To
Mom and Dad,
Bruce,
Jennie,
and Tim

# ALKYLATION OF KETONES WITH 3-BROMOMETHYL-1,2-BENZISOTHIAZOLES

Thesis by

Robert Allen Gillham, Jr.

In Partial Fulfillment of the Requirements

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## ABSTRACT

The synthesis of 3-bromomethyl-1,2-benzisothiazole and its 5- and 7-methoxy derivatives has been accomplished. In alkylation reactions, these bromides were found to behave much like benzylic bromides; and in this respect they have been used successfully to alkylate strongly basic enolates, thus introducing a latent β-phenylethyl moiety in situations where β-phenylethyl bromide and phenacyl bromide give at best poor yields of alkylated product. In several cases, degradative procedures have been devised to remove the heteroatoms from the benzisothiazoyl system to provide the actual β-phenylethyl fragment; however, no generally applicable degradative method has yet been developed.

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# HISTORICAL INTRODUCTION

Today, at a time when the synthetic chemist is accepting the challenge inherent in ever larger and more complex molecules, synthetic schemes containing upward of thirty separate transformations are no longer uncommon. In fact, for the natural product chemist who has chosen the synthetic challenge presented by the pentacyclic triterpenes, schemes of such magnitude are the rule rather than the exception. Clearly, if such an involved synthetic sequence is indeed to be realized, it must contain a series of consistently high yield reactions; otherwise, the efficacy of the scheme will quickly succumb to the law of diminishing returns.

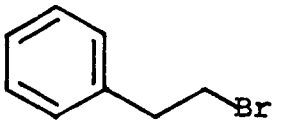
Viewed as a class, the pentacyclic triterpenes exhibit two striking characteristics which the synthetic chemist must consider. These compounds possess a series of contiguous asymmetric centers which are situated more or less regularly along the backbone of a polycarbocyclic system. The presence of these numerous, adjacent centers of asymmetry demands a synthetic scheme that promises a high degree of stereochemical control, while the presence of a series of five interconnected ring systems implies the need for an efficient method of constructing the gross structure of the molecule.

Efficient construction of a gross structure necessarily involves the efficient formation of new carbon-carbon bonds. To accomplish this task, the synthetic chemist often resorts to a quite simple, yet widely applicable reaction, namely the alkylation reaction. Within the general realm of alkylation reactions, the alkylation of methylene groups activated by ketones and ketone derivatives has seen repeated use, due largely to the frequent appearance of the carbonyl functional group in synthetic intermediates.

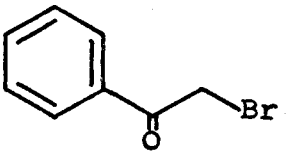
Acknowledging the importance of the alkylation of ketones in forming new carbon-carbon bonds, one particular type of alkylating agent has special appeal to the natural product chemist who is concerned with fabricating 6-membered carbocyclic ring systems. This class of reagent, containing an actual or latent β-phenylethyl moiety, introduces an eight carbon fragment in a single reaction. Furthermore, as will become apparent shortly, in many situations the newly acquired β-phenylethyl sidechain represents the elements sufficient for the formation of two additional 6-membered carbocyclic rings. This last property fits in nicely with the steroidal approach of progressive ring additions, a concept frequently employed in these laboratories. It also helps satisfy the requirement

for rapid and efficient construction of the gross skeleton of molecules such as the pentacyclic triterpenes.

The two most widely used of the β-phenylethyl bearing alkylating agents are β-phenylethyl bromide (i) and phenacyl bromide (ii). These two reagents and various of

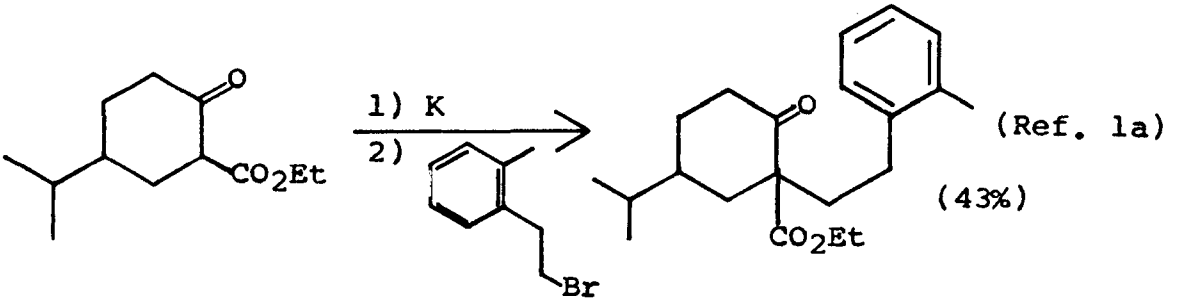



i



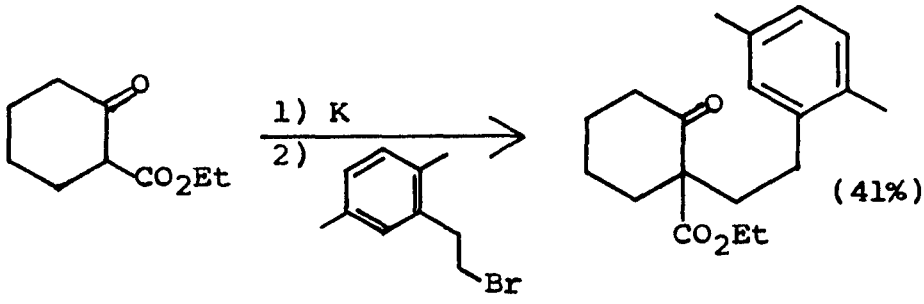

ii

their derivatives have been used to aklylate a variety of synthetically useful ketones and ketone derivatives. For example, the chemist intent on constructing phenanthrene skeletons has often used β-phenylethyl bromides in conjunction with cyclohexanone derivatives.




(Ref. 1a)

(43%)

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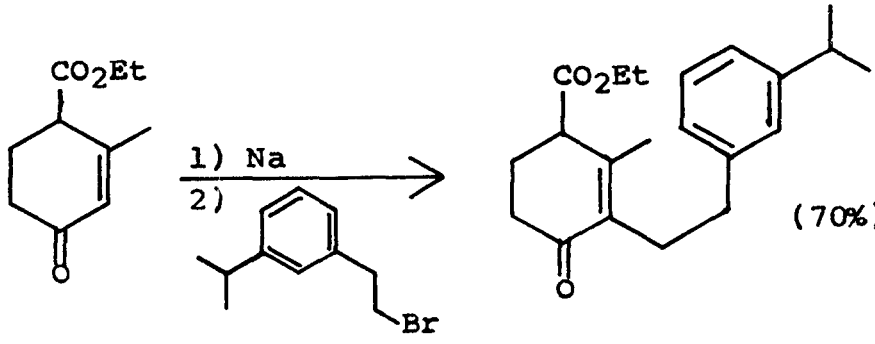


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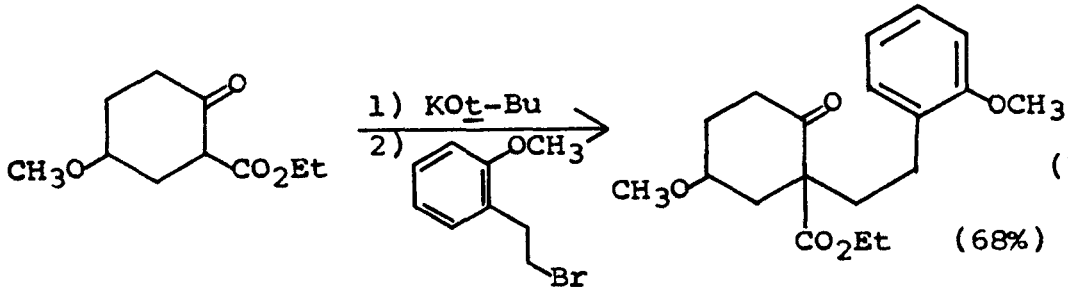


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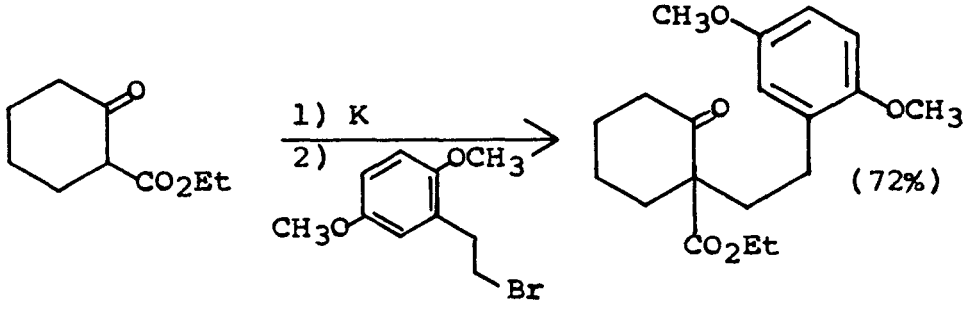
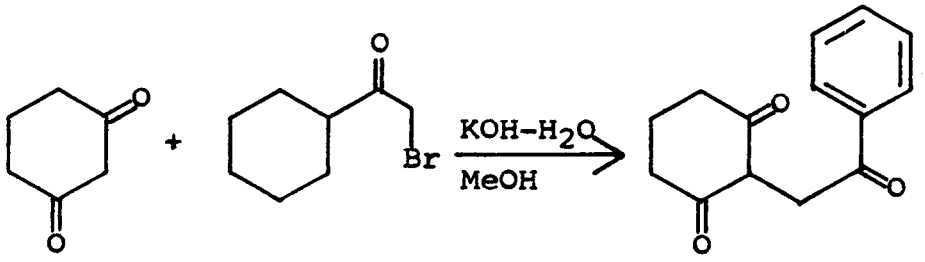



(Ref. 4)

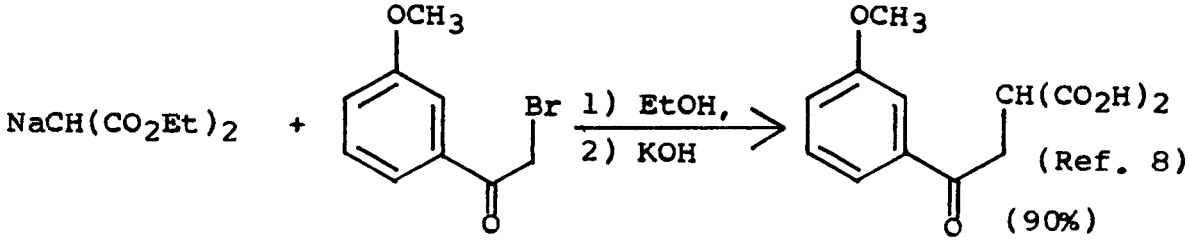
In addition to these representative cases, diethyl malonate (5) and ethyl cyclopentanone-2-carboxylate (6) have been alkylated with β-phenylethyl bromides in yields of 70-75%.

The chemical literature also contains many references to the synthetic use of phenacyl bromides, including the examples listed below:




(Ref. 7)

(44%)

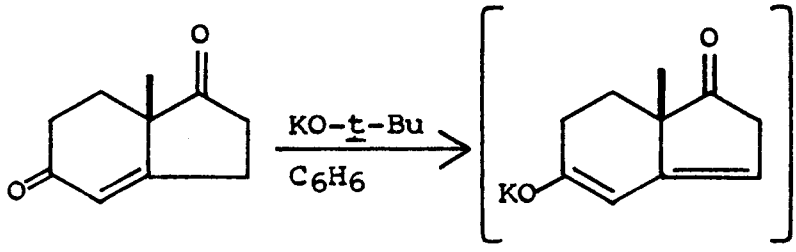



(Ref. 8)

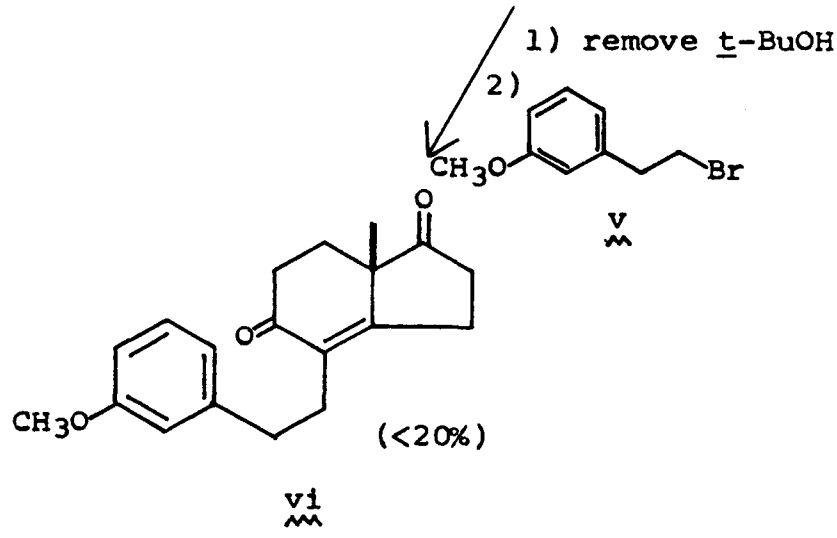
(90%)

The reactions illustrated above all have one feature in common. They all involve the alkylation of enolate anions derived from relatively acidic compounds. The activated methylene groups in β-diketones, β-keto esters, and malonic esters have $pK_a$'s in the range 9-13. Consequently, the enolate anions derived from them are not

particularly strong bases, in fact not strong enough to frustrate the alkylation by interacting with bromides i or ii in ways that do not lead to the desired alkylated products. Unfortunately, these alternate modes of reaction come sharply to the forefront when the chemist attempts to employ these alkylating agents together with strongly basic enolates. For example, Smith and co-workers (9) reported that alkylation of the heteroannular enolate from iii, obtained under equilibrating conditions, gave a very low return of the desired adduct vi. In this case,



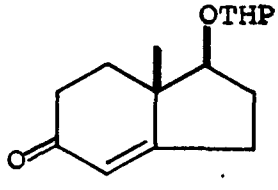

iii iv



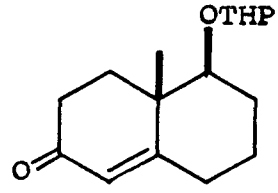

v vi

enolate iv is sufficiently basic ($pK_a$ 18-20) to effect appreciable dehydrobromination of alkylating agent v. This result is not totally unexpected, as β-phenylethyl bromides are known to suffer $E_2$ elimination in the presence of strong base. Bromide i in a warm solution of tert.-butyl alcohol containing potassium tert.-butoxide ($pK_a$ 19) eliminates to give a quantitative yield of styrene (10). Under similar conditions, the less nucleophilic methoxide ion [sodium methoxide in methanol ($pK_a$ 16)] gives a mixture of products arising from both elimination and substitution: 64% styrene, 12% β-phenylethyl methyl ether (11).

Crispin and Whitehurst (12) report the successful alkylation of enone vii with bromide v but do not comment on the yield. However, the yield is probably low, as Smith and McLoughlin (9b) report little success using the same bromide with the analogous enone viii.



