test solution.

The course of the base-catalyzed rearrangement is dependent upon the presence or absence of oxygen. The diosphenolic product is isolated in the absence of oxygen. The presence of a trace amount of oxygen results in the formation of a number of oxidation products. The mixture consisted mainly of diketone C-4 and the anhydride formed from 1,8-dehydrodiacid C-1.

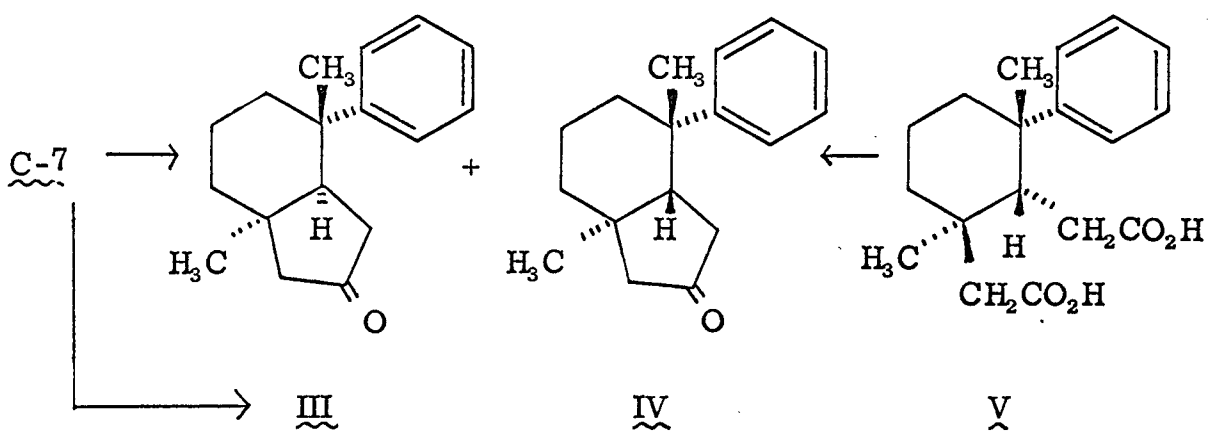
Oxidation of the rearrangement product did not produce a diacid identical with the one derived from oxidation of hydroxyketone C-2 (i.e., diacid C-1). Oxidation of the rearrangement product with hydrogen peroxide--aqueous sodium hydroxide and subsequent reaction with acetic anhydride afforded an anhydride[14]. Comparison of both melting point and infrared spectral data indicates that the tricyclic keto acid, obtained by conversion of the anhydride using polyphosphoric acid, was not identical with 7-ketodesoxypodocarpic acid (C-5). This indicates that the diosphenolic product does not have the structure indicated by formula C-6. A similar comparison of compounds in the 5-isopodocarpic acid series with the corresponding compounds in the rearrangement product series indicates that the rearrangement product cannot be the corresponding trans-fused diosphenol (i.e., compound C-6 with the C-8 hydrogen β).

DISCUSSION

The current research program has been concerned with the determination of the structure of the rearrangement product and a study of the mechanism of the rearrangement.

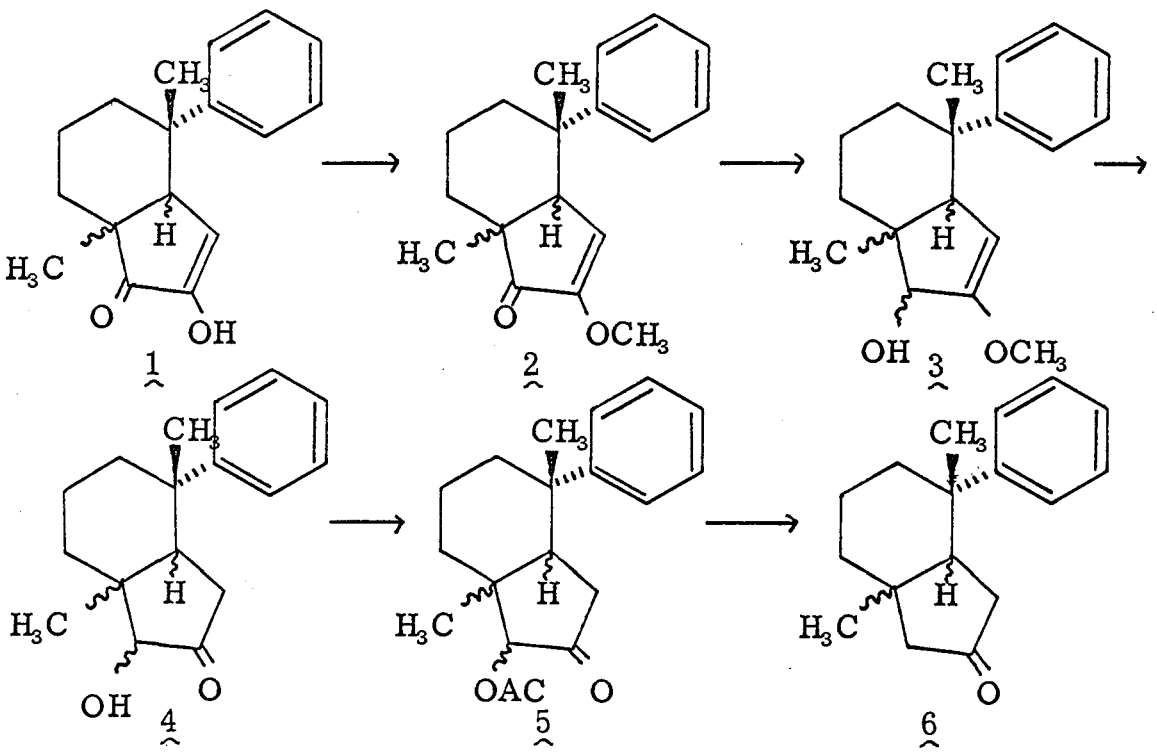
A reinvestigation of the potassium t-butoxide initiated rearrangement indicated that the conversion to the diosphenol was quantitative when the reaction components were stirred at 45° for one hour. Quantitative conversion was also effected upon heating the hydroxyketone C-3 in aqueous methanolic sodium hydroxide for thirty minutes under carefully deoxygenated conditions.

Confirmation that the diosphenol was neither compound C-6 nor its epimer with the C-8 hydrogen β was selected as the initial goal. This confirmation would be accomplished by transformation of the rearrangement product, now assigned structure D-1 only for the ease of visual presentation, to hydrindanone D-6 by a series of reactions that would neither affect the stereochemistry of center 8 nor that of 9 (Chart D). A lack of identity between both ketone III and IV and ketone D-6 would prove that the rearrangement product was neither



diosphenol C-6 nor its C-8 epimer. The solid cis-fused ketone III and the liquid trans-fused ketone IV are formed during lithium--ammonia reduction of unsaturated ketone C-7 (in a 2:3 ratio)[7], and consequently are available for comparative study.

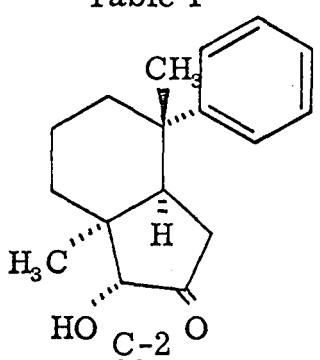
Chart D



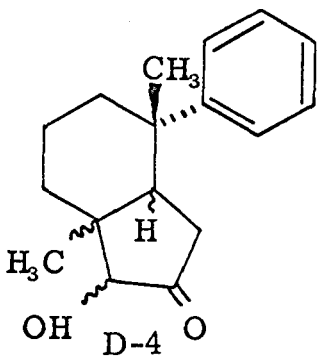
The rearrangement product D-1 was converted to the acetoxyketone D-5 in 79% overall yield. The diosphenol D-1 was first quantitatively converted to the corresponding keto enol ether D-2 with the aid of dimethyl sulfate--potassium carbonate[15]. The keto enol ether was reduced by lithium aluminum hydride to the hydroxy enol ether D-3 which was hydrolyzed to the hydroxyketone D-4. A com-

parison of the melting point and spectral data of the hydroxyketone D-4 of the rearrangement series with the catalytic reduction product C-2 of the podocarpic acid series as presented in Table I below indicates that these two compounds are not the same.

Table I



C-2



D-4

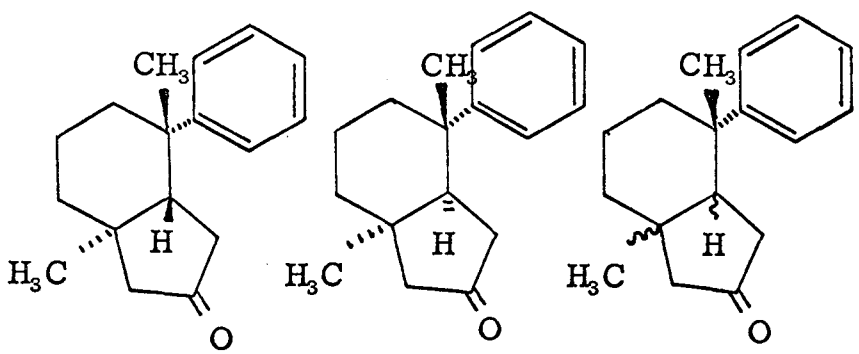
		C-2	D-4
mp (°C)		173-174.	122-124.5
ir (cm^{-1})	ν $CHCl_3$ max	3600 (m) 3450 (w) 1735 (s)	3550 (m) 3450 (w) 1748 (s)
nmr (ppm)	δ $CDCl_3$ TMS		
C-9 methyl		0.67 (s)	1.43 (s) and
C-7 methyl		1.14 (s)	1.45 (s)

The hydroxyketone D-4 was esterified with acetic anhydride and pyridine in 83% yield, and the resultant acetoxyketone D-5 was reduced with lithium--ammonia[16]. The resultant crude reaction mixture of ketone D-6 and alcohol reduction product was oxidized with chromic acid[17] to the hydrindanone D-6.

A comparison of both the spectral and melting-point data of the degradation ketone D-6 of the rearrangement series with the trans-fused ketone IV and the cis-fused ketone III is presented in

Table II below. The stereochemistry of ketones III and IV was ascertained through independent synthesis of the trans-locked isomer from the diacid V of known[18] configuration in 98% yield. The trans-ketone IV, obtained by pyrolysis of the lead salt[19] of this diacid, proved to

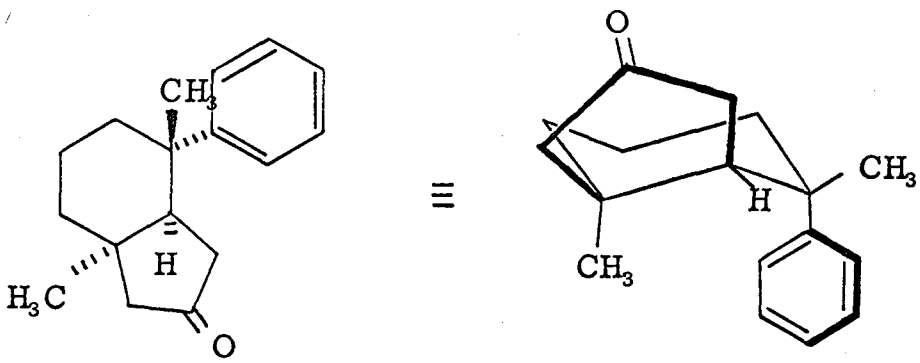
Table II



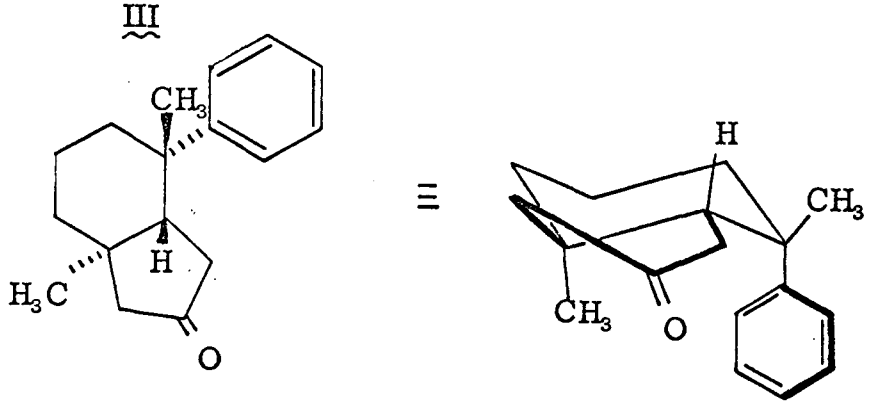
	IV	III	D-6
ketone mp (°C)	oil	100.5-101	100.5-101
ketone mmp (°C)		III + D-6 melted between 70 and 102°	
semicarb. mp (°C)	221-223	241-243	220.5-222
semicarb. mmp (°C)	IV + D-6 melted between 208° and 243°		
ir (cm^{-1}) ν $CHCl_3$ max	1735	1738	1738
nmr (ppm) δ CCl_4 TMS			
C-9 methyl	0.33 (s)	0.53 (s)	1.33 (s)
C-7 methyl	1.28 (s)	1.06 (s)	1.40 (s)

be identical to the liquid ketone obtained on lithium--ammonia reduc-

tion of the enone C-7. This was accomplished through direct spectral comparisons as well as mixture melting point determination of their semicarbazones[7]. This conclusion meant that the crystalline saturated ketone from the lithium--ammonia reduction was the cis-locked ketone III. This cis-ketone was selectively obtained by catalytic hydrogenation[7] of the enone C-7. The C-9 methyl protons of both cis-fused ketone III and trans-fused ketone IV are highly shielded. This is easily recognized in the conformational study shown below. The ketone D-6 is neither the cis-fused ketone III nor the trans-fused ketone IV. The



III

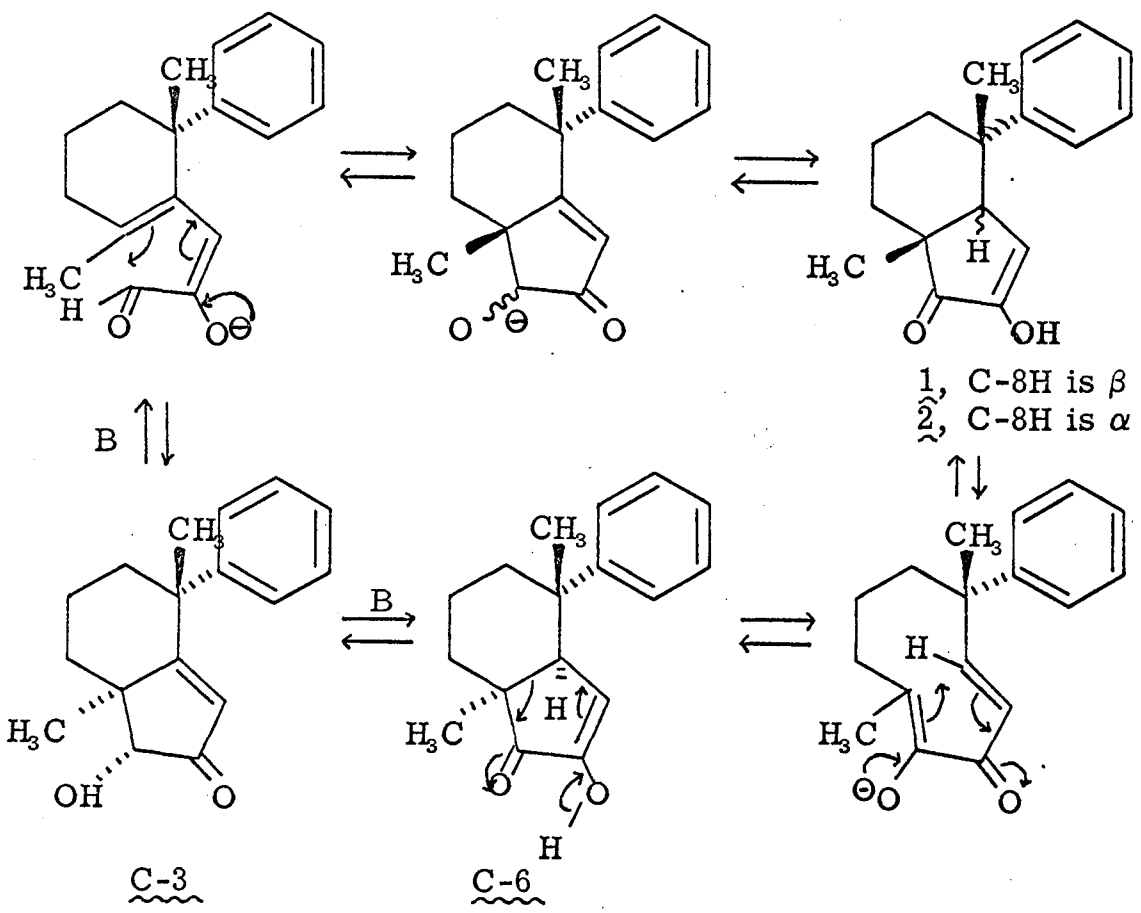


IV

rearrangement product D-1 is therefore neither the cis-fused diosphenol C-6 nor the C-8 epimeric trans-fused diosphenol, since the transformation of the rearrangement product D-1 to the ketone D-6 involved isomerization of neither the C-8 nor C-9 assymetric centers.

Our attention was drawn to the possibility that the rearrangement product D-1 was a stereoisomeric diosphenol. Evidence for this belief included the spectral properties of the rearrangement product D-1, its response to the ferric chloride test, and the analogy of the rearrangement in the androstane series already cited[11]. Interest

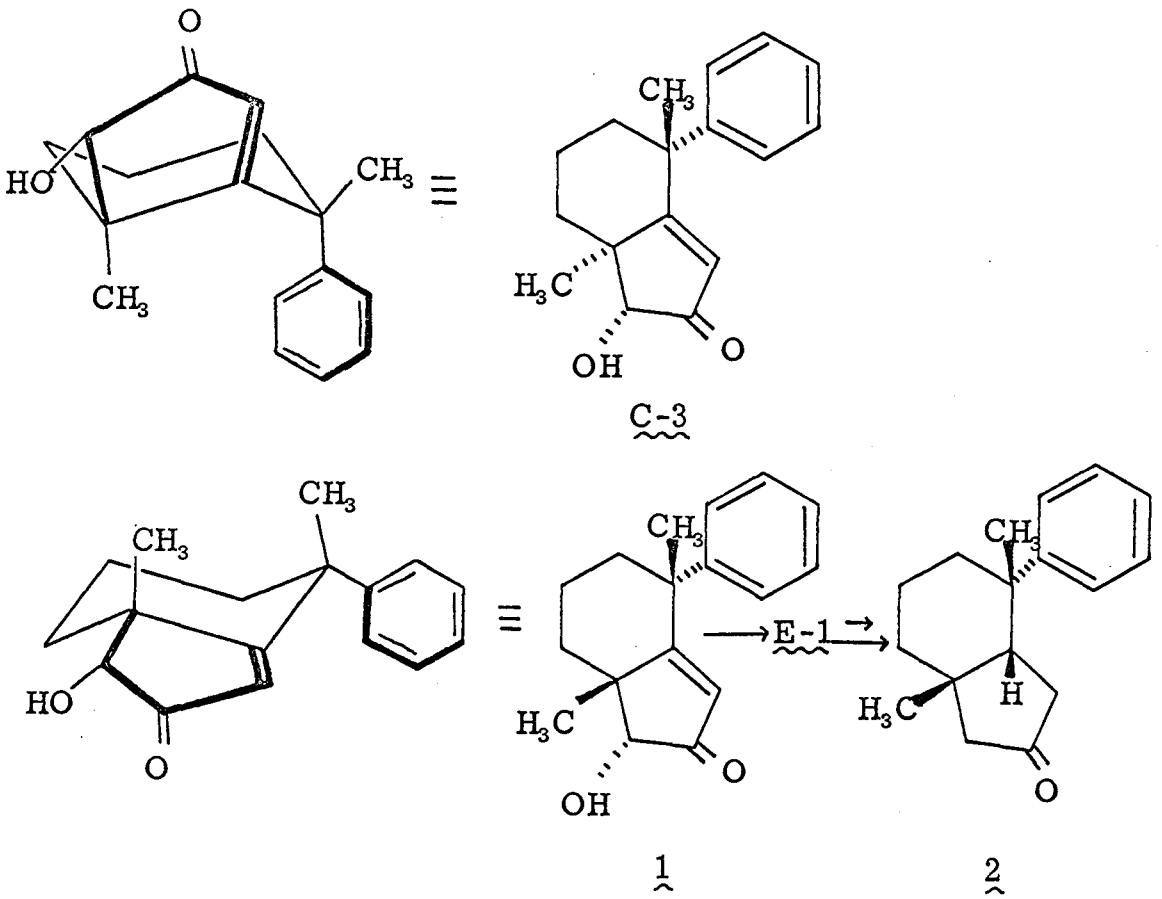
Chart E



became centered on the possibility that the rearrangement product was the diosphenol E-1. Isomerization of hydroxyketone C-3, as indicated in the alternative mechanistic routes shown above in Chart E, would afford either diosphenol E-1 or epimeric diosphenol E-2. Cis-fused hydrindones being more stable than their trans-fused epimers[20], the formation of diosphenol E-1 would seem to be preferred to that of E-2. Diosphenol E-1 can be formed as indicated by an initial retro-aldolization performed on hydroxyketone C-3. Subsequent recyclization would yield the C-9 epimeric methylated hydroxyketone F-1. This hydroxyketone would then rearrange to diosphenol E-1 by the mechanism originally postulated. Considerations of steric effects in a study of molecular models shown in Chart F indicate that the cis-fused hydroxyketone F-1 is equally as stable as the cis-fused hydroxyketone C-3. The relative stability of hydroxyketone C-3 and F-1 would not therefore present a barrier to the formation of hydroxyketone F-1 by the retro-aldolization reaction. Diosphenol E-1 can also be formed by an alternative route which would afford the initially desired diosphenol C-6 as a reactive intermediate. Rearrangement of diosphenol C-6 to a dienic 9-membered ring compound and subsequent cyclization would afford diosphenol E-1.

If diosphenol E-1 is the rearrangement product, then its degradation by the route already described would result in the formation of hydrindanone F-2. Hydrindanone F-2 has been synthe-

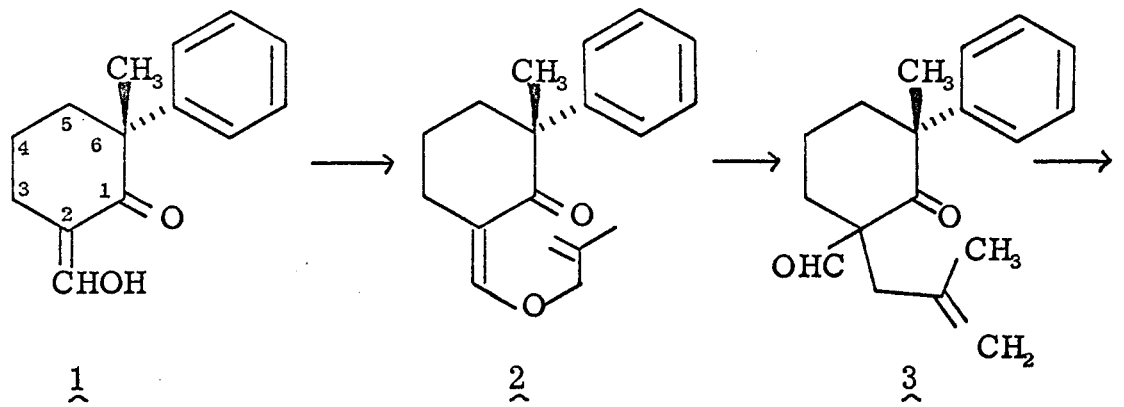
Chart F



sized by the route shown in Chart G on the following page. Comparison of ketone F-2 with that of D-6 would firmly establish whether diosphenol E-1 is indeed the rearrangement product.

A number of observations pertaining to thermal rearrangements, stereoselectivity of alkylation, and lithium--ammonia reductions either noted in this laboratory or cited in the literature indicated that this synthetic approach was feasible. Reports by both Claisen and Burgstahler offered support for the postulated thermal isomerization of allyl vinyl ether G-2 to the aldehydic ketone G-3.

Chart G



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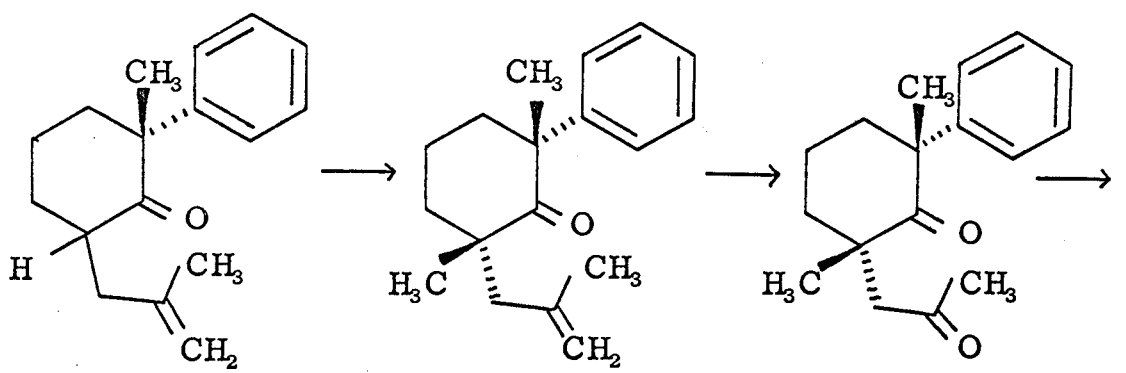

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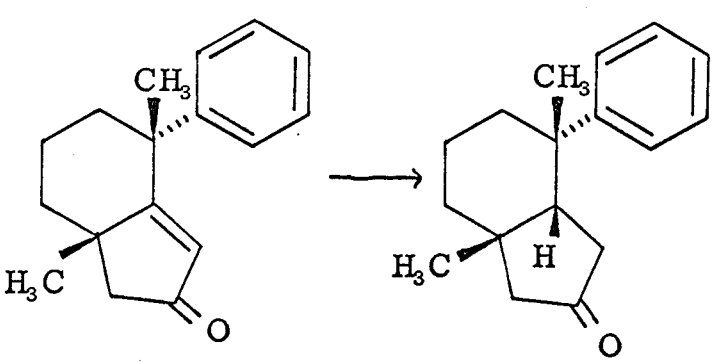
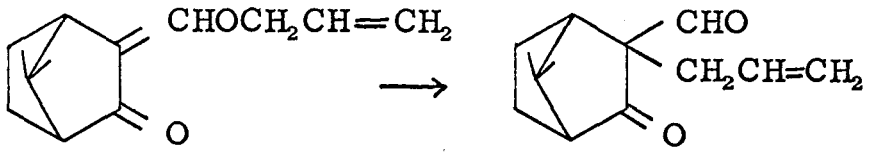


7 F-2

Claisen in his original note[21] disclosed the rearrangement of 3-allyloxymethylene camphor VI to the C-allyl derivative VII. Burgstahler later expanded this synthetic technique by incorporating

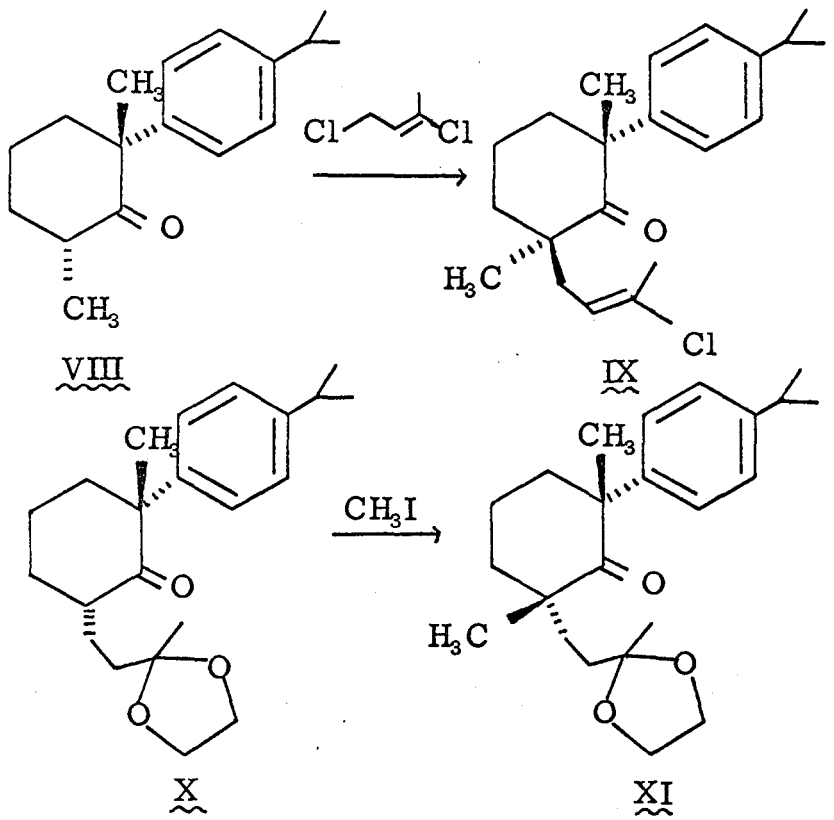


VI VII

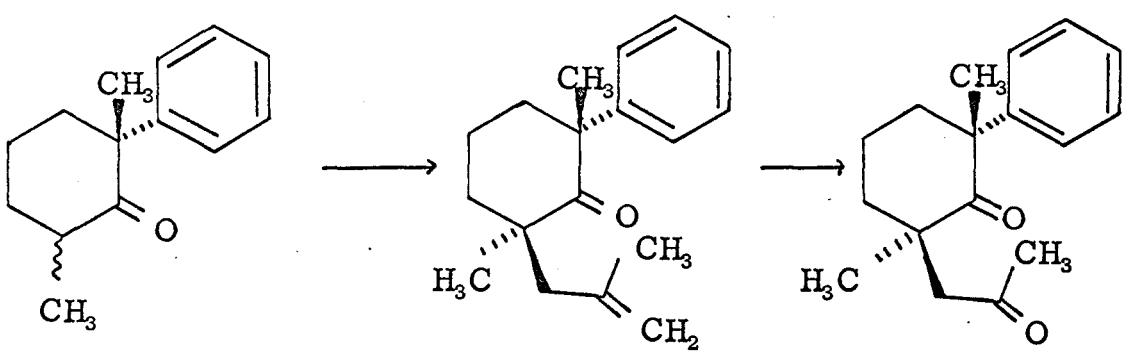
the participating allyl group into the ring[22].

It was felt that ketone G-4 could be stereoselectively alkylated in a manner to afford the β axially oriented alkylating agent residue. Ireland and Kierstead found that 2α, 6β-dimethyl-6α-(p-isopropyl-phenyl)-cyclohexanone (VIII) upon alkylation with 1,3-dichlorobutene-2 afforded the axially oriented 3-chloro-2-butenyl substituted cyclo-hexanone IX in 69% yield[18]. When they treated 2α-(3,3-ethyl-enedioxybutyl)-6α-(p-isopropylphenyl)-6β-methylcyclohexanone (X) with methyl iodide, the axial 2β-methylated ketone XI was produced in 89% yield. Ireland has also found the same results with analogous compounds in which the phenyl group does not contain an isopropyl substituent.

An earlier stage in the synthesis of dl-Desoxypodocarpic acid (ii) in our laboratories[7] involved the alkylation of 2,6-dimethyl-6-phenylcyclohexanone (XII) with methallyl chloride. The alkylated



product XIII was again shown to be the one derived from axial attack.



The lithium-ammonia reduction of enone G-7 was expected to lead to both ketone F-2 and the trans-fused epimer (with the C-8 hydrogen α). This expectation is based on the observation that ketone C-7 yields a mixture of both hydrindanones III and IV under similar conditions[7]. Both ketones would therefore be available for comparison with the degradation ketone D-6.

The synthesis was effected as follows. Selective O-alkylation of the formyl ketone G-1, prepared in the manner reported by Ireland and Kierstead[18], with methallyl alcohol and p-toluenesulfonic acid afforded the allyl vinyl ether G-2 in 81% yield. Claisen rearrangement of the enol ether G-2 yielded the methallyl aldehydic ketone G-3, which was converted to the methallyl ketone G-4 upon mild base treatment in 80% overall yield. Alkylation of methallyl ketone G-4 in 95% yield was effected with methyl iodide. Potassium t-butoxide was employed as the base.

The major alkylation product was the expected axial β-methylated ketone G-5. The minor product was determined to be the α-methylated epimer XIII as follows. The minor product was eluted from a silicic acid column immediately prior to ketone G-5, but quantitative separation was difficult to achieve. The nmr spectral analysis of the crude product indicated that the ratio of β-methylated material G-5 to the minor product was 5:1 (e.g., absorption of C-2 methyl singlets at 1.10 ppm vs. 0.68 ppm respectively). The attempt to separate what was assumed to be the epimeric methylated product

through silicic acid chromatography resulted in an early cut whose ratio of trans-dimethyl XIII to cis-dimethyl G-5 was 9:1. This material, oxidized with osmium tetroxide and p-periodic acid[23], afforded a compound which was shown to be identical with authentic diketone XIV (obtained from F.F. Giarrusso[7]) by infrared and nmr spectral analyses and mixture melting point.

A reinvestigation of the quantitative alkylation of ketone XII with methallyl chloride indicated the presence of both epimeric ketones G-5 and XIII. The ratio, as determined by nmr spectroscopy, was 9:1 in favor of the trans-dimethylated ketone XIII. The C-2 methyl group absorption of ketone XIII occurs at 0.68 ppm and the corresponding absorption of ketone G-5 occurs at 1.10 ppm. This ratio was confirmed by gas chromatographic analysis which indicated that the cis-dimethylated ketone G-5 is eluted from the SE-30 column after 675 sec. and that the trans-dimethylated ketone XIII is eluted from the column after 735 sec. (152° oven temperature).

The factors controlling the direction of alkylation of an enolate anion are difficult to quantify, and differing viewpoints and observations have consequently been reported. House, in a recently reported study[24] concerning the stereochemistry of alkylation of 4-t-butylcyclohexanone, concludes "that there is no inherent factor which strongly favors the alkylation of a cyclohexanone enolate anion from that direction which will form a product with an axial alkyl substituent." But a high degree of stereoselectivity during alkylation of a number of cyclohexanone compounds in these laboratories has been observed.