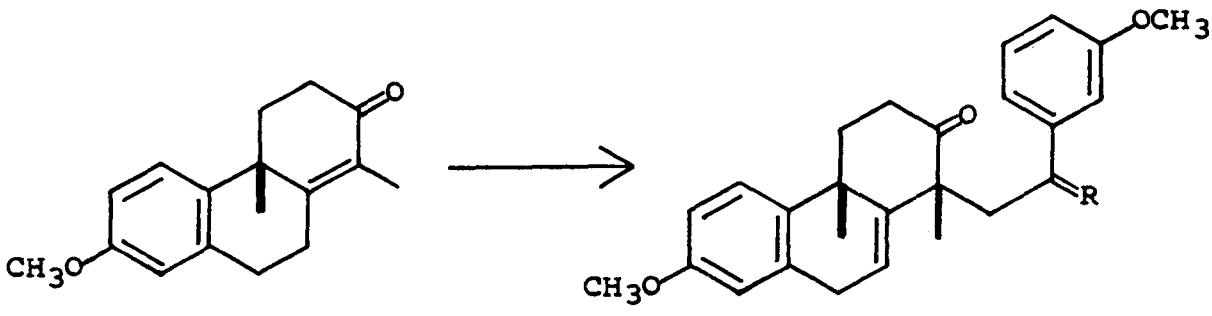

vii




viii

More recently in this laboratory, Evans (13) encountered the same difficulty when he attempted to alkylate

the heteroannular enolate of enone ix with bromide v. This transformation, although attempted under a variety

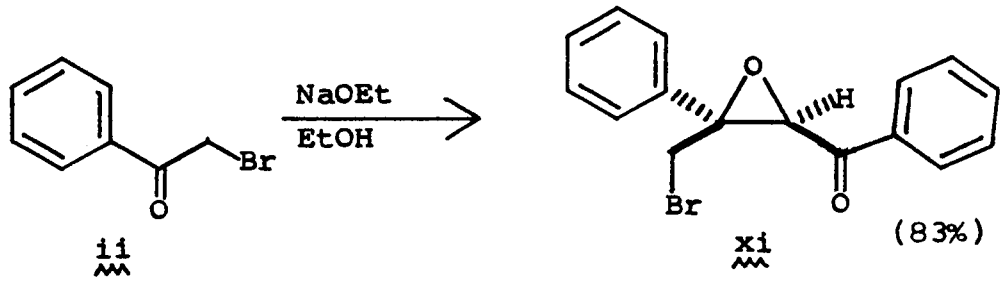



ix

x a: R=H2
b: R=O
c: R=CH2

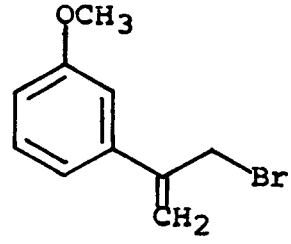
of conditions, was never successful. Evans, too, noted only dehydrobromination of the alkylating agent. The corresponding iodide responded likewise. Thwarted with the direct approach, Evans next explored an alternate route leading to x-b by using m-methoxyphenacyl bromide as the alkylating agent. At first glance, the great reactivity of this halide as well as its inability to undergo dehydrobromination made it an attractive choice. However, at the time Evans did not realize that the phenacyl bromide (estimated $pK_a$ 17) was a weaker conjugate base than the heteroannular enolate of enone ix. Consequently, when this bromide was used to alkylate enone ix,

the reaction returned unchanged starting material and condensation products derived from the alkylating agent. The work of Wasserman and co-workers (14) provides some insight into the probable nature of these condensation products. They found that bromide ii, in ethanolic sodium ethoxide at room temperature, rapidly condensed with itself to give the stable epoxide xi.




ii xi (83%)

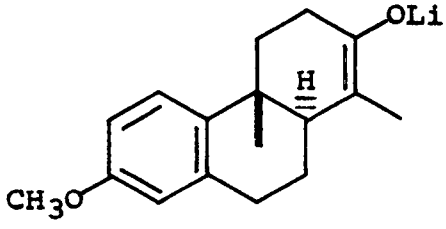
Evans was able to obtain the keto olefin x-c from ix in 48% yield through the efficacy of the α-bromomethylstyrene xii. However, efforts to remove the exomethylene



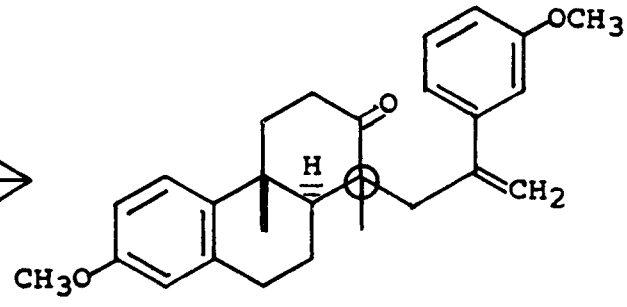

xii

fragment without disturbing the rest of the molecule were unsuccessful and this route was ultimately abandoned.

As a final note, attempts to quench the enolate xiii (estimated $pK_a$ >20), formed by the reduction of enone ix with lithium in ammonia, with the β-phenylethyl bromide and the phenacyl bromide were also unsuccessful. With

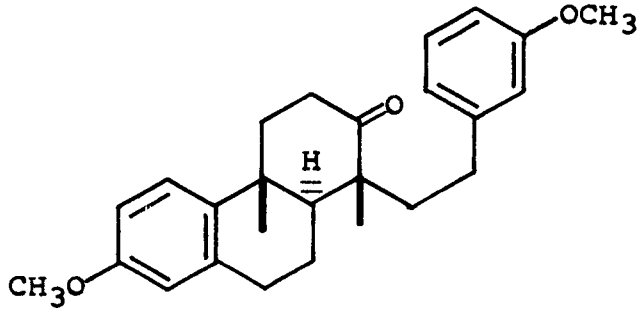



xiii




xiv

the same intermediate, allylic halide xii afforded a 91% yield of a 3:2 mixture of ketones xiv isomeric at C-1. By the efficient manipulation of a twelve step sequence beginning with alkylation of enone ix with ethyl bromoacetate (estimated $pK_a$ 22), Evans was able to obtain the elusive phenylethyl ketone xv. This stepwise procedure




xv

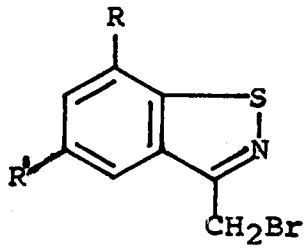
notwithstanding, there would still seem to be a place for an alkylating agent that could introduce a β-phenylethyl moiety and yet be used in conjunction with strongly basic enolates.

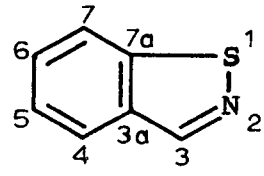
## DISCUSSION

Past chemical experience would indicate that for an alkylating agent to be capable of introducing a β-phenylethyl fragment and yet be used successfully with strongly basic enolates, it must not be able to dehydrohalogenate as does β-phenylethyl bromide (i) nor contain protons acidic enough to quench the enolate as is the case with phenacyl bromide (ii). However, an alkylating agent that satisfies these requirements must necessarily contain a latent β-phenylethyl moiety; and for such a reagent to be synthetically useful it must be more than just an efficient alkylating agent. After the alkylation reaction, the newly acquired residue must be willing to release the desired β-phenylethyl fragment under conditions that will not unduly perturb the rest of the molecule. The application of α-bromomethyl styrene xii described earlier is a particular example of an alkylating agent that satisfied the first two requirements, but not the third. As was noted, Evans (13) encountered considerable difficulty in his efforts to remove the exomethylene group in the styrryl sidechain of molecule x-c.

Possible alkylating agents which appear to satisfy all three requirements set forth above are the related

3-bromomethylbenzisothiazoles I*. Although the chemical literature contains few references to benzisothiazole




I a: R=R'=H

b: R=$OCH_3$, R'=H

c: R=H, R'=$OCH_3$

chemistry (15), the sparse evidence that was available indicated that the bromides I were likely candidates for

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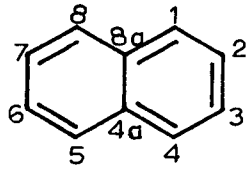
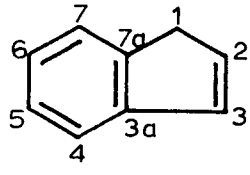
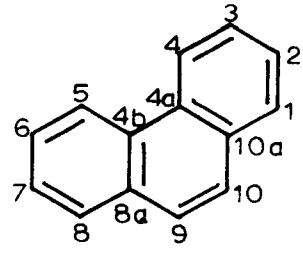
*The 1,2-benzisothiazole ring system is No. 1150 in the Ring Index. Bicyclic compounds discussed herein are named and numbered as derivatives of naphthalene (No. 1754) or indene (No. 1391). Tricyclic compounds are treated as derivatives of phenanthrene (No. 3619). (A. M. Patterson, L. T. Capell, D. F. Walker, "The Ring Index", American Chemical Society Special Issue Sales, 1960).

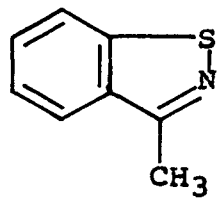


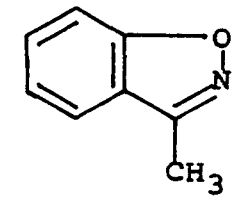



further investigation. The parent compound, 1,2-benzisothiazole itself, was first prepared in the 1920's, and while it has been synthesized more recently (16), most of the chemistry of this class of compounds is confined to that earlier decade. A number of polysubstituted 1,2-benzisothiazoles were prepared during this period, and from their reported chemistry one can obtain some idea of the reactivity of the 1,2-benzisothiazole ring system. It is apparently stable to mild oxidation and reduction procedures. Fries (17) compared these heteroaromatic compounds with naphthalene and its derivatives with reference to their ability to undergo electrophilic aromatic substitution. Carrying this similarity one step further, one might expect the reactivity of bromides I to be not unlike that of the benzylic bromides, a class of very hot alkylating agents (18).

In 1966, Crawford and Woo (19) had prepared 3-methyl-1,2-benzisothiazole (II) by the sequence shown in Chart A.

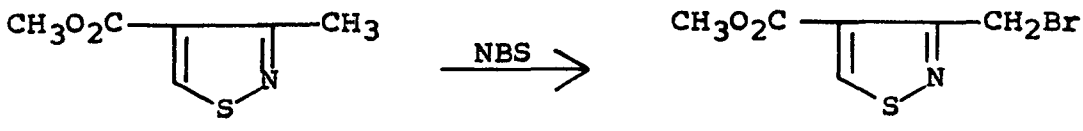



II




III

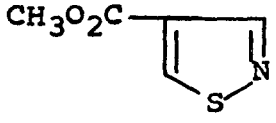
By analogy to the known chemistry of its oxygen analogue, 3-methyl-indoxazene (III) (20), we expected that II would mono-nitrate at C-5 and/or C-7; and this substitution pattern would provide a possible route to methyl ethers Ib and Ic. As Woodward (21) had earlier prepared 3-bromomethylisothiazole IV for use in his total synthesis of colchicine, a similar conversion of II to bromide Ia should present no difficulties.



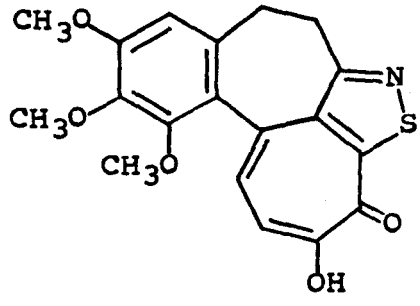

IV

Confident that we could obtain the bromide Ia and that it would be an efficient alkylating agent, we were still challenged to find a suitable way to unmask the β-phenylethyl moiety via the orderly destruction of the 1,2-benzisothiazole nucleus. The literature contains no reference to any degradation of this heteroaromatic system, however one key to its dismantlement was suggested by the work of Adams and Slack (22) and Woodward (21) who had successfully degraded isothiazoles V and VI,

respectively. Treatment of these molecules with Raney nickel had stripped them of sulfur and reduced the carbon-nitrogen double bond to generate the appropriate primary amine. As it is possible to remove primary amines via



V

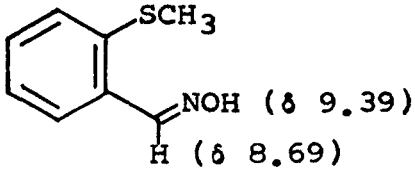


VI

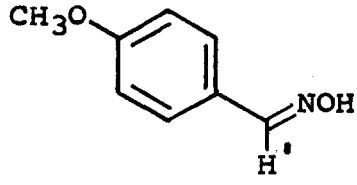
decomposition of their diazonium salts (23) and tertiary benzylic amines via catalytic hydrogenolysis (24), we decided to proceed with a conscientious investigation to determine the utility of bromides I as "phenylethylating" agents.

The synthesis of 3-methyl-1,2-benzisothiazole (II) was accomplished without difficulty following the general procedure of Crawford and Woo (19) outlined in Chart A. Commercially available thiosalicyclic acid (A-1) was converted in routine fashion to o-methylthiobenzoic acid (A-2) with dimethyl sulfate in aqueous sodium hydroxide.

In a three step sequence, benzoic acid A-2 was transformed into acetophenone A-3. The acid chloride was formed with thionyl chloride in benzene, and this in turn was caused to react with ethoxymagnesium malonic ester to generate the corresponding acyl malonate. Methyl ketone A-3 was obtained from this β-keto diester by acid catalyzed hydrolysis and decarboxylation. The yield for this sequence was 67%. The ketoxime A-4, prepared from ketone A-3 with hydroxylamine hydrochloride in ethanol-pyridine, was esterified with p-nitrobenzoyl chloride in dry pyridine to provide oxime benzoate A-5. Crawford and Woo (19) have assigned the syn configuration to oximes A-4 and A-5 by comparing the nmr spectrum of the analogous benzaldoxime V with those of benzaldoximes of known configuration.




V

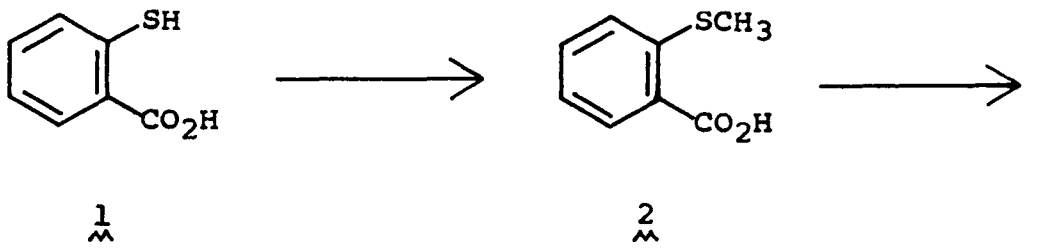



VI

| | syn (δ) | anti |
|---|---|---|
| H | 9.23 | 7.37 |
| H' | 8.17 | 7.31 |

In the syn configuration, both the aldehydic and hydroxylic protons occur at much lower field than when they are in the anti configuration. Oxime VI is presented to illustrate

CHART A

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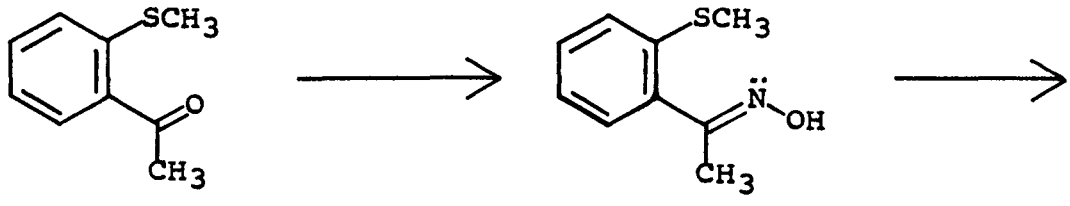


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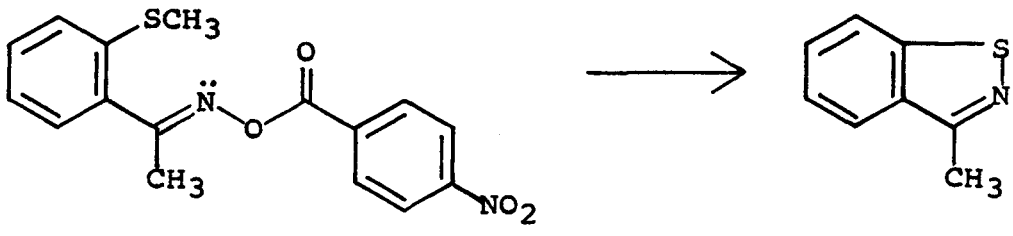
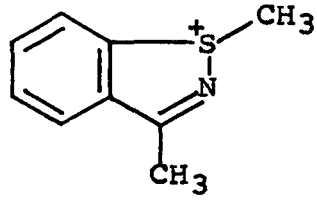
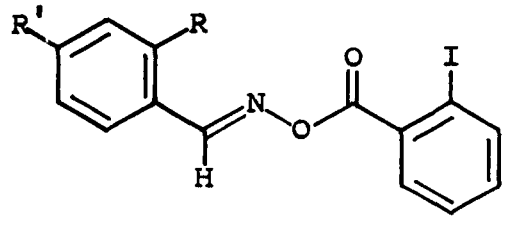



5 II

this phenomenon. The oxime benzoate A-5, a stable crystalline solid (mp 95-99°), decomposed smoothly in refluxing tetrachloroethane to afford a fine 89% yield of 3-methyl-1,2-benzisothiazole (II). Crawford and Woo (19b) have evidence that the decomposition of the oxime benzoate proceeds with ortho sulfur participation via the sulfonium intermediate VII, which in the presence of a good



VII



VIII a: R=$SCH_3$, R'=H

b: R=H, R'=$SCH_3$

nucleophile such as the p-nitrobenzoate anion, gives II and methyl p-nitrobenzoate. They have observed that the aldoxime ester VIIIa, in 50% dioxane, decomposes to the corresponding nitrile 11,000 times faster than does ester VIIIb.

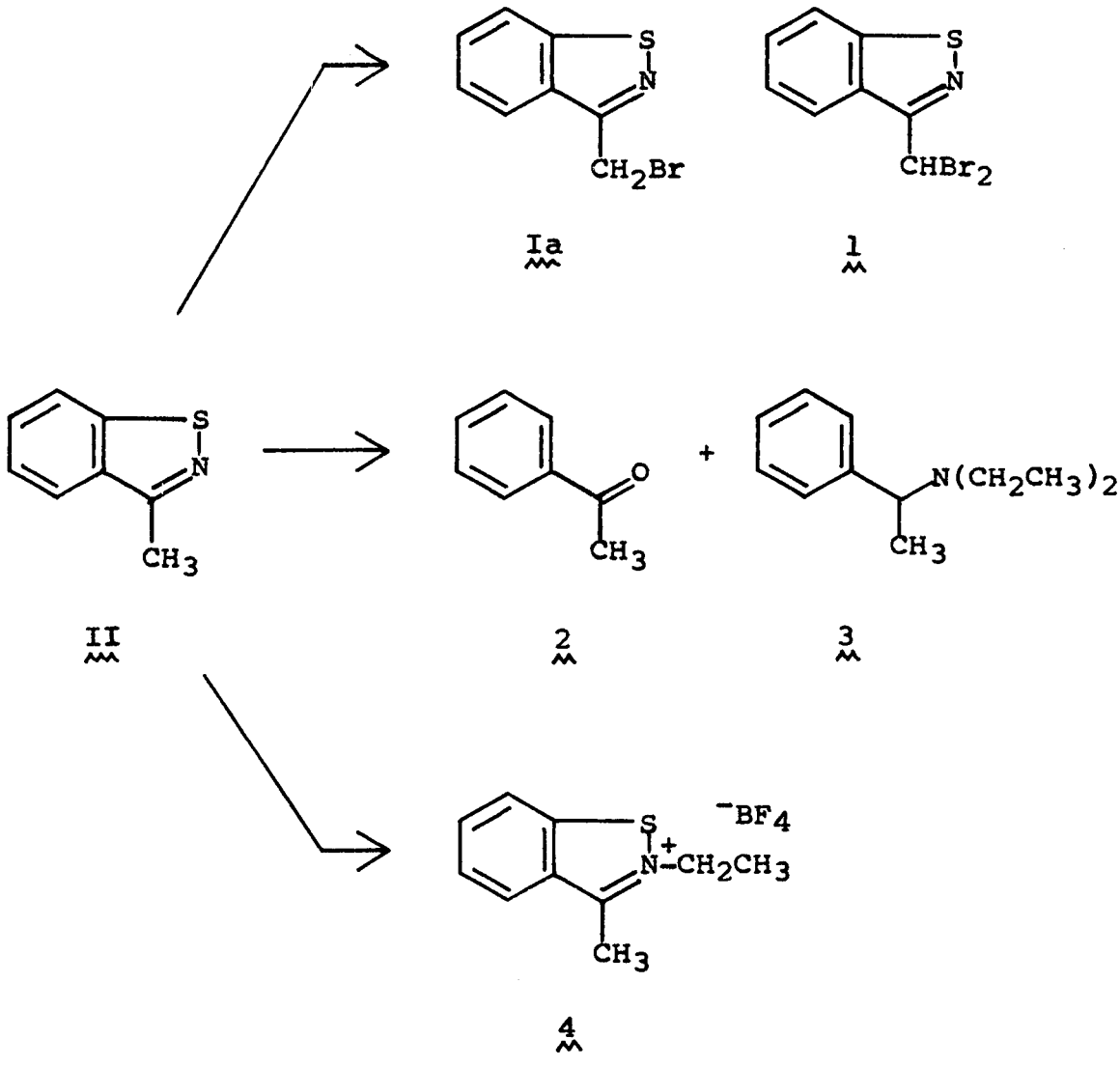
In addition to the evidence presented earlier, further indication of the similarity between 1,2-benzisothiazoles and naphthalenes is provided by a comparison of the

positions of the methyl resonances of II and 1-methylnaphthalene in their nmr spectra. The former appears as a sharp singlet at δ 2.61, the latter at δ 2.63 (25).

Earlier reports on the stability of the benzisothiazole ring system were well-founded. Benzisothiazole II was recovered unchanged after being exposed in a 1:1 solution of glacial acetic acid—concentrated hydrochloric acid for prolonged periods at reflux. A refluxing solution of 40% potassium hydroxide in aqueous ethanol did not alter II, nor did sodium borohydride in methanol.

With an ample supply of benzisothiazole II now at our disposal, we could begin our work in earnest. As anticipated, II could readily be transformed into its monobromide Ia when treated with N-bromosuccinimide in refluxing carbon tetrachloride solution in the presence of light (21). By following the progress of the reaction by gas chromatography, it was possible to terminate the reaction at the first appearance of dibromide B-1. In this fashion, the yield of monobromide Ia was normally 80-85% based on the usual 10-15% yield of recovered starting material. Experience had shown that this was clearly the method of choice, as once dibromide B-1 began to form, the absolute yield of Ia did not increase. While light from an ordinary light bulb was sufficient to

CHART B



initiate the bromination reaction, two attempts to employ a heat lamp in the dual capacity of radical initiator and heat source led to the recovery of an intractable solid that proved to be highly insoluble in the common organic solvents. After that misadventure, an oil bath was used routinely as the heat source.

Initial attempts to degrade benzisothiazole II with 10- to 20-fold excesses of W-2 Raney nickel catalyst in refluxing ethanol or methanol were unsuccessful as an acceptable material balance could not be maintained. On the presumption that this discrepancy was due primarily to strong adsorption by the products on the relatively large amount of catalyst, subsequent reactions were conducted with only three- to five-fold excesses of catalyst. The new results were encouraging. By stirring an ethanolic solution of II at reflux in the presence of three times its weight of catalyst, consistently high yields of a mixture of ketone B-2 and amine B-3 could be obtained. With freshly prepared catalyst, the N,N-diethyl amine B-3 was the predominant product, while less active catalyst favored the ketone B-2. The formation of these two products is well within the capability of Raney nickel, a truly versatile catalyst which can promote desulfurization, hydrogenation, and dehydrogenation, apparently all in the same reaction.

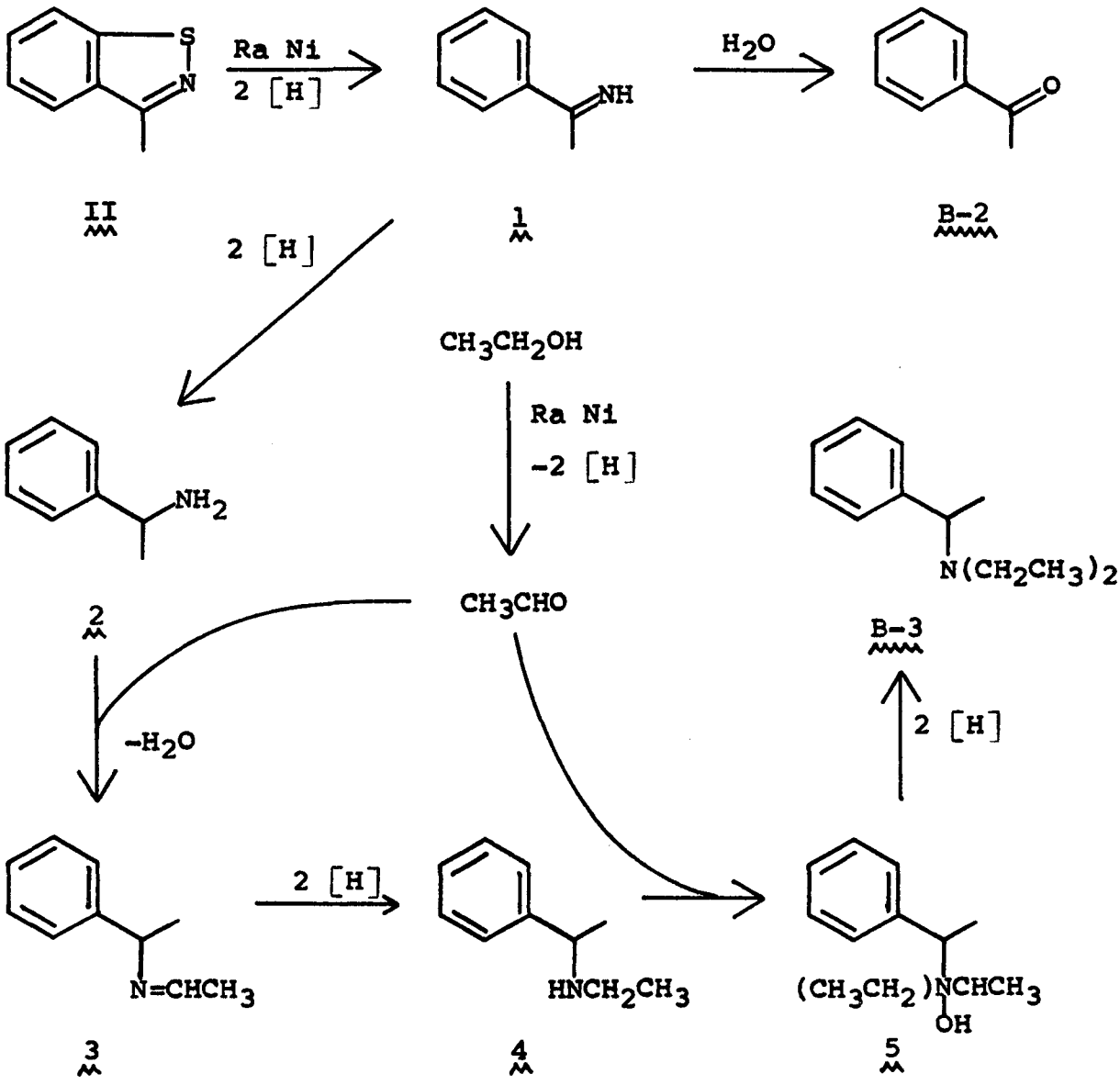
In harmony with the results of previous workers, the scheme presented in Chart C depicts the probable pathways leading from benzisothiazole II to ketone B-2 and amine B-3. Several workers (26, 27) have noted the ability of Raney nickel to catalyze the dehydrogenation of alcohols to aldehydes or ketones at reflux temperatures whether or not a sulfur compound or other hydrogen acceptor is present. In fact, Bonner (26) isolated acetaldehyde in 11% yield from such an experiment with ethanol. This low yield prompted him to conclude that the source of the hydrogen responsible for reductive desulfurization is not the dehydrogenation of ethanol, but rather the W-2 catalyst itself.

The Raney nickel catalyzed alkylation of amines with alcohols is not restricted to ethanol. Rice and Kohn (28) have employed W-2 catalyst to promote dialkylation of benzidine with ethyl, n-propyl, n-butyl, n-amyl, and benzyl alcohols. This process appears to be merely a variation of the normal reductive alkylation reaction in which an amine is combined with an aldehyde or ketone in the presence of a reducing agent (frequently hydrogen) and a metal catalyst (29).