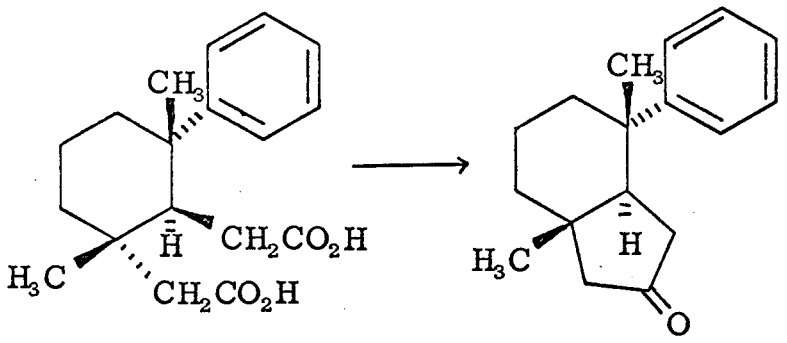
Ireland concludes[18] "that during the transition from enolate to product, the lower energy pathway is that which maintains the maximum orbital overlap between the carbonyl π system and the negative charge on the α carbon. The population of that conformation wherein the phenyl group is more equitorially oriented is probably very great. Therefore, the maintenance of overlap between the orbitals of the carbanion and the carbonyl group dictates the formation of only one product and is more important in determining the lower energy pathway than steric consideration in the enolate. In cases where the conformation of the enolate is not nearly so fixed, this stereoelectronic requirement may be satisfied in more than one conformation, and then other considerations will become more important in determining product stereochemistry."

The synthesis of ketone F-2 was completed by first formation of the diketone G-6 in 85% yield; the oxidation of the methallylated ketone G-5 being effected with osmium tetroxide and p-periodic acid[23]. The indenone G-7 was then prepared in quantitative yield through an internal aldolization reaction of the dione with the aid of potassium t-butoxide.

The reduction of indenone G-7 and subsequent chromic acid oxidation[17] of the crude product afforded an isomerically pure white crystalline solid in 90% yield. It is to be recalled that lithium--ammonia reduction of the indenone C-7 did not selectively lead to the thermodynamically more stable cis-fused indanone III, but to a mix-

ture of both cis-fused III and trans-fused IV indanones in the ratio of 2:3[7]. Stork observes[25] "the relative energies of the stereoelectronically allowed transition states, rather than those of the reduction products, will determine the stereochemistry of the products." In other words, if conformational interactions do not forbid overlap of the anion with the enolate system, the reduced product will reflect that β-carbanion which can maintain most efficient overlap with the enolate. An examination of molecular models of the carbanions generated by lithium--ammonia reduction of indenone C-7 indicates that both β-carbanions can effectively overlap with the enolate. The formation of an isomeric mixture is consequently reasonable to expect. A molecular model study of the carbanions generated by the lithium--ammonia reduction of the indenone G-7 also indicates that a mixture of both the trans-fused ketone XVI and the desired cis-fused ketone F-2 could be expected. The results would seem to indicate that consideration of subtle factors, whose effects are difficult to weigh, play an important role in metal--ammonia reductions. Since the energy difference between the two possible β-carbanions in each reduction is quite small, factors such as relative molecular solvation and steric interactions in the transition state probably control the product mix.

The hydrindanone product was assumed to be either ketone F-2 or XVI. Authentic trans-fused ketone XVI was obtained by pyrolysis of the lead salt[19] of diacid XV of known[18] configuration.

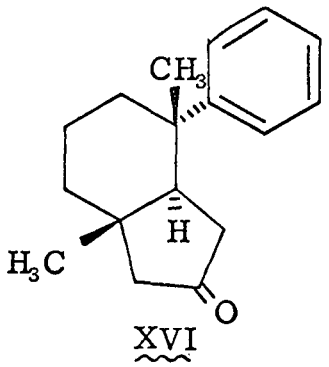
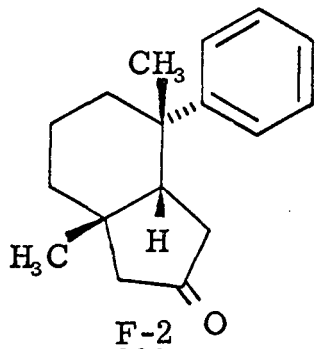


XV XVI

A comparison of both spectral and melting-point data of the trans-fused ketone XVI and the reduction product shown in Table III on the following page indicates that they are not identical. A comparison of both the spectral and melting-point data of the indanone formed in 90% yield by lithium--ammonia reduction and the degradation ketone D-6 indicate that they are identical - both being hydrindanone F-2. This proves that the compound prepared by potassium t-butoxide rearrangement is indeed the diosphenol E-1.

The relative merits of the alternative mechanisms proposed for the formation of diosphenol E-1 (shown in Chart E) could be investigated by the determination of the stability of the originally desired diosphenol C-6 to the potassium t-butoxide rearrangement conditions. The conversion of diosphenol C-6 to diosphenol E-1 with the aid of potassium t-butoxide would strengthen the possibility that diosphenol C-6 is an intermediate in the conversion of hydroxyketone C-3 to

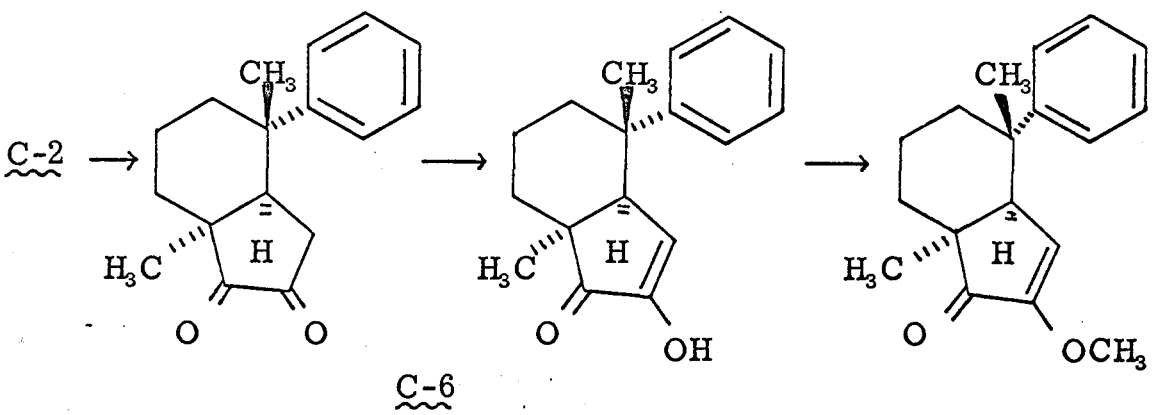
Table III

		 XVI	 F-2
ketone mp (°C)		79.5-80.5	100.5-101
ketone mmp (°C)		XVI + F-2 melted between 79 and 93°	
ir (cm^{-1})	ν $CHCl_3$ max	1735	1738
nmr (ppm)	δ CCl_4 TMS		
C-9 methyl		1.09 (s)	1.33 (s)
C-7 methyl		1.39 (s)	1.40 (s)

diosphenol E-1. Diosphenol C-6 was prepared in 56% yield by chromic acid[17] oxidation of hydroxyketone C-2 at 0°. Diosphenol C-6 was shown to be stable to the potassium t-butoxide conditions. This fact eliminates the possibility that diosphenol C-6 is an intermediate in the rearrangement, and consequently strengthens the mechanism involving the retro-aldolization. Diosphenol E-1 was also shown to be stable to potassium t-butoxide.

The sensitive nature of the hydroxyketone system C-2 with respect to oxidative cleavage is indicated by the following observations.

Mainly starting material was recovered when the oxidation was performed at -10°, and the major products when the reaction was performed at +10° seemed to be a mixture of the diacid C-1 and the corresponding anhydride. A compound, isolated in 14% yield from the product mixture when the reaction was performed at 0°, was shown to be the diacid C-1 by both infrared spectral comparison and mixture



keto enol XVII

melting point. Another portion of the product mixture was thought to be the corresponding anhydride.

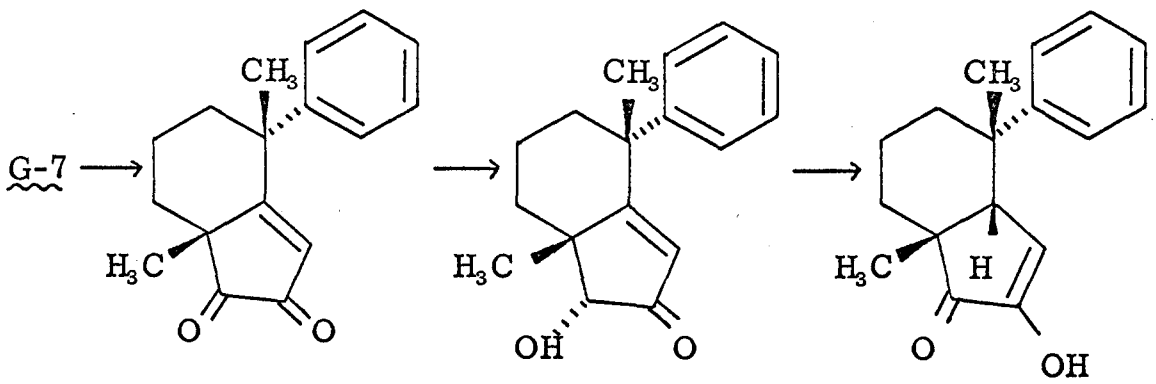
The spectral and chemical properties of the oxidation product aided in its assignment as diosphenol C-6. The infrared spectrum of diosphenol C-6, which exhibited a purple color with ferric chloride test solution[13], displayed absorption bands at 3480 and 3240 cm^{-1} (enolic -OH), and 1695 and 1652 cm^{-1} (enolic dione). A maximum

was exhibited at 259 mμ (ε 9,620) in the ultraviolet. The nuclear magnetic resonance spectrum exhibited signals at δ0.93 (s, 1, C-9 -CH_3); 1.20 (s, 1, C-7 -CH_3); 3.22, 3.24, 3.28, and 3.30 (q, 1, the secondary splitting being caused by W coupling, J_{1-8} = 3.4 Hz, C-8 H); and 6.68 (d, 1, J = 3.4 Hz, vinyl H). The white crystalline α-cis-fused diosphenol C-6, which melted at 121-123°, started melting at 105° when mixed with the β-cis-fused diosphenol E-1. The formation of the enol ether XVII, quantitatively prepared from α-cis-diosphenol C-6 with dimethyl sulfate employed as the alkylating agent, is a confirmation of the presence of the diosphenolic grouping.

Smaller scale chromic acid oxidations, worked up by extracting the chromic salts into water, afforded a yellow crystalline solid instead of the white diosphenol C-6. Preparation of diosphenol C-6 involved the technique of filtering off the chromic salts and concentrating the filtrate in the presence of sodium bicarbonate. The yellow color is characteristic of α-diketones. A solution of the yellow compound in chloroform did not impart any color upon the addition of ferric chloride test solution. A drop of pyridine was then added to the solution, which was heated on the steam bath for thirty seconds; the system now turned purple. The infrared spectrum of this compound in a chloroform solution exhibited a carbonyl absorption band at 1748 cm^{-1}, with a shoulder observed at 1758 cm^{-1}; the absence of hydroxylic absorption was noted. The nuclear magnetic resonance spectrum displayed signals at δ 0.89 and 1.09 (two s, 6, C-9 and C-7 -CH_3) and

2.52, 2.60, 2.61, and 2.72 (d of d, 2, C-1 -$C\underset{\sim}{H}_2$-); vinylic absorption was absent. The yellow crystalline solid, which can be converted to diosphenol C-6 upon stirring with sodium bicarbonate, most likely is the corresponding non-enolized α-diketone.

The conversion of hydroxyketone F-1, the intermediate in the retro-aldolization mechanism, to diosphenol E-1 upon the addition of potassium t-butoxide would offer additional support for this mechanism. Hydroxyketone F-1 was consequently synthesized, as shown below. Selenous acid effected the quantitative oxidative conversion of



XVIII F-1 E-1

the unsaturated ketone G-7 to the dione XVIII. The reduction of the dione to the unsaturated hydroxyketone F-1 in 90% yield was effected by sodium borohydride. This hydroxyketone was quantitatively converted to the diosphenol E-1 upon being caused to reflux with an

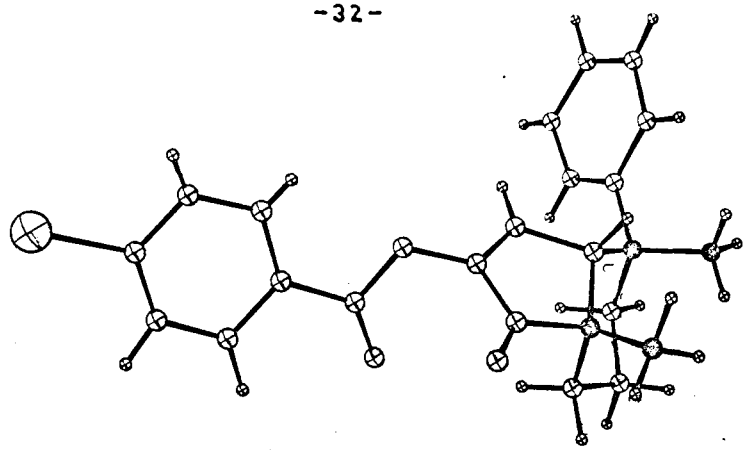
excess of sodium hydroxide. Hydroxyketone F-1 was also converted to diosphenol E-1 in the presence of potassium t-butoxide approximately five times as quickly as the starting material hydroxyketone C-3 was converted to diosphenol E-1. Aliquots, extracted with a syringe at suitable intervals, were quenched with hydrochloric acid and worked up as usual. The rate of the rearrangement was determined by vapor phase chromatography at 275°--diosphenol E-1 eluted after 40 sec. and hydroxyketone F-1 eluted after 46 sec.

The proposed structure of diosphenol E-1 was confirmed by the heavy-atom single-crystal x-ray crystallographic technique. This technique was also applied to hydroxyketone C-3[26] and hydroxyketone F-1. All three substances were studied as their p-bromobenzoate derivatives. Inspection of the conformational drawings below indicates the presence of a 1,3-methyl-phenyl interaction in the p-bromobenzoate derivative XIX of hydroxyketone C-3. The non-bonded distance from the carbon atom of the methyl group to the closest carbon atom of the benzene ring is 3.35 Å. Inspection of the p-bromobenzoate derivative XX of hydroxyketone F-1 indicates the presence of a 1,3-methyl-methyl interaction. The non-bonded distance from the carbon atom of one methyl group of derivative XX to the carbon atom of the other methyl group is 3.33 Å; the corresponding closest H-H interaction is 2.14 Å. A similar methyl-methyl interaction is also present in the p-bromobenzoate derivative XXI of diosphenol E-1. The non-bonded distance from the carbon atom of one methyl group of deriva-

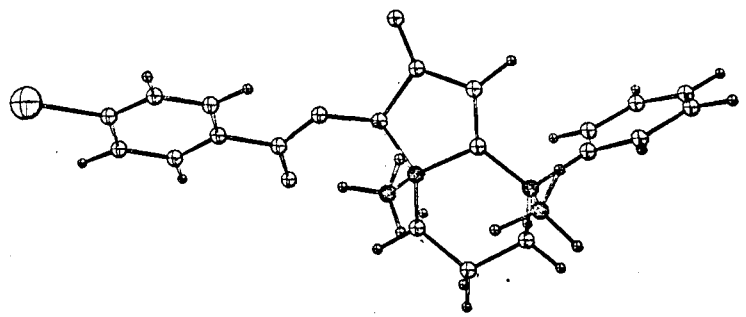
tive XXI to the carbon atom of the other methyl group is 3.43 Å; the corresponding closest H-H interaction is 2.03 Å. The non-bonded distance cited above refers to the static crystalline state in which the plane of the benzene ring is "frozen" such that it is spatially as far removed from the methyl group as possible. The freely rotating benzene ring in solution would impose a more serious steric interaction than is indicated by the non-bonded crystalline interactions. A possible driving force for the initial retro-aldolization and subsequent recyclization is the conversion of hydroxyketone C-3 containing the 1,3-steric interaction of the methyl and phenyl groups to the hydroxyketone E-1 which contains a less sterically encumbered 1,3-methyl-methyl interaction.

Since the rearrangement product has been shown to be 7β, 9β-Dimethyl-2-hydroxy-7α-phenylhexahydro-8βH-1,2-indene-3-one (E-1), the previously described tricyclic keto acid formed by oxidation of the rearrangement product and subsequent cyclization would therefore seem to be 7-keto-5-isodesisopropyldehydroabietic acid (H-2). Inversion of the configuration of the C-5 hydrogen of acid H-2, possibly through palladium catalysis[27], would allow entry into the natural abietic acid series. Hydroxyketone C-3 could consequently be employed as the common starting material for entry into two different terpenoid series, the podocarpic and abietic acid series, if the assignment of the tricyclic keto acid as H-2 is correct.

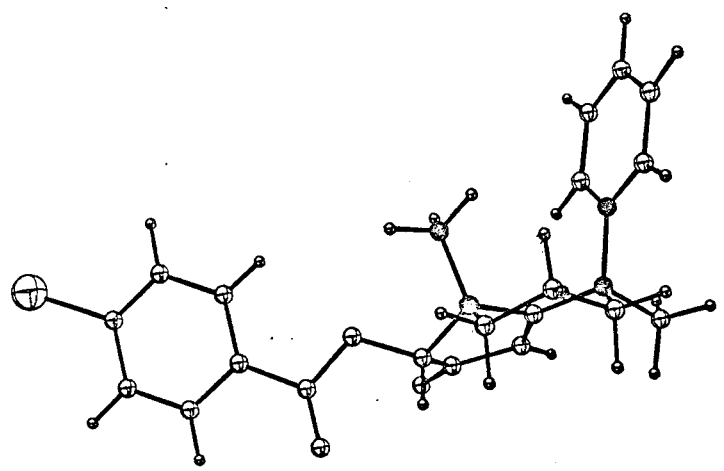
It was therefore decided to prove that the tricyclic keto acid



XXI



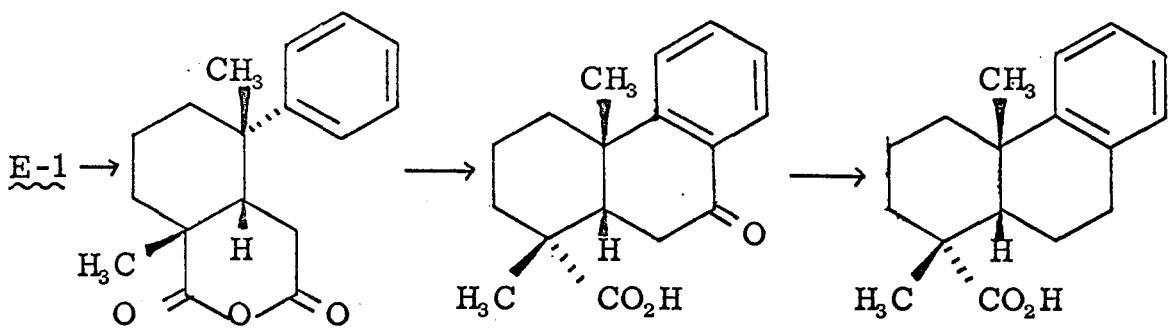
XX



XIX

is indeed H-2. The conversion of diosphenol E-1 to the known tricyclic acid H-3, as shown in Chart H, would confirm the assignment of the tricyclic keto acid as 7-keto-5-isodesisopropyldehydroabietic acid (H-2). The anhydride H-1 was formed in 92% yield from the

Chart H



1 2 3

diosphenol E-1 by initial oxidative cleavage with the aid of hydrogen peroxide--sodium hydroxide[28], and subsequent cyclization with acetic anhydride. Intramolecular acylation was effected by cyclization of the anhydride H-1 in polyphosphoric acid[29a, 29b] to the tricyclic keto acid H-2 in 86% yield. The spectral and physical properties of keto acid H-2 are indicated in Table IV. Hydrogenolysis resulted in the quantitative conversion of tricyclic keto acid H-2 to tricyclic acid H-3. The spectral and physical properties of tricyclic acid H-3

are also indicated in Table IV. Melting points of 146-147°[30a] and

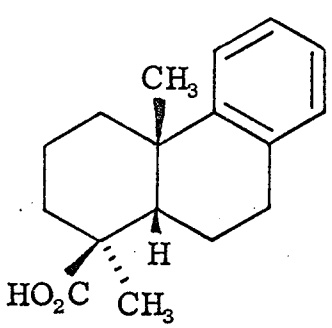
Table IV

PPA Series

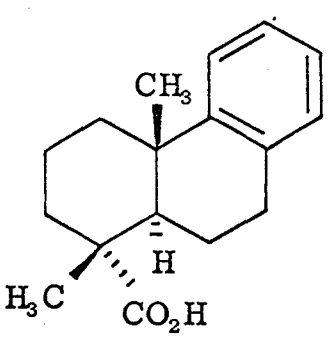
		tricyclic keto acid	tricyclic acid
melting point (°C)		172-173.5	162-164
ir (cm^{-1})	ν $CHCl_3$ max		
acid hydroxyl		3560-2224	3540-2320
monomer acid carbonyl shoulder		1750 (m)	1750 (m)
dimer acid carbonyl		1710 (s)	1710 (s)
ketone carbonyl		1675 (s)	
aromatic double bond		1599 (s)	1600 (w)
uv (mμ)	λ CH_3OH max	253 (ε 10,750)	
nmr (ppm)	δ $CDCl_3$ TMS	1.23 (s)	1.01 (s)
		1.49 (s)	1.39 (s)
		2.25 (d, J = 1.5 Hz)	2.22 (m)
			2.66 (s with w coupling)

145-147°[30b] have been reported in the literature for 5-isodesisopropyldehydroabietic acid. The melting point of the hydrogenolysis product was determined to be 162-164°. Examination of the nmr spectra confirms that the polyphosphoric acid cyclization product is not 7-keto-5-isodesisopropyldehydroabietic acid (H-2) and that the hydrogenolysis product is also not 5-isodesisopropyldehydroabietic acid (H-3). The chemical shift of the two C-6 methylene hydrogens

of keto acid H-2 would be expected to occur at approximately 3.0 ppm. The methyl absorption of acetophenone occurs at 2.59 ppm[31]; the C-6 methylene hydrogens of 7-ketodesoxypodocarpic acid (C-5) occurs at 3.10 ppm[14]. No such adsorption is present in the spectrum of the cyclization product. The absorptions at 2.25 ppm in the cyclization product and 2.22 ppm in the hydrogenolysis product would not be expected in 7-keto-5-isodesisopropyldehydroabietic acid and 5-isodesisopropyldehydroabietic acid respectively. A comparison of reported melting points indicates that the hydrogenolysis product also cannot be any of the three other C-4 and/or C-5 isomeric acids. The melting point of desoxypodocarpic acid (ii) has been reported as 232-233°[32] and 233-235°[7]. The melting point of 5-isodesoxypodocarpic acid (XXII) has been reported as 206-207°[32] and 210-211°[18]. The melting point of desisopropyldehydroabietic acid (XXIII) has been reported as 177-179°[30b] and 174.5-175°[18].



XXII



XXIII

An alternative mode of cyclization of anhydride H-1 is illustrated in Chart I. The chart employs diacid I-1 (corresponding to anhydride H-1) for descriptive purposes. An examination of molecular models of diacid I-1 indicates that the conformation necessary for cyclization to form keto acid I-2 results in a diaxial carboxyl-aromatic ring interaction. A diaxial dimethyl interaction and an axial $-CH_2CO_2H$ grouping are noted in the diacid conformation required for cyclization to form keto acid H-2. The relative energies of the two conformations are difficult to assign.

Inspection of the nuclear magnetic resonance spectrum (re Table IV) of the tricyclic keto acid indicates that acylation involved the C-4 carboxyl grouping. Absorption of the keto acid at 2.25 ppm can be ascribed to the methylene grouping adjacent to the carboxyl group. The methyl group of acetic acid exhibits a signal at 2.10 ppm[31]. A corresponding methylene grouping would be expected at approximately 2.50 ppm, but a molecular model examination of keto acid I-2 indicates that the $-CH_2CO_2H$ grouping is somewhat shielded by the aromatic ring. The maintenance of this signal (at 2.22 ppm), and the addition of a signal at 2.66 ppm (assigned to the two benzylic hydrogens), are additional confirmation of the assignment of the tricyclic acid as I-3.

Spectral observations of compounds obtained in the degradative scheme described in Chart J (page 38) corroborated the assignment of the tricyclic acid as structure I-3. The conditions for the

Chart I

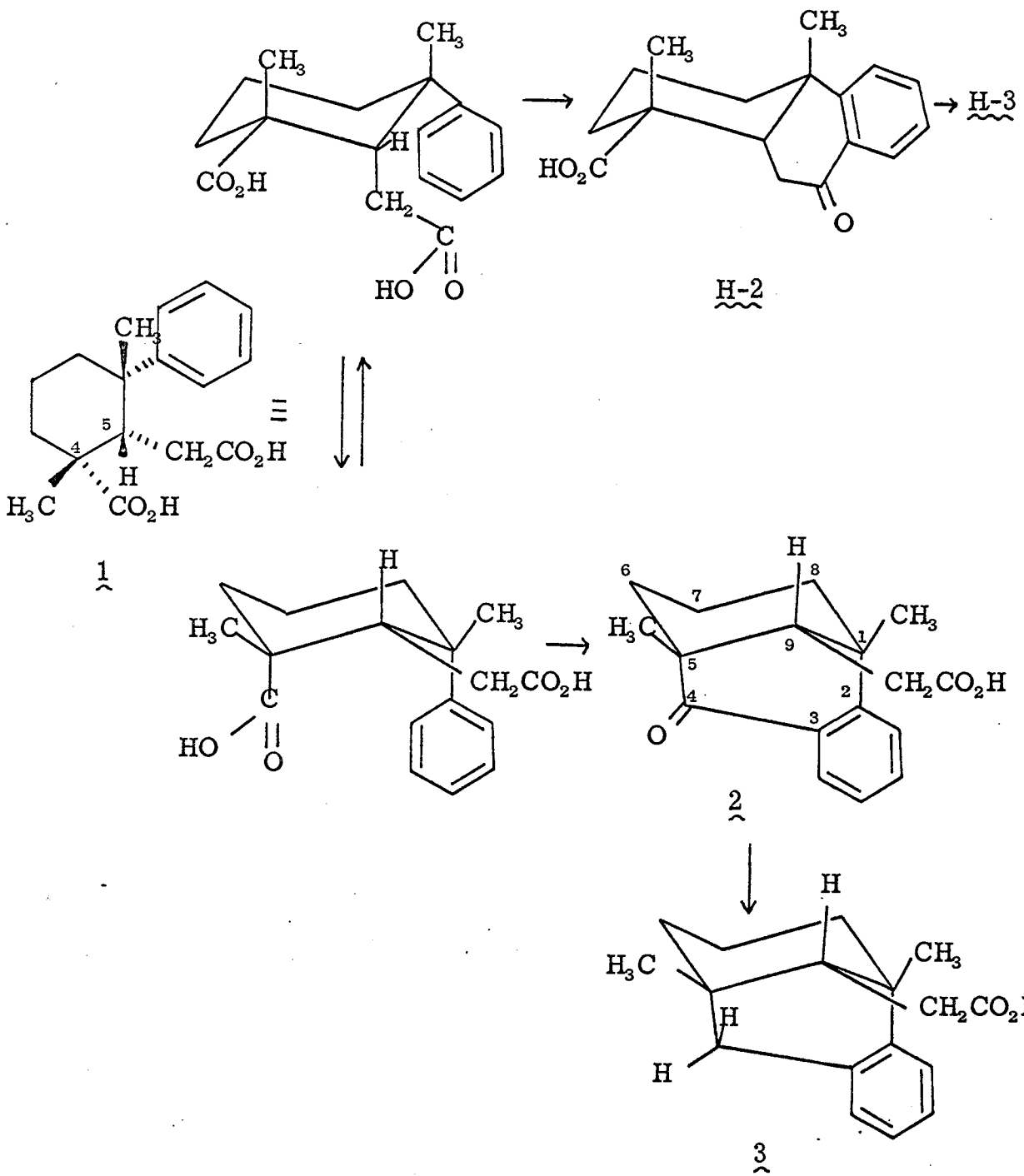
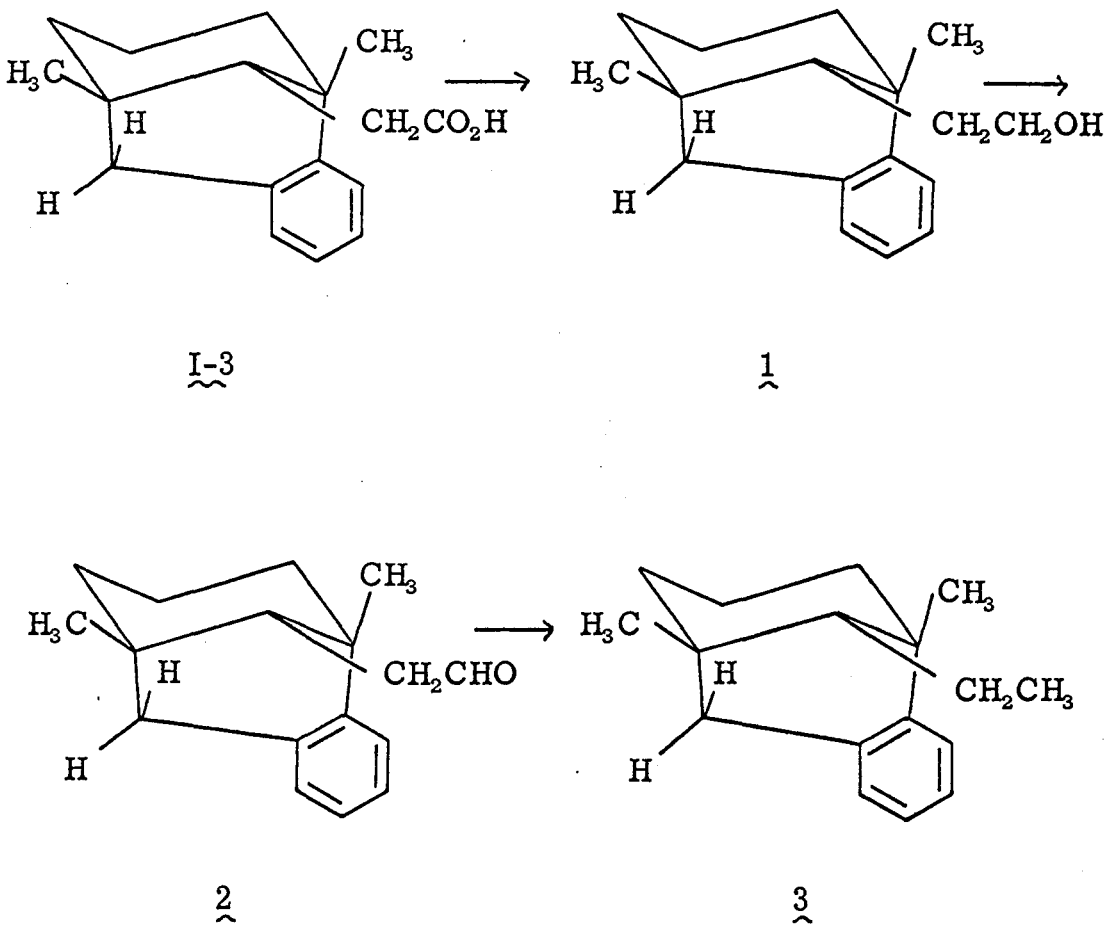

CH3
CH3
H
CO2H
CH2
C
HO
O
H-2
H-3
HO2C
O
CH3
5
4
CH2CO2H
H
H3C
CO2H
1
H
H3C
CH3
C
HO
O
CH2CO2H
2
H
6
7
8
H3C
CH3
1
9
5
4
2
3
CH2CO2H
O
3
H
H3C
CH3
H
CH2CO2H
H

Chart J

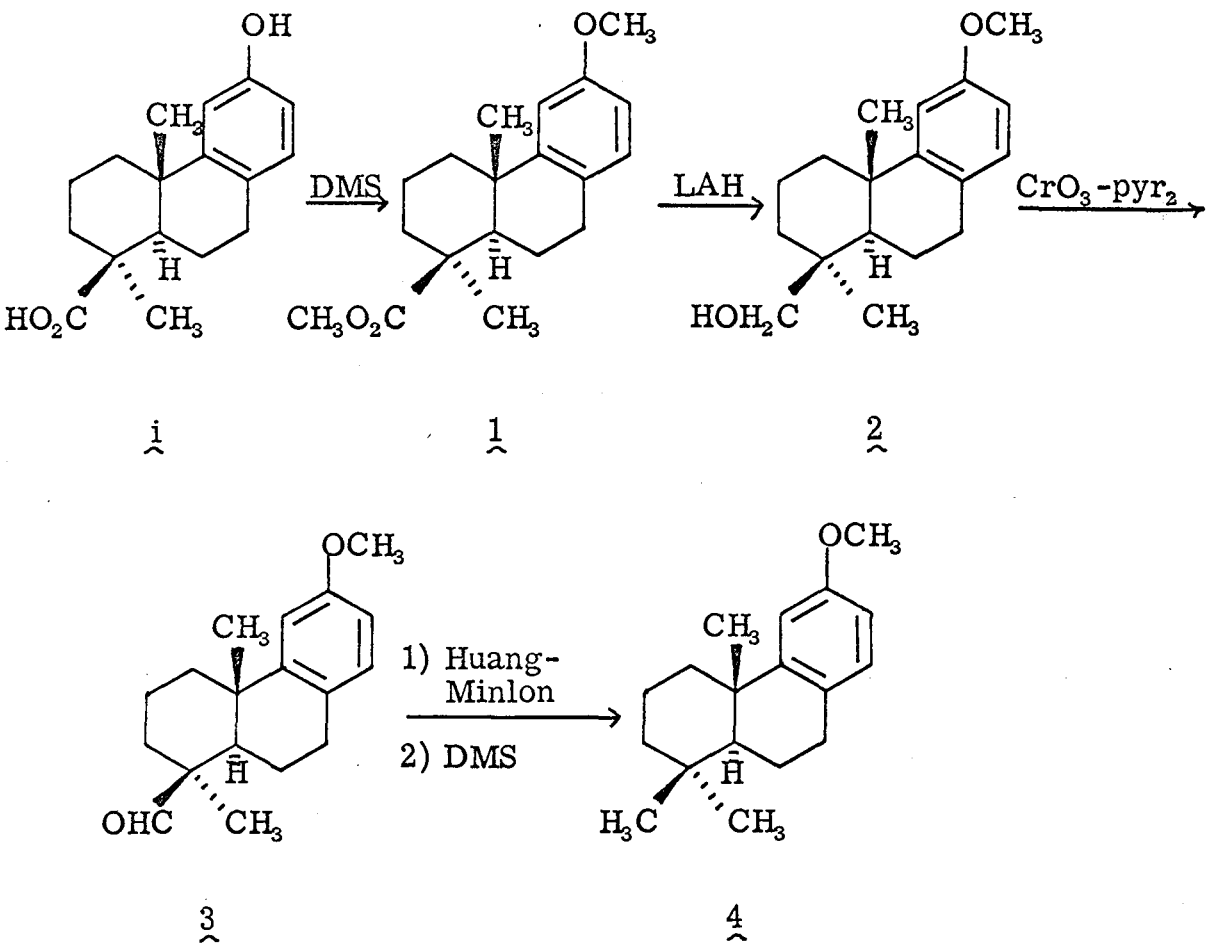


I-3 1

2 3

degradative sequence employed were initially applied and worked out on the model series shown in Chart K. The starting material for the sequence was podocarpic acid[33] (i). The overall yield was 91%. Reduction of podocarpic acid over a four-day period at room temperature affords podocarpinol in only 56% yield[34]. The acid

Chart K



i 1 2

3 4

was therefore esterified prior to lithium aluminum hydride reduction. Oxidation of the alcohol K-2 to the aldehyde K-3 was accomplished with the recently reported solid chromic oxide-dipyridine complex[35]. Huang-Minlon reduction[36] and subsequent remethylation resulted in the formation of O-methylpodocarpane (K-4). A comparison of the

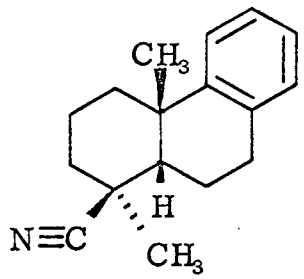
spectral properties of the reduction product with that of authentic O-methylpodocarpane (K-4) reported in the literature[37] indicates that they are the same. The infrared spectrum of the reduction product taken in chloroform exhibits absorption bands at 1605 cm^{-1} (m) and 1570 cm^{-1} (w). The assymetric methyl bending of the gem-dimethyl group is split into a doublet[38] at 1372 and 1367 cm^{-1}. The absorption bands reported in the literature (spectrum taken in chloroform) occur at 1607 cm^{-1} (m) and 1566 cm^{-1} (w). The ultraviolet spectrum of the reduction product exhibited $\lambda_{max}^{95\% C_2H_5OH}$ = 280 mμ (ε 1,490), λ shoulder = 286 mμ (ε 1,320). The ultraviolet spectrum reported in the literature exhibited $\lambda_{max}^{95\% C_2H_5OH}$ = 279 mμ (ε 1,500), λ shoulder = 284 mμ (ε 1,390). The reduction product was an oil. O-methylpodocarpane, reported in the literature, occurs as an oil which crystallizes (mp 31-32°) upon standing.