The ketone B-2 and the tertiary amine B-3 both represent useful intermediates in route to the desired

CHART C

Degradation of 3-methyl-1,2-benzisothiazole (II) with Raney Nickel in Ethanol

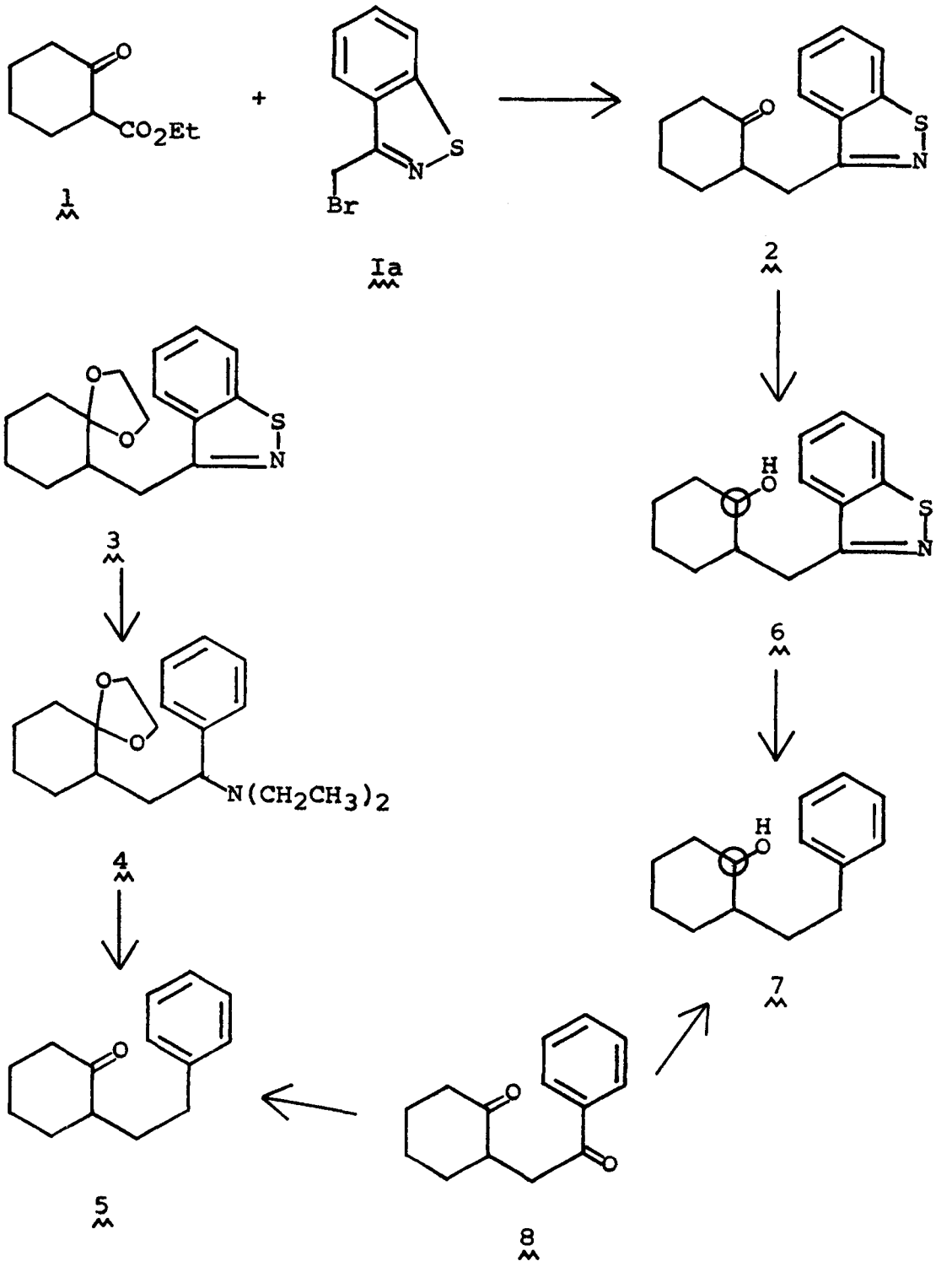


β-phenylethyl moiety, in this case ethylbenzene. As catalytic hydrogenolysis of both benzylic ketones and benzylic tertiary amines is well-documented in the literature (24, 30), we anticipated no difficulty in removing either group. Results to be presented shortly bear out this expectation.

The benzisothiazolium salt B-4 was prepared by the addition of triethyloxonium fluoroborate to a solution of II in dichloromethane. Alkylation was assumed to have occured on nitrogen by analogy to similar reactions of indoxazenes and isothiazoles (31). After several cursory attempts to decompose this salt with dilute aqueous base produced only highly colored, intractable oils, no further attempts were made to explore a chemical means of degrading the 1,2-benzisothiazole ring system.

Our first full-scale investigation of a combined sequence of alkylation followed by degradation is outlined in Chart D. The β-keto ester D-1 was a logical starting material since its enolate was expected to alkylate routinely and provide us with an appropriate model ketone with which to thoroughly investigate the desulfurization and hydrogenolysis reactions. As an important bonus, the anticipated final degradation products would be known compounds.

CHART D



Addition of bromide Ia to a solution of the enolate of β-keto ester D-1 in benzene—N,N-dimethylformamide (32) afforded a 90-95% yield of crude alkylated β-keto ester which, without purification, was hydrolyzed and decarboxylated in a refluxing solution of glacial acetic acid—concentrated hydrochloric acid. In this fashion, benzisothiazoyl ketone D-2 could be obtained in overall yield of 70-75%.

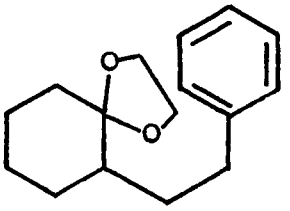
The initial experiments to degrade ketone D-2 were conducted concomitantly with those described previously involving parent benzisothiazole II. At that time we were not aware of the consequences that ensue when both an amine and ketone are present in a reaction mixture with Raney nickel catalyst. Suffice it to say that all direct attempts to degrade benzisothiazoyl ketone D-2 in the presence of Raney nickel produced a multitude of products (as adduced by gas chromatographic analysis). The presence of a very weak carbonyl absorption in the infrared spectra of the crude mixtures indicated that there had been appreciable interaction between the carbonyl group and the nascent amine functionality that arises after the initial desulfurization.

Once we recognized the similarity between our reaction conditions and those employed in a normal reductive

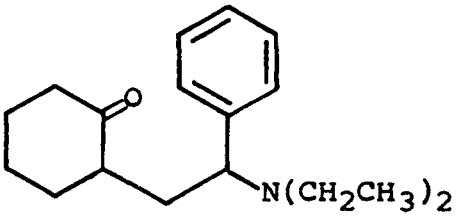
alkylation (29), the solution to our predicament became obvious: prohibit the undesired amine-ketone interaction by suitably masking the ketone prior to treatment with Raney nickel.

Protecting the obtrusive ketone as the corresponding ketal appeared to be a perfect choice. This derivative lacked the electrophilic property inherent in the carbonyl group, and it offered the advantage of being quite stable to the weakly alkaline conditions that prevail in reactions with W-2 Raney nickel. Subsequent experiments confirmed the efficacy of this choice.

Ethylene ketal D-3 was derived from ketone D-2 in the usual manner and deserves no further comment. An ethanolic solution of this ketal was stirred at reflux in the presence of Raney nickel for 24 hours to provide a crude product which exhibited two major peaks by gas chromatography. These components could be separated by thin layer chromatography on alumina. The major product so obtained was identified as ketal amine D-4 by virtue of its distinctive nmr spectrum; the minor product, although not conclusively identified, was thought to be ketal IX arising from Raney nickel catalyzed hydrogenolysis of benzylic amine D-4. From this point, acid hydrolysis of ketal D-4 followed by catalytic hydrogenolysis under one atmosphere of hydrogen in the presence of 10% palladium-on-charcoal afforded the



IX




X

desired β-phenylethyl ketone D-5. The identity of ketone D-5 was verified by independent synthesis. The benzylic tertiary amine residue, stable to hydrogenolysis at room temperature, had departed smoothly when the ethanol solvent was maintained at reflux for several hours.

Subsequent experiments indicated that the degradative procedure was most efficient if the intermediate purification step was omitted. In this way, β-phenylethyl ketone D-5 could be obtained from benzisothiazoyl ketal D-3 in 85% yield *via* the three step sequence of Raney nickel treatment—hydrolysis—hydrogenolysis.

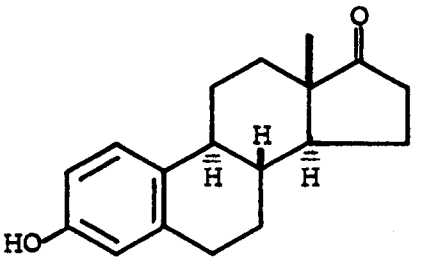
While completely satisfied with the effectiveness of the ketal derivative during the degradation process, we elected to investigate still another possibility. Reduction of ketone D-2 with sodium borohydride in methanol solution afforded a quantitative yield of epimeric alcohols

D-6. This mixture of hydroxy benzisothiazoles was treated successively to the Raney nickel and catalytic hydrogenolysis procedures to afford a 61% yield of β-phenylethyl alcohols D-7. The alcohols D-7 were epimeric at C-1 as determined by the presence of two carbinyl hydrogens in the nmr spectrum, each integrating for one-half of a proton. Although this second route was not as efficient as the first, we now had two acceptable procedures for stripping the heteroatoms from a 1,2-benzisothiazole ring system.

Having established a suitable degradative method, it was now necessary to incorporate our newly acquired techniques into some simple yet informative synthetic schemes. As described previously, the bicyclic enones vii and viii and the tricyclic enone ix had all proven exceptionally recalcitrant to attempted alkylations with the traditional "phenylethylating" agents, the β-phenylethyl bromides and the phenacyl bromides. Therefore, the results obtained by utilizing each of these synthetic intermediates in an alkylation—degradation sequence with benzisothiazoyl bromide Ia would be amenable to direct comparison with the results obtained previously with the standard alkylating agents. Furthermore, the three enones offered us the opportunity to evaluate bromide Ia in three different types of alkylation reactions. The tricyclic

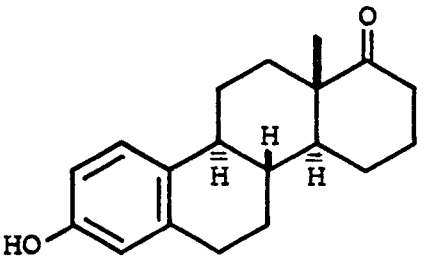
enone ix, an α-monosubstituted α,β-unsaturated ketone, could be alkylated directly without fear of dialkylation. On the other hand, any direct alkylation of enone vii, which bears no α-substituent, must consider dialkylation as a potential side reaction. Enone viii appeared well-suited for use in a Birch reduction—alkylation sequence.

The enones vii and viii were utilized by several British groups (9, 12) in their investigations leading to the total syntheses of estrone (XI) and some related steroidal estrogens. Therefore, we chose to direct our efforts along these same lines.




XI

Estrone

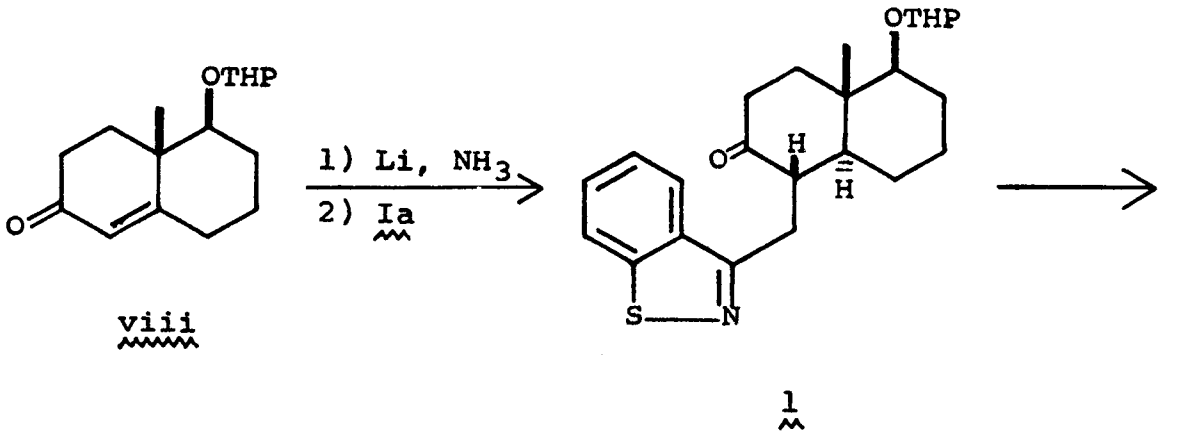



XII

Homo-estrone

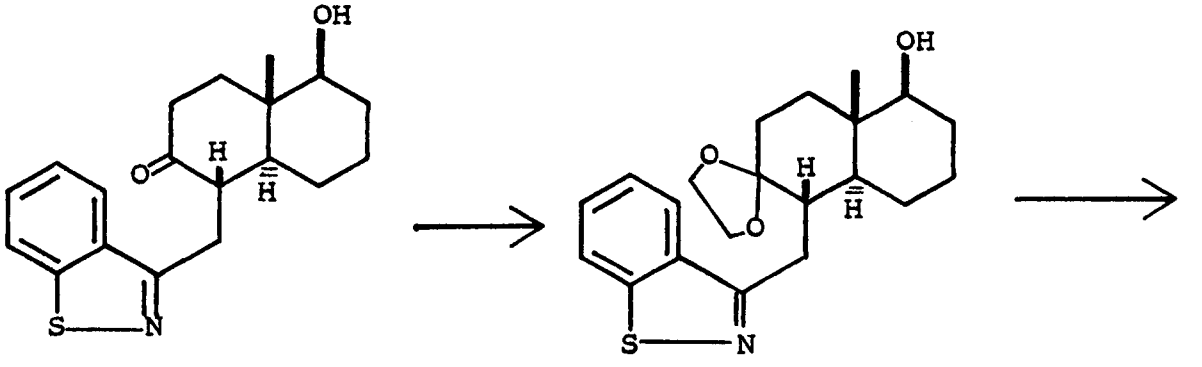
Starting with enone viii, the most direct route to the homo-estrone ring system (XII) is via the Birch reduction—alkylation reaction shown at the beginning of Chart E. This reaction put our approach into immediate harmony with

CHART E



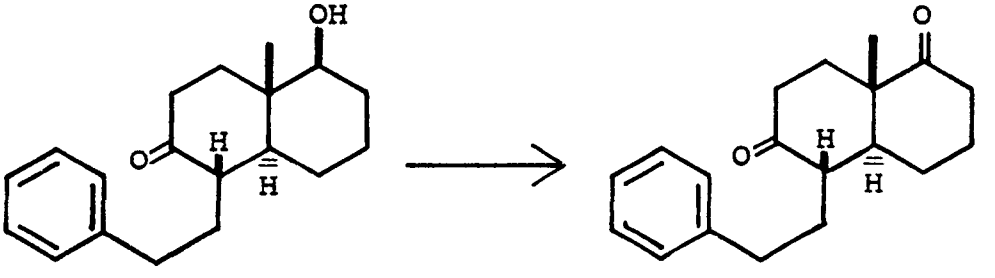

viii

1




2

3




4

5

that followed earlier by the Smith group (9) and permitted us to arrive at dione E-5 which they had characterized. The decalin system in enone viii is particularly suited to a reductive alkylation sequence. The initial reduction with lithium in liquid ammonia generates both the desired trans ring fusion and the kinetic enolate which, in the absence of a proton source, cannot equilibrate. This enolate can then be quenched with bromide Ia.

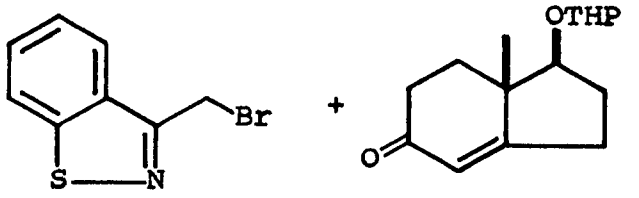
The reduction of enone viii was accomplished by adding two equivalents of lithium to a solution of viii in liquid ammonia containing one equivalent of tert.-butyl alcohol. The enolate formed in situ during the reduction (33) was then quenched with bromide Ia to provide, after alumina chromatography, the acetal ketone E-1. This compound was an unattractive gum; however the hydroxy ketone E-2, obtained by acid catalyzed hydrolysis of the tetrahydropyranyl ether linkage, existed as fine white crystals. The yield for the two step process was an unpretentious 39%. By the requirements set forth earlier, it now became necessary to protect the keto group of E-2 prior to degrading the benzisothiazole system. To this end, the hydroxy ketal E-3 was prepared in 83% yield by standard methods. When this benzisothiazoyl ketal was subjected to the sequence of Raney nickel treatment—hydrolysis—hydrogenolysis previously described for the conversion of D-3 to

D-5, a crude product was obtained which, after purification by thin layer chromatography on silica gel, afforded an 18% yield of crystalline hydroxy ketone E-4. The synthetic scheme was completed by oxidizing this hydroxy ketone to the previously characterized dione E-5 with Jones' reagent. While the reductive alkylation step could undoubtedly be improved, the low yield for the degradative process was discouraging.

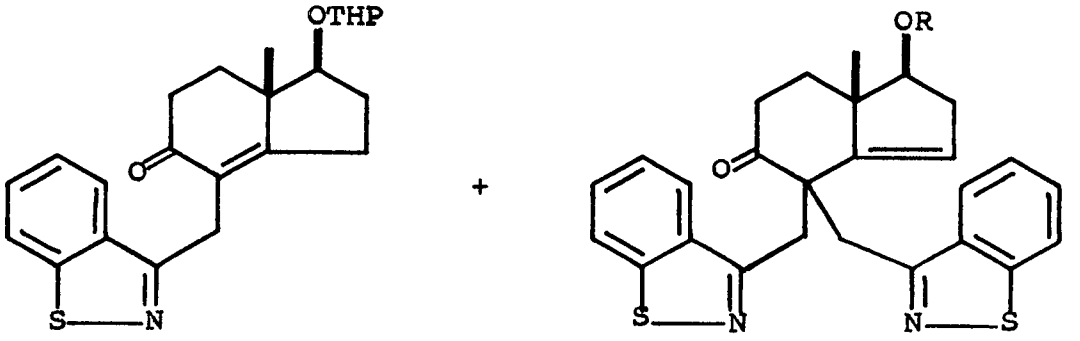
We next turned our attention to the indenone vii (Chart F). In this case an initial Birch reduction—alkylation reaction was not feasible, because lithium and ammonia reduction of several related hydrindenones was known to produce mixtures of both cis- and trans-fused products (33). We chose, instead, the Smith procedure (9) of direct alkylation leading to enone F-1. This approach required subsequent hydrogenation of the olefinic double bond as well as degradation of the benzisothiazole ring in order to gain entry into the desired estrone skeleton (XI).

The heteroannular enolate G-1, generated by stirring a solution of enone vii in refluxing 1,2-dimethoxyethane in the presence of sodium hydride, was alkylated at room temperature by the slow addition of bromide Ia. The monoalkylated product F-1, thus obtained, could be

CHART F



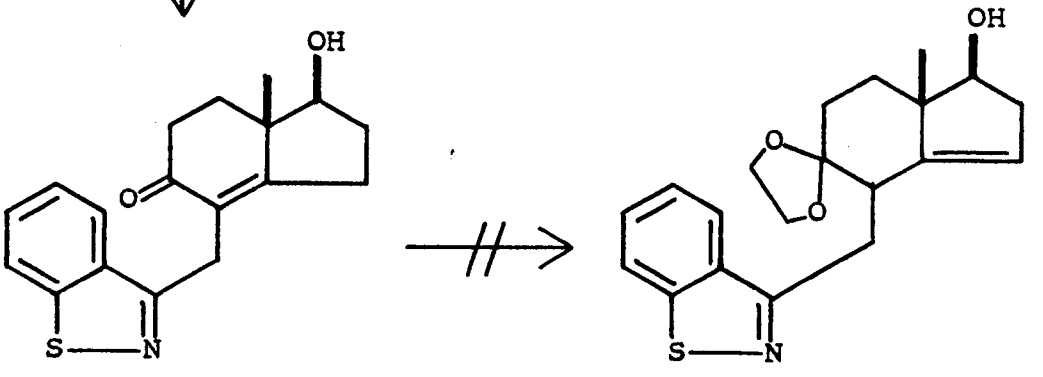

Ia vii




1 2

a: R=THP

b: R=H

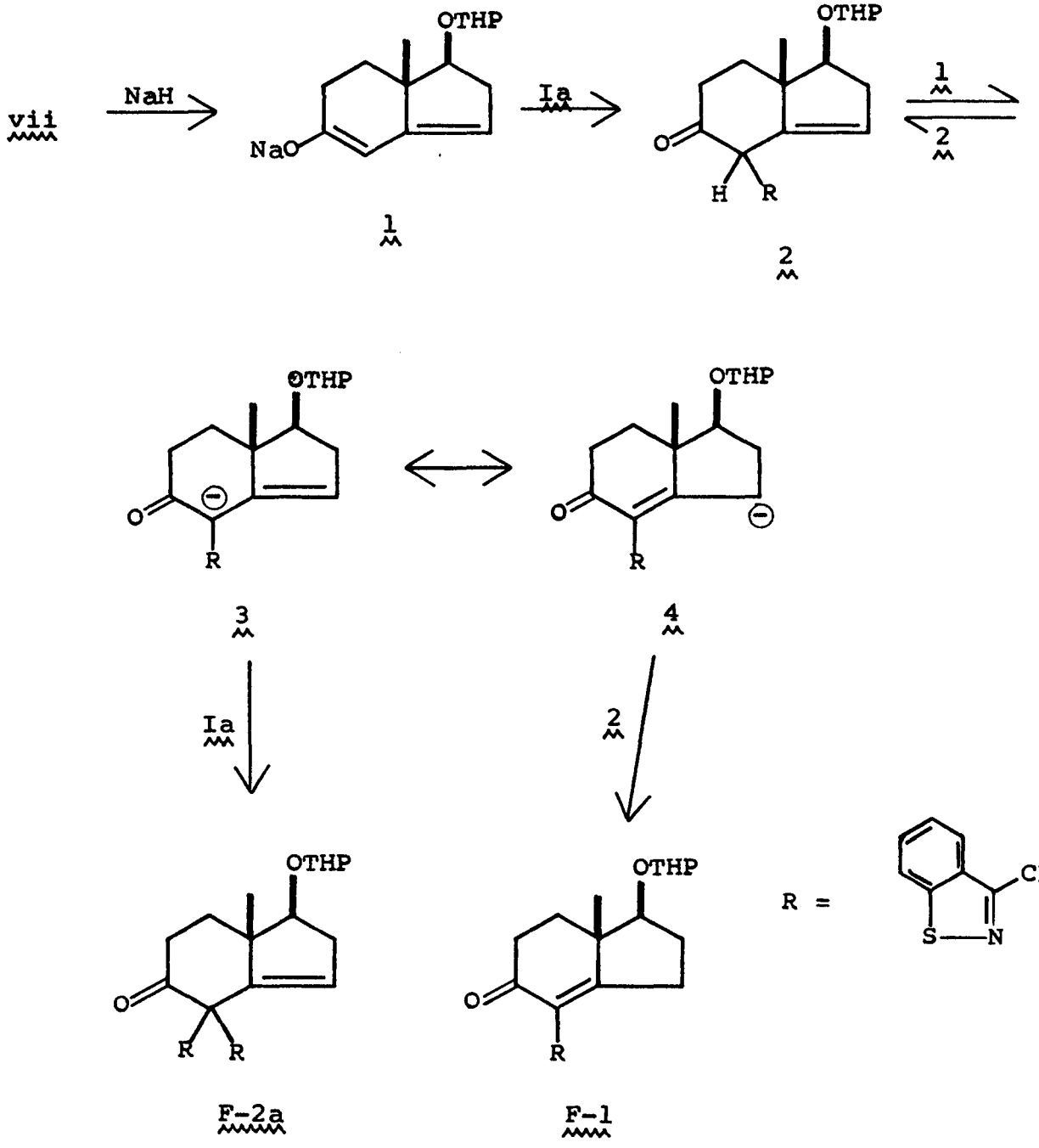



3 4

separated from recovered starting material vii and dialkylated product F-2a by chromatographing the crude product on neutral alumina. Acid hydrolysis of the tetrahydropyranyl ethers F-1 and F-2a afforded the highly crystalline hydroxy ketones F-3 and F-2b, respectively. From this alkylation—hydrolysis sequence the yield of monoalkylated hydroxy enone F-3 was usually in the range 35-45%, while the dialkylated hydroxy ketone F-2b normally was obtained in 5-10% yield. Assuming the hydrolysis reaction is virtually quantitative, the yield of F-3, albeit not noteworthy, is in keeping with the typical yields for monoalkylation of α-unsubstituted α,β-unsaturated ketones (34a, b). The reaction is complicated by the fact that it is practically impossible to avoid dialkylation of these types of enones, and this wasteful side reaction becomes particularly bothersome when the alkylating agent is highly reactive, *e.g.* benzylic or allylic (35a, b). As depicted in Chart G, dialkylated product F-2a arises when bromide Ia attacks the intermediate anion G-3 before it has a chance to isomerize. The extensive work of Ringold and Malhotra (34b-e) involving both protonation and alkylation of these enone systems provides some idea of the relative importance of the steps in this scheme. Protonation occurs at C-4 in G-3 much more frequently

CHART G

Alkylation of Enone vii.



than at C-3 in G-4. However when G-4 is protonated, the result is formation of F-1 which is resistant to further reaction; whereas rapid protonation of G-3 merely constitutes an equilibrium process between itself and G-2. Theoretically, slow addition of bromide Ia should lower the yield of dialkylated product F-2a by allowing the sequence G-2→G-3→G-4→F-1 to occur without disruption by excess alkylating agent. In practice this method reduces, but does not eliminate, dialkylation (34a).

Not unexpectedly, treatment of benzisothiazoyl enone F-3 with Raney nickel in ethanol afforded a myriad of products as determined by gas chromatography. By analogy with our previous results, interaction between the enone moiety and the nascent amino group was assumed to be responsible for this gross mixture; and in fact the infrared spectrum of the crude product exhibited only a weak carbonyl absorption.

An attempt to protect the carbonyl group of enone F-3 as the corresponding ketal F-4 was unsuccessful. Analysis by nmr indicated that while some of the anticipated ketal F-4 had been formed, it was contaminated with equal amounts of starting material and a second, unidentified ketal. A likely candidate for this second product is the allylic ketal that arises when ketalization is unaccompanied by

double bond migration. An effort to purify the product mixture by thin layer chromatography on silica gel resulted in appreciable decomposition of the ketal products to enone F-3. This last result emphasizes the sensitivity of ketals derived from α,β-unsaturated ketones relative to those derived from saturated ketones, as we have routinely purified the latter by silica gel thin layer chromatography without noticeable decomposition.

Recognizing the necessity of blocking the ketone in F-3 prior to treatment with Raney nickel, we apparently had reached an impasse. Although we never did circumvent this problem, subsequent experiments with the 7'-methoxy analogue of F-3 did provide us with an opportunity to test an alternate approach. This latter endeavor will be discussed shortly.

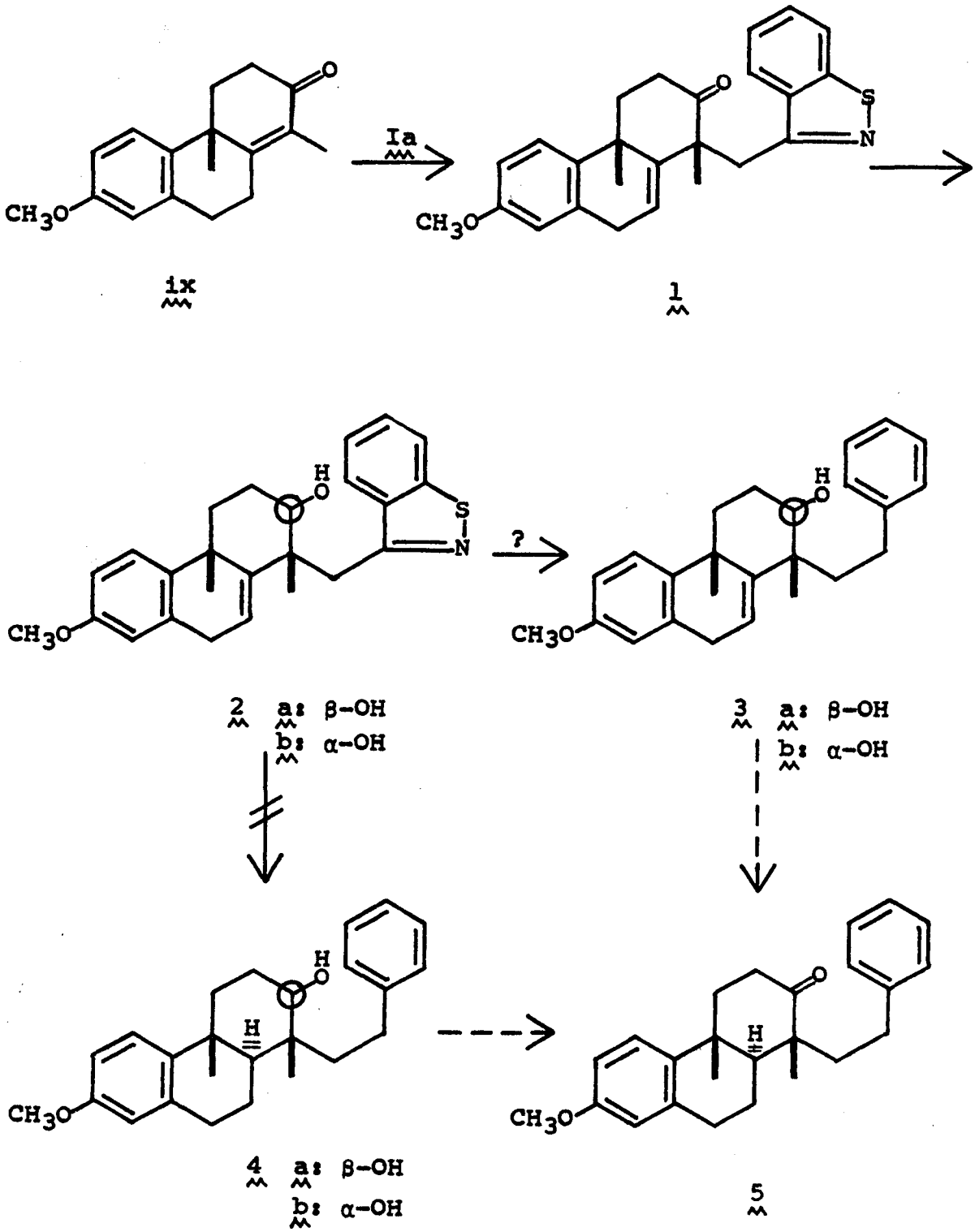
In the case of tricyclic enone ix, we had the opportunity to compare the efficacy of benzisothiazoyl bromide Ia with that of α-bromomethyl styrene xii, which Evans had used previously to alkylate this α-methyl α,β-unsaturated ketone (13). We elected to use the general alkylation procedure described by Evans (36). He had found it much more convenient to generate the enolate of ix with sodium hydride rather than by the classical, but considerably more involved, method with potassium and tert.-butyl

alcohol. Thus, the desired heteroannular enolate was generated by stirring a mixture of enone ix and sodium hydride in refluxing 1,2-dimethoxyethane for five hours. The resulting dark-colored enolate was alkylated at 0° with a slight excess of bromide Ia. The crude product from this reaction, purified by alumina chromatography, afforded a gratifying 84% yield of benzisothiazoyl keto olefin H-l. Evans reported a 48% yield of x-c from the alkylation of enone ix with α-bromomethyl styrene xii (13).