The tricyclic acid I-3 was reduced to the tricyclic alcohol J-1 in 83% yield with the aid of lithium aluminum hydride. The nuclear magnetic resonance spectrum ($CDCl_3$) of the alcohol exhibited a triplet at 3.60 ppm (J = 8 Hz). The triplet was assigned to the two hydrogens attached to the carbon atom containing the hydroxyl group. The corresponding signal would be expected to be a singlet if the alcohol was in the isoabietic acid series.

The tricyclic alcohol J-1 was oxidized to the tricyclic aldehyde J-2 in 97% yield with the aid of the solid chromic oxide-dipyridine reagent[35]. The nuclear magnetic resonance spectrum ($CDCl_3$) of the

aldehyde exhibited two singlets at 0.94 ppm and 1.32 ppm assigned to the two methyl groups, and a triplet at 9.83 ppm (J = 1 Hz) assigned to the aldehydic hydrogen. The corresponding aldehydic signal would be expected to be a singlet if the aldehyde was in the isoabietic acid series.

The Huang-Minlon procedure[36] was employed to reduce the tricyclic aldehyde J-2 to the tricyclic hydrocarbon J-3 in 94% yield. The infrared spectrum ($CHCl_3$) of the tricyclic hydrocarbon exhibited a singlet absorption band at 1373 cm^{-1} (m). The corresponding signal would be expected to be a doublet (indicative of the gem-dimethyl grouping[38]) if the hydrocarbon was in the isoabietic acid series. The 60 Mc nuclear magnetic resonance spectrum ($CDCl_3$) of the hydrocarbon exhibited two single peaks at 2.54 ppm and 2.72 ppm assigned to the two benzylic hydrogens. Two much smaller peaks at 2.28 ppm and 3.01 ppm (J = 18 Hz) were assumed to be the remainder of the Ab d of d pattern. This section of the spectrum resolved itself into a more recognizable AB pattern (2.90, 2.72, 2.54, 2.36 ppm) when the spectrum was retaken on the Varian Associates HA-100 spectrometer. The corresponding benzylic signal would be expected to be a complicated multiplet if the hydrocarbon was in the isoabietic acid series. The nitrile XXIV[39] exhibits a multiplet assigned to the benzylic hydrogens centered at 2.83 ppm. O-methylpodocarpane K-4 exhibits a multiplet assigned to the benzylic hydrogens centered at 2.82 ppm. Methyl absorptions in the 60 Mc spectrum of the hydro-

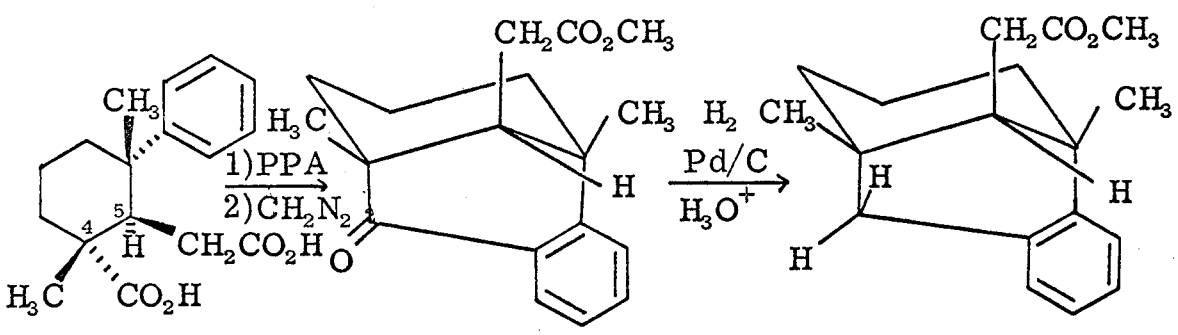


XXIV

carbon J-3 occurred at 1.00 ppm and 1.40 ppm. Integration indicated that two methyl groups were present at 1.00 ppm. The methyl group of the ethyl chain would be expected to exhibit a triplet signal. This signal was not sufficiently resolved.

A survey of the nuclear magnetic resonance spectra[14] of the polyphosphoric acid cyclization product L-2 of the diacid L-1 in the pimaric acid series, and subsequent hydrogenolysis product L-3[40], indicates that the C-4 carboxyl group participated in this cyclization. Diacids L-1 and I-1 have the necessary cis-1,3-carboxyl-phenyl re-

Chart L



1 2 3

lationship required for this "abnormal" cyclization. The diacid C-1 and its epimer at the $-CH_2CO_2H$ center do not have this relationship. Models indicate that the signals which correspond to the methylene group adjacent to the carboxyl group in both L-2 and L-3 would be expected to be downfield relative to the corresponding methylene absorption in J-1 and J-2. This is because only the methylene groups of J-1 and J-2 are shielded by the aromatic ring. This has been found to be the case. An indication of the purity of keto acid L-2 and acid L-3 was not given[14]. A signal at approximately 3.0 ppm, characteristic of the C_6 hydrogens α to the carbonyl group of the keto acid which would be formed if cyclization had occurred in the "normal" manner, was absent. A signal, ascribable to the methylene group adjacent to the ester gouping of keto ester L-2, was centered at 2.52 ppm. It consisted of an unsymmetrical doublet (J = 2.5 Hz) and four smaller peaks which integrated for a total of approximately three protons. The signal, ascribable to the same methylene grouping of ester L-3, was centered at 2.40 ppm. It consisted of a singlet peak and four smaller peaks which integrated for a total of approximately three protons. The benzylic hydrogens exhibited two clean single peaks at 2.70 ppm and 2.83 ppm.

EXPERIMENTAL

Melting points, unless otherwise noted, were taken on a Kofler Hot Stage and are uncorrected. Boiling points are also uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infrared Spectrometer Model 237B; and ultraviolet spectra were recorded on a Cary Recording Spectrometer Model 11M. Nuclear magnetic resonance spectra were recorded on a Varian Associates Model A-60A Nuclear Magnetic Resonance Spectrometer. All gas chromatographic analyses were taken on an F and M Model 810 Gas Chromatograph using a 6 ft silicone gum rubber (SE-30) column. The pressures of the gases employed during the vapor phase chromatographic analyses were helium, 50 psi; hydrogen, 22 psi; and compressed air, 24 psi. A Buerger precession camera and General Electric-Datex diffractometer were employed in the X-ray analyses. Petroleum ether, unless otherwise noted, refers to the fraction boiling in the range 30-60°. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Michigan; and Elek Microanalytical Laboratories, Torrance, California.

7β,9β-Dimethyl-2-hydroxy-7α-phenylhexahydro-8βH-1,2-indene-3-one(E-1) (a) Potassium t-butoxide rearrangement from hydroxyketone C-3: To a stirred solution of 1.31 g (11.7 mmoles) of potassium t-butoxide in 60 ml of t-butyl alcohol (freshly distilled from calcium hydride) contained in a nitrogen-protected flame-dried flask was dropwise added a solution of 1.50 g (5.85 mmoles) of unsaturated

hydroxyketone C-3 in 60 ml of t-butyl alcohol (dried as above). The blood-red colored solution was stirred for an additional 1 hr at approximately 45°, acidified with iced concentrated hydrochloric acid, and diluted with 100 ml of water. The mixture was thrice extracted with 100 ml portions of an ether--benzene solution (4:1). The combined organic layers were washed three times with 40 ml portions of water, twice with 25 ml portions of a saturated salt solution and then dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 1.50 g of solid diosphenol E-1. Gas chromatographic analysis of the crude product at 285° indicated the presence of a single peak with a retention time of 25 sec accounting for 95% of the material and two minor impurities. Chromatography on silicic acid afforded 1.37 g (91%) of diosphenol E-1 on elution with 3 l. of a 10% ether--petroleum ether solution. The analytical sample, obtained as colorless plates melting at 162-164°, was prepared by two crystallizations of a portion of this material from ether--petroleum ether. Anal (Spang) calc'd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86%. Found: C, 79.61; H, 7.84%[7]. ir ($CHCl_3$) 3500, 3350 (OH), 1700, 1650 cm^{-1} (enolic dione); uv max (MeOH) 262 mμ (ε 9,038); nmr ($CDCl_3$) δ 1.32 (s, 3, C-9 CH_3), 1.48 (s, 3, C-7 CH_3), 2.85 (d, 1, J = 3 Hz, C-8 H), 5.65 (d, 1, J = 3 Hz, C-1 vinyl H), 6.22 (s, 1, OH).

By the same procedure as described above 0.100 (0.195 mmole) of the unsaturated hydroxyketone C-3 underwent rearrangement to the diosphenol E-1 in a mixture of 0.088 g (0.390 mmole) of potassium t-butoxide and 8 ml t-butyl alcohol upon being stirred in a nitrogen atmos-

phere for 1 hr at room temperature. There resulted 0.100 g of a pale yellow crystalline solid which was shown by vpc analysis at 300° to consist of equal amounts of hydroxyketone C-3 (18 sec) and diosphenol E-1 (14 sec).

(b) Potassium t-butoxide rearrangement from hydroxyketone F-1: To a stirred solution of 0.106 g (0.934 mmole) of potassium t-butoxide in 6 ml of t-butyl alcohol (freshly distilled from calcium hydride) contained in a nitrogen-protected flame dried flask was dropwise added a solution of 0.120 g (0.467 mmole) of unsaturated hydroxyketone F-1 in 6 ml of t-butyl alcohol (dried as above). The blood-red colored solution was stirred at room temperature. Four equal aliquots, removed and quenched with iced concentrated hydrochloric acid, were worked up as described above. The progress of the reaction was followed by vapor phase chromatography--the retention time of diosphenol E-1 was 40 sec and the retention time of hydroxyketone F-1 was 46 sec sec at an oven temperature of 275°. The diosphenol/hydroxyketone ratio of the 0.030 g oil isolated after 10 min was 1/4. The ratio of the partially crystalline oil was 3.5/5.0 after 20 min, 4/1 after 43 min, and 6.5/1.0 after 80 min.

(c) and (d) Sodium hydroxide rearrangements from hydroxyketones C-3 and F-1: To a stirred solution of 2.4 ml of 40% aqueous sodium hydroxide solution in 10 ml of methanol in a nitrogen atmosphere, repeatedly degassed at 0.03 mm with the aid of liquid nitrogen, was added dropwise 0.400 g (1.58 mmoles) of hydroxyketone C-3 in 10 ml of methanol. The red colored solution, which turned pale yellow in 15 min, was heated under reflux for 30 min, cooled, quenched with

iced concentrated hydrochloric acid, and then diluted with 100 ml of water. The mixture was thrice extracted with 25 ml portions of ether--benzene (4:1), and the combined ethereal extracts were washed three times with 10 ml portions of a saturated brine solution and dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 0.400 g of a white solid--exhibiting a single peak (100% yield) with retention time of 23 sec by gas chromatographic analysis at 285°. The infrared spectrum, melting point, and mixture melting point with diosphenol E-1, prepared from the potassium t-butoxide rearrangement described above, indicated that the isolated product and diosphenol E-1 were identical.

By the same procedure as described above 0.040 g (0.158 mmole) of the unsaturated hydroxyketone F-1 underwent rearrangement to the diosphenol E-1 in a degassed solution of 0.25 ml of 40% aqueous sodium hydroxide in 2 ml of methanol. There resulted 0.040 g of an off-white crystalline solid which produced a single peak on vpc analysis at 270° with a retention time of 33 sec. The infrared spectrum, melting point, and mixture melting point with authentic diosphenol E-1 indicated that the isolated product was identical with diosphenol E-1.

7β,9β-Dimethyl-2-methoxy-7α-phenylhexahydro-8βH-1,2-indene-3-one (D-2): A stirred mixture of 1.40 g (5.46 mmoles) of diosphenol E-1, 5.96 ml (62.2 mmoles) of dimethyl sulfate[15], 19.95 g (144 mmoles) of anhydrous potassium carbonate, and 100 ml of anhydrous acetone was heated under reflux in a nitrogen atmosphere

for 22 hr. The two phase system was cooled, and the mixture was then concentrated on the rotary evaporator under reduced pressure until approximately 20 ml of acetone remained. The cooled mixture, diluted with 400 ml of water, was placed in the refrigerator for 2 hr. The pale yellow solid, separated from the aqueous solution by filtration, was washed four times with 20 ml portions of water. The residue was heated at 56° in a vacuum (0.1 mm) until a constant weight of 1.470 g (100% yield) was achieved and maintained. Gas chromatographic analysis of the crude product, (melting at 109-111°) at 285° indicated a single peak with retention time of 28 sec. The analytical sample, prepared by two recrystallizations of a portion of this material from ether--petroleum ether (60-75°), consisted of thick colorless platelets melting at 110.5-111.5°. Anal (Spang) calc'd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20%. Found: C, 80.03; H, 8.28%[14]. ir ($CHCl_3$) 1710 (C=O) 1628 (double bond linked to oxygen) 1250, 1075 cm^{-1} (vinyl ether); uv max (MeOH) 257 mμ (ϵ 8,410); nmr ($CDCl_3$) δ 1.34 (s, 3, C-9 $C\underset{\frown}{H}_3$), 1.50 (s, 3, C-7 $C\underset{\frown}{H}_3$), 2.97 (d, 1, $\underline{J}$ = 3 Hz, C-8 $\underset{\frown}{H}$), 3.46 (s, 3, $OC\underset{\frown}{H}_3$), 5.38 (d, 1, $\underline{J}$ = 3 Hz, vinyl $\underset{\frown}{H}$).

7β,9β-Dimethyl-3ξ-hydroxy-7α-phenylhexahydro-8βH-indan-2-one (D-4): To a suspension of 0.577 g (15.2 mmoles) of lithium aluminum hydride in 35 ml of tetrahydrofuran (freshly distilled from lithium aluminum hydride) was added 0.412 g (1.52 mmoles) of unsaturated ketone D-2 in 35 ml of tetrahydrofuran (dried as above), and the reaction was heated under reflux in a nitrogen atmosphere for 1.5 hr. After treatment of the cooled solution with 0.15 ml of 10%

aqueous sodium hydroxide solution, the precipitated salts were removed by filtration, and the filtrate was diluted with 100 ml of ether. The ethereal solution was washed three times with 15 ml portions of water, two times with 10 ml quantities of saturated salt solution, dried (Na_2SO_4), and concentrated at reduced pressure. Gas chromatographic analysis of the 0.407 g oily residue indicated the presence of a single peak with the retention time of 24 sec accounting for 98° of the material. ir ($CHCl_3$) 3594, 3470 (OH), 1650 cm^{-1} (double bond linked to oxygen). A solution of 1.00 g (11.1 mmoles) of oxalic acid in 10 ml of water was added to the 0.407 g residue dissolved in 60 ml of acetone. The mixture was stirred at room temperature for 48 hr. The solution was concentrated on the rotary evaporator under reduced pressure until approximately 10 ml of acetone remained and 100 ml of 9:1 ether--benzene was added. The system was washed three times with 10 ml portions of 10% aqueous sodium bicarbonate, twice with 10 ml quantities of water, twice with 10 ml quantities of saturated salt solution and dried (Na_2SO_4). Removal of the solvent at reduced pressure yielded 0.390 g (95% overall yield) of an off-white colored solid, exhibiting a single peak with retention time of 26 sec by gas chromatographic analysis at 278°, which melted at 120-124°. The analytical sample, obtained after four recrystallizations of a portion from ether--petroleum ether, consisted of small colorless plates melting at 122-124°. Anal (Spang) calc'd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58%. Found: C, 78.85; H, 8.44%. ir ($CHCl_3$) 3550, 3450 (OH), 1748 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.43,

1.46 (two s, 6, C-9 and C-7 CH_3), 3.15 (s, 1, OH), 3.83 (s, 1, C-3 H).

7β,9β-Dimethyl-3α-acetoxy-7α-phenylhexahydro-8βH-indan-2-one (D-5): A solution of 0.412 g (1.60 mmoles) of hydroxyketone D-4 in 8.6 ml (107 mmoles) of anhydrous pyridine was treated with 10 ml (107 mmoles) of acetic anhydride and stirred at room temperature for 15 hr. A nitrogen stream was employed to blow off the major portion of the solution. The residue, taken up in 100 ml of ether--benzene solution (4:1), was successively washed three times with 8 ml portions of 5 N sulfuric acid, three times with 10 ml portions of water, three times with 10 ml quantities of aqueous sodium bicarbonate, two times with 10 ml portions of water, two times with 10 ml portions of saturated salt solution, and dried (Na_2SO_4). Removal of the solvent at reduced pressure yielded 0.446 g of a pale yellow solid. Crystallization from acetone--hexane afforded 0.319 g of a white crystalline solid, mp 172-176°. Chromatography of the mother liquor on 15 g florisil (60-100 mesh) afforded an additional 0.055 g (83% combined yield) of crystalline material, mp 174-177°, on elution with 350 ml of ether. The analytical sample, a colorless hexagonal tubular solid, was prepared by three additional recrystallizations of a portion of the once recrystallized material from acetone--hexane and melted at 175-176.5°. Anal (Spang) calc'd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05%. Found: C, 75.98; H, 8.13%. ir ($CHCl_3$) 1763 (ester C=O), 1738 (C=O), 1215 cm^{-1} (ester); nmr ($CDCl_3$) δ 1.38, 1.46 (two s, 6, C-9 and C-7 CH_3), 2.13 (s, 3, $OCOCH_3$), 5.13 (s, 1, C-3 H).

7β-9β-Dimethyl-7α-phenylhexahydro-8βH-indan-2-one (D-6): After 0.155 g (22.3 atoms) of lithium wire had been allowed to dissolve in ca 100 ml of liquid ammonia (dried over sodium immediately preceding the reaction), a solution of 0.270 g (1.100 mmole) of the acetoxy ketone D-5 in 10 ml of tetrahydrofuran (dried over lithium aluminum hydride immediately preceding the reaction) was added dropwise. The reaction mixture was stirred for 1 hr. Solid ammonium chloride was then added to discharge the blue color, and the ammonia was allowed to evaporate. The resulting solid white residue was taken up in 100 ml of ether--benzene (4:1). The ethereal solution was washed with 10 ml of 3 N hydrochloric acid, thrice with 10 ml portions of water, twice with 10 ml portions of saturated salt solution and dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 0.232 g of a yellow oil, whose infrared spectrum (e.g., carbonyl absorption at 1735 cm^{-1} and hydroxy absorption at 3590 and 3420 cm^{-1} in chloroform) indicated partial reduction of ketone D-6 to the corresponding alcohol. Consequently an ice-cooled mixture of the 0.232 g crude product in 5 ml of acetone was oxidized with 0.23 ml of 8 N aqueous chromic acid solution[17]. After the mixture had been stirred in the cold for 15 min, isopropyl alcohol was added to destroy the excess oxidant, and the mixture was diluted with 100 ml of water and thrice extracted with 60 ml portions of ether--benzene (4:1). The combined organic layers were washed two times with 5 ml quantities of 10% aqueous sodium bicarbonate, two times with 10 ml portions of water, two times with 10 ml portions of

brine and dried (Na_2SO_4). Removal of the solvent at reduced pressure yielded 0.205 g of an orange oil which crystallized overnight. The infrared spectrum indicated the absence of hydroxylic absorption. The crude product was purified by preparative thin layer chromatography on a 2 mm silicic acid plate (20× 20 cm), on elution with 30% ether--petroleum ether. The 0.129 g (59% yield) white crystalline solid, which exhibited a single peak with retention time of 24 sec by vapor phase chromatography at 300°, was isolated from a band whose R_f was 0.60. A sample of analytical purity, obtained as thin plates after two recrystallizations of a portion from hexane, melted at 100.5-101°. A mixture of this material and the cis-fused ketone III, mp 100.5-101°, melted between 70 and 102°. The semicarbazone, formed by the procedure of Fieser[41], afforded a yellow crystalline solid of melting point 220.5-222° after two recrystallizations from a mixture of methanol and ethanol. A mixture of this material and the semicarbazone of the trans-fused ketone IV, mp 221-223°, melted between 208 and 243°. Anal (Elek) calc'd for $C_{18}H_{25}N_3O$: C, 72.20; H, 8.42; N, 14.04%. Found: C, 72.18; H, 8.56; N, 13.94%.

7β-9β-Dimethyl-7α-phenylhexahydro-8αH-indan-2-one (XVI): An intimate mixture of 0.200 g (0.658 mmole) of diacid XV (sample obtained from R. E. Ireland) and 0.214 g (0.798 mmole) of lead carbonate[19], contained at the sealed end of a 7 mm pyrex tube was heated at 285° (at 5 mm pressure) for 2 hr, the ketone immediately distilling as it was formed. The distillate was taken up in 100 ml of ether--petroleum ether (4:1), and the solution was washed three times with 5 ml portions of 5% potassium hydroxide solution, two

times with 5 ml portions of saturated salt solution and then dried (Na_2SO_4). The solution, concentrated under reduced pressure, afforded 0.133 g of an off-white colored solid residue. The crude product, placed on a 2 mm thick silicic acid plate (20 × 20 cm) and developed with 40% ether--petroleum ether, yielded 0.107 g (67% yield) of a white colored crystalline solid (exhibiting a single peak with retention time of 97 sec by vapor phase chromatography at 256°) which was extracted from the major band, R_f 0.44. The analytical sample, obtained from two recrystallizations of a portion from hexane, melted at 79.5-80.5°. The trans-fused ketone XVI and ketone F-2 exhibited the same vapor phase chromatograph retention time and could therefore not be distinguished by this technique. The thin layer (i.e., silicic acid analytical plate developed with 50% ether--petroleum ether) chromatographic R_f value of the trans-fused ketone XVI was 0.51 and that of ketone F-2 was 0.49. Anal (Elek) calc'd for $C_{17}H_{22}O$: C, 84.25; H, 9.15%. Found: C, 84.25; H, 9.22%. ir ($CHCl_3$) 1710 cm^{-1} (C=O); nmr (CCl_4) δ 1.09 (s, 3, C-9 CH_3), 1.39 (s, 3, C-7 CH_3).

7β-9α-Dimethyl-7α-phenylhexahydro-8βH-indan-2-one (IV): An intimate mixture of 0.060 g (0.197 mmole) of diacid V (sample obtained from R. E. Ireland) and 0.064 g (0.240 mmole) of lead carbonate[19], contained at the sealed end of a 7 mm pyrex tube was heated at 281° (at 5 mm pressure) for 15 min, the ketone distilling as it was formed. The glassy white oily pyrolysate, which resisted attempts at crystallization, was formed in a yield of 98% (0.047 g). The combustion analysis of the semicarbazone derivative, mp

221-223°, was correct[7]. ir ($CHCl_3$) 1743 cm^{-1} (C=O); nmr (CCl_4) δ 0.33 (s, 3, C-9 CH_3), 1.28 (s, 3, C-7 CH_3).

6-Methyl-2-(3'-methallyloxy-1')methylene-6-phenylcyclohexane (G-2): A solution of 21.6 g (100 mmoles) of formyl ketone G-1, prepared in the manner reported by Ireland and Kierstead[18], 8.30 g (115 mmoles) of methallyl alcohol, and a trace of p-toluene sulfonic acid were dissolved in 100 ml of benzene. The solution was heated under reflux in a nitrogen atmosphere for 10 hr, cooled, and then diluted with 100 ml of ether. The organic solution was then washed four times with 10 ml portions of 10% aqueous potassium hydroxide solution, four times with 10 ml portions of saturated salt solution and dried (Na_2SO_4). Removal of the solvent at reduced pressure yielded 25.0 g of a yellow oil. Chromatography of the crude product on silicic acid afforded 21.9 g (81%) of the desired allyl vinyl ether G-2, a pale yellow oil which crystallizes upon standing, on elution with 15 l. of a 12.5% ether--petroleum ether solution. Allyl vinyl ether G-2 decomposes on the column during vpc analysis. The analytical sample, obtained as platelets, was prepared by two recrystallizations of a portion of the material from ether--isopentane and melted at 66.5-67.5°. Anal (performed by H. King, U.C.L.A. Microanalytical Laboratories) calc'd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20%. Found: C, 79.69; H, 8.24%. ir (neat) 1675 (C=O), 1582 (double bond linked to oxygen), 1078 cm^{-1} (vinyl ether); uv max (MeOH) 278 mμ (ε 11,960); nmr ($CDCl_3$) δ 1.43 (s, 1, C-2 CH_3), 1.70 (m, 3, vinylic CH_3), 4.37 (s, 2 -O-CH_2), 4.96 (m, 2 $>C=CH_2$), 7.41 (m, 1,

$\geq C=\underset{\wedge}{CH}-O-$).

6-Methyl-2-(3'-methallyl)-6-phenylcyclohexanone (G-4): Heating of 15.1 g (55.8 mmoles) of allyl vinyl ether G-2 under nitrogen in an oil bath at 190° for 1 hr resulted in the formation of 14.9 g of a yellow-orange oily product. ir (neat) 1731 and 1697 cm^{-1} (C=O) indicates that the material is the product of Claisen rearrangement[21], 2-formyl-2-methallyl-6-methyl-6-phenylcyclohexanone (G-3). A solution of 30.0 g (217 mmoles) of potassium carbonate in 30 ml of water was added to the crude product dissolved in 450 ml of methanol. The mixture was stirred for 9 hr at room temperature, and then concentrated under reduced pressure to approximately 150 ml of solution. The reaction mixture, diluted with 400 ml of water, was thrice extracted with 10 ml portions of ether--benzene (1:1). The combined ethereal layers were washed three times with 25 ml portions of saturated salt solution and then dried (Na_2SO_4). Removal of the solvent at reduced pressure yielded 13.5 g of a yellow-orange oil. Chromatography of the residue on silicic acid afforded 10.8 g (80%) of the desired deformylated ketone G-4, a clear colorless oil, on elution with 3 l. of 10% ether--petroleum ether. The oil exhibited a single peak with retention time of 66 sec at 237° during vpc analysis. The analytical sample, obtained by evaporative distillation of a portion of the material at 0.05 mm pressure (15 cm path length) boiled at 54-57°. Anal (Spang) calc'd for $C_{17}H_{22}O$: C, 84.25; H, 9.15%. Found: C, 84.35; H, 9.25%. ir (neat) 1718 (C=O), 1651, 889 cm^{-1} ($C=CH_2$); nmr ($CDCl_3$) δ 1.23 (s, 3, C-2 $C\underset{\wedge}{H}_3$), 1.56 (s, 3,

vinylic $C\underset{\sim}{H}_3$), 4.52, 4.63 (two m, 2, $C{=}C\underset{\sim}{H}_2$).

2β,6β-Dimethyl-2α-(3'-methallyl)-6α-phenylcyclohexanone (G-5): To a suspension of 23.6 g (207 mmoles) of potassium t-butoxide in 700 ml of dry benzene in a nitrogen atmosphere was added with stirring at room temperature a solution of 10.0 g (41.3 mmoles) of methallyl ketone G-4 in 300 ml of dry benzene. After the reaction mixture had stirred for 15 min (generating a pale yellow colored enolate), it was cooled in an ice-water bath for 3 min and then 25.0 ml (56.8 g, 400 mmoles) of methyl iodide was added all at once. The reaction mixture was then allowed to stir overnight as the cooling bath came to room temperature. An additional 75 ml of methyl iodide was then added, and the reaction mixture was stirred and maintained at reflux for 2.5 hr. The cooled mixture was concentrated under reduced pressure to approximately 30% of its original volume, and 200 ml of water and 100 ml of ether were added. The aqueous layer was twice washed with 70 ml portions of ether--benzene (4:1). The combined ethereal layers were washed two times with 40 ml portions of a saturated salt solution and dried (Na_2SO_4). The 238° vapor phase chromatographic analysis of the 10.5 g (100%) pale yellow oily residue remaining after the solvent was removed under reduced pressure indicated the presence of a single peak (75 sec). The peak was assigned to the methylated product and accounted for 95% of the material. The α-methylated isomer XIII is eluted from a silicic acid column immediately prior to the β-methylated epimer G-5 upon increasing the polarity of the eluent from 70-99% benzene--petroleum

ether, but quantitative separation is quite difficult to achieve. The nmr spectral analysis of the crude product indicates that the ratio of β-methylated material G-5 to α-methylated epimer XIII (e.g., C-2 methyl absorption at 1.10 ppm vs. 0.68 ppm, respectively) is 5:1. The analytical sample, obtained by distillation of a portion of the material at 0.05 mm pressure, boiled at 84-87°. Anal (Spang) calc'd for $C_{18}H_{24}O$: C, 84.32; H, 9.44%. Found: C, 84.57; H, 9.66%. ir (neat) 1698 (C=O), 1643, 890 cm^{-1} ($C=CH_2$); nmr ($CDCl_3$) δ 1.10 (s, 3, C-2 CH_3), 1.33 (s, 3, C-6 CH_3), 1.54 (d, 3, J = 1 Hz, vinylic CH_3), 4.48, 4.77, (two m., 2, $C=CH_2$).

2α, 6β-Dimethyl-2β-(3'-methallyl)-6α-phenylcyclohexanone (XIII)[7]: To a rapidly stirred nitrogen protected mixture of 0.300 g (1.48 mmoles) of methylated ketone XII[42], 0.252 g (2.24 mmoles) of potassium t-butoxide, and 4 ml of dry benzene was added 0.435 ml (0.402 g, 4.34 mmoles) of methallyl chloride (distilled between 70.5-71° immediately preceding the reaction). The pale yellow colored mixture was stirred for an additional 10 hr at room temperature, and then heated under reflux for an additional 5 hr. The cooled solution was diluted with 40 ml of water and thrice extracted with 30 ml portions of ether--benzene (4:1). The combined ethereal layers were washed three times with 7 ml portions of water, one time with 10 ml of saturated salt solution and dried (Na_2SO_4). Removal of the solvents at reduced pressure afforded 0.381 g (100% yield) of a pale yellow oil. Gas chromatographic analysis of the crude product indicated quantitative methylative conversion. The ratio of the two epimeric

methylated ketones, as determined by nmr spectroscopy, was 9:1 in favor of the trans-dimethylated ketone XIII. This ratio was confirmed by the gas chromatographic analysis which indicated that the cis-dimethylated ketone G-5 is eluted from the column in 675 sec, and the trans-dimethylated ketone XIII is eluted from the column in 735 sec at the following machine settings-oven at 152°, injection port at 317°, and detector at 302°. ir (neat) 1698 (C=O), 1643, 890 cm^{-1} ($C=CH_2$); nmr ($CDCl_3$) δ 0.68 (s, 3, C-2 CH_3), 1.31 (s, 3, C-6 CH_3), 1.71 (d, 3, J = 1 Hz, vinylic CH_3), 4.67, 4.88 (two m, 2, $C=CH_2$).

2β,6β-Dimethyl-2α-acetonyl-6α-phenylcyclohexanone (G-6): A solution of 6.45 g (25.2 mmoles) of the terminal methylene olefin G-5 (nmr analysis indicates the presence of 94% G-5 and 6% epimeric XIII) in 650 ml of dioxane (distilled immediately preceding the reaction from lithium aluminum hydride), 64.5 ml of glacial acetic acid, and 129 ml of water was treated with 0.065 g of solid osmium tetroxide[23], and the resulting solution was allowed to stir 10 min, during which time it became dark brown. There was then added in small portions, over a period of 25 min, 22.9 g (101 mmoles) of crystalline p-periodic acid. After stirring for 24 hr, the reaction mixture was diluted with 100 ml of water and the system was extracted four times with 500 ml portions of chloroform. The combined organic layers were then successively washed three times with 300 ml portions of water, three times with 70 ml portions of 10% aqueous potassium hydroxide solution, 200 ml of water, saturated salt solution and then dried (Na_2SO_4). The solution, concentrated to dryness under reduced

pressure, yielded 6.50 g of a yellow oil. Chromatography of the crude product on silicic acid afforded 5.52 g (85% yield) of the desired diketone G-6, a pale yellow crystalline solid, on elution with 12 l. of 30% ether--petroleum ether. Two successive crystallizations of a portion from petroleum ether afforded colorless crystalline analytically pure platelets melting at 88.5-89.5° (Thomas Hoover capillary silicone oil bath). Anal (Spang) calc'd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58%. Found: C, 79.13; H, 8.60%. ir ($CHCl_3$) 1712, 1692 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.22 (s, 3, C-2 CH_3), 1.44 (s, 3, C-6 CH_3), 1.90 (s, 3, vinylic CH_3), 2.42, 2.58 (two s, 2, $-CH_2-COCH_3$). The assumption that the minor product of the methylation reaction was the epimeric trans-dimethylated cyclohexanone XIII was confirmed as follows. The attempt to separate what was assumed to be epimeric methylated product through the aid of silicic acid chromatography resulted in an early cut whose ratio of trans-dimethylated ketone XIII to cis-dimethylated ketone G-5 was 9:1. The material, weighing 1.013 g, oxidized with osmium tetroxide and p-periodic acid and worked up as above yielded a crystalline solid (mp 92-93.5°). The melting point of authentic 2β-acetonyl-2α, 6β-dimethyl-6α-phenylcyclohexanone XIII is 92-93.5°, and the mixture melting point is 92-94°. The ir and nmr spectra of both compounds were identical. ir ($CHCl_3$) 1715, 1690 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.63 (s, 3, C-2 CH_3), 1.29 (s, 3, C-6 CH_3), 2.06 (s, 3, $-CO-CH_3$).