Our product was judged to be isomerically pure by nmr analysis, since only two sharp angular methyl resonances were present. Based on the work of Stork and Schulenberg (37) in the synthesis of dehydroabietic acid, entry of the benzisothiazoyl moiety was assumed to have occurred from the underside of the tricyclic enolate to give the stereochemistry indicated for H-l.

The chromatographic purification procedure had provided ketone H-l in the form of a pale yellow gum, and all efforts to induce it to crystallize were unsuccessful. In this noncrystalline state, H-l decomposed noticeably when exposed to air; however, it was stable when stored under nitrogen in a refrigerator. It was subsequently characterized as its highly crystalline semicarbazone, which melted with decomposition at 205-207°.

CHART H




ix

1

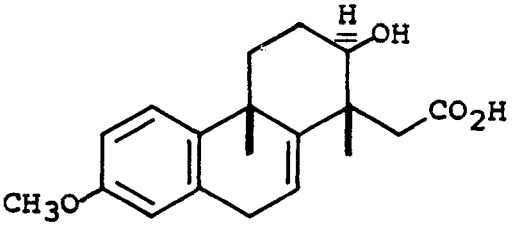
2 a: β-OH
b: α-OH

3 a: β-OH
b: α-OH

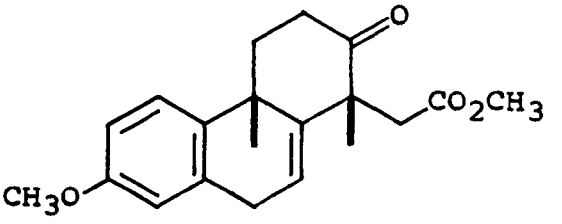
4 a: β-OH
b: α-OH

5

As Evans (38) had not been able to form the ethylene ketal of X-C, we were not surprised when ketone H-1 also resisted attempts to ketalize it. At this point we formulated a plan, outlined in Chart H, in which we envisaged a concise route to ketone H-5, the desmethoxy analogue of the alnusenone intermediate XV described earlier. In this scheme, formation of the alcohol derivative of H-1 would serve two important purposes. According to previous results, the alcohol group would adequately protect the C-2 oxygen functionality during the Raney nickel catalyzed degradation of the benzisothiazole system. Secondly, we anticipated, from the work of Evans, that a tetrahedral center would be necessary at C-2 in order to achieve stereospecific α-hydrogenation of the C-10 double bond. Evans (13) presents a convincing analysis for the observed difference in the catalytic hydrogenation of olefins XIII and XIV under the same conditions, i.e. 10% palladium-on-charcoal in acetic acid. Under these conditions, the




XIII




XIV

hydroxy acid XIII afforded only trans-fused product, while the keto ester XIV gave predominantly cis-fused product.

The reduction of ketone H-1 with sodium borohydride in methanol produced a 2:1 mixture of epimeric alcohols H-2 in 85-95% yield. This mixture of alcohols was non-crystalline and proved to be unstable in air. Separation of the two components was effected by thin layer chromatography using deoxygenated solvents in a nitrogen atmosphere. Even with these precautions, this process dropped the combined yield of alcohols to below 65%. The major alcohol recovered from the chromatography was deemed to be the equatorial alcohol H-2a (43%) as it had the lower $R_f$. Furthermore, the resonance assigned to the C-2α-hydrogen in the nmr had a half-width of 12 Hz which is appropriate for a carbinyl hydrogen in an axial orientation. The minor component, having the higher $R_f$, was judged to be the axial alcohol H-2b (21%). Unfortunately, the carbinyl hydrogen of this epimer did not appear as an isolated resonance in the nmr. Even in a pure state these two alcohols were non-crystalline and unstable in air.

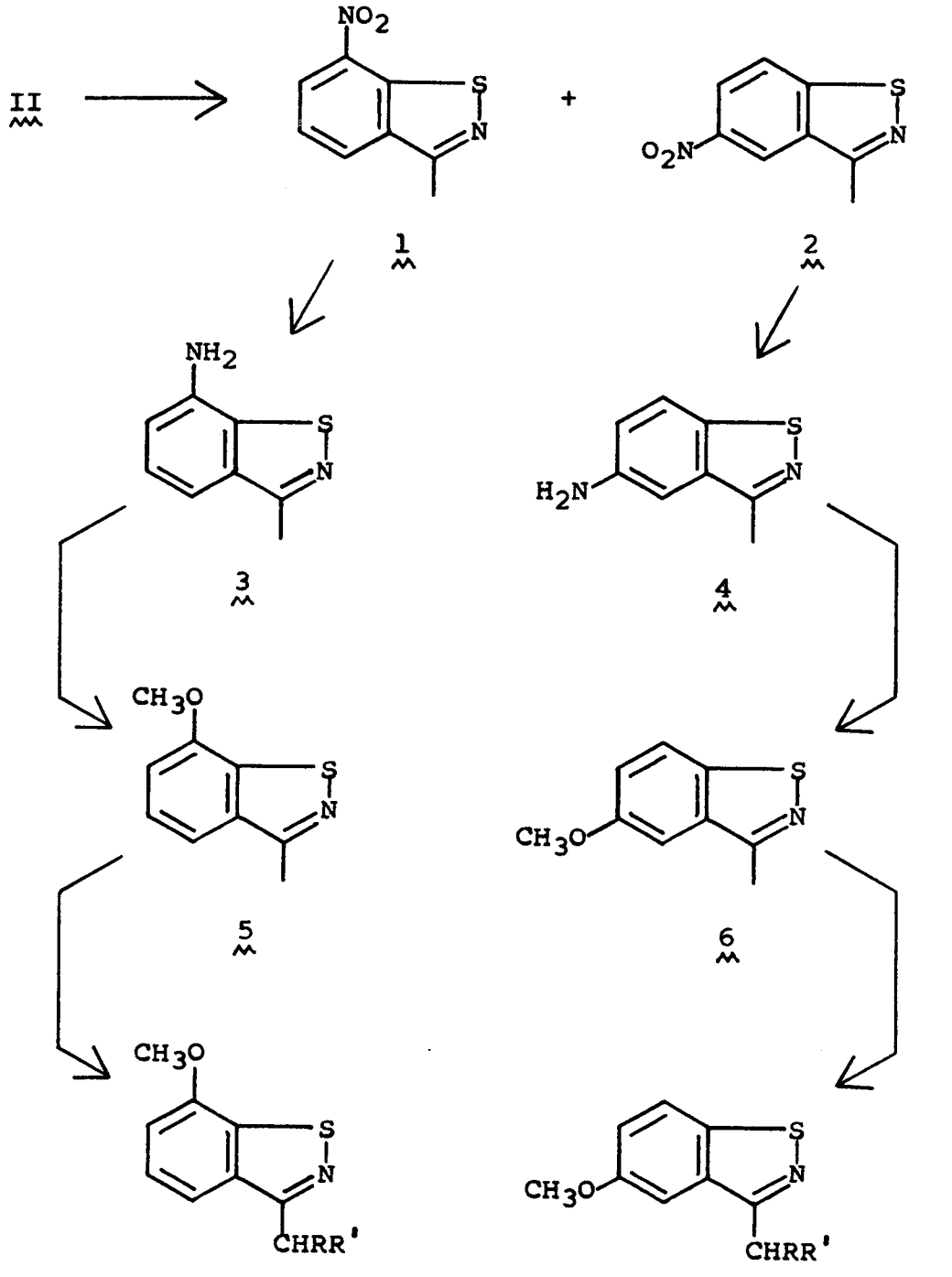
The results obtained when each of the pure alcohols, as well as the mixture, was subjected to the degradative sequence of Raney nickel treatment and hydrogenolysis were at best discouraging. We had anticipated that the

hydrogenolysis conditions used to cleave the benzylic nitrogen would be sufficient to hydrogenate the C-10 olefinic bond as well. Such was not the case. In no instance was there any appreciable hydrogenation of the double bond. Furthermore, we were not able to determine with certainty whether or not we had completely removed the benzylic nitrogen. In one instance, sodium fusion analysis of the crude product obtained from the degradative sequence gave a positive test for nitrogen. Frustrated by these vagarious results and the general instability of the compounds in this series, we decided to concentrate our efforts in other more promising areas.

Concomitantly with much of the preceding work involving benzisothiazoyl bromide Ia, we were developing a synthetic route to the potentially more versatile bromides Ib and Ic. As outlined in Chart I, the synthetic scheme leading to these bromides exhibits an outwardly classical bent; however, in several instances we were able to utilize some rather interesting reaction conditions in order to effect these simple transformations.

By analogy to the substitution pattern of indoxazene III in electrophilic aromatic substitution reactions (20), we anticipated that mono-nitration of benzisothiazole II would occur at C-5 and/or C-7. This pattern is consistent with the ortho-para directing influence of a thioether

CHART I


II
NO2
S
N
+
O2N
1
2
NH2
H2N
3
4
CH3O
5
6
CHRR'
Ib: R=H, R'=Br
7: R=R'=Br
Ic: R=H, R'=Br
8: R=R'=Br

substituent on a benzene ring, and it would provide entry into either or both of the positions that are located meta to the ethyl moiety in II.

In actual fact, nitration of benzisothiazole II with potassium nitrate and sulfuric acid in the cold afforded an 85-95% yield of a crystalline product consisting of a 45:55 mixture of the two isomeric nitro benzisothiazoles I-1 and I-2, as determined by gas chromatographic analysis. These two components could be separated by careful column chromatography on silica gel. The two crystalline products were identified by a comparison of their nmr spectra. In each case, all three aromatic hydrogens appeared as well-defined resonances, so it was possible to identify each hydrogen as well as the appropriate coupling constants. These data are presented in Table I accompanied by the corresponding data obtained from the other compounds in this series.

In all observed cases, the coupling constants decreased in the order ortho, meta, para. The ortho coupling constants fell in the range 6.1-9.2 Hz, the meta coupling constants in the range 1.0-2.8 Hz, and the para coupling constants in the range 0.6-1.2 Hz. These J values are in good agreement with those commonly observed between ortho-, meta-, and para-situated hydrogens in simple benzene

Table I: NMR Data for the Aromatic Hydrogens of 5- and 7-Substituted 3-Methyl-1,2-benzisothiazoles.

| Compd | Substituent | Chemical Shifts (δ) $H_4$ | $H_5$ | $H_6$ | Coupling Constants (Hz) $J_{4,5}$ | $J_{5,6}$ | $J_{4,6}$ |
|---|---|---|---|---|---|---|---|
| I-1 | 7-$NO_2$ | 8.30 | 7.66 | 8.48 | 7.6 | 7.6 | 1.0 |
| I-3 | 7-$NH_2$ | (7.22) | (7.22) | 6.75 | - | 6.1 | 2.4 |
| I-5 | 7-OMe | 6.83 | a | a | 6.8 | - | 1.8 |
| Ib | 7-OMe (3-$CH_2Br$) | 7.70 | 7.39 | 6.89 | 8.3 | 7.5 | 1.2 |
| I-7 | 7-OMe (3-$CHBr_2$) | 8.09 | 7.50 | 6.91 | 8.4 | 7.9 | 1.0 |
| | | $H_4$ | $H_6$ | $H_7$ | $J_{6,7}$ | $J_{4,6}$ | $J_{4,7}$ |
| I-2 | 5-$NO_2$ | 8.82 | 8.36 | 8.06 | 8.6 | 1.9 | 0.6 |
| I-4 | 5-$NH_2$ | 7.17 | 6.98 | 7.72 | 8.8 | 2.2 | 0.8 |
| I-6 | 5-OMe | b | b | 7.72 | 8.6 | - | 1.2 |
| Ic | 5-OMe (3-$CH_2Br$) | 7.45 | 7.21 | 7.80 | 8.8 | 1.2 | 0.8 |
| I-8 | 5-OMe (3-$CHBr_2$) | c | 7.22 | c | 9.2 | 2.8 | 0.6 |

a) multiplet at δ 7.20-7.55. b) multiplet at δ 7.04-7.22. c) partially overlapping resonances at δ 7.72 and 7.87.

derivatives (39). Identification of 7-nitro-benzisothiazole I-1 was particularly easy because its C-5 hydrogen appeared as a simple triplet. This was the only observed case in the 7-substituted series in which $J_{4,5} = J_{4,6}$.

The conversion of the two nitro derivatives into the corresponding amines I-3 and I-4 was accomplished in good yield by a modification (40) of the classical aluminum amalgam reduction (41). This mild procedure makes use of the fact that commercial aluminum foil, activated by aqueous mercury(II) chloride, reacts with water at room temperature to liberate hydrogen. Our reductions were conducted by adding pieces of activated aluminum foil to a solution of the appropriate nitro compound in ether containing the calculated amount of water. The reductions, normally complete after 12-20 hours stirring at room temperature, returned a clean product in 75-85% yield. The utility of this procedure was only limited by the fact that it became somewhat unwieldy to handle more than 15-20 g of aluminum foil.

The 7-amino benzisothiazole I-3 was found to have a much greater $R_f$ on silica gel thin layer chromatography than did the isomeric 5-amino benzisothiazole I-4. This phenomenon can be explained by invoking hydrogen bonding between the 7-amino hydrogens and the adjacent sulfur atom

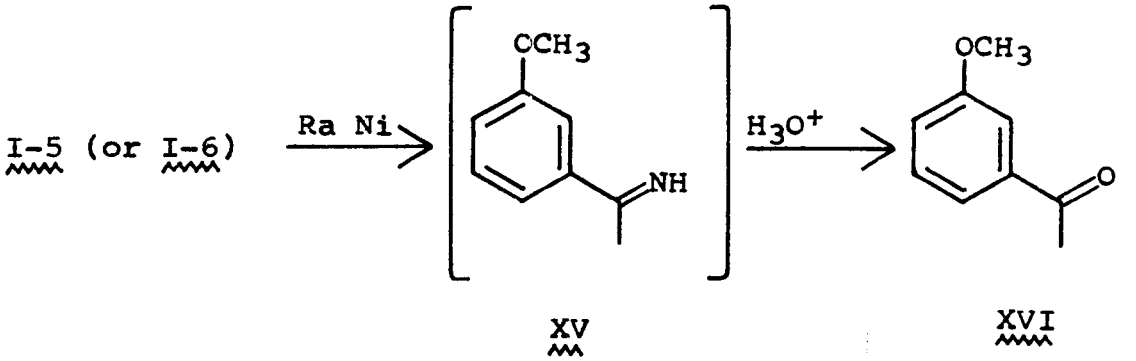
in I-3, a situation not sterically permitted in the 5-amino isomer I-4. By extending this finding to column chromatography, it was found that the two amines could be obtained most efficiently by chromatographing the mixture of amines obtained from a reduction of the original mixture of nitro benzisothiazoles. This approach allowed us to replace the difficult separation of I-1 and I-2 with a facile chromatographic separation of amines I-3 and I-4.

Each amine was converted to its respective methyl ether I-5 or I-6 by a two-step process in which its diazonium salt, formed in the cold with iso-amyl nitrite and hydrochloric acid in methanol, was decomposed in situ by gently warming the methanolic solution under an atmosphere of oxygen. The presence of oxygen effectively inhibits homolytic cleavage of the carbon-nitrogen bond and thereby minimizes formation of benzisothiazole II which arises via the radical process (42).

In each instance, the diazotization—methanolysis sequence afforded the crude product as an intensely red oil. However, when subjected to alumina chromatography, these oils surrendered the appropriate methyl ether as a white crystalline solid. In this manner, we were able to obtain the 7-methoxy benzisothiazole I-5 in 68% yield and the 5-methoxy benzisothiazole I-6 in 86% yield.

The methoxy bromides Ib and Ic were obtained in good yields by allowing their respective 3-methyl progenitors I-5 and I-6 to react with N-bromosuccinimide exactly as described previously for the transformation of benzisothiazole II to its bromide Ia. As was true for all compounds in this series, both bromides were nice, crystalline compounds.

For reasons which will become apparent very shortly, we chose to degrade methoxy benzisothiazoles I-5 and I-6 under milder conditions than those previously employed to degrade their desmethoxy analogue II. Instead of conducting the Raney nickel treatment under forcing conditions (i.e., refluxing ethanol) that would lead to a diethylated amine such as B-3, we selected conditions that would limit this reaction to the desulfurization step only. Thus, by treating an ethanolic solution of either I-5 or I-6 with a five-fold excess of Raney nickel at room temperature, we were able to generate the intermediate imine XV. After



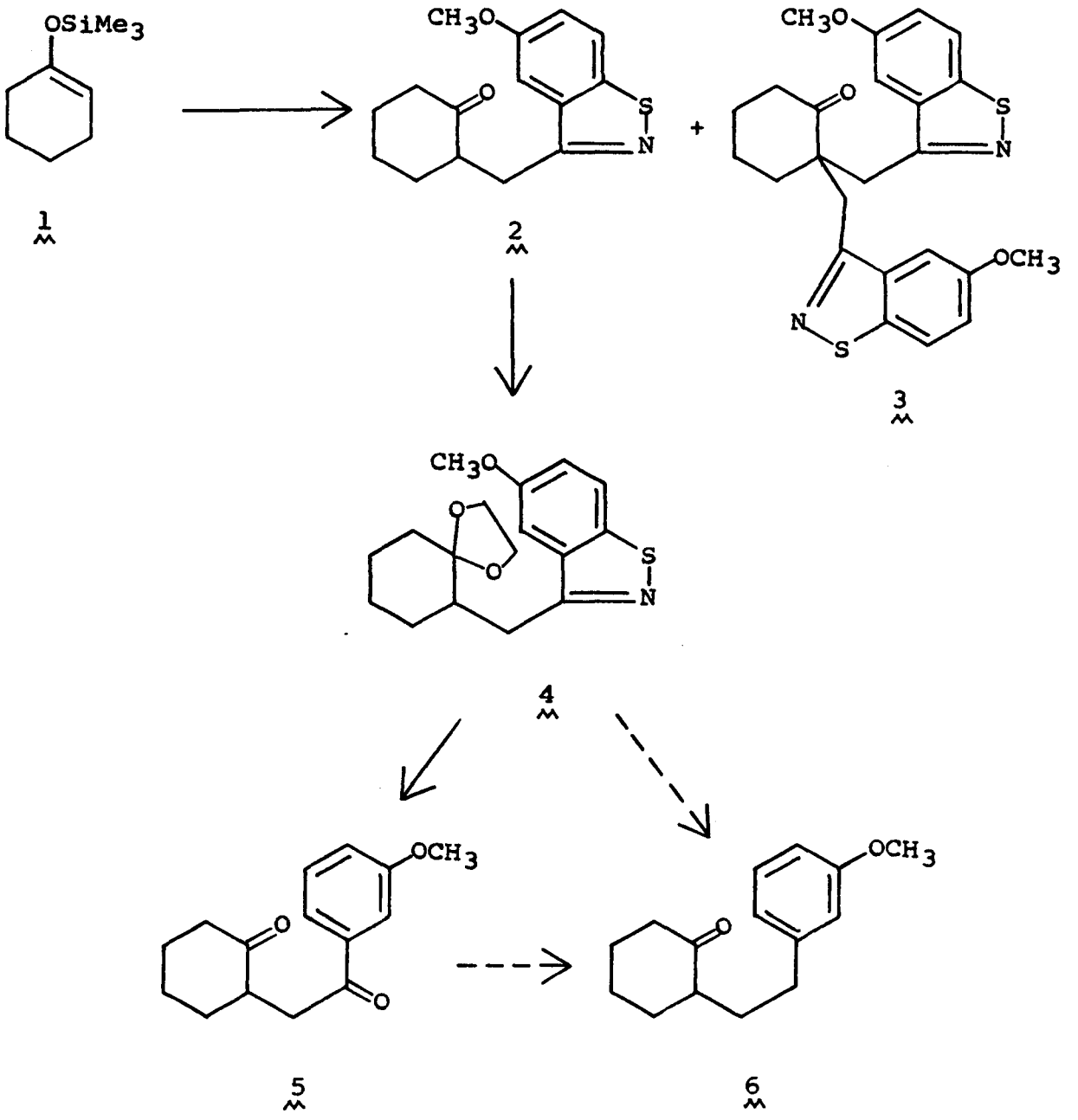

XV XVI

removal of the catalyst, this imine was hydrolyzed directly to acetophenone XVI, which was isolated in yields of 45-55%. At this point, catalytic hydrogenolysis of the benzylic ketone (30) would complete the degradation sequence.

On the basis of the results just presented, we employed this mild degradative process in route to the diketone J-5, as outlined in Chart J. As the initial step in this sequence, a solution of the lithium enolate of silyl enol ether J-1 (58) in 1,2-dimethoxyethane at room temperature was quenched by the rapid addition of bromide Ic. This alkylation afforded a 38% yield of the non-crystalline benzisothiazoyl ketone J-2 as well as several polyalkylated products. The major product in this latter category was the 2,2-dibenzisothiazoyl ketone J-3 which was isolated in 19% yield as a highly crystalline solid. The ketal J-4, mp 100-101.5°, was obtained from ketone J-2 in 97% yield by conventional methods.

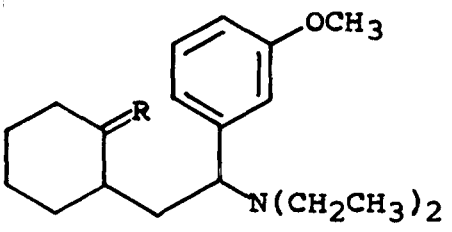
We approached the next step, the crucial conversion of J-4 to J-6 with the premonition that the same techniques that had been used to effect the analogous transformation of D-3 to D-5 would not be applicable in this present situation. This hunch was predicated on the following train of thought. Applying the previous Raney nickel

CHART J




1 2 3 4 5 6

procedure to J-4 should provide ketal amine XVIIa which, upon mild acid hydrolysis, would yield keto amine XVIIb.




XVII a: R=$-OCH_2CH_2O-$

b: R=O

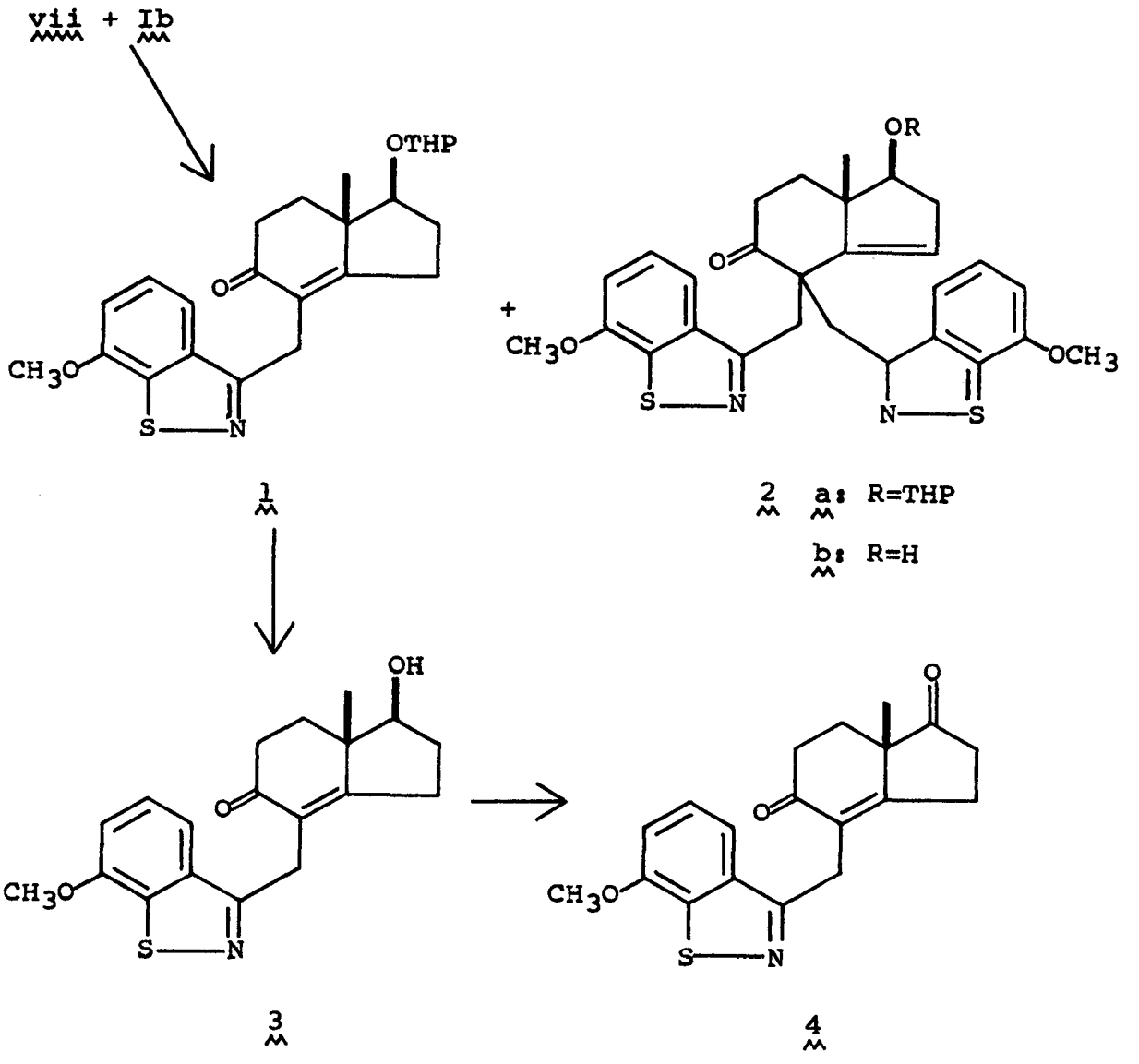
The conditions required to hydrogenolyze the benzylic amine linkage in XVIIb (i.e., refluxing an ethanolic solution of the amine with an equilvalent of acid in the presence of 10% palladium-on-charcoal under one atmosphere of hydrogen) would be more than sufficient to bring about concomitant cyclization of the methoxy-activated phenyl ring into the carbonyl functionality.

As the uncontrolled cyclization reaction would considerably limit the versatility of this entire sequence, we chose an alternate route by way of diketone J-5. This approach was based on the facile cleavage of benzylic ketones under mild hydrogenolysis conditions and should not be afflicted with accompanying cyclization (43).

Having anticipated the need for just such a route, the previously described conversions of methoxy benziso-thiazoles I-5 and I-6 to acetophenone XVI had been worked out ahead of time. It was a simple matter to adapt this mild degradative process to our present needs. Thus, an ethanolic solution of benzisothiazoyl ketal J-4 was treated with Raney nickel at room temperature. The crude product from the desulfurization, presumably the appropriate ketal imine, was hydrolyzed with dilute acid to afford a 33% yield of diketone J-5. A second product, soluble in aqueous acid and exhibiting a medium intensity band at 1650 $cm^{-1}$ in the infrared, was also obtained from the hydrolysis. However, it decomposed when an attempt was made to purify it by thin layer chromatography on silica gel. As just explained, the final transformation of diketone J-5 to ketone J-6 should present no problem.

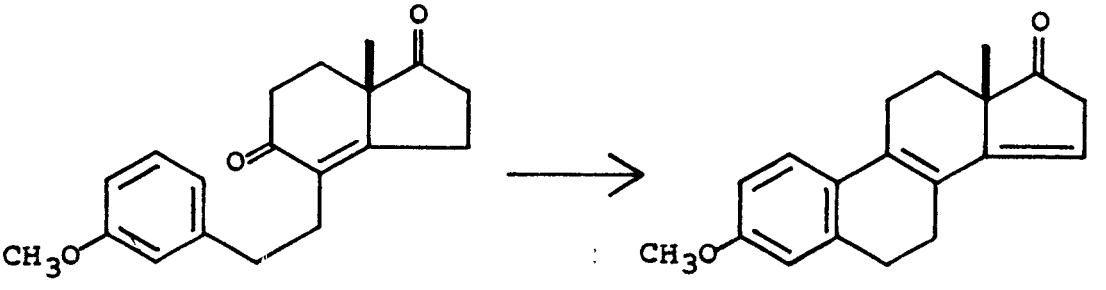
With a reasonable supply of methoxy bromide Ib at hand, we next undertook a re-examination of the estrone problem that was discussed previously. (Refer to Chart F.) In that earlier investigation we had been stymied by our inability to realize ketal F-4, a prerequisite compound for degrading the benzisothiazole ring in this series. However, with the aid of Ib we envisaged a way to circum-vent this former obstruction. To this end, we prepared hydroxy enone K-3 by the route outlined in Chart K. The

CHART K


vii + Ib
OTHP
O
CH3O
S
N
1
+
OR
O
CH3O
OCH3
S
N
N
S
2 a: R=THP
b: R=H
OH
O
CH3O
S
N
3
O
O
CH3O
S
N
4

method of preparation paralleled that described previously for the preparation of the desmethoxy analogue F-3. In this instance, alkylation followed by hydrolysis afforded K-3 in 40% yield. As expected, it was accompanied by a small amount of K-2b arising from dialkylation of vii. Subsequent oxidation of hydroxy ketone K-3 with dipyridine—chromium trioxide complex (44) provided the crystalline dione K-4, mp 164-165.5°, in 78% yield. Because we knew that the C-5 carbonyl group in K-4 would interfere with the degradation of the benzisothiazole ring, we intended to remove it first by cyclizing K-4 prior to initiating the degradation process.

The dione K-4 is comparable to the dione XVIII which the Smith group (9) and Crispen and Whitehurst (12) had previously cyclized to keto diene XIX. Their cyclization




XVIII XIX

conditions, polyphosphoric acid at 60°, did not affect dione K-4; however, in polyphosphoric acid at 120°, K-4 was transformed into two products as evidenced by gas chromatography. From one experiment we were able to isolate the major product by thin layer chromatography in sufficient quantity to obtain infrared and nmr spectra. The infrared spectrum indicated that we had completely lost the 5-membered ring ketone (1745 $cm^{-1}$) as well as the $\alpha,\beta$-unsaturated ketone (1660 $cm^{-1}$). These former bands in the infrared spectrum of K-4 had been replaced by a strong absorption at 1700 $cm^{-1}$ indicative of a saturated 6-membered ring ketone. Furthermore, the intensity and complexity of the absorptions in the C=C and aromatic region, specifically 1600, 1575, and 1475 $cm^{-1}$, had increased. Such a change usually implies increased conjugation. Although the nmr spectrum was relatively clean, we were largely unable to correlate its data with that supplied by the infrared spectrum. One point is noteworthy: two resonances that could be assigned to two of the hydrogens on the benzisothiazole ring each still appeared as a doublet of doublets. This splitting pattern indicates that the third benzisothiazoyl hydrogen is also present, which in turn implies that cyclization did not occur. Unfortunately, we exhausted our supply of dione

K-4 before we could determine the identity of this compound. In view of the fact that conditions which were required to consume starting material did not appear to give the desired cyclization product, we concluded our work in this area.