7β, 9β-Dimethyl-7α-phenylhexahydro-1, 8-indene-2-one (G-7): A solution of 2.00 g (7.75 mmoles) of dione G-6 in 17 ml of

azeotropically dried benzene was added dropwise to a stirred, nitrogen protected, incomplete solution of 2.62 g (23.2 mmoles) of potassium t-butoxide in 25 ml of t-butyl alcohol (freshly distilled from calcium hydride), and the reaction mixture was stirred at room temperature for 24 hr in a nitrogen atmosphere. The orange colored solution was acidified with 2.5 ml of 3 N hydrochloric acid and most of the t-butyl alcohol was removed at reduced pressure. The residue was then partitioned between 100 ml of ether--benzene (4:1) and 20 ml of water. The organic layer was washed three times with 10 ml portions of water, once with 10 ml of saturated salt solution and then dried (Na_2SO_4). The solution, concentrated under reduced pressure, left a 0.190 g (100% yield) white crystalline solid residue shown to be pure by both vapor phase (i.e., exhibiting a single peak with retention time of 90 sec at 275°) and thin layer chromatography (i.e., exhibiting a single spot with R_f value of 0.42 upon being developed in 50% ether--petroleum ether on a silicic acid plate). The analytical sample, obtained as colorless thick platelets after three recrystallizations of a portion from ether--hexane, melted at 90-91°. Anal (Spang) calc'd for $C_{17}H_{20}O$: C, 84.96; H, 8.39%. Found: C, 84.95; H, 8.49%. ir ($CHCl_3$) 1690 (C=O), 1593 (C=C); nmr ($CDCl_3$) δ 1.47 (s, 3, C-9 $C\underset{\frown}{H}_3$), 1.71 (s, 3, C-7 $C\underset{\frown}{H}_3$), 2.33 (s, 2, $-C\underset{\frown}{H}_2-CO-$), 5.13 (s, 1, $C=C\underset{\frown}{H}-CO-$).

7β-9β-Dimethyl-7α-phenylhexahydro-8βH-indan-2-one (F-2): After 0.852 g (12.2 g atoms) of lithium wire had been allowed to dissolve in ca 250 ml of liquid ammonia (dried by distillation from

sodium immediately preceding the reaction), a solution of 0.600 g (2.50 mmoles) of α,β-unsaturated ketone G-7 in 90 ml of dry ether (distilled from lithium aluminum hydride immediately preceding the reaction) was added dropwise. The reaction mixture was stirred for 1 hr. Solid ammonium chloride was then added to discharge the blue color, and the ammonia was allowed to evaporate. The resulting solid residue was partitioned between 200 ml of ether--benzene (4:1) and 40 ml of water. The organic layer was successively washed three times with 20 ml portions of water, two times with 10 ml portions of a saturated salt solution and dried (Na_2SO_4). Removal of the solid at reduced pressure afforded 0.588 g of an off-white colored solid. Both hydroxylic and carbonyl absorptions were noted in the ir spectrum. An ice-cooled mixture of the ketone--alcohol mixture in 15 ml of acetone was consequently oxidized with 1.5 ml of 8 N aqueous chromic acid solution[17]. After the mixture had been stirred in the cold for 10 min, isopropyl alcohol was added to destroy the excess oxidant, and then the mixture was diluted with 100 ml of water and extracted four times with 40 ml portions of ether--benzene (4:1). The combined ethereal layers were washed two times with 7 ml portions of 10% aqueous sodium bicarbonate, two times with 10 ml portions of water, two times with 10 ml quantities of saturated salt solution and then dried (Na_2SO_4). Removal of the solvent at reduced pressure yielded 0.567 g of an off-white colored crystalline solid. Analysis of the vapor phase chromatogram of the crude oxidation product taken with an oven temperature of 264° indicated complete absence of the alcohol, 97%

ketone F-2 exhibiting a retention time of 82 sec, and 3% unreacted unsaturated ketone G-7 exhibiting a retention time of 91 sec. Separation of the mixture was achieved on three 2 mm silica gel plates (20 × 20 cm) on elution with 40% ether--petroleum ether. The 0.526 g (90% yield) white crystalline solid extracted from the R_f 0.56 bands was shown to be pure by gas chromatographic analysis. The analytical sample, obtained as thin platelets after two recrystallizations of a portion from hexane, melted at 99.5-100°. (Thomas Hoover capillary silicone oil bath). The melting point of ketone D-6, obtained by degradation from diosphenol B-1 was 99-100° (Hoover), the mixture melting point (Hoover) exhibited no depression. Both the infrared and nmr spectra of both compounds are identical. The thin layer chromatogram of both these compounds on silicic acid, employing 40% ether--petroleum ether as developer, exhibited the identical R_f value of 0.56; the gas chromatographic peak enhancement study also indicated that these compounds are identical. The mixture melting point with the trans-fused ketone XVI mp 81.5-82.5 (Hoover), occurred between 79 and 93°. These facts indicate that the potassium t-butoxide rearrangement product has the structure E-1. Anal (Spang) calc'd for $C_{17}H_{22}O$: C, 84.25; H, 9.15%. Found: C, 84.33; H, 9.21%. ir ($CHCl_3$) 1738 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.33, 1.40 (two s, 6, C-7 and C-9 CH_3).

7β,9α-Dimethyl-2-hydroxy-7α-phenylhexahydro-8αH-1,2-indene-3-one (C-6): An ice-cooled mixture of 0.980 g (3.78 mmoles) of hydroxyketone C-2 in 100 ml of acetone was oxidized with 4 ml of

8 N aqueous chromic acid solution[17]. After the mixture had been stirred at 0° in a nitrogen atmosphere for 45 min, isopropyl alcohol was added to destroy the excess oxidant. To the filtered reaction mixture was added 5 ml of saturated sodium bicarbonate solution and the resultant mixture was concentrated on the rotary evaporator at 40° at reduced pressure until 20 ml of liquid remained. The filtered chromic salts were twice washed with 250 ml portions of water and the aqueous washings were extracted three times with 50 ml portions of ether--benzene (4:1). The combined ethereal washings were added to the concentrated rotary evaporator mixture and the resultant system was washed three times with 15 ml portions of saturated salt solution and dried (Na_2SO_4). Removal of the solvent at reduced pressure yielded 0.860 g of an off-white colored oily solid. Chromatography on silicic acid afforded 0.545 g (56%) of diosphenol C-6 on elution with 900 ml of 12% ether--petroleum ether. The analytical sample, obtained as platelets after two recrystallizations of a portion from ether--petroleum ether melted at 121-123°. The compound exhibited a purple color upon the addition of ferric chloride test solution. The mixture melting point with diosphenol E-1, obtained from potassium t-butoxide rearrangement (mp 162-164°), exhibited a depression - the mixture starting to melt at 105°. Separation of both diosphenols was obtained on the gas chromatograph with the oven temperature at 268°--cis-α-diosphenol C-6 eluting after 112.5 sec and the cis-β-diosphenol E-1 after 121.5 sec. Anal (Spang) calc'd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86%. Found: C, 79.77; H, 7.86%.

ir ($CHCl_3$) 3480, 3240 (OH), 1695, 1652 cm^{-1} (enolic dione); uv max (MeOH) 259 mμ (ϵ 9,620); nmr ($CDCl_3$) δ 0.93 (s, 3, C-9 $C\underset{\frown}{H}_3$), 1.20 (s, 3, C-7 $C\underset{\frown}{H}_3$), 3.26 (d of d, 1, $\underline{J} = 3.4_{H_1\text{-}H_8}$ Hz, $\underline{J} = 1.5_{\text{w coupling}}$ Hz, C-8 $\underset{\frown}{H}$), 6.68 (d, 1, $\underline{J}$ = 3.4 Hz, vinyl $\underset{\frown}{H}$). An off-white colored oily solid which weighed 0.150 g and crystallized to an off-white colored solid upon being seeded with authentic diacid $\underset{\sim\sim}{C\text{-}1}$ was isolated from the above aqueous layer. Its infrared spectrum exhibits peaks both at 3540-2270 (acid OH) and 1700 cm^{-1} (C=O) which are characteristic of diacid $\underset{\sim\sim}{C\text{-}1}$. The compound, obtained after three recrystallizations of a portion from ether--petroleum ether, melted at 206-208°. The mixture melting point with authentic diacid $\underset{\sim\sim}{C\text{-}1}$, 207-209°, was 205-208°. Smaller scale chromic acid oxidations worked up by extracting the chromic salts into water (as opposed to filtering off the chromic salts and concentrating the filtrate with sodium bicarbonate as performed above) yielded a yellow crystalline solid. ir ($CHCl_3$) 1758 (shoulder) and 1748 cm^{-1} (carbonyls), hydroxylic absorption absent; nmr ($CDCl_3$) δ 0.89, 1.09 (two s, 6, C-9 and C-7 $C\underset{\frown}{H}_3$), 2.52, 2.60, 2.61, 2.72 (d of d, 2, C-1 $C\underset{\frown}{H}_2$). This compound did not impart a color to ferric chloride test solution[13], but exhibited a purple color when the chloroform solution of the compound containing a drop of pyridine is heated on the steam bath for 30 sec before the addition of ferric chloride. A white solid is obtained after 0.030 g of yellow crystalline solid, probably the non-enolized α-diketone $\underset{\sim\sim}{C\text{-}6}$, is stirred at room temperature in 8 ml of acetone with 1 ml aqueous saturated sodium bicarbonate solution for 2 hr in a

nitrogen atmosphere. The purified white solid, obtained after two recrystallizations of a portion from ether--petroleum ether, melted at 120-122°. The mixture melting point with authentic diosphenol C-6, whose melting point is 121-123°, is 120-122°.

7β,9α-Dimethyl-2-methoxy-7α-phenylhexahydro-8αH-1,2-indene-3-one (XVII): A stirred mixture of 0.205 g (0.798 mmole) of diosphenol C-6, 0.75 ml of dimethyl sulfate[15], 2.5 g of anhydrous potassium carbonate, and 50 ml of anhydrous acetone was heated under reflux in a nitrogen atmosphere for 14 hr. The mixture was concentrated to near dryness under reduced pressure and the residue, diluted with 120 ml of ether--petroleum ether (4:1), was washed three times with 15 ml portions of a saturated salt solution and then dried (Na_2SO_4). The solution, concentrated to dryness on the rotary evaporator, afforded 0.217 g (100% yield) of a pale yellow oil which crystallized upon standing. The ether exhibited a single peak with retention time of 118 sec by vapor phase chromatography at 300°. The analytical sample, obtained as white platelets melting at 73-75°, was prepared by one recrystallization of a portion of this material from ether--petroleum ether. Anal (Elek) calc'd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20%. Found: C, 79.87; H, 8.13%. ir ($CHCl_3$) 1710 (C=O), 1628 (double bond linked to oxygen), 1258, 1080 cm^{-1} (vinyl ether); uv max (MeOH) 256 mμ (ε 8,110); nmr ($CDCl_3$) δ 0.83 (s, 3, C-9 CH_3), 1.09 (s, 3, C-7 CH_3), 3.16 (d, 1, J = 3 Hz, C-8 H), 3.68 (s, 3, OCH_3), 6.36 (d, 1, J = 3 Hz, vinyl H).

7β,9β-Dimethyl-7α-phenylhexahydro-1,8-indene-2,3-dione (XVIII): A solution of 0.800 g (3.36 mmoles) of unsaturated ketone G-7, 1.16 g (10.4 mmoles) of selenium dioxide and 0.188 ml (10.4 mmoles) of water in 40 ml of glacial acetic acid was heated under reflux for 4 hr. Filtration of the cooled reaction mixture and removal of the acetic acid from the filtrate at reduced pressure left an orange-colored oil. The oily residue, diluted with 200 ml of ether--benzene (4:1) was washed five times with 20 ml portion of water, three times with 20 ml portion of 5% aqueous sodium bicarbonate, three times with 15 ml portions of saturated salt solution and then dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 0.843 g (100% yield) of a yellow crystalline solid - exhibiting a single spot with an R_f value of 0.46 on a silicic acid thin layer chromatogram upon being developed with 35% ether--petroleum ether. Diketone XVIII decomposes in the vapor phase chromatograph when the oven temperature is 274°. Two successive crystallizations of a portion from ether--petroleum ether afforded analytically pure thin yellow platelets which melted at 111.5-112.5°. Anal (Spang) calc'd for $C_{17}H_{18}O_2$: C, 80.25; H, 7.13%. Found: C, 80.38; H, 7.25%. ir ($CHCl_3$) 1765 (C=O) 1717 (conjugated C=O), 1622 cm^{-1} (C=C); uv max (MeOH) 278 mμ (ε 5,720); nmr ($CDCl_3$) δ 1.53, 1.80 (two s, 6, C-9 and C-7 CH_3), 5.97 (s, 1, C=C$\underset{\sim}{H}$-CO).

7β,9β-Dimethyl-3α-hydroxy-7α-phenylhexahydro-1,8-indene-2-one (F-1): An ice-water cooled solution of 0.889 g (3.49 mmoles) of diketone XVIII in 25 ml of methanol was treated with 0.033 g

(0.873 mmole) of sodium borohydride in 4 ml of water and the mixture was stirred at room temperature in a nitrogen atmosphere for 3.5 hr. The reaction mixture was diluted with 150 ml of water and extracted with three 50 ml portions of ether--benzene (4:1). The combined organic extracts were washed with three 15 ml portions of a saturated salt solution, dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The 0.887 g pale yellow solid residue, eluted from 50 g of silicic acid (60-200 mesh) with 1300 ml of 50% ether--petroleum ether, afforded 0.823 g (90% yield) of a white crystalline solid - exhibiting a single spot whose R_f value is 0.82 on silicic acid thin layer chromatography when developed with ether. The hydroxyketone F-1 decomposes in the gas chromatographic column when the oven is maintained at 246°. The analytical sample, obtained as fine thin platelets after one crystallization of a portion from ether--petroleum ether, melted at 116.5-118.5°. Anal (Spang) calc'd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86%. Found: C, 79.69; H, 7.87%. ir ($CHCl_3$) 3514, 3370 (OH), 1710 (C=O), 1585 cm^{-1} (C=C); uv max (MeOH) 235 mμ (ϵ 10,790); nmr ($CDCl_3$) δ 1.37, 1.75 (two s, 6, C-9 and C-7 CH_3), 3.16 (s, 1, OH), 4.04 (d, 1, J = 1 Hz, C-3 H), 5.29 (s, 1, vinyl H).

7β,9α-Dimethyl-3α(p-bromobenzoyl)-7α-phenylhexahydro-1,8-indene-2-one (XIX): A solution of 0.618 g (2.81 mmoles) of p-bromobenzoyl chloride in 20 ml of dry pyridine was added to 0.600 g (2.31 mmoles) of hydroxyketone C-3 dissolved in 30 ml of dry pyridine - the system being maintained at 0° during addition, and then

stirred at room temperature for 18 hr in a nitrogen atmosphere. A nitrogen stream and reduced pressure were employed to remove the major portion of pyridine. The residue, taken up in 200 ml of ether--petroleum ether (4:1), was successively washed three times with 10 ml portions of 5 N sulfuric acid, three times with 10 ml portions of water, twice with 10 ml portions of saturated salt solution and then dried (Na_2SO_4). Removal of the solvent at reduced pressure yielded 1.02 g of an off-white colored solid. The crude product, placed on four 2 mm silicic acid plates (20 × 20 cm) and developed with 45% ether--petroleum ether, yielded 0.712 g (70% yield) of a white crystalline solid exhibiting a single peak with retention time of 340 sec by vapor phase chromatographic analysis at 303° which was extracted from the major band, R_f 0.60. The analytical sample, obtained as tiny thin plates after one recrystallization of a portion from ether--methanol and a second recrystallization from acetone--petroleum ether, melted at 177.5-179°. Anal (Spang) calc'd for $C_{24}H_{23}BrO_3$: C, 65.61; H, 5.28; Br, 18.19%. Found: C, 65.66; H, 5.21; Br, 18.07%. ir ($CHCl_3$) 1720-1715 (C=O), 1592 (aromatic ring C=C), 1270 cm^{-1} (ester); uv max (MeOH) 246 mμ (ε 31,100); nmr ($CDCl_3$) δ 0.62 (s, 3, C-9 $C\underset{\sim}{H}_3$), 1.44 (s, 3, C-7 $C\underset{\sim}{H}_3$), 5.37 and 6.39 (two s, 2, C-3 $\underset{\sim}{H}$ and vinyl $\underset{\sim}{H}$), 7.75 (A_2B_2, 4, $\underline{J}$ = 23.5 Hz, $\underline{J}$ = 8.5 Hz, p-bromobenzoate ring).

7β,9β-Dimethyl-2-(p-bromobenzoyl)-7α-phenylhexahydro-8βH-1,2-indene-3-one (XXI): A solution of 1.26 g (4.50 mmoles) of p-bromobenzoyl chloride in 40 ml of dry pyridine was added to 0.400 g

(1.56 mmoles) of diosphenol E-1 dissolved in 20 ml of dry pyridine - the system being maintained at 0° during addition and then stirred at room temperature for 15 hr in a nitrogen atmosphere. A nitrogen stream and reduced pressure were employed to remove the major portion of pyridine. The residue, taken up in ether--benzene (4:1), was successively washed with 5 N sulfuric acid, water, saturated salt solution and then dried (Na_2SO_4). Removal of the solvent at reduced pressure yielded 0.850 g of a yellow oily crystalline solid. The crude product, eluted from 50 g of silicic acid (60-200 mesh) with 600 ml of 15% ether--petroleum ether yielded 0.533 g of a white oily solid shown by vapor phase chromatography at 305° to be composed of 90% of the desired bromobenzoate XXI (with a retention time of 145 sec) and a single impurity present in 10% yield with a retention time of 3 sec, and 0.189 g of pure white crystalline XXI. Washing the 0.533 g oily white solid with cold petroleum ether resulted in the isolation of 0.457 g [yielding 0.646 g (94% yield) of combined pure solid] of additional bromobenzoate XXI. The analytical sample, obtained as needles after one recrystallization of a portion from acetone--petroleum ether, melted at 139.5-140.5°. Anal (Spang) calc'd for $C_{24}H_{23}BrO_3$: C, 65.61; H, 5.28; Br, 18.19%. Found: C, 65.69; H, 5.35; Br, 18.25%. ir ($CHCl_3$) 1743, 1723 (C=O), 1643 (enol ester C=C), 1590 (aromatic ring C=C), 1262 cm^{-1} (ester); uv max (MeOH) 238 mμ (ϵ 34,850); nmr ($CDCl_3$) δ 1.42, 1.53 (two s, 6, C-9 and C-7 CH_3), 3.02 (d, 1, J = 2.4 Hz, C-8 H), 6.48 (d, 1, J = 2.4 Hz, vinyl H), 7.75 (A_2B_2, 4, J = 21.5 Hz, J = 8.8 Hz, p-bromobenzoate ring).

7β,9β-Dimethyl-3α-(p-bromobenzoyl)-7α-phenylhexahydro-1,8-indene-2-one (XX): A solution of 0.230 g (1.05 mmoles) of p-bromobenzoyl chloride in 5 ml of dry pyridine was added to 0.150 g (0.585 mmole) of hydroxyketone F-1 dissolved in 5 ml of dry pyridine - the system being maintained at 0° during addition and then stirred at room temperature for 17 hr in a nitrogen atmosphere. A nitrogen stream and reduced pressure were employed to remove the major portion of pyridine. The residue, taken up in ether--benzene (4:1), was successively washed with 5 N sulfuric acid, water, saturated salt solution and dried (Na_2SO_4). Removal of the solvent at reduced pressure yielded 0.237 g of an off-white colored solid. The crude product, placed on two 2 mm silicic acid plates (20× 20 cm) and developed with 30% ether--petroleum ether yielded 0.166 g (67%) of a white crystalline solid. The analytical sample, obtained as a needle matte after two recrystallizations of a portion from ether--methanol, melted at 107.5-108.5°. The sample was heated at 143° at 0.03 mm pressure for 1.5 hr before the melting point was taken because the bromobenzoate XX occludes ether upon crystallization. Anal (Spang) calc'd for $C_{24}H_{23}BrO_3$: C, 65.61; H, 5.28; Br, 18.19%. Found: C, 65.81; H, 5.33; Br, 18.15%. ir ($CHCl_3$) 1725-1715 (C=O), 1592 (aromatic ring C=C), 1270 cm^{-1} (ester); uv max (MeOH) 246 mμ (ε 29,620); nmr ($CDCl_3$) δ 1.41, 1.77 (two s, 6, C-9 and C-7 CH_3), 5.36, 5.47 (two s, 2, C-3 H and vinyl H), 7.81 (A_2B_2, 4, J = 23.4 Hz, J = 8.7 Hz, p-bromobenzoate ring).

2α-Carboxymethyl-1β,3β-dimethyl-3α-phenylcyclohexanecarboxylic acid anhydride (H-1): To a stirred solution of 0.942 g (3.66 mmoles) diosphenol E-1 in 40 ml of methyl alcohol was separately added 1.5 ml of 10% aqueous sodium hydroxide solution and 4 ml of 30% hydrogen peroxide. The solution was heated at reflux for 1 hr, cooled, and 1.5 ml of 10% sodium hydroxide and 4 ml of 30% hydrogen peroxide were again added. The solution was heated at reflux for 1 hr, cooled and an additional 4 ml of 30% hydrogen peroxide was again added. The solution was heated for an additional 1 hr. To the cooled solution was added 100 ml of 4:1 ether--benzene. The ethereal solution was twice extracted with 50 ml portions of 3% aqueous sodium hydroxide solution. The combined aqueous layers were acidified with iced concentrated hydrochloric acid, and then thrice extracted with 30 ml portions of 4:1 ether--benzene. The combined ethereal layers were washed four times with 10 ml portions of saturated salt solution, and then dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 1.10 g of a pale yellow crystalline solid. ir ($CHCl_3$) 3530-2326 (acid OH), 1775 (acid C=O monomer), 1725-1700 cm^{-1} (acid C=O dimer). Gas chromatographic analysis of the crude product at 300° indicated the presence of a single peak with a retention time of 106 sec accounting for 94% of the material. The crude product was combined with 30 ml of acetic anhydride and refluxed under nitrogen for 2 hr. The solution was concentrated under reduced pressure to 1.030 g of an orange oily residue which readily crystallized upon being triturated with ether. The crude product, recrystallized from

ether--petroleum ether, afforded 0.337 g of a white crystalline product, mp 122-124°. The concentrated mother liquor afforded 0.338 g of a white crystalline solid, mp 121-124°. Gas chromatographic analysis of the combined crystalline solids at 300° indicated the presence of a single peak with a retention time of 66 sec accounting for 99% of the material. Gas chromatographic analysis of the mother liquor, a pale yellow oily solid, at 300° indicated that this mixture contained 70% anhydride H-1 (combined yield of 92%). A single crystallization of a portion of the solid material from ether--petroleum ether afforded a white crystalline solid melting at 124-125° (reported[14] mp 124-125°). Anal (Spang) calc'd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40%. Found: C, 75.01; H, 7.26%. ir ($CHCl_3$) 1804, 1759 cm^{-1} (anhydride C=O); nmr[14] ($CDCl_3$) δ 1.42, 1.53 (two s, 6, C-1 and C-3 CH_3).

syn-9-(1,5-Dimethyl-4-oxo-2,3-benzobicyclo[3.3.1]nonane)-acetic acid (I-2): To 38.4 ml of 85% phosphoric acid under nitrogen was added 48 g of phosphorous pentoxide. After stirring for 1 hr, 0.320 g of anhydride H-1 was added and the mixture was heated with stirring at 90° for 1 hr. While still warm, the brown colored reaction mixture was poured over approximately 100 g of crushed ice, and the precipitate was extracted into ether (upon being thrice washed with 50 ml portions of 4:1 ether--benzene). The combined ethereal layer was twice washed with 15 ml portions of water, washed four times with a saturated salt solution, and then dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 0.310 g of a yellow solid. Keto acid I-2 did not elute from the SE 30 vpc column. Crystallization

of the crude product from ethyl acetate--hexane afforded 0.275 g (86% yield) of a white crystalline solid, mp 171-174°. The analytical sample, obtained as white platelets melting at 172-173.5°, was prepared by two further crystallizations from ethyl acetate--hexane. Anal (Elek) calc'd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40%. Found: C, 74.91; H, 7.28%. ir ($CHCl_3$) 3560-2224 (acid OH), 1710 (acid C=O), 1675 (ketone C=O), 1599 cm^{-1} (C=C); uv max (MeOH) 253 mμ (ε 10,750), 292 mμ (ε 1,620); nmr ($CDCl_3$) δ 1.23 (s, 3, C-5 $C\underset{\frown}{H}_3$), 1.49 (s, 3, C-1 $C\underset{\frown}{H}_3$), 2.25 (d, 2, $\underline{J}$ = 1.5 Hz, $-C\underset{\frown}{H}_2-CO_2H$), 10.65 (s, 1, $CO_2\underset{\frown}{H}$).

syn-9-(1,5-Dimethyl-2,3-benzobicyclo[3.3.1]nonane)acetic acid (I-3): To a suspension of 0.1 g of 10% palladium on carbon in 5 ml of glacial acetic acid was added a solution of 0.197 g (0.722 mmole) of keto acid I-2 and 4 drops of 60% aqueous perchloric acid in 10 ml of glacial acetic acid, and the mixture was stirred in a hydrogen atmosphere until the uptake of hydrogen gas ceased (2 hr). During this period 36.5 ml of hydrogen was absorbed. The catalyst was removed by filtration and washed with 50 ml of benzene. The filtrate was diluted with 100 ml of water, and the benzene layer was separated. The aqueous layer was thrice extracted with 30 ml portions of 1:1 ether--benzene. The combined organic layers were thrice washed with 15 ml portions of water, thrice washed with 15 ml portions of a saturated brine solution, and then dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 0.189 g (100% yield) of an off-white colored crystalline solid, mp 159-163°. The

analytical sample, obtained as white platelets melting at 162-164°, was prepared by two further crystallizations from ethyl acetate--hexane. Anal (Elek) calc'd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58%. Found: C, 78.94; H, 8.48%. ir ($CHCl_3$) 3540-2320 (acid OH), 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.01 (s, 3, C-5 $C\underset{\sim}{H}_3$), 1.39 (s, 3, C-1 $C\underset{\sim}{H}_3$), 2.22 (m, 2, $-C\underset{\sim}{H}_2-CO_2H$), 2.56 (s, 2, w coupling causes pattern to look like d of d, $J_{w\ coupling}$ = 0.6 Hz, benzylic $C\underset{\sim}{H}_2$), 11.23 (s, 1, $CO_2\underset{\sim}{H}$).

syn-9-(1,5-Dimethyl-2,3-benzobicyclo[3.3.1]nonane)-2'-ethyl alcohol (J-1): A solution of 0.300 g (1.16 mmoles) of acid I-3 in 20 ml of tetrahydrofuran (freshly distilled from lithium aluminum hydride) was dropwise added to 0.228 g (6.00 mmoles) of lithium aluminum hydride in 80 ml of tetrahydrofuran (dried as above). The stirred mixture was heated at reflux in a nitrogen atmosphere for 3 hr. To the cooled mixture was cautiously added 5 ml of 10% aqueous sodium hydroxide, and the resultant granular sodium aluminate salts were separated by filtration. The filtrate was concentrated at reduced pressure to near dryness. The residue was taken up in 100 ml of 1:1 ether--benzene, twice washed with 10 ml portions of water, thrice washed with 10 ml portions of a saturated salt solution, and then dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 0.260 g of a yellow oil. Gas chromatographic analysis of the crude product at 260° indicated the presence of a single peak with a retention time of 58 sec accounting for 90% of the material. A 0.060 g portion of the crude product, placed on a 2 mm thick silicic acid plate (20 × 20 cm) and developed with 50% ether--petroleum ether, afforded 0.055 g

(83% yield) of a clear colorless oil which was extracted from a band centered at R_f 0.65. Gas chromatographic analysis indicated that alcohol J-1 was pure. The analytical sample, obtained as a clear colorless oil by evaporative distillation over a 10 cm path length, exhibited bp 100-102° (0.20 mm). Anal (Elek) calc'd for $C_{17}H_{24}O$: C, 83.55; H, 9.90%. Found: C, 83.64%; H, 9.98%. ir ($CHCl_3$) 3606 and 3420 cm^{-1} (shoulder) (OH); nmr ($CDCl_3$) δ 0.99 (s, 3, C-5 CH_3), 1.18 (s, 1, OH), 1.39 (s, 3, C-1 CH_3), 3.60 (t, 2, J = 8 Hz, $-CH_2OH$).

syn-9-(1,5-Dimethyl-2,3-benzobicyclo[3.3.1]nonane)-acetaldehyde (J-2): To 0.207 g (90% pure, 0.760 mmole) of alcohol J-1 dissolved in 24 ml of methylene chloride was added 1.31 g (5.06 mmoles) of solid chromic oxide--dipyridine complex[35]. The dark brown colored mixture was stirred at room temperature for 15 min, and then filtered through 25 g of Merck acid-washed alumina with 100 ml of methylene chloride. The clear colorless eluent was concentrated at reduced pressure to almost dryness and taken up in 150 ml of 1:1 ether--benzene. The ethereal solution was successively washed two times with 5 ml portions of 1 N hydrochloric acid, two times with 10 ml portions of water, 3 times with 10 ml portions of a saturated salt solution and then dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 0.197 g of a yellow oil. Gas chromatographic analysis of the crude product at 270° indicated the presence of a single peak with a retention time of 41 sec accounting for 88% of the material (100% yield). ir ($CHCl_3$) 1722 cm^{-1} (C=O); nmr ($CDCl_3$)

δ 0.94 (s, 3, C-5 $C\underset{\frown}{H}_3$), 1.32 (s, 3, C-1 $C\underset{\frown}{H}_3$), 9.83 (t, 1, $\underline{J}$ = 1 Hz, -$C\underset{\frown}{H}$O). The aldehyde was converted into its semicarbazone derivative by the procedure of Fieser[41]. An analytical sample of the semicarbazone prepared by two crystallizations from methanol--ether melted at 159-160°. Anal (Elek) calc'd for $C_{18}H_{25}N_3O$: C, 72.21; H, 8.42; N, 14.03%. Found: C, 72.05; H, 8.54; N, 13.58%. ir ($CHCl_3$) 3530, 3474, 3402, 3350 (NH), 1690, 1635, 1567 cm^{-1} (amide bands).

syn-9-Ethyl-1,5-dimethyl-2,3-benzobicyclo[3.3.1]nonane (J-3): To 0.090 g (88% pure, 0.326 mmole) of aldehyde J-2 was added 0.224 g (3.40 mmoles) of 85% potassium hydroxide dissolved in 10 ml of triethylene glycol, and 0.192 g (5.70 mmoles) of 95% hydrazine was added to the resultant clear pale yellow solution. The stirred solution was first heated at 105° for 2.5 hr in a nitrogen atmosphere, and then at 205° for 4 hr. A Dean-Stark trap was employed to remove the excess hydrazine and water. The solution was cooled and 100 ml of 4:1 petroleum ether--ether was added. The ethereal mixture was thrice extracted with 50 ml portions of water. The combined aqueous layers were back-extracted with three 30 ml portions of 1:1 ether--benzene. The combined ethereal layers were washed with three 10 ml portions of water, one 10 ml portion of a saturated salt solution, and dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 0.085 g of a yellow oil. Gas chromatographic analysis of the crude product at 280° indicated the presence of a single peak with a retention time of 26 sec accounting for 80% of the material. The crude product

was purified by preparative thin layer chromatography on a 2 mm silicic acid plate (20 × 20 cm) by elution with 10% benzene--petroleum ether. The 0.058 g (94% yield) clear colorless oil, which exhibited a single peak during vapor phase chromatography, was isolated from a band whose R_f was 0.69. Evaporative distillation (over a path length of 15 cm) afforded a clear colorless oil of analytical sample purity, bp 55-57° (0.06 mm). Anal (Elek) calc'd for $C_{17}H_{24}$: C, 89.41; H, 10.59%. Found: C, 89.37; H, 10.68%. ir ($CHCl_3$) 1373 cm^{-1} (singlet, CH_3); $nmr_{60\,Mc}$ ($CDCl_3$) δ 1.00 (s + smaller spikes, 6, two $C\underset{\sim}{H}_3$), 1.40 (s, 3, $C\underset{\sim}{H}_3$), 2.63 (d of d, 2, $\underline{J}$ = 26 Hz, $\underline{J}$ = 18 Hz, benzylic $C\underset{\sim}{H}_2$); $nmr_{100\,Mc}$ ($CDCl_3$) δ 2.63 (d of d, 2, $\underline{J}$ = 36 Hz, $\underline{J}$ = 18 Hz, benzylic $C\underset{\sim}{H}_2$).

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APPENDIX

Data Employed in the Determination of the Structure of 7β, 9α-Dimethyl-3α-(p-bromobenzoyl)-7α-phenylhexahydro-1, 8-indene-2-one (XIX) by X-ray Analysis

Experimental

Crystals suitable for an x-ray analysis were grown utilizing the slow evaporative technique employing a mixture of ether and methyl alcohol. The resulting crystals were surveyed on a precession camera. The unit cell dimensions (Å) were: a = 24.80, b = 12.62, c = 13.09. The corresponding bond angles (°) were: α = 90.00, b = 93.64, γ = 90.00. The systematic extinctions were: hkl, h+k odd; hol, l odd. The space group was $C_{2/c}$. There are 8 molecules in the unit cell. The calculated density is 1.426 g/cm^3, and the observed density is 1.43 g/cm^3. The number of reflections recorded were 2146, of which 2071 were non-zero reflections.

One angstrom intensity data was collected for the compound on the General Electric-Datex diffractometer using nickel filtered copper radiation. A θ-2θ scan technique was employed, background was counted for 10 sec at each end of the scan, and the scan rate was 2° per min in 2θ. A single check reflection was monitored every 30 reflections. The check reflection indicated no crystal damage and was reproducible well within counting statistics.

The diffractometer output was processed using subprograms of

the CRYRM crystallographic computer system[1]. The processing included corrections for background and for Lorentz and polarization effects. It also included calculation of the F^2 value and its standard deviation for each of the reflections. The standard deviations were assigned on the basis of the following equation:

$$\sigma^2(I) = S + (B_1 + B_2)\alpha^2 + (dS)^2$$

Where S is the scan count, B_1 and B_2 are the background counts, d is an empirical constant equal to 0.02, and $\alpha = n/2\,mt$ where n = scan range, m = scanning speed, and t = time for background count in seconds. Finally, the data were placed on an absolute scale by means of Wilson statistics.

Structure Determination and Refinements

The trial structure was derived by the usual Patterson and Fourier techniques in three dimensions. Full matrix least-squares refinement of coordinates, isotropic temperature factors, and scale factor reduced the R-index to 11.5% after the refinement. A difference Fourier indicated no misplaced or missing Br, C or O atoms. The difference Fourier was also utilized to locate the hydrogen atoms. The addition of the hydrogen atoms to the structure factor calculation and the application of anisotropic temperature factors to the refinement reduced the R-index to its final value, 7.2%. The observed and calculated structure factors are listed in Table I. The final refined atomic parameters and their standard deviations are presented in

Table II. The bond lengths and angles of the structure are given in Tables III and IV. The standard deviations in the coordinates, derived from the residuals and the diagonalized elements of the inverse matrix of the final least-squares cycle, correspond to positional uncertainties of about 0.0009 Å for the C and O atoms. The uncertainties for the Br, C, and O bonds are about 0.007 Å. Uncertainties in the bond angles involving the C, O, and Br atoms are approximately 0.5°. Since the hydrogen positions were not refined, no error estimates will be made for distances and angles involving these atoms. The coordinates of the hydrogen atoms are listed in Table V.

The three structures obtained were stereographically plotted using the ORTEP computer program of C. K. Johnson[2].

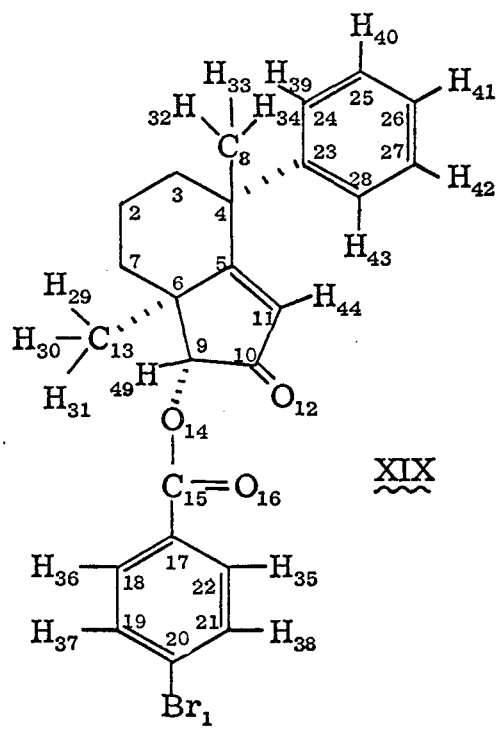

Table I

The Observed and Calculated Structure Factors.
Within each group are values of 1, $10F_o$, $10F_c$.
Reflections indicated with asterisk were assigned zero weights in the final least squares cycle.

Table I (Cont'd)

The Observed and Calculated Structure Factors.
Within each group are values of 1, $10F_o$, $10F_c$.
Reflections indicated with asterisk were assigned zero weights in the final least squares cycle.

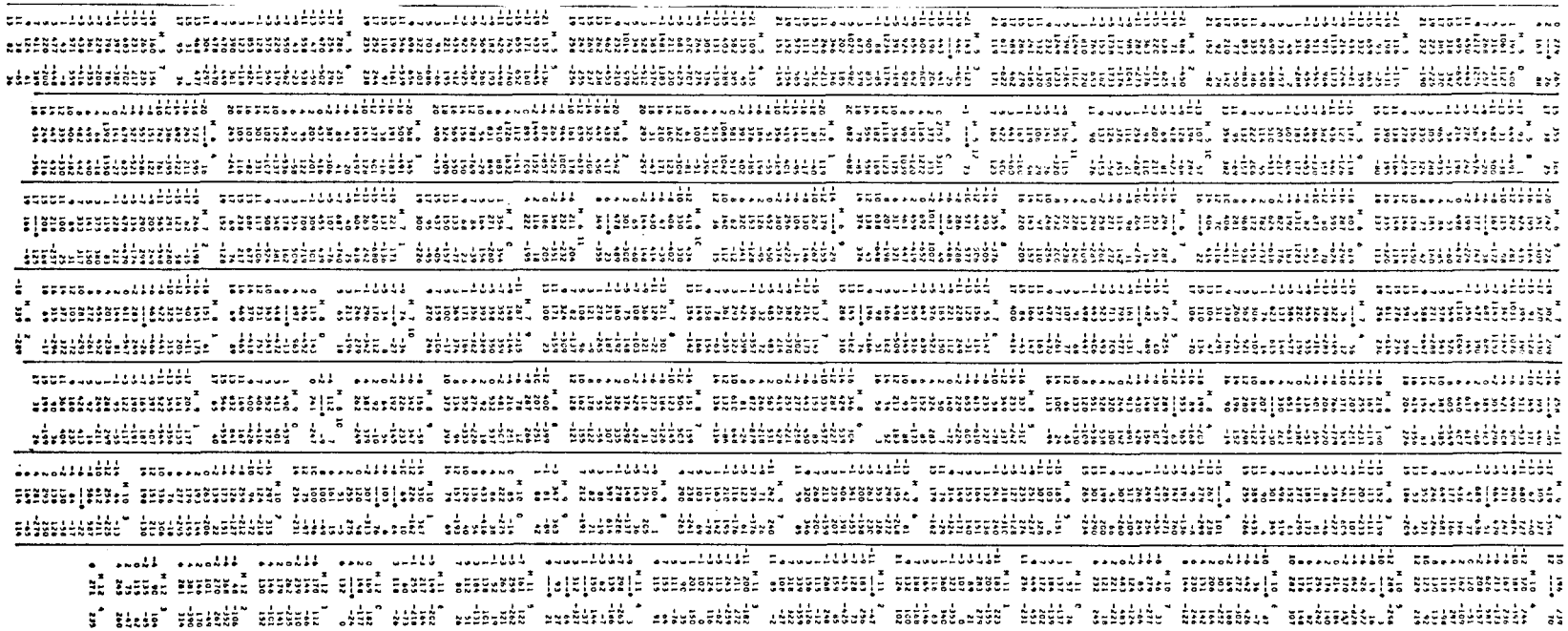

Table II

The Final Refined C, O, Br Parameters and Their Standard Deviations.

Values for bromine atom have been multiplied by 10^5, for the other atoms, by 10^4.
The temperature factor is in the form $T = \exp\{-(b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{12}hk + b_{13}hl + b_{23}kl)\}$.

Atom	x	y	z	b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
Br (1)	37703(3)	3277(7)	-4767(6)	204(2)	1496(10)	822(6)	-279(6)	252(4)	385(13)
C (2)	230(2)	1634(4)	4168(4)	11(1)	92(5)	69(5)	- 7(4)	- 5(4)	- 17(8)
C (3)	307(2)	1347(5)	5303(5)	15(1)	95(5)	65(5)	- 18(4)	13(4)	9(8)
C (4)	789(2)	1916(4)	5875(4)	14(1)	71(5)	42(4)	- 13(4)	2(4)	29(8)
C (5)	1285(2)	1705(4)	5262(4)	11(1)	57(5)	45(4)	- 7(4)	0(3)	- 6(7)
C (6)	1247(2)	1853(4)	4094(4)	11(1)	72(5)	33(4)	- 0(4)	2(3)	8(7)
C (7)	736(2)	1323(4)	3626(4)	16(1)	72(5)	54(5)	- 6(4)	- 5(4)	- 12(8)
C (8)	870(2)	1414(5)	6951(5)	20(1)	95(5)	57(5)	- 4(4)	16(4)	37(9)
C (9)	1754(2)	1250(4)	3831(4)	14(1)	55(5)	46(4)	1(4)	6(4)	7(7)
C (10)	2118(2)	1242(4)	4809(4)	12(1)	50(5)	67(4)	3(4)	0(4)	20(7)
C (11)	1765(2)	1405(4)	5636(4)	12(1)	75(5)	48(4)	- 8(4)	2(4)	6(7)
O (12)	2601(1)	1125(3)	4841(3)	14(1)	99(4)	72(3)	8(3)	0(3)	2(6)
C (13)	1270(2)	3028(4)	3777(4)	19(1)	62(5)	48(4)	6(4)	8(4)	30(8)
O (14)	2032(1)	1715(3)	3006(3)	18(1)	52(3)	47(3)	5(3)	20(2)	11(5)
C (15)	2340(2)	1045(5)	2487(4)	19(1)	52(5)	46(4)	6(4)	5(4)	16(9)

Table II (Cont'd)

Atom	x	y	z	b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
C (15)	2340(2)	1045(5)	2487(4)	19(1)	52(5)	46(4)	6(4)	5(4)	16(9)
O (16)	2340(2)	107(3)	2600(3)	36(1)	52(3)	70(3)	5(3)	49(3)	12(6)
C (17)	2671(2)	1606(4)	1770(4)	14(1)	46(5)	40(4)	1(4)	2(3)	- 4(7)
C (18)	3038(2)	1027(5)	1251(4)	23(1)	60(5)	60(5)	15(4)	13(4)	- 1(9)
C (19)	3379(2)	1532(5)	597(4)	19(1)	97(6)	51(5)	11(4)	16(4)	- 20(9)
C (20)	3318(2)	2602(4)	429(4)	14(1)	74(5)	46(4)	- 14(4)	4(4)	2(8)
C (21)	2950(2)	3181(4)	910(4)	15(1)	55(5)	55(4)	- 11(4)	4(4)	- 2(8)
C (22)	2627(2)	2689(4)	1596(4)	14(1)	51(5)	53(4)	0(4)	9(4)	- 20(8)
C (23)	701(2)	3125(4)	6025(4)	17(1)	82(5)	29(4)	5(4)	5(4)	2(8)
C (24)	1144(2)	3760(5)	6262(4)	20(1)	70(6)	62(5)	3(4)	5(4)	- 13(9)
C (25)	1071(3)	4834(5)	6481(5)	29(2)	89(7)	74(6)	- 2(5)	9(5)	- 26(10)
C (26)	188(2)	3547(5)	6021(5)	17(1)	102(7)	71(5)	19(5)	6(4)	- 24(10)
C (27)	129(3)	4625(6)	6229(5)	32(2)	134(8)	91(6)	83(6)	- 9(6)	- 54(12)
C (28)	573(3)	5243(5)	6458(5)	43(2)	83(7)	69(6)	20(6)	-11(6)	- 43(10)

Table III

Atomic Distances

(The numbering scheme represents a convenient crystallographic one and is not the correct organic nomenclature)

Atom	Atm	Distance (Å)	Atom	Atom	Distance (Å)
Br (1)	C (20)	1.89	C (24)	C (25)	1.40
C (2)	C (3)	1.53	C (25)	C (28)	1.34
C (2)	C (7)	1.53	C (26)	C (27)	1.40
C (3)	C (4)	1.55	C (27)	C (28)	1.37
C (4)	C (5)	1.53	C (2)	H (50)	1.06
C (4)	C (8)	1.55	C (2)	H (51)	1.04
C (4)	C (23)	1.56	C (3)	H (45)	1.08
C (5)	C (6)	1.54	C (3)	H (46)	1.08
C (5)	C (11)	1.31	C (7)	H (47)	1.08
C (6)	C (7)	1.53	C (7)	H (48)	1.05
C (6)	C (9)	1.53	C (8)	H (32)	1.06
C (6)	C (13)	1.54	C (8)	H (33)	1.04
C (9)	C (10)	1.52	C (8)	H (34)	1.08
C (9)	O (14)	1.44	C (9)	H (49)	1.03
C (10)	C (11)	1.45	C (11)	H (44)	1.07
C (10)	O (12)	1.20	C (13)	H (29)	1.09
O (14)	C (15)	1.35	C (13)	H (30)	1.03
C (15)	O (16)	1.19	C (13)	H (31)	1.04
C (15)	C (17)	1.47	C (18)	H (36)	1.02
C (17)	C (18)	1.38	C (19)	H (37)	1.03
C (17)	C (22)	1.39	C (21)	H (38)	1.00
C (18)	C (19)	1.39	C (22)	H (35)	1.00
C (19)	C (20)	1.38	C (24)	H (39)	1.00
C (20)	C (21)	1.35	C (25)	H (40)	1.02
C (21)	C (22)	1.39	C (26)	H (43)	1.01
C (23)	C (24)	1.38	C (27)	H (42)	1.08
C (23)	C (26)	1.38	C (28)	H (41)	1.05

Table IV

Bond Angles

Atom	Atom	Atom	Angle (°)	Atom	Atom	Atom	Angle (°)
Br (1)	C (20)	C (19)	119	C (11)	C (10)	C (9)	106
Br (1)	C (20)	C (21)	120	O (12)	C (10)	C (9)	124
C (3)	C (2)	C (7)	109	C (5)	C (11)	C (10)	110
C (4)	C (3)	C (2)	114	C (15)	O (14)	C (9)	116
C (5)	C (4)	C (8)	110	O (16)	C (15)	C (17)	124
C (5)	C (4)	C (23)	111	O (16)	C (15)	O (14)	124
C (5)	C (4)	C (3)	107	C (17)	C (15)	O (14)	112
C (8)	C (4)	C (23)	107	C (18)	C (17)	C (22)	119
C (8)	C (4)	C (3)	108	C (18)	C (17)	C (15)	118
C (23)	C (4)	C (3)	114	C (22)	C (17)	C (15)	123
C (6)	C (5)	C (11)	114	C (19)	C (18)	C (17)	120
C (6)	C (5)	C (4)	120	C (20)	C (19)	C (18)	119
C (11)	C (5)	C (4)	126	C (21)	C (20)	C (19)	122
C (7)	C (6)	C (9)	112	C (22)	C (21)	C (20)	120
C (7)	C (6)	C (13)	111	C (17)	C (22)	C (21)	120
C (7)	C (6)	C (5)	110	C (24)	C (23)	C (26)	120
C (9)	C (6)	C (13)	112	C (24)	C (23)	C (4)	119
C (9)	C (6)	C (5)	99	C (26)	C (23)	C (4)	121
C (13)	C (6)	C (5)	113	C (25)	C (24)	C (23)	120
C (2)	C (7)	C (6)	113	C (28)	C (25)	C (24)	120
C (10)	C (9)	O (14)	110	C (27)	C (26)	C (23)	119
C (10)	C (9)	C (6)	105	C (28)	C (27)	C (26)	120
O (14)	C (9)	C (6)	114	C (25)	C (28)	C (27)	121
C (11)	C (10)	O (12)	130				

Table V

Hydrogen Coordinates

Values for hydrogen atoms have been multiplied by 10^4.
Isotropic temperature factor for all hydrogens equals 4.0.

Atom	x	y	z
H (29)	1619	3396	4184
H (30)	1330	3095	3008
H (31)	920	3425	3963
H (32)	979	610	6868
H (33)	1166	1827	7380
H (34)	495	1455	7323
H (35)	2348	3086	1961
H (36)	3096	235	1381
H (37)	3657	1086	234
H (38)	2910	3967	811
H (39)	1505	3416	6254
H (40)	1414	5263	6636
H (41)	540	6055	6619
H (42)	261	5015	6220
H (43)	160	3161	5839
H (44)	1932	1321	6406
H (45)	388	507	5336
H (46)	61	1446	5685
H (47)	780	471	3640
H (48)	681	1497	2844
H (49)	1654	490	3610
H (50)	241	2477	4171
H (51)	140	1434	3797

XIX

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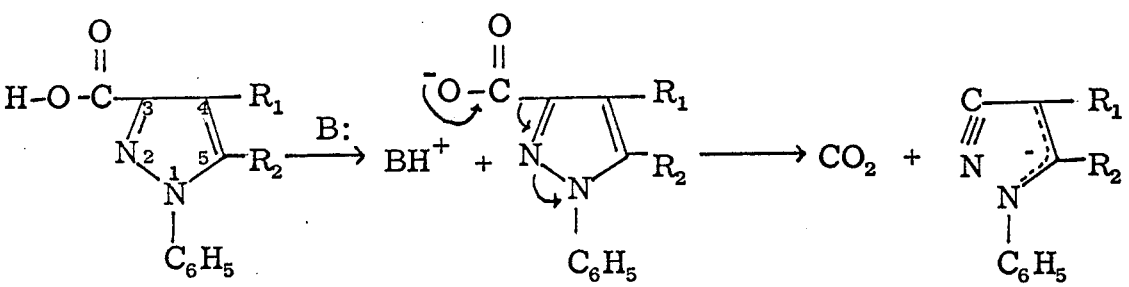
PROPOSITION I

It is proposed that the use of negative ion mass spectrometry as a mechanistic tool in the study of elimination reactions be studied.

The ring opening of 3-carboxy and 3-unsubstituted pyrazoles, each substituted with different electron-attracting substituents in the 4-position, has been studied by heating the acids in boiling quinoline for 90 minutes and by heating the 3-unsubstituted pyrazoles with potassium t-butoxide in t-butyl alcohol for several hours[1]. The authors found that the relative ratio of β-anilino-acrylo-nitrile to decarboxylated 4-substituted pyrazole increased as the electron-attracting capability of the 4-substituent increased. These experiments support the reaction mechanism hypothesis of the pyrazole ring cleavage described in Chart A.

Chart A

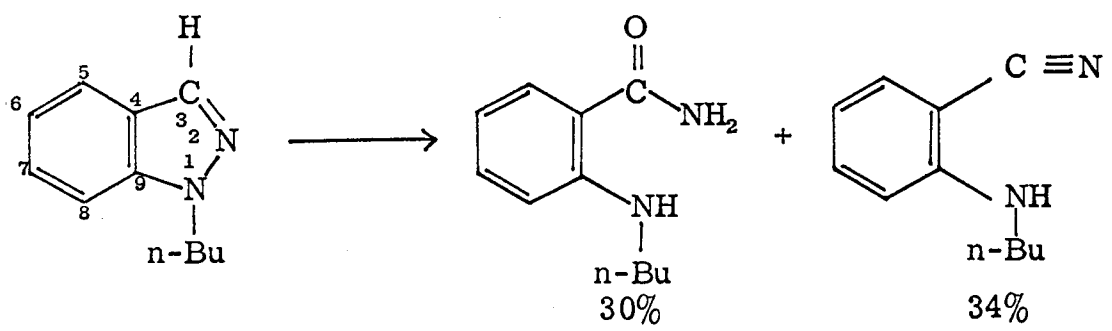


The electron-attracting substituents in the 4-position were acetyl, benzoyl, cyano, nitro, and hydrogen. The substituents in the 5-position were methyl, phenyl, and hydrogen.

Many of the arguments used to rationalize and predict the course of organic reactions in solution have been applied to the study of unimolecular decomposition of ions in the gas phase. It is proposed to study the above system in an attempt to determine whether a corrolation exists between electron-impact decarboxylation and ring-opening, and solution chemistry decarboxylation and cleavage by comparing the ratio of the abundance of the p-45 fragment to the abundance of the p-1 fragment peak heights as the electron-attracting 4-substituent is varied. The corrolation should exist because the probability of occurrence of a particular gas phase electron impact initiated reaction is increased if it produces a more stable ion. A positive corrolation would have the result of greatly broadening the application of negative ion mass spectrometry by employing it as an easily applied non-solution chemistry mechanistic tool for the study of certain elimination reactions.

Recently it has also been reported that 3-unsubstituted-1-alkyl-indazoles are cleaved to the corresponding N-alkyl-anthranilonitrile by reaction with sodium amide and caustic soda in boiling xylene[2] as shown in Chart B.

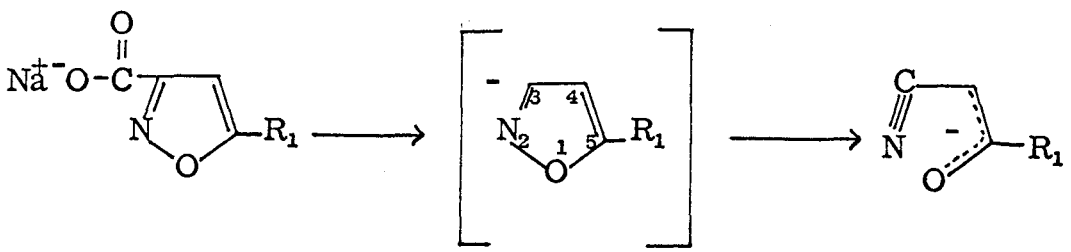
Chart B



A correlation between both solution and electron impact decarboxylation and ring opening of either 3-unsubstituted or 3-carboxyl indazoles substituted in either the 6- or 8-position with various electron-attracting substituents should exist.

The sodium salts of 5-alkyl isoxazole-3-carboxylic acids on mild thermolysis readily undergo decarboxylation followed by ring cleavage[3,4] as shown in Chart C.

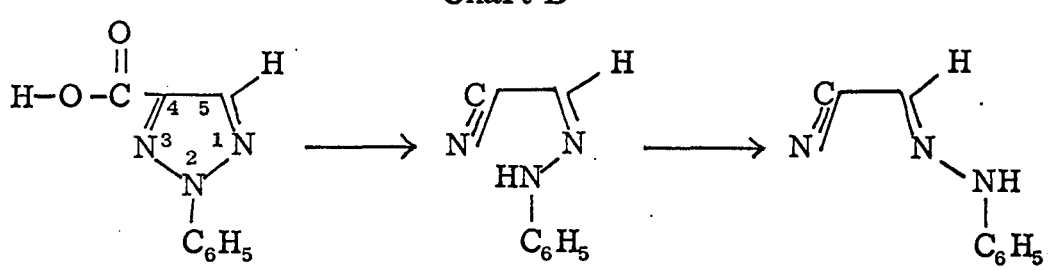
Chart C



5-alkyl isoxazole-3-carboxylic acids substituted with various electronegative substituents in the 4-position consequently lend themselves to a similar study.

The same type of decarboxylative ring cleavage has recently been reported upon distillation of 2-phenyl-1,2,3-triazole-4-carboxylic acid from barium hydroxide[5] as shown in Chart D.

Chart D



Two recent positive ion mass spectral studies have demonstrated the mass spectrometers ability as a mechanistic elucidation tool. A linear relationship between the intensities of the fragments corresponding to the benzoyl and acetyl ions in the positive ion mass spectra of substituted benzophenones and acetophenones has been found[6]. Much of the data can be corrolated by the common relationships of solution chemistry. The ratio of the intensities of the 2-norbornyl radical carbonium ion fragment peak to the two exo- and endo-2-norbornyl bromide molecular ion peaks determined from electron-impact studies in the gas phase has been found to be comparable to the corresponding ratio obtained from solvolytic studies[7].

Negative ion mass spectra have neither been tabulated to any large degree nor applied to analytical problems. The apparent lack of extensive fragmentation has negated its use as a structural elucidation tool. It has been found that the formation of positive ions is about four orders of magnitude more probable than the formation of negative ions when using 70 ev ionizing electrons[8a, 8b], the standard energy beam. Negative ions are often formed with excess kinetic energy which greatly reduces the collection efficiency for them by mass spectrometers. Ion-molecule reactions sometimes result, yielding substances whose mass is greater than the molecular ion. Another frequently introduced objection is that the negative ions are produced by four independent non-concurrent modes of mono-energetic electrons[8b].

In addition to the fact that negative ion mass spectrometry possesses unique advantages for certain mechanistic studies, many of the disadvantages cited are easily corrected. If the elimination pathway is energetically favorable then the lack of extensive fragmentation results in a faster assignment and easier study. Considering the instrumental conditions to be used for the decarboxylative ring-opening study, it is felt that the only two major peaks will be the p-1 and p-45 peaks. Exotic molecular rearrangements frequently found in positive ion mass spectrometry have not been noted in negative ion spectral studies. High detector sensitivity is achieved by the use of a 10-20 stage electron multiplier which can usually increase the detection sensitivity for both positive and negative ions by a factor of 10^4 or more over conventional electrometer techniques. Both positive and negative ions are produced upon impact with the electron beam in the ionization chamber. Spectra of negative ions may be obtained principally in the same way as positive ions with a normal mass spectrometer after reversing the potentials in both the ion source and analyzer tube. A small negative potential between the back wall of the ion source and the first accelerator plate pushes the negative ions toward the accelerating region, attracting at the same time the positive ions which are then discharged at the repeller plate. The study will probably be performed at electron energies lower than the appearance potential of the positive molecular ion and no positive ions will therefore be generated. The four modes of negative ion formation occur at different energies (i.e., experimental conditions), and each of the mechanisms can therefore be

studied separately.

Ropp [9a, 9b] has applied the arguments used to predict and rationalize the ionization of formic, acetic, and propionic acids in solution to the negative ion mass spectrometric study of these acids. The cracking of deuterated formic acid yields a positive ion at mass 45 by loss of either hydrogen attached to oxygen or carbon with equal facility. The negative ion generated by loss of a single hydrogen from formic acid is formed almost entirely by loss of hydrogen from oxygen and not carbon. The negative ion observation is expected based on the resonance stabilization of the carboxylate anion and the inductive effect of the oxygen atoms. The ratio of the loss of the acidic proton to yield the base peak ion RCO_2^- (R = H, CH_3, C_2H_5) from both acetic acid and proprionic acid compared to the proton lost from formic acid was 4/10. This is in accordance with the inductive effect of methyl and ethyl versus hydrogen in carboxylic acids. Acetic acid would be expected to form the carboxylate anion more readily than proprionic acid, although the difference should be much smaller than the difference between formic acid and acetic acid.

Decarboxylation can occur by both the pyrolytic and electron impact routes. The decarboxylation should be controlled so that a single route is being studied throughout the experiment. Melton found in his study of formic acid that the temperature of the ionization chamber had to be reduced to 120°C since the formic acid sample decomposed into hydrogen and carbon dioxide at higher temperatures[9a, 9b]. M. von Ardenne, in his negative ion mass spectrometric

study of the stable high-melting fatty acids, noted no thermal decarboxylation[10]. M. von Ardenne also noted the presence of low relative abundance peaks which he ascribes to the loss of acetic acid from acetoxy steroids and water from sterols[11]. He feels that these peaks result from pyrolytic decomposition due to the high vaporization temperature required. Vaporization of the cyclic compounds to be studied should not present the problem that was encountered in the high molecular weight fatty acids and steroids.

Thermal decarboxylation can be achieved by injecting the sample into the normal sample inlet system--maintained at a temperature high enough for decarboxylation. Electron impact decarboxylation can be achieved by injecting the sample into the normal sample inlet system--maintained at a temperature low enough to preclude decarboxylation; or preferentially, injection of the sample directly into the ion source. The temperature of the ion source compartment at which no thermal decarboxylation and ring opening occurs can be determined by observing the relative ratio of the p-45 to the p-1 peak as the temperature is both increased and decreased in small increments. Partial thermal decomposition is indicated by slight increases in the product ion intensity ratios for several substituted compounds relative to the parent compounds as the temperature is raised. Thermal decomposition is absent if the ratios do not decrease as the temperature is lowered.

Negative ions are known to be formed in the gas phase by four different mechanisms, three of which can be initiated directly by electron impact.

The electron-impact-initiated reactions are:

a. dissociative resonance capture, $AB + e \longrightarrow A + B^-$

b. resonance capture , $AB + e \longrightarrow AB^-$

c. ion pair production , $AB + e \longrightarrow A^+ + B^- + e$

Tabulations of negative ion mass spectra carried out at the usual operating pressures of less than 10^{-6} mm and the usual electron energies of 50 to 75 ev would include only negative ions produced by pair production, mechanism (c). Conversely, negative ion mass spectra produced by 2 to 10 ev electrons[8b] would be concerned mainly with ions produced by dissociative resonance capture, mechanism (a), and the relative abundance of each ion would be critically dependent upon the electron energy in this range. The appearance potential of B^- (the appearance potential being the minimum electron energy necessary to produce a given ion from its neutral precursor) is equal to the dissociation energy of the AB bond minus the electron affinity of the B atom plus the excess energy (e.g., the sum of both the kinetic energy and the electronic excitation of the fragments). Since the dissociation energies of most chemical bonds lie in the range of 3 to 5 ev and the electron affinities of most atoms lie in the range of 1.5 to 3.5 ev, it follows that the values of the appearance potential of B^- will be expected to lie in the range of 1.5 to 4 ev[12]. By the same process we see that the appearance potentials of negative ions arising by an ion pair process will generally lie in the range of 6 to 13 ev. At electron energies less than approximately 2 ev, only negative ions produced by mechanism (b), resonance capture, would

be detected. The decarboxylative ring opening study, an example of the dissociative resonance mechanism, will be studied over the ionizing range of 2 to 6 ev.

The intensity of the bombarding electron beam would be adjusted to a value which results in a spectrum sufficiently intense to display peaks for all the fragments of interest. The intensity has to be kept constant over the whole scan of the spectrum if reproducible spectra are to be obtained. The study of carboxylic acids, which have a low vapor pressure, and the use of a low electron energy, two factors which result in a much lower ionization efficiency, may require ionizing currents of 50 to 100 μamp in order to obtain a high ion yield. But the injection of the sample directly into the ionization chamber and the use of the electron multiplier detector probably will allow the use of the normal 10 μamp ionizing current.

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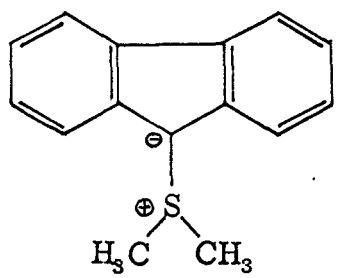
PROPOSITION II

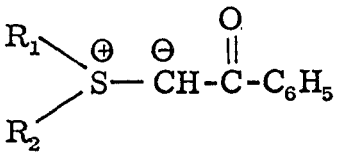
The existence, stability, and synthetic usefulness and versatility of phosphorous ylids have resulted in a search for other molecular systems containing the same general features. The investigation has led to the synthesis of many sulfur, nitrogen, arsenic, and antimony ylids of varying stability[1]. Relatively little is known about the physical properties of sulfonium ylids because many of them are noticeably unstable, and have therefore been generated and used in situ without any attempt to isolate and characterize them. The decreased reactivity of fluorenylidenedimethylsulfurane (1)[2a, 2b], the first stabilized sulfonium ylid, and the less highly reactive 2-nitro-[2c] and 2, 7-dinitro-[2c] derivatives is a result of the decrease in basicity and nucleophilicity due to the delocalization of the negative charge by the aromatic system.

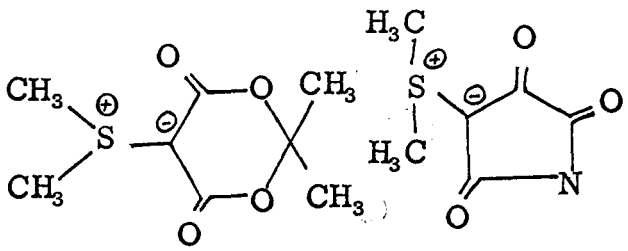


1

The preparation and study of the chemical reactivity of a number of stabilized sulfonium ylids have recently been reported. These include phenacylidenemethylphenylsulfurane (2a)[3a] and phenacyclidenedimethylsulfurane (2b)[3b, 3c], a cyclic bis ester ylid 3 [3d], 3-dimethylsulfuranylidene-2, 4, 5-pyrollidinetrione (4)[3e], dicyanomethylenedi-

methylsulfurane (5)[3f], and cyclopentadienylidenedimethylsulfurane (6)[3g].

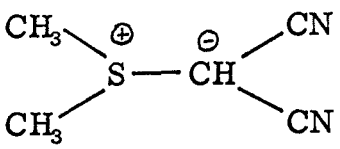


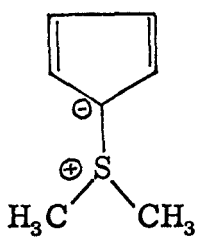


3 4

2a , $R_1 = CH_3$, $R_2 = C_6H_5$

2b , $R_1 = CH_3$, $R_2 = CH_3$





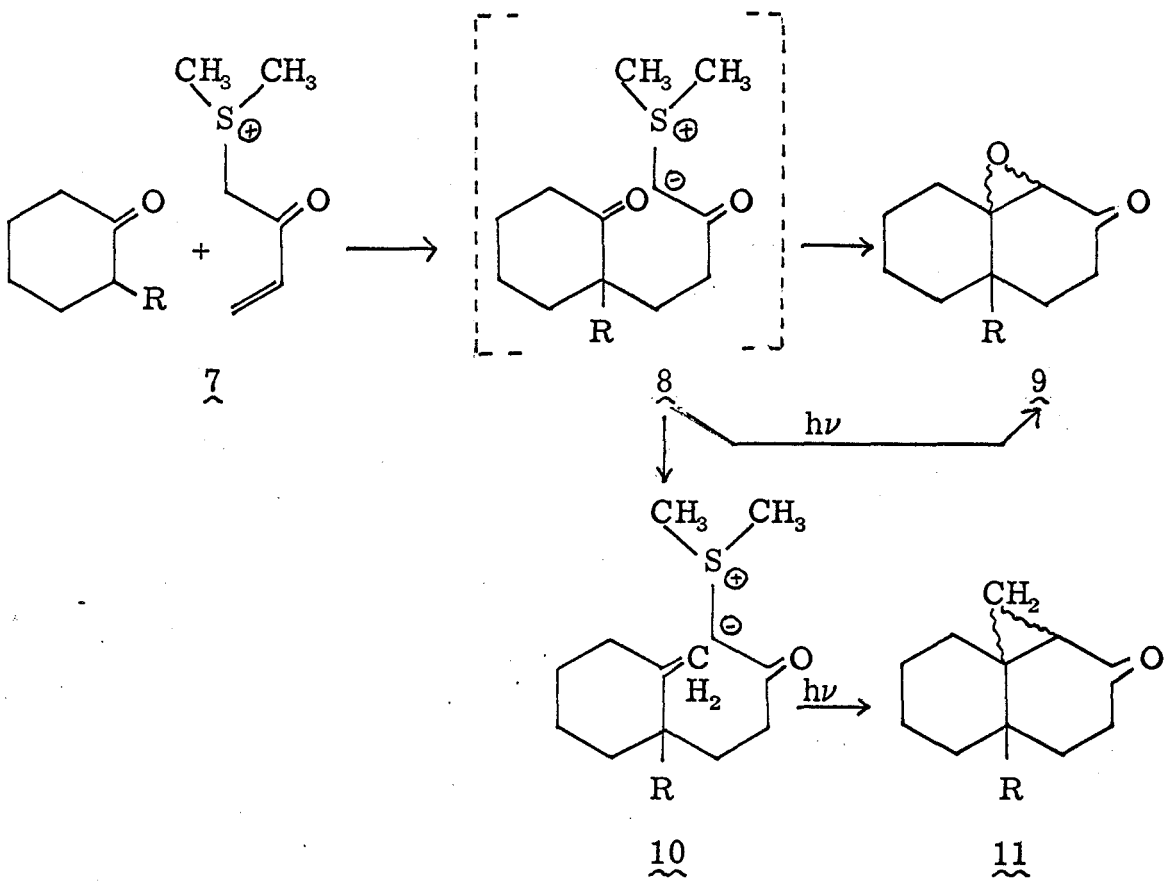
5 6

The various methods of ylid stabilization (e.g., carbonyl and cyanide conjugation, generation of aromatic character) produce a decrease in nucleophilicity and basicity.

Sulfonium ylids are, in the simplest sense, really nothing more than carbanions, and would be expected to undergo normal carbanionic reactions. It is proposed to make use of this fact, the difference in stability of reactive and stabilized sulfonium ylids towards carbonyl compounds, the relative acidity of various ylid protons, and the excellence of dimethylsulfide as a leaving group, in the study of a new condensation technique for the construction of bicyclic, bridged-

bicyclic, and spiro systems; thereby making use of sulfonium ylids as a synthetic tool. The technique involves the introduction of a four carbon keto-carbene precursor in a very simple manner. Chart A delineates one aspect of the proposed study.

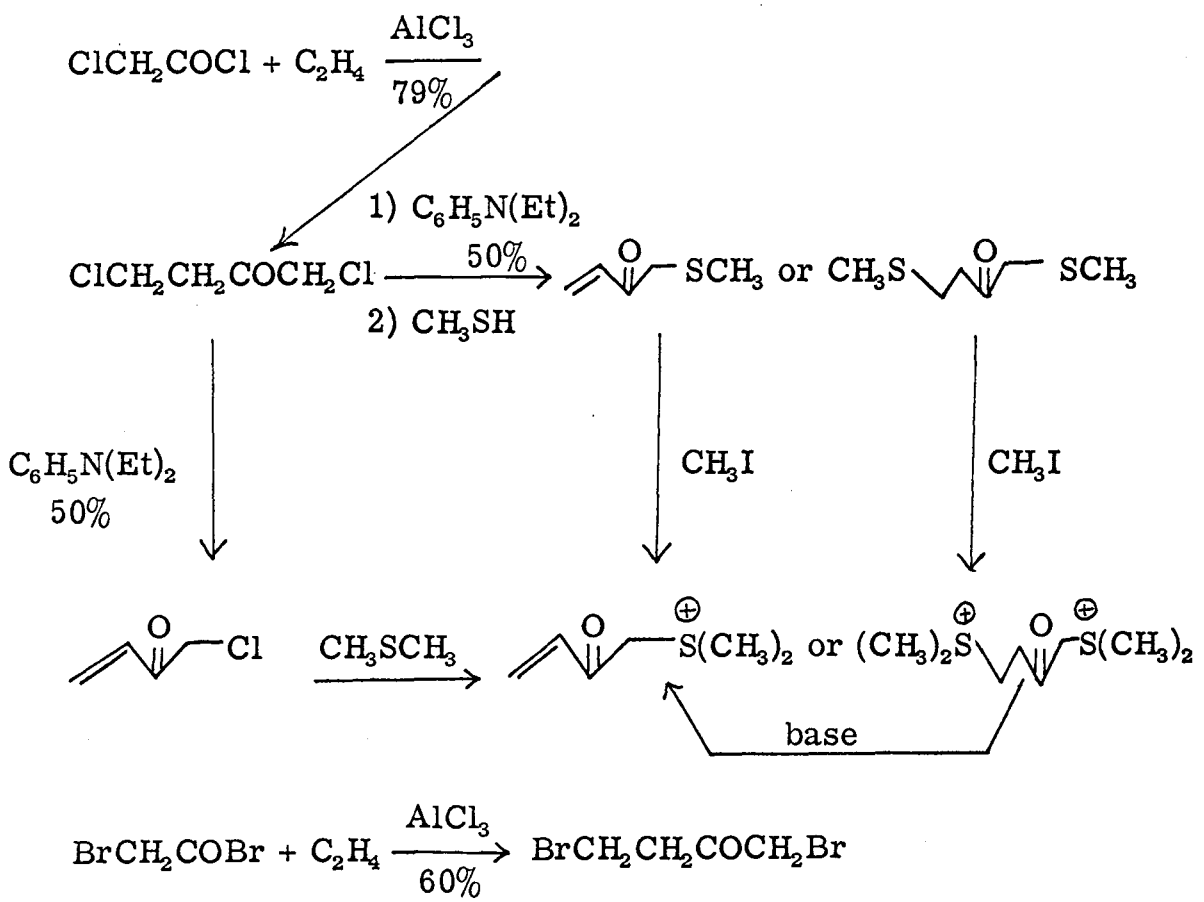
Chart A



The base-catalyzed Michael condensation of substituted cyclohexanones with the sulfonium salt 7 (or the corresponding sulfide which would later be converted to the sulfonium salt by reaction with methyl iodide) will yield the ylid 8. A literature survey indicates

that the synthesis of neither the sulfonium salt 7 nor corresponding sulfide has been reported. The synthesis of these compounds is indicated in Chart B.

Chart B



Chloromethyl vinyl ketone has been prepared from the dichloroketone[4a, 4b]. It is proposed to convert it to the monosulfide with methyl mercaptol as shown. Two equivalents of mercaptol will insure the formation of the disulfide if the mercaptide initially adds to the vinyl ketone in the Michael manner. The disulfonium salt can be converted to the monosulfonium salt through the base-catalyzed

Hofmann elimination of dimethyl sulfide[5]. Cyclopentadienylidene-dimethylsulfurane (6) was synthesized[3g] by elimination of dimethyl sulfide from the disulfonium salt. The dibromoketone has also been synthesized by the Friedel-Crafts reaction[4b], and can be substituted for the dichloride in the above sequence.

Epoxides have been prepared by the reaction of non-stabilized sulfonium ylids with carbonyl compounds. Corey has reacted dimethylsulfoniummethylide[6a], ethylide, and butylide[6b] with a variety of carbonyl compounds including benzaldehyde, benzophenone, carvone, and cyclohexanone. Johnson has reacted benzylidenediphenylsulfurane[2b] with benzaldehyde, benzaldehyde carrying substituents ranging in electronic effect from nitro to methoxyl, and aliphatic aldehydes. The reaction with cyclohexanone was not successful.

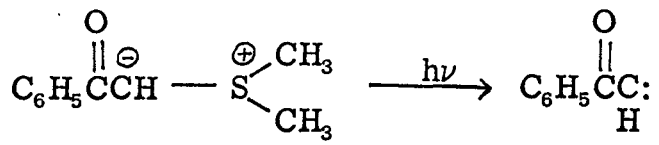
Aromatic and carbonyl stabilization of sulfonium ylids produce a decrease in reactivity because of the ability of these electron-attracting groups to efficiently disperse the electron density of the ylid carbanion. Fluorenylidenedimethylsulfurane (1) reacted only with benzaldehydes carrying electron-withdrawing substituents[2b]. It did not react with cyclohexanone. The stability of the recently reported phenacylidenephenylmethylsulfurane (2a)[3a] was such that it could not be thermally decomposed. It was also claimed not to react with p-nitrobenzaldehyde. This is contrary to the behavior of phenacylidene-dimethylsulfurane[3b] which formed an oxirane, although in low yield, upon reaction with p-nitrobenzaldehyde. It has been suggested[7] that stable sulfonium ylids are of limited synthetic utility since nucleo-

philic reactivity is weak and reaction with carbonyl compounds sluggish or nonexistent. Future discussion in this proposition will disprove this observation.

The reactivity of ylid 8 towards epoxide formation cannot be predicted with any great degree of certainty. But it is felt that based on the analogies described above it will be a fairly stable ylid, resistant to reactivity even upon being heated for a short length of time.

The stereochemistry of the ketol intermediate in the Robinson annelation of 2-substituted cyclohexanones with methyl vinyl ketone has been determined[8a, 8b]. Extrapolation to the analogous sulfonium ylid situation results in the prediction that the epoxide will be trans-fused when the R-substituent is hydrogen and cis-fused when it is methyl or another larger group.

The formation of substituted cyclopropanes and alkenes from ylid decomposition has been ascribed to the generation of an intermediate carbene[1, 2b, 3a]. The formation of the phenacyl carbene (12), generated by the photolysis of phenacylidenedimethylsulfurane (2b), has recently been reported[3c]. The photolytic decomposition of diazoacetophenone[9] produced the same products in very similar ratios as



2b 12

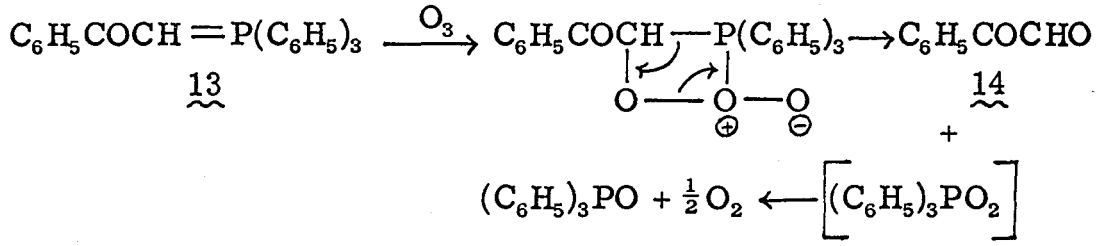
the ylid decomposition. This observation indicates that the same

intermediate carbene 12 is formed in both cases. The butene trapping experiments of the carbene indicated that it exists in the triplet state. If, as expected, the sulfonium ylid 8 is unreactive with respect to carbonyl attack, the photolysis of the ylid would yield the keto-carbene which would add to the carbonyl double bond to form the epoxide 9. This method would therefore be an excellent technique for the generation of a four carbon keto-carbene precursor. The use of cyclic and acyclic amines and alcoholate anions instead of enolates would greatly generalize the approach.

The formation of cyclopropyl ketone 11 from ylid 8 would expand and generalize the usefulness of the ylid. The keto-ylid 8 would be converted to the exomethylene compound by the use of methylenetriphenylphosphorane. Photolysis of the resulting ylid would yield the cyclopropyl ketone 11. It is felt that initial attack of the phosphonium ylid will occur at the carbonyl carbon and not the sulfur atom. If initial attack does occur at the sulfur atom then the generated betaine would either reverse to reform starting material (which would eventually form the desired methylene ketone with irreversible elimination of triphenylphosphine oxide) or "ylid-interchange" would occur yielding methylenedimethylsulfurane and a new keto phosphonium ylid (e.g., a new ylid generation technique).

It was found that phosphonium ylids which were not reactive enough to be cleaved by oxygen would react with ozone. Thus phenacylidenetriphenylphosphorane 13 reacted with ozone at -70° C in methylene chloride solution to afford phenylglyoxal (14) and triphenyl-

phosphine oxide in high yield[10]. It would be interesting to explore the analogy between ketophosphonium ylids and ketosulfonium ylids,

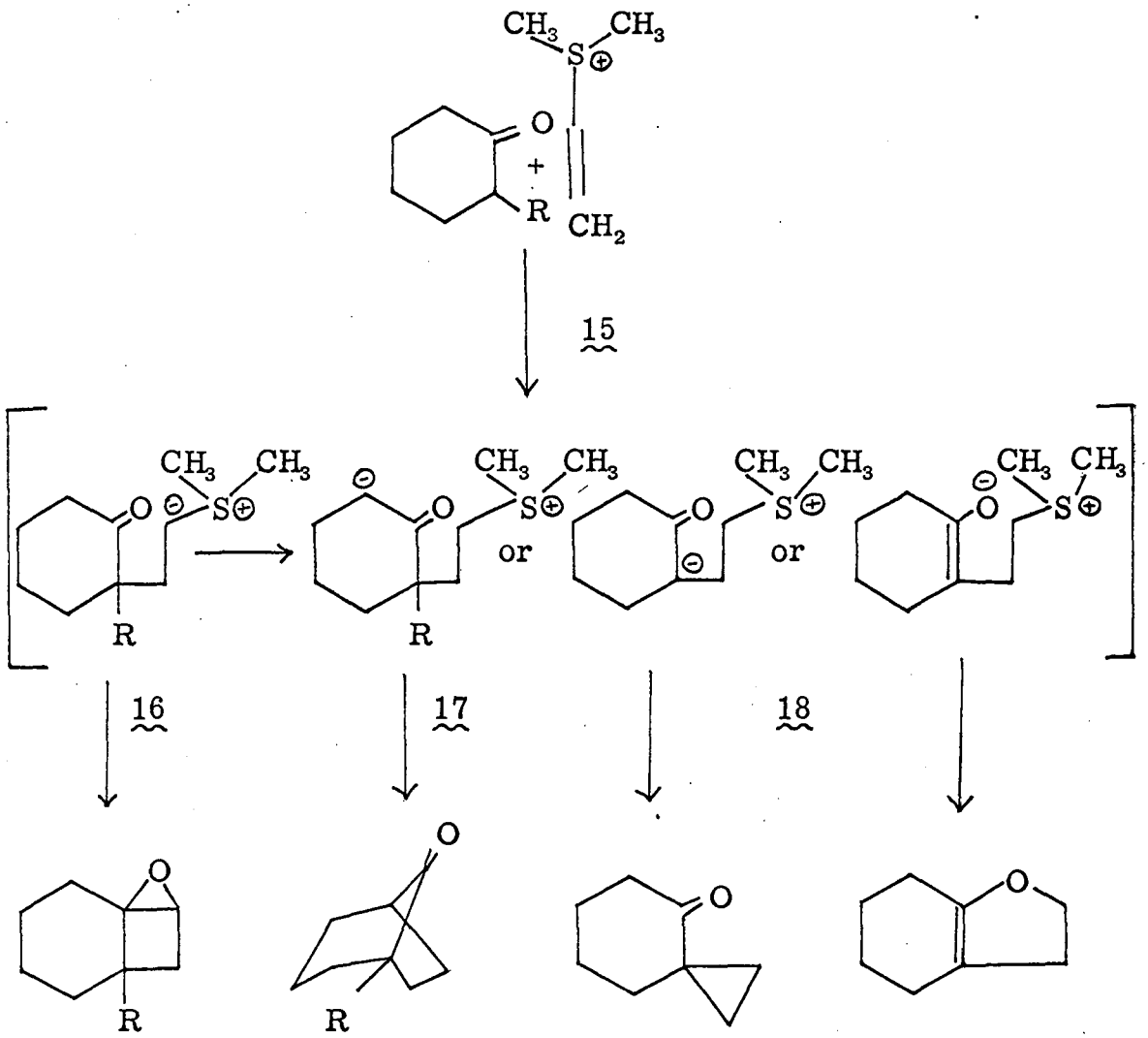


as the applicability of reactions involving the more broadly investigated phosphonium ylids to sulfonium ylids such as 8 would broaden the synthetic utility of these compounds.

Vinyldimethylsulfonium salts have been shown to undergo typical Michael addition reactions with a variety of nucleophiles including hydroxide, ethoxide, and sodiomalonic ester[11]. It is proposed to study the alkylation of 2-substituted cyclohexanones with the vinyldimethylsulfonium salt 15 as shown on the following page in Chart C.

The ylid 16, not being stabilized by the carbonyl group, is quite reactive. It can hypothetically react through any of the intermediates shown below to yield any of the described products. The protons alpha to the carbonyl are more acidic than those on the alkyl chain alpha to the sulfur atom. This is shown by the fact that very strong bases such as the dimethyl sulfoxide anion are required to generate the ylid from the trimethylsulfonium salt[12]. It is therefore felt that a prototropic shift will occur in the ylid 16 forming the enolate-salt 17 or 18 at the expense of the formation of the 6,4-epoxide.

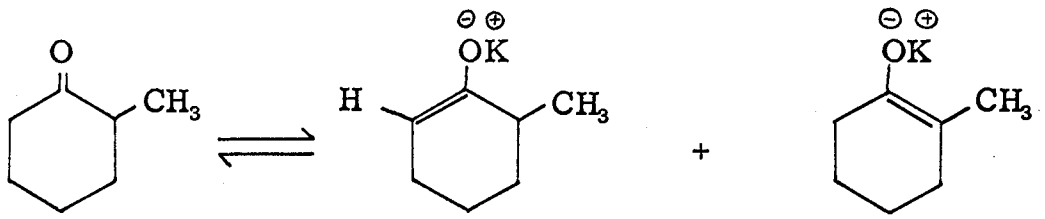
Chart C



It is difficult to predict the equilibrium concentration of enolate anions as many subtle factors must be taken into consideration. These factors include the relative acidity of the involved alpha protons, the effectiveness of the leaving group, the relative rates of ring closure, the nature of the solvent and base, and the tendency for C- versus

O-alkylation[13a, b, c]. House found that there was little preference for the initial removal of the axial proton at C-2 rather than the axial proton at C-6 in 2-methylcyclohexanone. In general, the relative rates of closure for rings of varying size follow the order three-, five-, and six-membered rings > seven-membered rings > four- and larger than seven-membered rings, and noncyclic compounds. The choice of reaction conditions may be of prime importance in determining the ratio of O-alkylated to C-alkylated products obtained. Nonhydroxylic polar solvents appear to favor O-alkylation. Alkylation at the more electronegative atom of the ambient anion is also favored by the use of a very reactive alkylation agent (i.e., one that contains a good leaving group such as dimethylsulfide, tosylate, iodide). Since the energy differences between many of the enolates studies are small (1 Kcal/mole or less), appreciable changes in the position of the enolate equilibrium are observed by changing the cation or solvent. The observations that changing from a lithium to a potassium or sodium enolate or changing the solvent from 1,2-dimethoxyethane to a more polar dimethyl sulfoxide shifts the equilibrium toward the more highly substituted enolate exemplify this point. The study of the Michael reaction with 2-methylcyclohexanone[13b] seems relevant to the control of the product distribution of the intramolecular alkylation of the anionic salt. The equilibrium concentrations for the enolate anions of 2-methylcyclohexanone are summarized in Chart D.

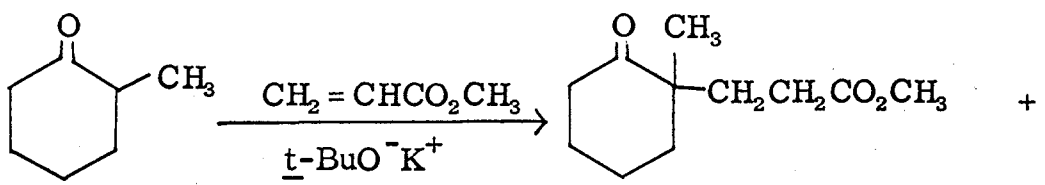
Chart D



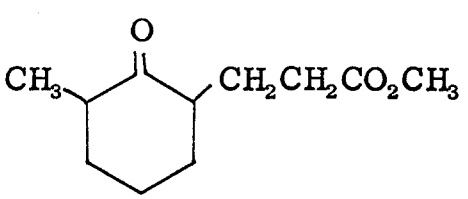
with $(C_6H_5)_3C^-K^+$, DME	ca. 35%	ca. 65%
with t-BuO^-K^+, t-BuOH	ca. 20%	ca. 80%
with t-BuO^-K^+, DME	ca. 22%	ca. 78%

It is seen that the positions of the relevant enolate anion equilibrium favors the more highly substituted isomer. This is borne out by the alkylation product ratio as shown in Chart E.

Chart E



a) 93% (t-BuOH)
b) 88% (DME)

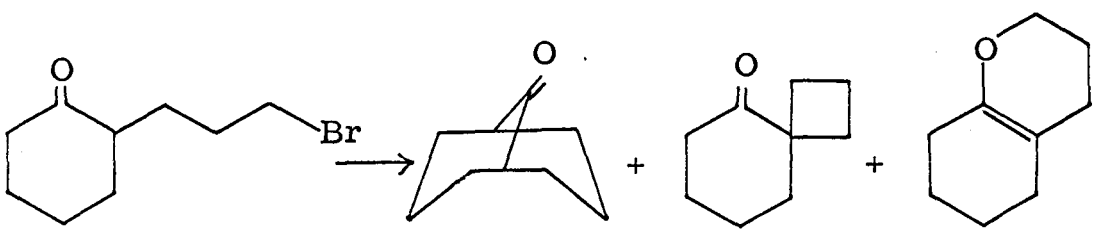


a) 7% (t-BuOH)
b) 12% (DME)

The total yield of monoalkylated products was 61%. It is suggested that the greater proportion of the approximately 15% higher molecular weight products is formed by further alkylation of the 2, 6-dialkylated ketone.

It would seem reasonable to conclude that reaction conditions could be controlled to lead to selective alkylation. The use of a non-polar solvent and a sodium or potassium base should lead to the spiro-cyclopropyl compound (when R = H)--cyclopropyl ring formation being kinetically favored and elimination of dimethylsulfide rendering the reaction irreversible. The intramolecular alkylation of bromoketone 19 yielded mainly the enol ether shown in Chart F,

Chart F



19 8% 78%

the reaction conditions being potassium t-butoxide and benzene[14]. Although the reaction conditions favored C-alkylation (e.g., spiro-cyclobutane formation), the formation of a four-membered ring is not favored. Formation of the bridged (3.3.1.) ketone involves a six-membered transition state, but the axial conformation of the side chain is required and considerable nonbonded interactions are built up in the transition state.

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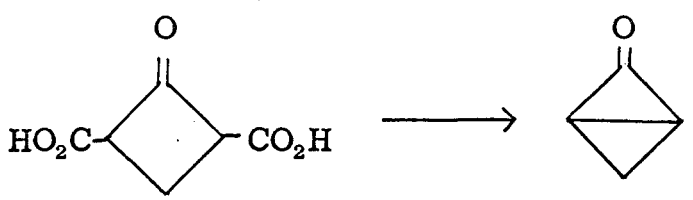
PROPOSITION III

Widespread interest in the chemical and physical properties of highly strained molecules has long been evident. The instability of these molecules is due to the extreme bond angle deformations. These compounds lend themselves nicely to a study of the effects of ring substituents on the properties of carbon-carbon bonds, on carbon-hydrogen bonds, and on the various orbitals. Chemical reactions involving strained systems have proven to be quite interesting. Strained small ring systems also serve as interesting models for testing the prediction of spectral properties. The system with the most strain per carbon atom thus far synthesized is bicyclobutane[1a, 1b]. The synthesis of a new highly strained system, the bicyclobutanone system, is proposed. The bicyclobutanone system can be converted to bicyclobutanes substituted in the methylene position. These compounds are quite difficult to prepare.

It is proposed that the bicyclobutanone system 2 be synthesized by the following reaction. Projected syntheses of the diacid 1 are

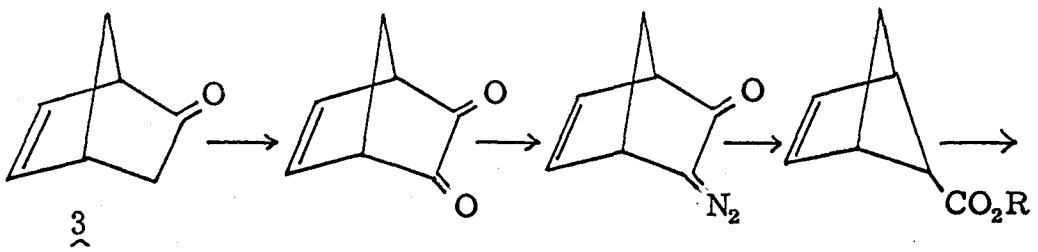


1 2

indicated in Chart A.

Chart A

a)



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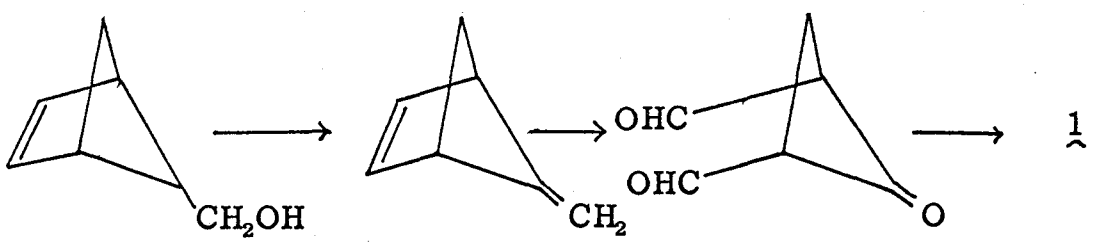

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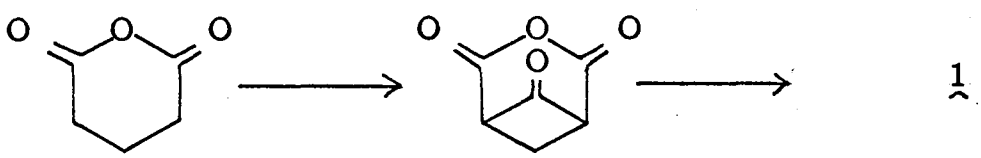
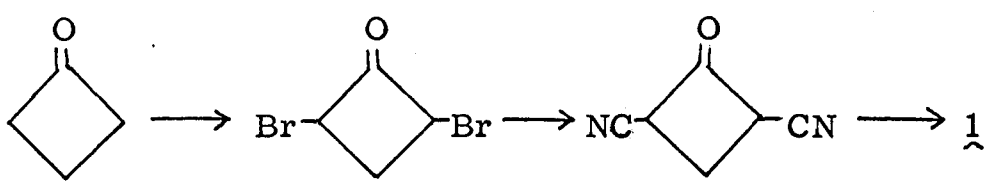
b)



4

1

c)

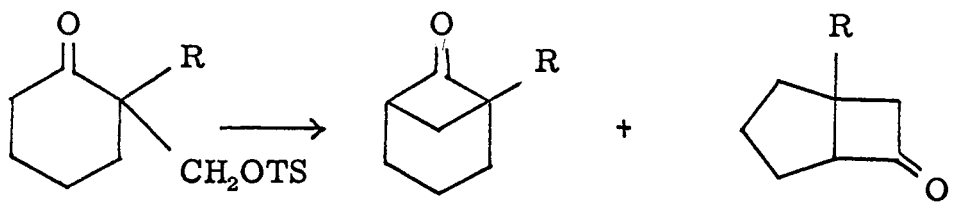


1

5-Norbornen-2-one[2] (3) can be converted by selenous acid to the α-dione, which is then converted to the diazo ketone (through the tosylhydrazone). Irradiative ring contraction yielding the acid (aqueous solvent) or ester (alcoholic solvent) is brought about by the Wolff rearrangement. Involvement of the double bond in the carbenic rearrangement would necessitate the protection of the bond, possibly as the acetonide or the thionocarbanate. The acid or ester can be reduced to the alcohol with lithium aluminum hydride and then dehydrated to yield the exo-methylene compound. The exo-methylene compound can also be synthesized by converting the acid to the substituted amide through the acid chloride, then to the amine through lithium aluminum hydride reduction, then to the amine oxide which is thermally eliminated to yield the terminal methylene compound. The terminal methylene is then oxidized to the ketone through the use of ozone or potassium periodate--potassium permanganate--potassium carbonate. This sequence is discussed and has been used by both Meinwald[3a] and Wiberg[3b] on similar systems. The dialdehyde can be oxidized to the diacid 1 with the aid of silver oxide.

The alkylative conversion of glutaric anhydride (4) to the cis-2,4-cyclobutanonecarboxylic acid anhydride would be accomplished by the use of diethyl carbonate, ethyl chloroformate, or phosgene (employing a base such as sodium hydride). Cis-1,2-cyclobutanecarboxylic acid anhydride is a known compound. The anhydride is readily hydrolyzed in water to the diacid. A literature search failed to turn up the corresponding cis-1,3-anhydride. A molecular model

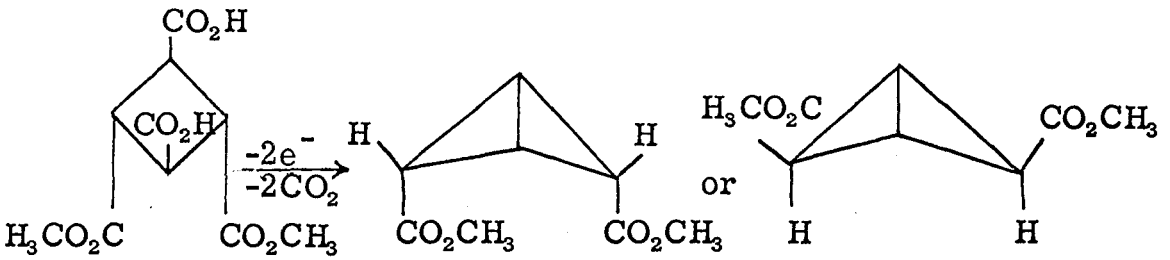
study indicates that the cis-1,3-anhydride is readily capable of existence. It should undergo hydrolysis much more readily than the cis-1,2-anhydride to yield the diacid 1. It is certainly conceivable that the second bond-forming reaction will reverse itself. The formation of a bridged cyclobutanone, bicyclo (3.1.1) heptanone, by alkylative SN^2 displacement has been reported by three groups[4a, 4b, 4c]. Wiberg[4d] though, in investigating this reaction with a variety of bases, found that the product is a mixture of two ketones, formed in about equal amounts. The possibility of decarboxylation must also be



protected against.

Another possible route to the diacid 1 involves the formation of the 2,4-dibromide of cyclobutanone through the employment of two equivalents of N-bromosuccinimide, and the subsequent conversion to the diacid (through the intermediacy of the dicyanide).

The conversion of diacid 1 to bicyclobutanone (2) would be accomplished by Kolbe anodic oxidative electrolysis[5a, 5b]. When trans, trans, trans, 1,3-decarboxy-2,4-dicarbomethoxycylobutane (5) was electrolyzed under Kolbe conditions 2,4-dicarbomethoxybicyclobutane (6), assumed to be cis, was the major product isolated (17% after gas chromatography)[6].



5 6

The usual procedure for carrying out reactions of the Kolbe type is to dissolve the starting acid in methanol containing sufficient sodium methoxide to neutralize a small portion (about 2%) of the acid, and then to electrolyze the solution between two platinum foil electrodes until it becomes slightly alkaline. As the electrolysis proceeds, the carboxylate ions are converted at the anode into products. The sodium liberated at the cathode reacts with the solvent, and the resulting alkali neutralizes some of the excess acid. The process continues in this way until all the starting material has been consumed. This procedure suffers from the fact that the nucleophilic methoxide ion formed could be expected to attack the generated bicyclobutanone system. An alternate procedure[7], which eliminates this potential problem, is to use sufficient base to neutralize all of the starting material and to electrolyze the resulting methanolic solution between a platinum anode and a mercury cathode. As long as a potential difference is applied across the electrodes the electro-

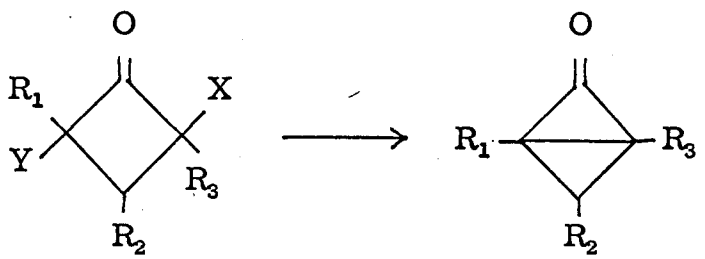
lyte does not turn alkaline. The excess sodium liberated at the mercury cathode is held there as the amalgam. Owing to the initial high carboxylate ion concentration, large currents can be used with a consequent saving in reaction time. The current drops as the carboxylate ion concentration is reduced by electrolysis, and the termination of the reaction is therefore readily detected.

Many successful Kolbe anodic oxidations of carboxylic acids have been reported to proceed without the use of any base. Acetonitrile (neat)[8a], acting as an ionizing agent producing carboxylate anions, and acetonitrile--methanol mixture[8b, 8c] are frequently employed. Acrylonitrile and triethyl amine[8d], triethyl amine and dimethyl formamide[8e], and methanol and pyridine[8b] have also been cited as suitable solvent systems.

The maintenance of the integrity of the carbonyl function during the electrolysis of diacid $\underset{\sim}{1}$ is a moot point. A literature review did not yield any pertinent data for electrolysis of β-keto acids, but successful electrolytic decarboxylative dimerizations of acyclic γ- and ϵ-keto acids have been reported[9a, 9b, 9c]. Alpha-alkylated keto acids decrease the efficiency of the electrolysis[5a, 5b]. Alkyl groups further removed from the carboxyl group than the α-position seem, in general, to exert little if any adverse influence. Phenyl groups in the α-position have been noted not to hinder the coupling reaction[2a, 2d, 2e].

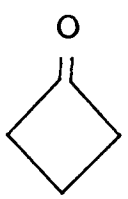
Bicyclobutanes, formed in good yields by the electrolytic cyclization of 1,3-dihalocyclobutanes, have recently been reported.

The electrolysis of 1-chloro-3-bromocyclobutane[10a] in dimethylformamide saturated with lithium bromide afforded a mixture of bicyclobutane (60%), cyclobutene (20%) and cyclobutane (10%). Similarly 1,3-dibromo-1,3-dimethylcyclobutane was electrolyzed to give 1,3-dimethylbicyclobutane in from 55 to 94% yield[10b, 10c]. The electrolytic cyclization of variously substituted 2,4-dihalo cyclobutanones would therefore seem to offer an effective alternative route to the bicyclobutanone system. The syntheses and successful

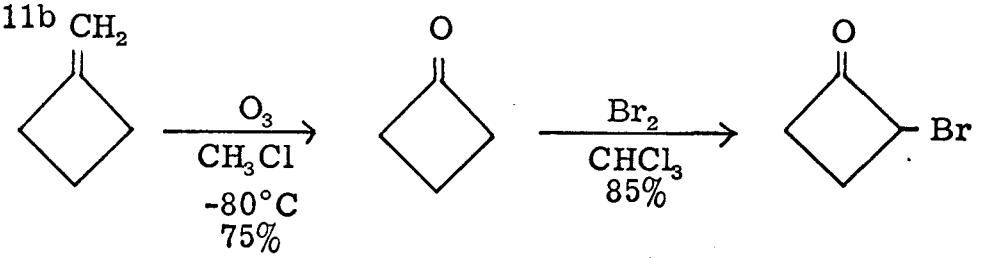


bromination of variously substituted cyclobutanones are described in Chart B.

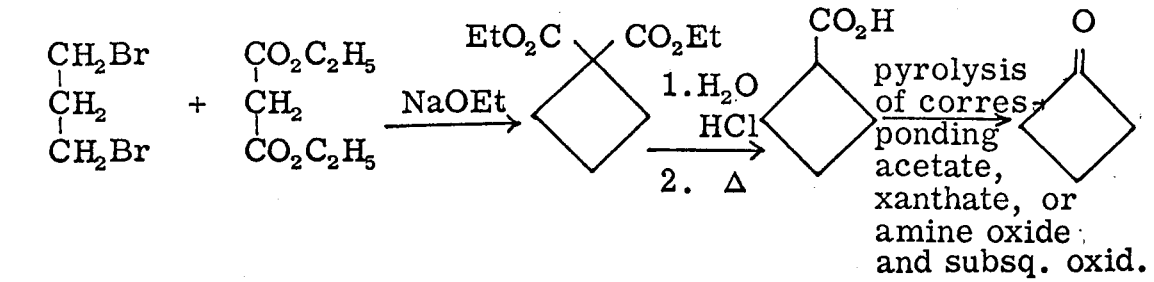
Chart B

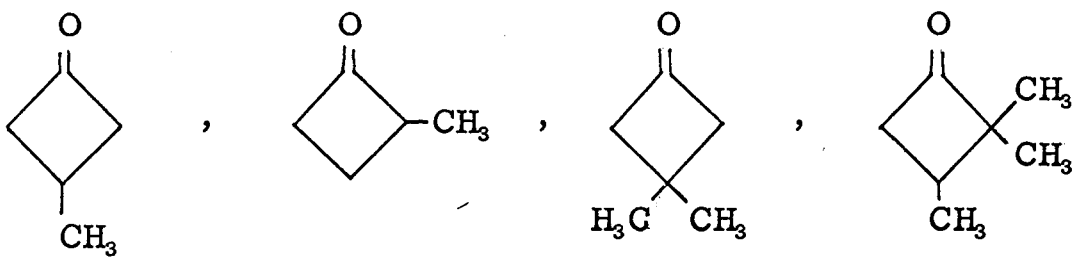
a) 

is commercially available from Aldrich (C-9600/ 1967-68 catalog).

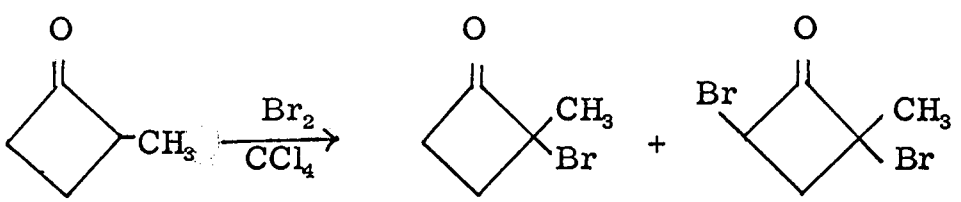
b)[11a, 11b] 

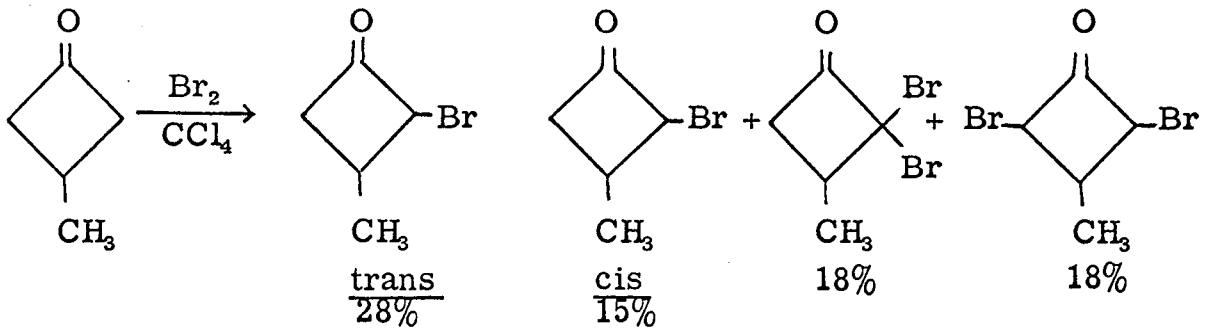
c)[11c, 11d]



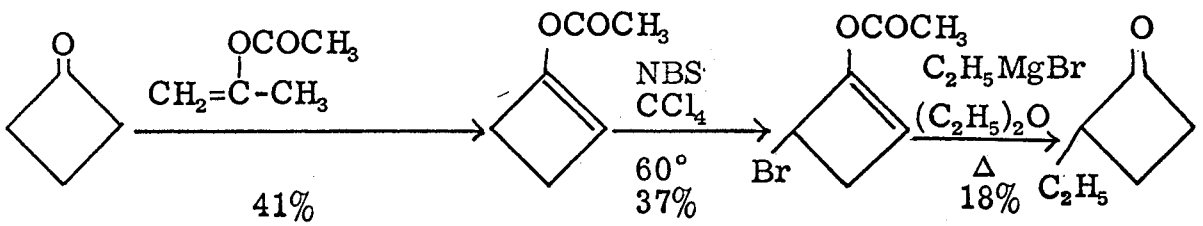


have also been prepared

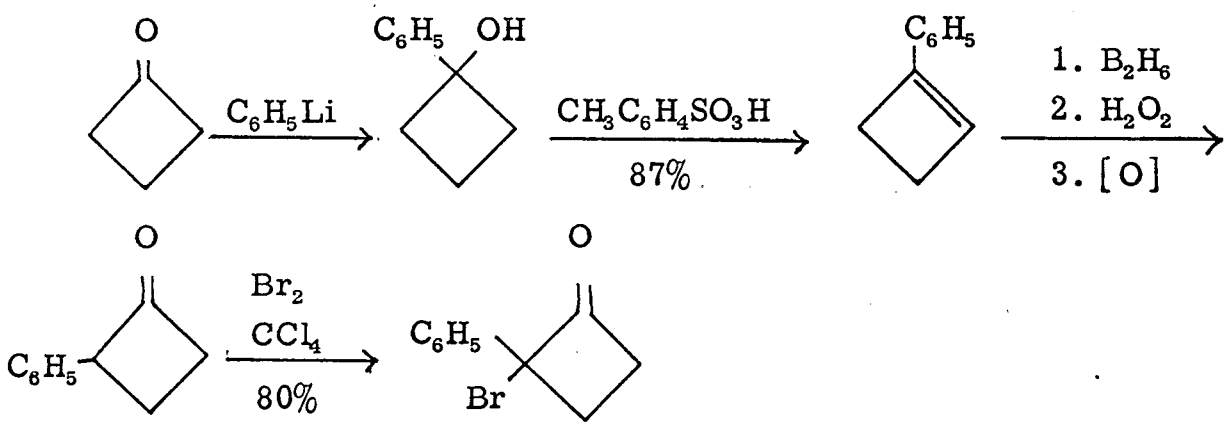




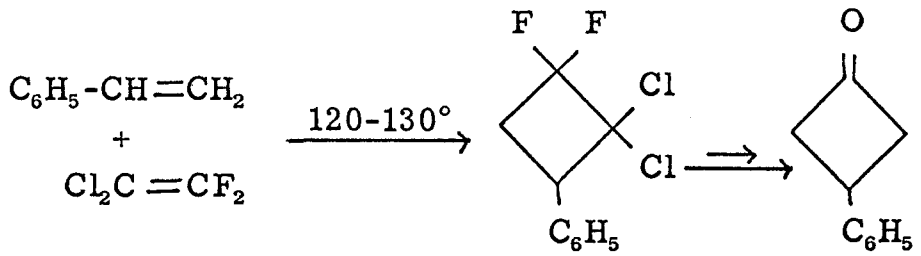
d)[11e]

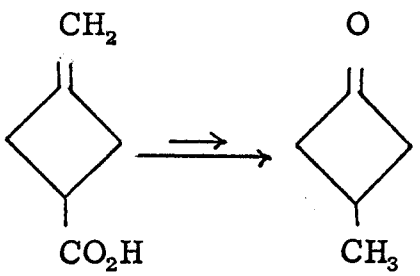


e)[11f, 11g, 11h]



f)[11i]





The chemistry of the bicyclobutanone system should prove to be quite interesting. Many chemical reactions of bicyclobutanones can be extrapolated from the reactivity of other similar systems. Cyclopropanone reacts smoothly with methanol at -78° to afford the hemiketal, and with diazomethane to yield the cyclobutanone[12a]. The lithium aluminum hydride reduction of tetramethylcyclopropanone yields the corresponding alcohol[12b]. Bicyclobutanones would be expected to react similarly. For instance, bicyclobutanone would react with diazomethane to yield the bicyclo (2.1.0) pentanone system. Bicyclobutanes substituted in the methylene position are difficult to prepare. The active carbonyl functionality of bicyclobutanones could be modified to generate such bicyclobutanes.

1,3-dimethyl bicyclo (1.1.0) butane reacts with methylene, generated photolytically from diazomethane, to give 2,4-dimethyl-penta-1,4-diene as well as the expected methylene insertion into the C-H methyl bond[13]. Bicyclobutanone would correspondingly be expected to yield penta-1,4-diene-3-one. C-H insertion would likewise also be expected with 2-methyl-bicyclobutanone.

Thermally or photochemically induced decarbonylation of the bicyclobutanone system would be expected to yield substituted cyclopropenes. Pyrolysis of methylcyclopropenone at 205° produces propyne[14]. The photolysis of tetramethyl-1,3-cyclobutanedione yields tetramethylethylene (tetramethylcyclopropanone being an intermediate product)[12b].

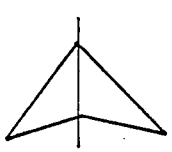
Reaction with nucleophilic bases would be expected to yield the cyclopropylcarboxylic acid derivative.

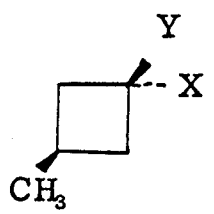
Cyclopropene has been noted to be a reactive dienophile in Diels-Alder reactions[15]. A literature search concerning the use of bicyclobutane as a Diels-Alder dienophile did not prove fruitful. The employment of the active central bond of bicyclobutanone as a dienophile would seem to be a possibility worthy of investigation--the conversion of the bicyclobutanone system to the bridged cyclobutanone system being driven by the release of strain.

The ability of the bicyclobutane system to conjugate with a double bond is indicative of its unsaturated character. A comparison of the ultraviolet spectra of methyl 3-methylbicyclo (1.1.0) butane-1-

carboxylate with methyl cyclopropane carboxylate is quite revealing in this respect[1a]. Whereas the latter has only a very weak absorption, the bicyclobutane ester has λ max 215 mu (ϵ = 12,500). Although all the carbon-carbon bonds of bicyclobutane contain π character, the 1,3-bond exhibits the greatest degree of unsaturation[16a, 16b]. Bicyclobutanones may in this context be viewed as substituted cyclopropenones. Good evidence for strong polarization of diphenylcyclopropenone is its dipole moment of 5.14 D. (benzophenone = 3.0 D.) Cyclopropene was found to have a dipole moment of 0.455 ± 0.01 D. It would be interesting to compare the dipole moment of the bicyclobutanone system with that of the cyclopropanone system.

Hydrogenation of bicyclobutanes leads to a variety of products when different catalysts are used. In one case both monocyclic and acyclic products are obtained[13]. Since it was shown that all the



$\xrightarrow{H_2/Pt}$ $CH_3CH_2CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_3$ + 

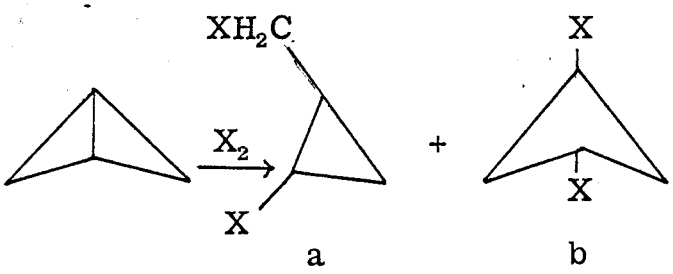
63%

When X is CH_3, and Y is H, yield is 32%
When X is H, and Y is CH_3, yield is 5 %

possible monocyclic products are stable to the hydrogenation conditions used, the two molecules of hydrogen must be added without desorption

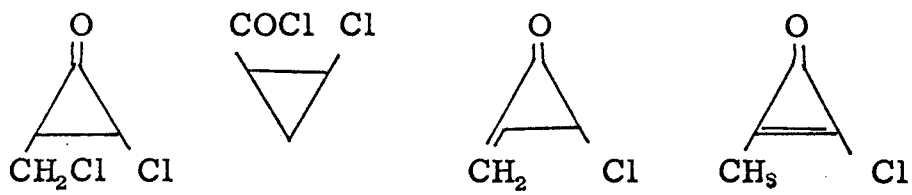
of the bicyclobutane from the catalyst surface. Reduction of bicyclobutanone with one mole of hydrogen would be expected to yield cyclobutanone. A literature search of the catalytic reduction of cyclobutanone was unsuccessful. Tetramethylcyclobutane-1,3-dione is catalytically reduced to 2,2,4,4-tetramethyl-3-hydroxy-cyclobutanone, and it would therefore seem reasonable that cyclobutanone (the reduction product of bicyclobutane) would be further reduced to cyclobutanol. Reduction of bicyclobutanone to either 2-butanone or butyraldehyde, corresponding to the reduction of bicyclobutane with two moles of hydrogen, cannot be predicted.

The reaction of bicyclobutane with halogens can take two different courses depending on the halogen employed[1b]. Iodination of bicyclo-



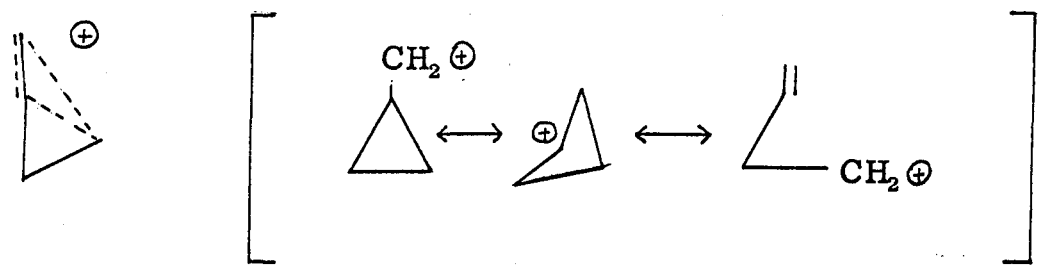
X	yield a	b
Cl	100	0
Br	mixture	
I	0	100

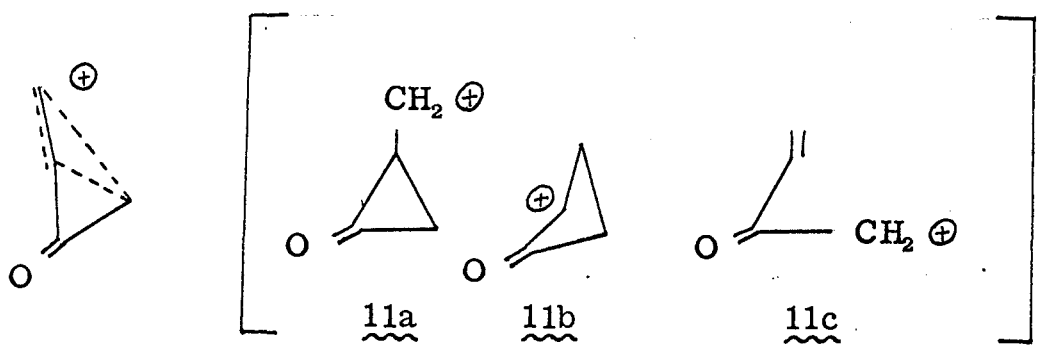
butanone would be expected to yield 2,4-diiodocyclobutanone. A possible initial chlorination product might be either ketone 7 or 8. Dehydrochlorination of ketone 7 would yield ketone 9, or less likely, ketone 10.



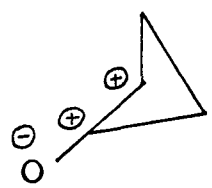
7 8 9 10

Bicyclobutane and most of its derivatives readily undergo hydration in dilute acid solution[1b]. The products of the hydration of bicyclobutane using 0.0001 N H_2SO_4 were found to be cyclobutanol (55%) and cyclopropylcarbinol (45%). The reaction of bicyclobutane-1-methanol with dilute acid (pH 4) occurs almost instantaneously and leads to 1-hydroxycyclobutanemethanol. As might be expected the addition of methanol across the central bond in 3-methylbicyclobutane-1-carboxylate gives one of the two isomeric 3-methyl-3-methoxy-cyclobutane-1-carboxylates. The type of products formed in these solvolyses reactions and the extraordinary lability toward acids suggests that the addition proceeds via a bicyclobutonium ion[17a]. The exact composition of the mixture obtained depends on the attacking reagent--water showing less preference than methanol in addition.

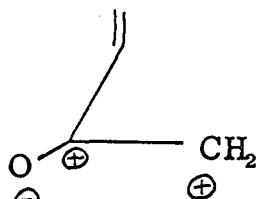




The exact structure of the bicyclobutonium ion would be expected to differ according to the substitution pattern of the substrate. Thus substituents which would stabilize one resonance form favor the products which are derived from that form. The solvolysis of 1-methyl cyclobutyl chloride yields only the corresponding cyclobutanol[17b, 17c]. The tertiary carbonium ion is sufficiently good as a classical ion that little extra stability would be derived from bicyclobutonium ion formation. The cyclobutanone carbonium ion 11b and methyl vinyl ketone carbonium ion 11c are destabilized relative to the cyclopropylcarbinyl carbonium ion 11a because of the contribution of 11d and 11e respectively. This would favor products derived from the cyclopropanone-



11d



11e

carbinyl carbonium ion 11a. Products derived from the cyclobutanone carbonium ion would be more significant if the α-position was substituted with either a methyl or phenyl group.

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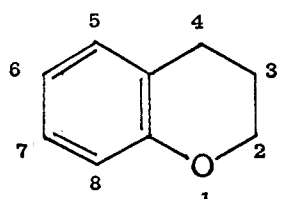
PROPOSITION IV

The chroman ring system[1a] 1, shown in Chart A, is found in a large group of plant products. Many of the plant and flower pigments, as well as some of the colored components produced by molds, are derived from this parent ring system. Coumarins[1b] 2 and chromones[1c] 3a are the most important divisions of this system. Flavones[1c] (i.e., 2-phenyl chromones) 3b, and isoflavones[1c] (i.e., 3-phenyl chromones) 3c, are widely distributed in plants as glycosides. A number of physiological, highly active substances possessing the α-pyrone[1d] nucleus 4 (α-pyrones can be viewed as nor-benzocoumarins) have been isolated. Substituted γ-pyrones[1d] 5, which can be viewed as nor-benzochromones, are widespread throughout nature. The pyrans (α-pyran[1d] 6 and γ-pyran[1d] 7) also offer a synthetic challenge, being enol ethers. Dihydropyran[1d] 8 has been employed as a model in carbohydrate chemistry.

Chart A



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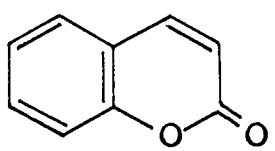

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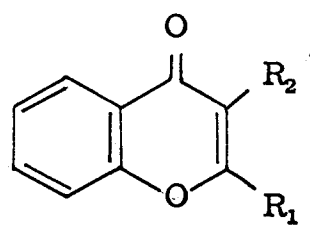
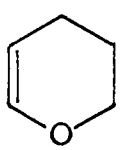


3 a, $R_1 = R_2 = H$

b, $R_1 = C_6H_5$, $R_2 = H$

c, $R_1 = H$, $R_2 = C_6H_5$



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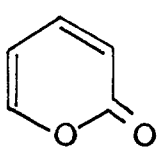

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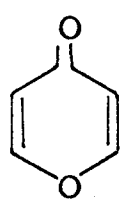

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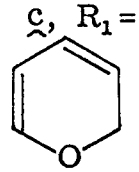

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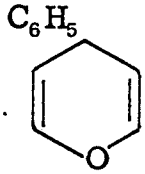
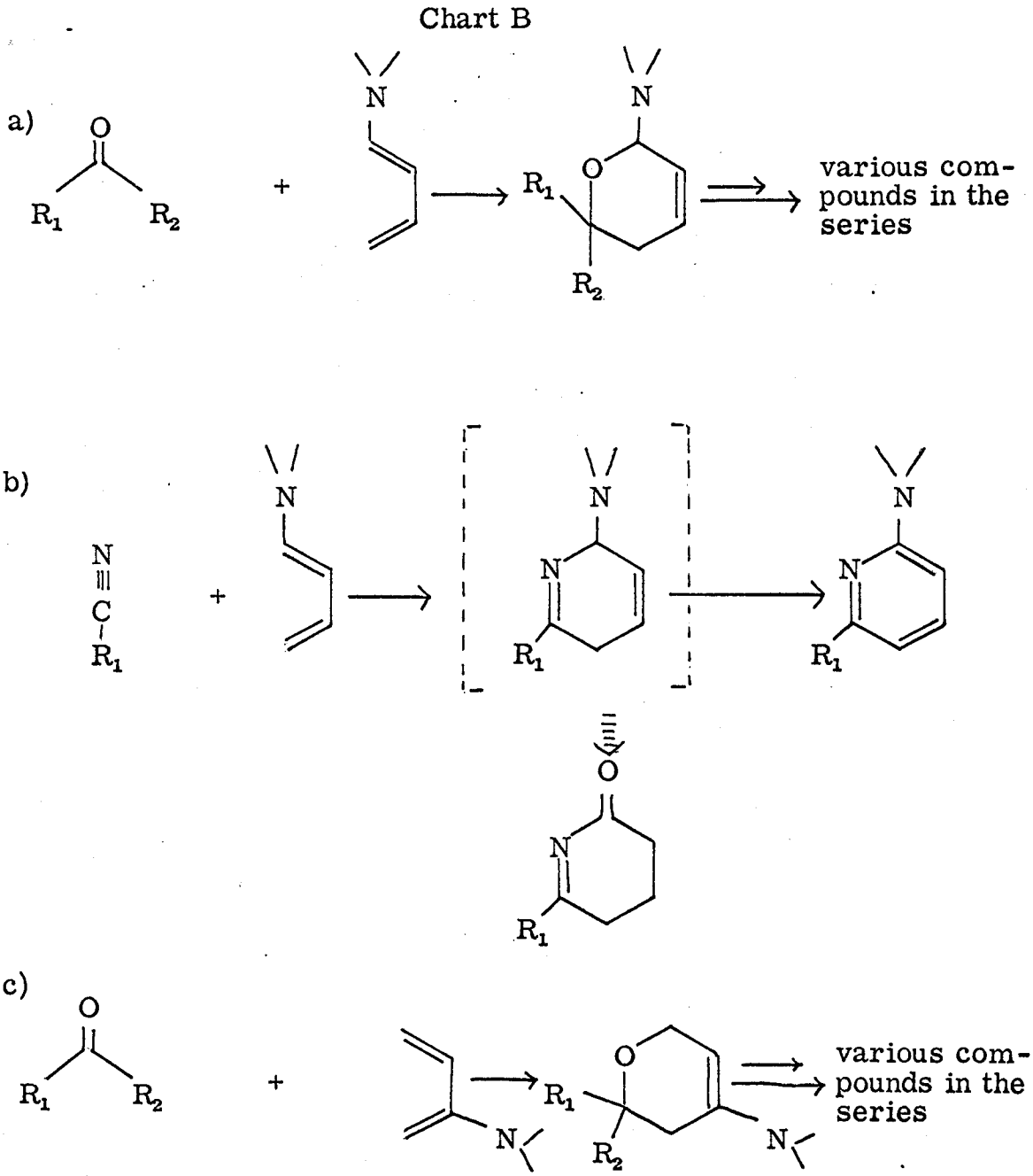


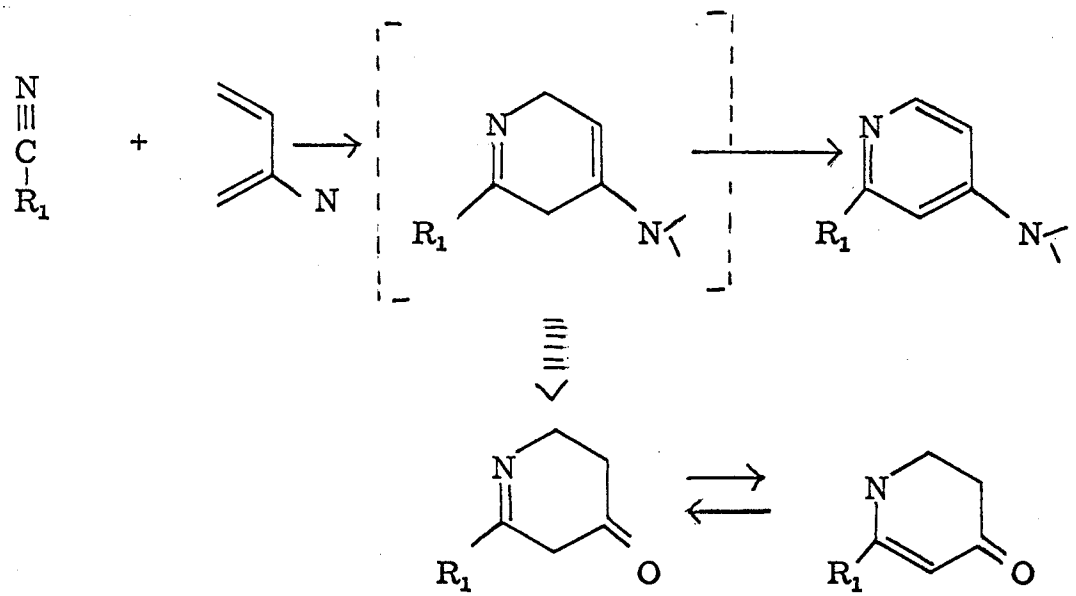
7

It is proposed to synthesize representatives of these classes of compounds by an enamine technique[2a, 2b, 2c] as shown below in Chart B.

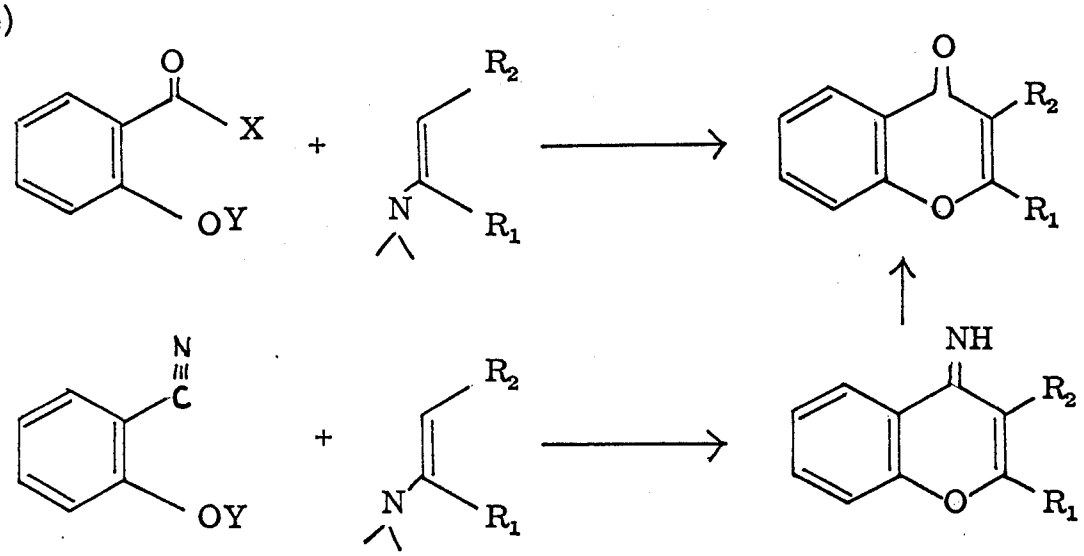
Chart B



d)



e)



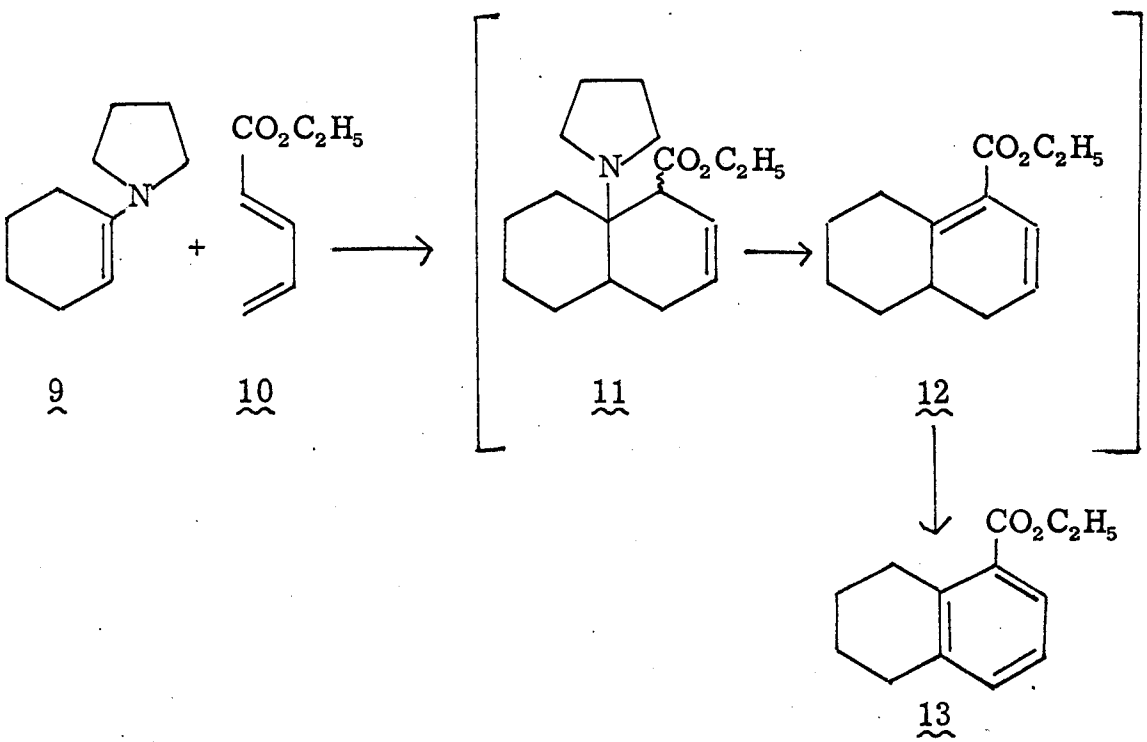
X = Cl

Y = $\overset{O}{\overset{\|}{C}}R_3$, H

The reactions to be cited, exhibiting high yields under mild conditions and incorporating nucleophilic enamine attack on various carbonyl and nitrile groupings, 1,4-cycloadditions, O-alkylation attack, amine elimination, and ease of aromatization, offer justification for the proposed routes delineated in Chart B by both flow and static methods.

Danishefsky[3a], aware that derivatives of β-vinyl acrylates are well known to undergo 1,6 addition preferably[3b], studied the reaction of the Δ^1-pyrrolidinocyclohexene (9) with ethyl trans-2,4-pentadienoate (10) as shown below in Chart C. In refluxing tetrahydrofuran a 1:1 molar ratio of (9) and (10) after 17 hours gave in

Chart C

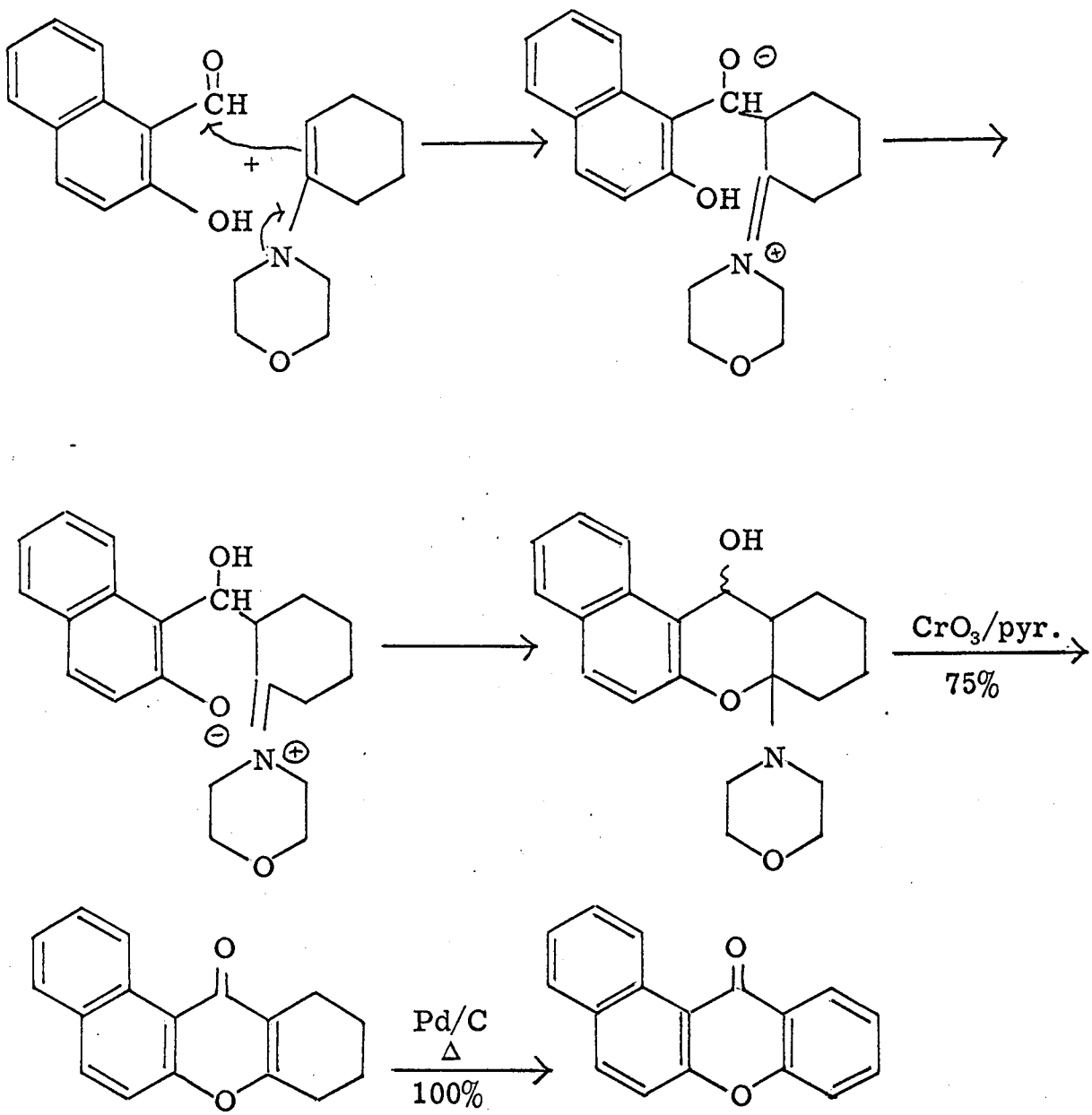


good yield a mixture composed of amino ester 11 and dienic ester 12. Under more vigorous conditions cycloaddition, retro-Michael elimination, and aromatization were realized, thus affording a one-step synthesis of aromatic ester 13 in 58% average yield. The authors note that the yellow color observed on admixture of the reactants is reminiscent of many types of Diels-Alder reactions. Berchtold[3c], who performed the study with a number of similar enamines, found that the enamines reacted with methyl trans-2,4-pentadienoate to give intermediate 1:1 adducts arising from 1,4-cycloaddition. These adducts were generally found to readily lose the elements of pyrrolidine or morpholine under the reaction conditions affording 3,4-dihydrobenzoate derivatives. The reaction has been shown to be general for pyrrolidine enamines of both cyclic ketones and simple aldehydes.

Paquette has reported[4] an interesting and germane zanthone synthesis which involves an enamine-initiated attack on an aldehydic group to form the alkoxide anion and O-alkylation of the resultant iminium salt as shown in Chart D on the following page. When equimolar quantities of 2-hydroxy-1-napthaldehyde and 1-morphilinocyclohexene were allowed to stand in benzene solution overnight at room temperature the crystalline adduct 14 was obtained in 91.5% yield.

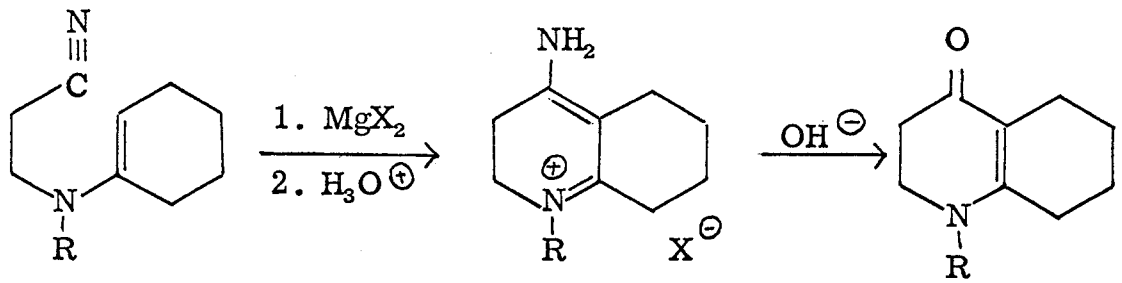
The facile cyclization of enamines containing a nitrile group

Chart D



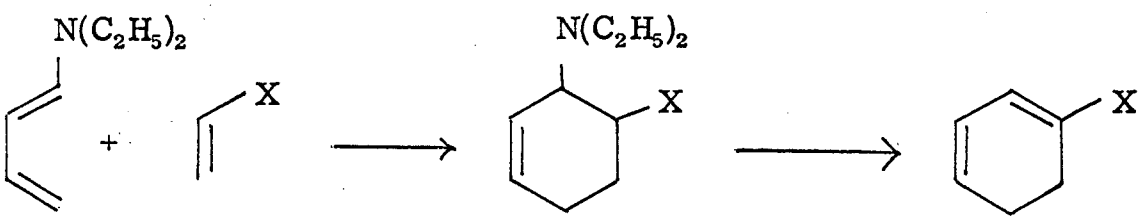
14

in the presence of magnesium has been reported to produce amino-dihydropyridinium salts in good yield[5a, 5b].



The 1,4-cycloaddition of 1-diethylamino-1,3-butadiene with electrophilic olefins to produce 4-substituted-3-diethylamino cyclohexenes[6] is described in Chart E. Yields are excellent and the experimental conditions quite mild.

Chart E

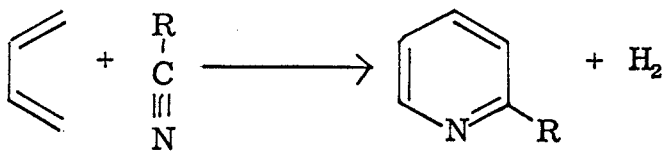


X	yield (%)	deamination
$CO_2C_2H_5$	94 (cis)	not reported
CN	93	no deamination noted
$COCH_3$	42 + some deamination product	spontaneously deaminates upon standing
CHO	84	deaminates quite easily

Hamer, in his instructive book "1,4-Cycloadditions--The Diels-Alder Reaction in Heterocyclic Synthesis"[7], notes that the mechanism of these 1,4-cycloaddition reactions remain a matter of debate. A number of interesting observations have been reported concerning the cycloaddition reaction of butadiene and substituted cyanides. The reader is referred to the chapter written by G.J. Janz[7] who also performed most of the experiments reported therein. The cycloaddition products obtained in the gas flow system are invariably the completely aromatized ring system (i.e., pyridines) rather than the primary diene addition products (i.e., dihydropyridines). Experimental conditions and yields for a variety of cyanides are reported in Chart F on the following page. These results indicate that although cyanides do undergo cycloaddition reactions with butadiene, only cyanides which contain polar groups adjacent to the dienophile able to enhance the polarizability of the reaction site are efficiently cyclized.

The previous studies cited, relevant to the proposal described in Chart B, resulted in good yields under mild reaction conditions upon reaction of a variety of activated and non-activated carbonyl and nitrile groupings with various nucleophilic monoenes and dienes (i.e., the enamines). These studies suggest that the employment of electron-rich 1-diethylamino-1,3-butadiene will be effectuated under mild conditions (i.e., low temperature, short reaction, non-activated dienophiles, etc.) in a static system. Repeating both the catalyzed and non-catalyzed type of gas flow system experiments

Chart F



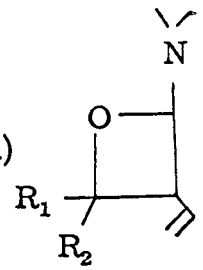
R	system	catalyst	temp. (°C)	contact time (hr.)	yield of pyr. pdt. (%)
H	homogen. gas phase rxn	none	404	15×10^{-4}	1.0
	heterogen. gas phase rxn	not noted	404	4.2×10^{-2}	1.01
CN	homogeneous	none	480	2×10^{-3}	34
	heterogeneous	not noted	400	6.3×10^{-2}	6.7
CH_3	homogeneous	none	395	12×10^{-4}	0.1
	heterogeneous	Al_2O_3	408	6×10^{-2}	3.6
C_6H_5	homogeneous	none	393	7.5×10^{-4}	1.4
	heterogeneous	Al_2O_3	400	6.5×10^{-2}	27
CF_3	homogeneous	none	400	44×10^{-2}	99

mentioned above with the various reactions shown in Chart B should also prove quite profitable. The dienamide technique could also be profitably applied with nitroso and azo dienophiles.

The formation of 4-membered rings is not competitive with the formation of 6-membered rings, especially if the reaction is considered to be initiated by nucleophilic attack and therefore fully

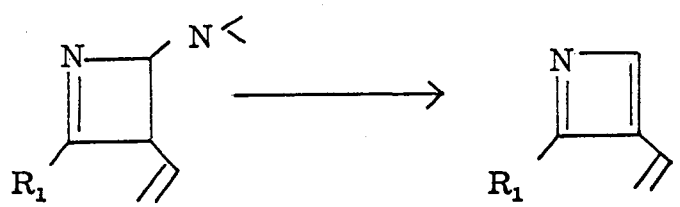
reversible. The corresponding 1,2-cycloaddition reactions, yielding an oxetane[8] by scheme Ba), substituted rare 1- or 2-azetines[8] by scheme Bb) and Bd), or oxetane[8] by scheme Bc), would not there-

scheme Ba)

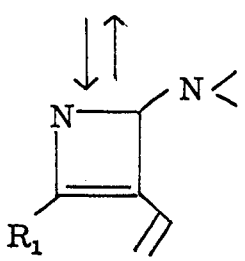


an oxetane

scheme Bb)

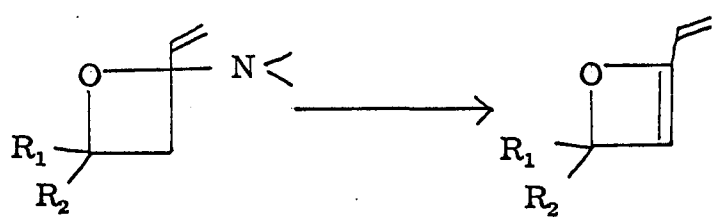


1-azetine azete



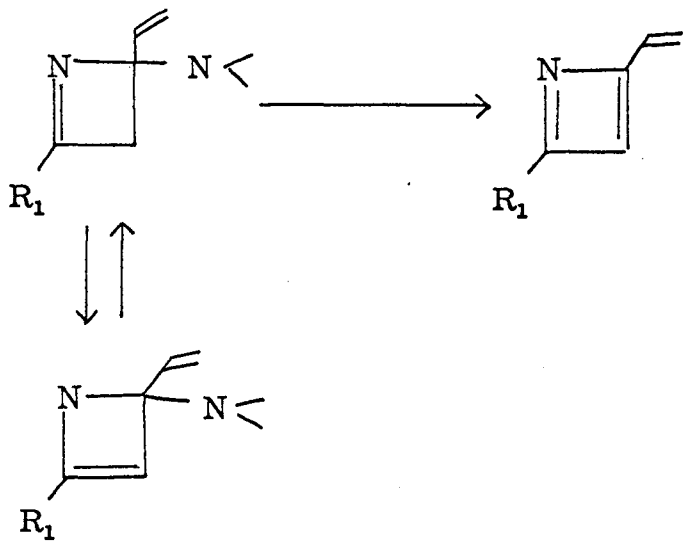
2-azetine

scheme Bc)



an oxete

scheme Bd)



fore seem to be competitive with the formation of six-membered rings obtained by 1,4-cycloadditions.

Appropriate R_1 and R_2 groupings in the nitrile and carbonyl starting materials shown in Chart B would seem to be H, CH_3, C_6H_5, and CN. Based on the observations already discussed it is felt that strong electron attracting groupings would not be necessary for satisfactory conversions. The presence of the cyanide group offers a good "handle" in the sequence as it can easily be converted to various functional groupings. Employment of various substituted crotonaldehydes also increase the generality of this synthetic approach. The use of phenyl methyl ketone and phenyl acetaldehyde as the enamine precursor in scheme Be) would result in the formation of the flavone and isoflavone systems, respectively.

The initial products of scheme Bb) and Bd) would be the dihydropyridines shown. Thermodynamic considerations indicate that spontaneous dehydrogenation of the dihydro adduct to the pyridine

adduct would be expected and this has been shown to be the case in the flow system studies[7] at 400°. Isolation of the amino dihydropyridines and subsequent hydrolysis would yield the trihydro- and dihydropyridones[9] shown in Chart B.

Conversion of the enamines formed in schemes Ba) and Bc) into the corresponding iminium salts and subsequent nucleophilic attack[2b, 2c] by hydride, cyanide, and grignard reagents would result in functionalization of the ring carbon atom attached to the nitrogen atom.

The α- and γ-pyrones $\underset{\sim}{4}$ and $\underset{\sim}{5}$ can be prepared from the enamine products of schemes Ba) and Bc) by first hydrolysis and then subsequent N-bromo succinimide[11] brominations and dehydrobrominations. Hydrolysis of the enamine formed in scheme Ba) would yield the lactone whose reduction and subsequent dehydration would form the dihydropyran $\underset{\sim}{8}$. Hydrolysis could also yield a hydroxy dihydropyran[11]. Hydrolysis of the imine prepared in scheme Be) would yield the desired chromone. The cyanide grouping (i.e., R_1 or R_2 in scheme Ba) or Bc)) is easily removed by first hydrolysis and then lead tetraacetate oxidative decarboxylation[12], thereby also introducing an additional double bond.

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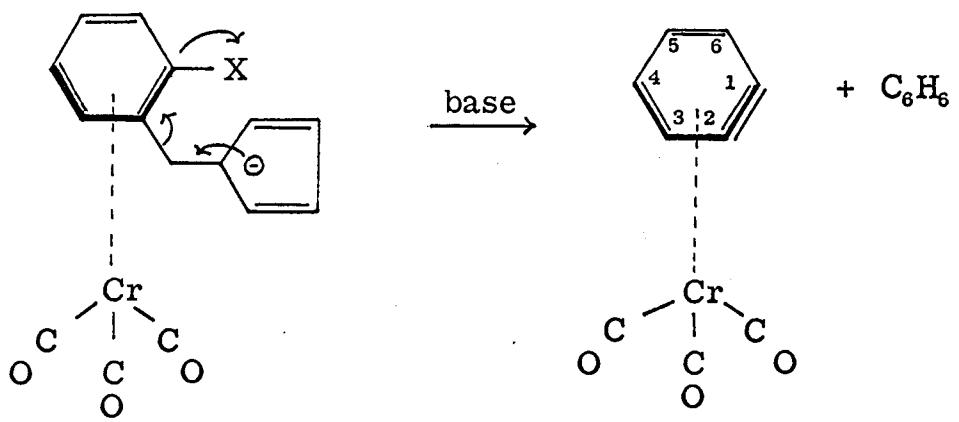
PROPOSITION V

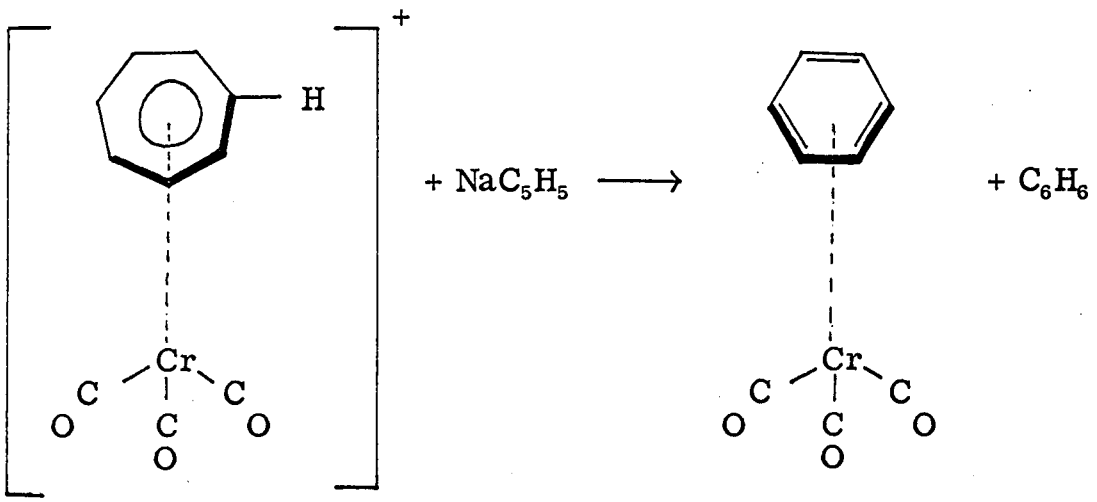
It is proposed to generate the benzyne-tricarbonyl-chromium complex (2) from the suitably substituted cyclopentadienyl benzene-tricarbonyl-chromium(0) complex 1 as shown below. The complex would be expected to exhibit a greater degree of stability than the benzyne molecule which is generated as a reactive intermediate by other techniques.



1 2

Salts of tropylium-tricarbonyl-chromium(0) (3) are prepared by hydride abstraction from cycloheptatriene-tricarbonyl-chromium(0)[1, 2a]. This method was previously employed for the preparation of tropylium-tricarbonyl-molybdenum(0) salts[3]. These salts undergo two types of reactions with nucleophiles depending on the character of the latter[2a, 2b]. With nucleophiles such as methoxide or phenyl anion, the products are

substituted (probably exo) cycloheptatriene-tricarbonyl-chromium(0) complexes. When the salt is added to excess sodium cyclopentadienide or sodiomalonic ester, a remarkable rearrangement occurs which leads to benzene-tricarbonyl-chromium(0) (4). The most favorable reaction conditions result in a 46% yield of the complex 4.

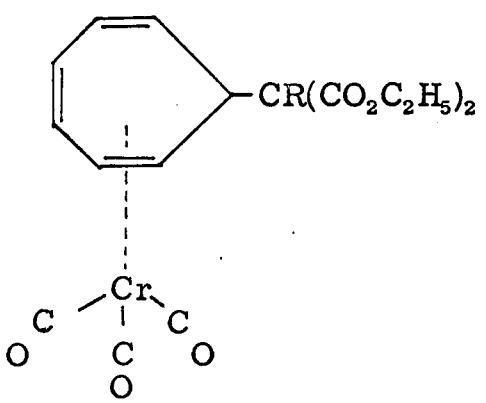


3 4

Munro and Pauson[2a] performed a number of experiments in order to establish whether the benzene ring attached to the chromium in the product was derived entirely from the seven-membered ring or in part from the cyclopentadiene ring. A decision in favor of the former view was reached qualitatively by repeating the reaction first with methylcyclopentadienylsodium, whereupon benzene-tricarbonyl-chromium(0) (4) was the only chromium complex isolated. Then, with methyltropylium-tricarbonyl-chromium, toluene-tricarbonyl-chromium(0)

was obtained. The conclusion that it is the seven-membered ring which produces the benzene complex by ring contraction (and thus, presumably, the five-membered ring which yields the free benzene molecule by ring expansion) was corroborated by labeling the tropylium complex 3 with tritium. The derived product 4 was shown to contain the expected tritium count.

The same ring contraction was again observed when the tropylium complex 3 was treated with an excess of diethylsodiomalonate. The simultaneous isolation of the malonate adduct 5 (R = H) suggested that the "normal" anion addition is an intermediate step in these rearrangements. This is confirmed by showing that ester 5 (R = H) is transformed into benzene complex 4 by the further action of sodiomalonate or by other bases such as sodium methoxide. The corresponding intermediate 6 (R = H) in the cyclopentadienide reaction was easily isolated when an excess of tropylium complex 3 was used and was



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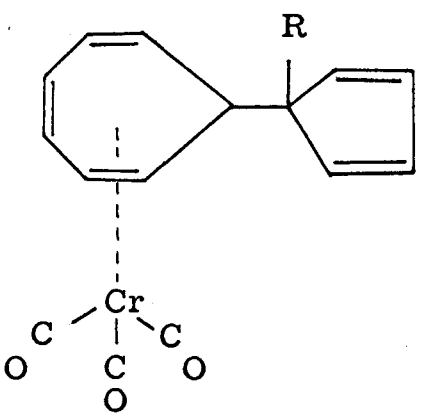
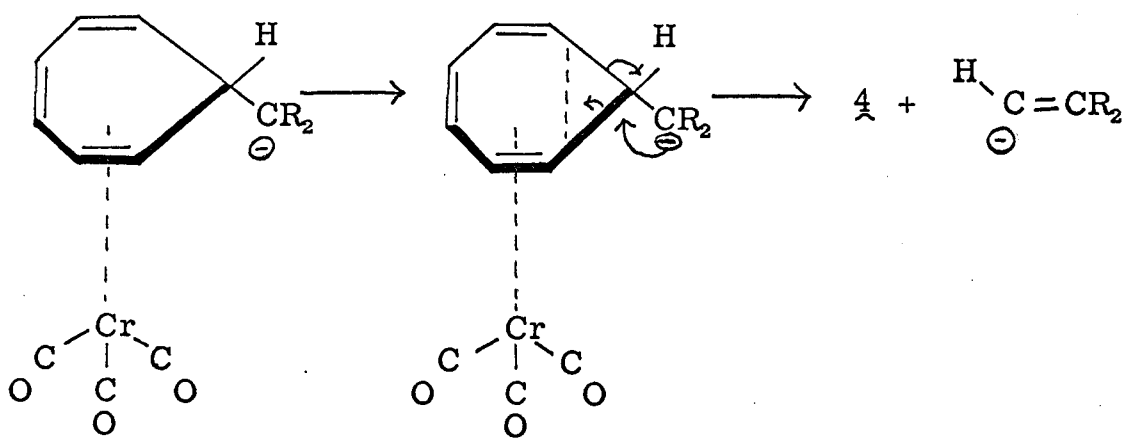


6

similarly transformed into benzene complex 4 by methoxide ion. Complex 6 (R = H) had a six degree melting range and was assumed to be a mixture of stereo-isomers. That the methylmalonate complex 5 (R = CH_3) fails to rearrange indicates that ionization of the acidic hydrogen (i.e., R in 5 and 6) induced by the basic catalyst is an essential step in the ring contraction. Munro and Pauson do not comment upon the fact that the rearrangement proceeds all the way to benzene complex 4 with sodium methylcyclopentadienide.

The above observations lead Munro and Pauson to propose that the electronic shifts indicated below represent "a possible mechanistic picture for this ring contraction". On this basis the "C_6H_6" fragment formed in the formation of complex 4 would be fulvene. Fulvene has not been isolated in this reaction and would not be expected to survive

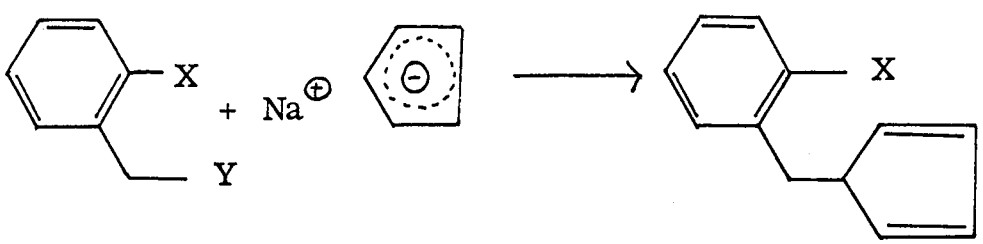


7

the reaction conditions. Munro and Pauson note in their 1961 article[2a] that attempts are in progress to find a situation where the corresponding product may be isolated. A survey of the subsequent literature indicates that a report of these attempts has not yet been published.

That formulation 7 is at best a first approximation of the actual mechanism is evident since it neglects the function of the tricarbonyl chromium grouping. Its importance to the reaction is, however, evident as cyclopentadienylcycloheptatriene is unaffected by sodium methoxide under the conditions employed for rearrangement of its complex 6 (R = H).

The synthesis of complex 1, X being a suitable leaving group, can be effected in various ways. An efficient approach would involve the reaction of ortho- and alpha-disubstituted toluenes with an equivalent amount (the equivalency determined either by salt isolation or employment of a standard solution) of sodium cyclopentadienide as indicated below.

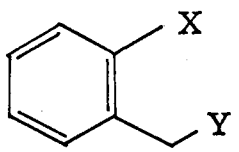


8 9

Disubstituted toluenes with X being halide, tosylate, or acetate and Y being halide or tosylate would be suitable substrates. Representative examples of innumerable syntheses of these compounds present in the

literature are shown in Chart I.

Chart I



8

X = F,	Y = Cl	[4a]
Br	Br	[4b]
Cl	Br	[4c]
Cl	OH	[4d]
Br	OH	[4d]

The complex 1 can be formed by either causing the cyclopentadienyl-benzene grouping to selectively react at the triene site with chromium hexacarbonyl or by preforming the complex with the reaction of chromium hexacarbonyl and the disubstituted toluene. Many mono- and di-substituted benzene complexes, such as chlorobenzene-tricarbonyl-chromium(0)[5a], phenol-tricarbonyl-chromium(0)[5b], benzyl alcohol-tricarbonyl-chromium(0)[5a], toluene-tricarbonyl-chromium(0)[5a], phenylacetate-tricarbonyl-chromium(0)[5c], ortho-toluidine-tricarbonyl-chromium(0)[5a], ortho-xylene-tricarbonyl-chromium(0)[5a], and meta-methoxybenzoic acid-tricarbonyl-chromium(0)[5d], have been prepared in yields from 20 to 90% by causing the substituted benzene to react with chromium hexacarbonyl.

Chromium tricarbonyl, requiring the donation of six electrons to fill the valence shell of chromium, will preferentially complex with

benzene rather than cyclopentadiene. Cyclo-octa-1,5-diene affords the yellow complex [$Cr(CO)_4(C_8H_{12})$] in only 2% yield after being refluxed for two days with a two-fold excess of chromium hexacarbonyl[6a]. Cais isolated 1-(phenyl-chromium tricarbonyl)-4-phenylbutadiene (60% yield) and a small amount of 1,4-di-(phenyl-chromium tricarbonyl) butadiene when 1,4-diphenylbutadiene was caused to react with chromium hexacarbonyl[6b]. The mono-complex could be converted to the di-complex in over 50% yield, but butadiene-complex formation was not noted. Iron pentacarbonyl, on the other hand, was shown to effectively complex with the butadiene moiety. No literature report of the reaction of chromium hexacarbonyl with cyclopentadiene to yield the diene-carbonyl complex was found. Cyclopentadiene will react with chromium hexacarbonyl under forcing conditions (i.e., 280-350° hot tube vapor phase experiment) to form bis-cyclopentadienylchromium(II) in 30% yield[6c].

Abstraction of the acidic cyclopentadienic proton in complex $\underset{\sim}{1}$ by base would be expected to readily occur based on the cyclohepta-trienic analogy. Subsequent elimination of the leaving group X would result in the formation of the desired benzyne complex $\underset{\sim}{2}$ and fulvene.

The most reasonable proposals for π-type bonding between a benzenoid compound and a transition metal involve donation of electrons to the metal -- the donated electrons allowing the metal to achieve the rare gas configuration. This direction of electronic transfer creates an electron deficienty on the arene and leaves it less prone to electrophilic attack than the free arene. These arene complexes, on the other hand,

undergo nucleophilic substitution much more readily than the corresponding arene. The facile reaction of chlorobenzene-tricarbonyl-chromium(0) with sodium methoxide to yield anisole-tricarbonyl-chromium[5a] demonstrates the enhanced reactivity of the π-bonded benzenoid nucleus towards nucleophiles. This enhanced reactivity should aid the proposed nucleophilic-type reaction required for the ejection of the leaving group.

The substitution of the malonate moiety for the cyclopentadienyl portion of complex 1 would also result in the formation of an effective precursor for the formation of benzyne complex 2.

It would be quite interesting to investigate the possibility of employing an anthranilic acid-tricarbonyl-chromium type compound as the benzyne complex precursor. Diazotization of the anthranilic acid-tricarbonyl-chromium complex would present a problem as arene-tricarbonyl-metal(0) complexes are, in general, unstable to strong acid. Benzenediazonium-2-carboxylate-tricarbonyl-chromium, prepared by the reaction of preformed benzenediazonium-2-carboxylate with chromium hexacarbonyl, would serve as a suitable substrate. Benzothiadiazole-1,1-dioxide, which has been employed to generate benzyne quite efficiently under very mild conditions[7], would also serve as an interesting substrate for benzyne complex formation.

Huisgen has shown with the aid of a series of Diels-Alder reactions[8] that the benzyne liberated by metals from benzene halides (which may exist as either the free alkyne or as a complex with a metal cation or anionic halide) and the intermediate generated by

thermolysis of benzenediazonium-2-carboxylate are identical. The benzyne complex $\underset{\sim}{2}$ could therefore be expected to generate the same intermediate.

It would be quite difficult to predict the relative stability of benzyne complex $\underset{\sim}{2}$. Benzyne[9a, 9b], although easy to generate, is quite unstable and has therefore been characterized only by the adducts it forms with other compounds and through labeling experiments. The only direct physical measurement of benzyne is the transcient absorption spectrum obtained by flash photolysis of the diazonium salt[10].

Numerous spectral investigations of arene-tricarbonyl-chromium complexes have been reported. A number of pronounced changes were found to occur in the infrared region upon complexing[11a]. These include shifting of the 1600 and 1500 bands, generally attributed to skeletal C-C stretching modes, from their normal position by 25-100 cm^{-1} and 30-40 cm^{-1} respectively toward lower energy. These changes also include the presence of two intense bands at 1990 and 1920 cm^{-1}--indicative of the tricarbonyl moiety. The carbonyl frequency is dependent on the extent of back-donation from the metal, carbonyl frequencies shifting to lower values when the electron density on the aromatic nucleus is increased. In general, three ultraviolet absorptions are quoted[11b] in the regions 218-221, 251-264 (shoulder), and 315-324 mμ with log ϵ of 4.4, 3.8, and 3.2 respectively. No efforts have been made to interpret these transitions, although from analogies to other carbonyl-metal complexes it appears that the absorptions below 300 mμ are due to the

carbonyl groupings. The ring protons in the nuclear magnetic resonance spectrum[11c] appear at higher field strength than in free benzenoid compounds. This is because the aromatic ring current is perturbed by π-bond formation to the metal.

The benzyne complex 2, if relatively unstable, could be trapped in the normal manner by compounds such as furan, anthracene, or carboxylic acids[9a, 9b], or nucleophiles such as thiophenoxide, anisole, anilide, triphenylmethide, or n-butide (from n-butyl lithium)[9a, 9b]. Heating of arene complexes with an excess of mesitylene results in arene exchange (i.e., formation of free arene and the corresponding mesitylene complex)[2a]. Distillation of toluene-tricarbonyl-chromium(0) at 200° resulted in the isolation of toluene in 76% yield[5a]. These observations would seem to indicate that the benzyne complex 1, if reasonably stable, could be converted to benzyne upon gentle heating in a relative stable solvent such as benzene[13] or the alkylated benzenes.

The bonding system of benzyne, which shows no reactions characteristic of radicals, is not well understood. But it is felt that the aromatic character of the cyclic system is reasonably undisturbed[9b]. Models of the electronic structure show that the ring strain is not excessively high and can be compared with that of the cyclopropene ring[9b]. It has been generally accepted[9a] that the two non-hydrogen carbon atoms maintain their sp^2 hybridization as in benzene; and that the electron pair of interest is resident in the two sp^2 orbitals ordinarily used for bonding with hydrogen or substituents. These orbitals are thought to have their axes in the plane of the ring and overlap sideways

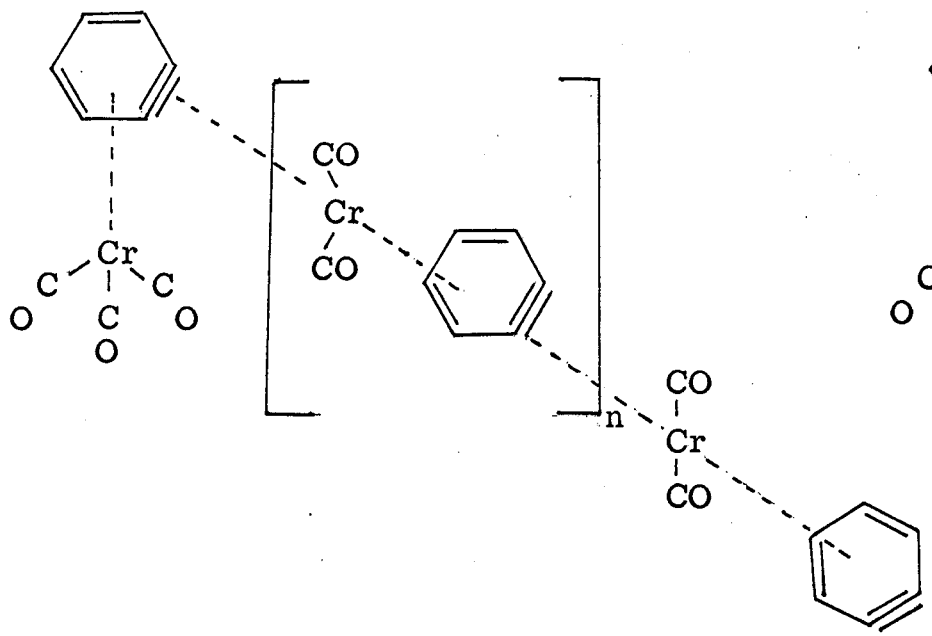
to some extent, creating a weak bond. Recently published calculations and observations by Hoffmann[12] also indicates that there is some overlap between the two half-occupied lone pairs. He considers these lobes as somewhat delocalized and quite different from sp^2 hybridization. Additional stabilization of the benzyne complex $\underset{\sim}{2}$ might be achieved by tilting of the benzyne plane such that carbon atoms 1 and 2 would be brought closer to the chromium atom than atoms 4 and 5. This would result in a slight destabilization due to the decreased electron donation of the C_3-C_4 and C_5-C_6 double bonds to chromium, but a greater stabilization of the "triple bond" (i.e., the unstable portion of the molecule) due to chromium back donation. Tilting the molecule such that carbon atoms 2 and 3 will be closer to the chromium atom will result in only a single double bond, the C_5-C_6 bond, being further removed from chromium. The degree of extra stabilization would probably not be such that a single carbonyl group would be lost from complex $\underset{\sim}{2}$.

The question of self condensation of complex 2 involving "triple bond" π-bonding with elimination of a single molecule of carbon monoxide is an intriguing one to consider. Stable complexes of formula [Arene $Cr(CO)_2$ $RC{\equiv}CR$] have been obtained by irradiation of solutions of hexamethylbenzene-tricarbonyl-chromium(0) or mesitylene-tricarbonyl-chromium(0) and diethylacetylenedicarboxylate or diphenylacetylene[14]. The complex prepared by irradiation of a solution of benzene-tricarbonyl-chromium(0) and diphenyl acetylene was also obtained. The yields varied from 30-55%. The performance of this

reaction

$$\text{Arene Cr(CO)}_3 + \text{R-C}\equiv\text{C-R} \xrightarrow{h\nu} \text{Arene Cr(CO)}_2\text{R-C}\equiv\text{C-R} + \text{CO}$$

by a thermal route has not been reported. It is therefore possible but unlikely that the benzyne complex 2 would be converted wholly or in part to polymeric complex 10 under the experimental conditions employed. It would be of interest to attempt to prepare complex 11 by reaction of complex 2 with chromium hexacarbonyl. The "triple bond" would then, of course, not be involved in stabilization with the tricarbonyl chromium grouping in complex 11. Benzyne should also be



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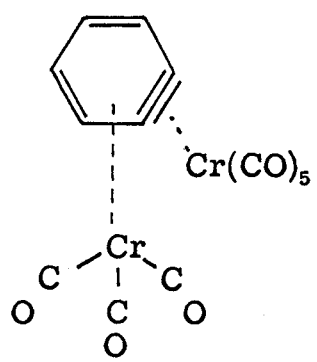

11

generated from either benzenediazonium-2-carboxylate or benzothiadiazole-1, 1-dioxide in the presence of hexacarbonyl chromium--two different possibly competitive complexing sites, the benzene ring and the "triple bond", being available.

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