In closing, several remarks seem appropriate. We initially stated that the benzisothiazoyl bromides I would have to satisfy two requirements in order to be qualified as synthetically useful reagents for introducing a β-phenylethyl moiety. Obviously, they would have to be efficient alkylating agents. In this respect, when used in conjuction with strongly basic enolates, the pseudo-benzylic bromides I performed as well as benzylic bromides and much better than β-phenylethyl bromides or phenacyl bromides. However, by virtue of the fact that these heteroaromatic compounds possess a latent β-phenylethyl moiety, a second requirement had to be met. The benzisothiazole ring system had to be degradable such that, once incorporated into a synthetic intermediate, the β-phenylethyl fragment could be realized. Unfortunately, we have not been able to satisfy this second requirement with consistency. While our degradative approach *via* benzylic tertiary amines proved satisfactory when applied to small, relatively flexible substrates, the facility

for hydrogenolytic cleavage of the benzylic C-N linkage appears to be compromised in larger, more structurally integrated synthetic intermediates.

Clearly, reliable methods for degrading the benzisothiazole ring in these larger molecules must be found before this heteroaromatic system can be of any general synthetic value. The success of our initial efforts to produce benzylic ketones from benzisothiazoles by mild Raney nickel desulfurization followed by hydrolysis of the intermediate imines indicates that that this approach is worthy of further investigation. The mild conditions necessary to effect the degradations make this an attractive method, particulary if the overall yield can be improved.

Another potential method for degrading benzisothiazoles is suggested by a recent publication of Corey and Achiwa (45). Their new technique for oxidizing primary amines to ketones through the intermediacy of isomeric Schiff bases is an extremely mild and highly efficient process. For example, oxidation of α-phenylethyl amine by 3-nitromesitylglyoxal followed by hydrolysis of the appropriate Schiff base afforded acetophenone in 98% yield. In our case, the corresponding α-phenylethyl amine can be generated from the benzisothiazole system in a simple sequence

involving mild Raney nickel desulfurization followed by reduction *in situ* of the intermediate imine with sodium borohydride. In his total synthesis of colchicine, Woodward (21) effected this very transformation with an isothiazole ring. After the benzylic ketone had been provided *via* the Corey oxidation, the degradation could be completed by facile catalytic hydrogenolysis of the carbonyl group.

## Experimental Section

(a) All compounds described in this section which contain asymmetric carbon atoms are racemic; the prefix "dl" has been omitted.

(b) Melting points (mp) were determined on a Kofler Micro Hot Stage melting point apparatus and are uncorrected.

(c) Infrared (ir) spectra were determined on a Perkin-Elmer 237B grating infrared spectrophotometer. Solution spectra were taken in 0.1 or 0.2 mm cavity cells using chloroform as solvent. The 1601.4 $cm^{-1}$ absorption band of polystyrene was used as the calibration band.

(d) Nuclear magnetic resonance (nmr) spectra were determined on a Varian A-60A spectrometer unless otherwise noted. Resonances were recorded in ppm ($\delta$) downfield from tetramethylsilane (tms).

(e) Vapor phase chromatographic (vpc) analyses were taken on an F & M Model 810 Research Chromatograph equipped with hydrogen flame detectors. Columns used were generally 6' x 1/8", 3-10% SE-30 on diatoport S. The carrier gas (helium) flow rate was maintained at 60 ml/min. Retention times (rt) were recorded in minutes.

(f) Unless otherwise noted, preparative thin layer chromatography (ptlc) was performed on 20 x 20 cm glass plates coated with a 1-2 mm layer of Silica Gel $PF_{254+366}$ (Brinkmann Instruments Co.). Amines were chromatographed on similar plates coated with Alumina Oxide $PF_{254+366}$ (Brinkmann Instruments Co.).

(g) Anhydrous solvents were dried immediately prior to use. Ether, tetrahydrofuran, and 1,2-dimethoxyethane were distilled from lithium aluminum hydride. Pyridine, N,N-dimethylformamide, and tert.-butyl alcohol were distilled from calcium hydride. Dichloromethane was distilled from phosphorus pentoxide, and benzene was dried by distillation of the benzene-water azeotrope. Petroleum ether refers to that fraction boiling in the range 30-60° as supplied by J. T. Baker Chemical Co. Absolute ethanol refers to that commercially available; no further steps were taken to insure its dryness.

(h) Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Michigan.

o-Methylthiobenzoic acid (A-2).—The procedure of Crawford and Woo (19b) was followed in the preparation of this compound. A solution of 125 g (0.81 mole) thiosalicylic acid (A-1) (46) and 68 g (1.70 moles) sodium hydroxide in 425 ml water was cooled to 10°, and 53.5 g (0.425 mole) dimethyl sulfate was added slowly with stirring. The mixture was refluxed for 3 hr, cooled, and acidified with 10% aqueous hydrochloric acid. The resulting precipitate was filtered, washed with water, and recrystallized from methanol-water to give 116 g (85%) thioether A-2 as white crystals, mp 169-171°, [lit (19b) mp 169-171°].

o-Methylthioacetophenone (A-3).— The general procedure of Crawford and Woo (19) was followed in the preparation of this compound.

a) Preparation of o-methylthiobenzoyl chloride.—A mixture of 164 g (0.98 mole) o-methylthiobenzoic acid (A-2), mp 169-171°, and 280 g (2.36 moles) thionyl chloride in 700 ml dry benzene was stirred at reflux for 2 hr resulting in a homogeneous solution. The benzene was removed under reduced pressure and excess thionyl chloride was removed by azeotropic distillation with added benzene. The resulting acid chloride crystallized upon cooling. This material was taken up in 500 ml dry benzene and set aside until the ethoxymagnesium malonic ester had been prepared as described below.

b) Preparation of ethoxymagnesium malonic ester.—A mixture of 48.6 g (2.0 g-atoms) magnesium turnings, 150 ml dry benzene, and 25 ml of 100% ethanol was placed in a three-necked flask fitted with a reflux condenser, dropping funnel, and mechanical stirrer. To this mixture was added a crystal of iodine and 10 ml carbon tetrachloride, followed by a small portion of a solution of 320 g (1.70 moles) diethyl malonate and 95 ml (2.25 moles) 100% ethanol in 400 ml dry benzene. The mixture was heated until a vigorous reaction began, and then the remainder of the diethyl malonate solution was added at a convenient rate. The mixture was refluxed until dissolution of the magnesium was complete and then distilled slowly to remove most of the free ethanol as an azeotrope with benzene (until the temperature reached 70°). The residue consisted of ethanol-free ethoxymagnesium malonic ester in benzene solution.

c) Formation of the methyl ketone.—The acid chloride solution prepared in (a) above was added with stirring and cooling to the benzene solution of the ethoxymagnesium malonic ester, and the resulting mixture was stirred overnight. The cooled mixture was added, with stirring, to a mixture of 1.5 l. of 10% sulfuric acid and 500 g crushed ice. The benzene solution was separated and the aqueous layer extracted twice with benzene. The combined benzene solutions were washed with water and brine, dried ($Na_2SO_4$), and con-

centrated at reduced pressure on a rotary evaporator. Excess malonic ester was removed at 1 mm on a steam bath.

To the crude acyl malonate was added 600 g propionic acid and 10 g concentrated sulfuric acid, and the mixture was refluxed for 4 hr. Then 350 ml of 4 N aqueous sulfuric acid was added to the slightly cooled mixture, and refluxing was continued for an additional 3 hr, at which point evolution of gas had ceased.

The reaction mixture was poured into 2.5 l. water containing 2.5 kg crushed ice. The mixture was neutralized with aqueous sodium hydroxide, and the ketone separated as an oil which crystallized upon cooling in an ice bath. The crystals were filtered, dissolved in petroleum ether-benzene, and filtered through an alumina (Merck) column to remove the dark colored impurities. The product was eluted with petroleum ether-benzene (4:1) as a pale yellow oil which crystallized upon cooling to afford 109 g (67%) ketone A-3, mp 43-45° [lit (19a) mp 45-47°]. ir ($CHCl_3$) 1674 $cm^{-1}$ (C=O); nmr ($CDCl_3$) δ 2.40 (s, 3, $-SCH_3$), 2.59 (s, 3, $CH_3CO$), and 7.00-7.88 (m, 4, aromatic hydrogens).

syn-Methyl o-methylthiophenyl ketoxime (A-4)—A solution of 104.3 g (0.63 mole) ketone A-3, mp 43-45°, and 104.3 g (1.53 moles) hydroxyl amine hydrochloride in 1 l. ethanol and 105 ml pyridine was refluxed for 1 hr. The solvent was

removed under reduced pressure at 50° and 500 ml water was added to the cooled product. The mixture was cooled in ice and shaken for several minutes until crystalline. The crystals were filtered, washed thoroughly with water, and air dried. Recrystallization of this material from benzene-n-hexane gave 77.5 g crystalline product. Three recrystallizations of the mother liquor from benzene-n-hexane afforded 14.3 g crystalline material, which when combined with the material from the initial crystallization gave 91.8 g (81%) oxime A-4, mp 116-119° [lit (19a) mp 121-123°]. ir ($CHCl_3$) 3585, 3290 (-OH), 1630, 915 $cm^{-1}$ (C=N).

syn-Methyl o-methylthiophenyl ketoxime p-nitrobenzoate (A-5). —To a solution of 103.5 g (0.56 mole) p-nitrobenzoyl chloride in 250 ml dry pyridine at 0° was added dropwise with stirring a solution of 91.8 g (0.51 mole) oxime A-4, mp 116-119°, in 250 ml dry pyridine. After addition was complete, the solution was stirred for an additional 30 min at 0°, and then stored in a refrigerator overnight. To this solution, cooled in ice, was added 1.2 l. of 5 N aqueous sulfuric acid. The resulting mixture was stirred for 1 hr, and then extracted with ether-benzene (1:1). The extract was washed with 5 N aqueous sulfuric acid and the acid wash was re-extracted with ether-benzene (1:1). The combined extracts were washed thoroughly with saturated aqueous bicarbonate followed by brine. Drying ($Na_2SO_4$), and concentration

provided a yellow solid which was recrystallized from n-hexane-benzene to give 153.2 g (92%) benzoate A-5 as yellow crystals, mp 95-99° [lit (19a) mp 94-96°]. ir ($CHCl_3$) 1760 $cm^{-1}$ (ester C=O); nmr ($CDCl_3$) δ 2.47 [s, 3, S-$CH_3$ or Ar$C(CH_3)$=N], 2.52 [s, 3, S-$CH_3$ or Ar$C(CH_3)$=N], 7.32 (m, 4, hydrogens on o-substituted aromatic ring), and 8.31 (s, 4, hydrogens on benzoate ring).

3-Methyl-1,2-benzisothiazole (II).-A procedure similar to that of Crawford and Woo (19a) was used in the preparation of this compound. A solution of 153.2 g (0.465 mole) oxime ester A-5, mp 95-99°, in 620 ml tetrachloroethane was refluxed for 3 hr, then cooled and the solvent removed on a rotary evaporator at 70°. To the residue was added 2 l. of 5% aqueous sodium hydroxide, and the resulting mixture was steam distilled. The benzisothiazole was extracted from the distillate with several portions of ether-benzene and the combined extracts were washed with brine, dried ($Na_2SO_4$), and concentrated to afford a yellow oil which was distilled under vacuum. The benzisothiazole II distilled as a colorless oil, bp 82-83° (0.75 mm) weighing 61.5 (89%). ir (film) 3050, 1595, 1495, 1435, 1380, 1340, 1320, 785, 755, 730, 710 $cm^{-1}$; nmr ($CDCl_3$) δ 2.61 (s, 3, C-3-$CH_3$), 7.30 (m, 2, aromatic hydrogens) and 7.75 (m, 2, aromatic hydrogens).

Stability of II to strong acid.—The procedure of Ritchie and Taylor (32) was employed in this reaction. A solution of 180 mg (1.21 mmoles) II, in 5 ml glacial acetic acid and 5 ml concentrated hydrochloric acid was heated at reflux with stirring for 24 hr, cooled to room temperature, and then partitioned between petroleum ether-brine. The organic solution was separated and washed with brine until neutral (litmus paper). Drying ($Na_2SO_4$) and concentration afforded 157 mg (87%) pale yellow oil, homogeneous by vpc (oven temp 140-200° @ 20°/min, rt 2.3 min). The ir spectrum of this oil was identical to that of the starting benzisothiazole II.

Stability of II to sodium borohydride.—To a solution of 105 mg (0.704 mmole) II in 4 ml methanol was added 50 mg (1.32 mmoles) sodium borohydride. The mixture was stirred at room temperature for 21 hr, then diluted with water and extracted with petroleum ether. The organic solution was separated and washed with water followed by brine. Drying ($Na_2SO_4$) and concentration provided a quantitative recovery of unchanged starting material II as determined by a comparison of the vpc record (oven temp 140-200° @ 20°/min, rt 2.4 min) and ir spectrum with those of authentic II.

Stability of II to strong base.—To a solution of 105 mg (0.704 mmole) II in 1.5 ml of 95% ethanol was added a solution of 2 g potassium hydroxide in 2 ml water and 1.5 ml

of 95% ethanol. This mixture was stirred at reflux for 6 hr, then cooled to room temperature. The two phase system was partitioned between petroleum ether-water. The organic solution was separated, washed with water until neutral (litmus paper), then with brine, and dried ($Na_2SO_4$). Concentration provided 89 mg (85%) pale yellow oil, homogeneous by vpc, (oven temp 140-200° @ 20°/min, rt 2.2 min). This oil was identified as unchanged II as its ir spectrum was identical to that of authentic starting material.

3-Bromomethyl-1,2-benzisothiazole (Ia).-To a solution of 5.0 g (33.5 mmoles) 3-methylbenzisothiazole II in 250 ml carbon tetrachloride was added 5.8 g (33.6 mmoles) N-bromosuccinimide (NBS) (recrystallized from acetone-water, mp 180-182°). The resulting mixture, heated with an oil bath, was stirred at reflux in the presence of a 150 W tungsten light. After 7 hr, visual inspection indicated that no NBS remained and analysis of a portion of the reaction mixture by vpc indicated a 1:3 mixture (oven temp 200-300° @ 20°/min, rt 1.0 and 1.8 min) of starting material to bromide Ia, so an additional 0.5 g (2.8 mmoles) NBS was added and the reaction allowed to continue for 4 hr more and then terminated when analysis by vpc showed three peaks (oven temp 140-300° @ 20°/min; rt 2.0, 3.8, and 4.9 min) in the approximate ratio of 3:12:2 (in order of increasing retention time) assigned to starting material, mono-bromide Ia, and di-bromide B-1, respectively.

The bulk of the carbon tetrachloride was removed under reduced pressure on a rotary evaporator. Petroleum ether was added to the residue and the insoluble succinimide was removed by filtration. The organic solution was washed in succession with 5% aqueous sodium hydroxide and water. Drying ($Na_2SO_4$) and concentration afforded 8.8 g yellow oil which was chromatographed on 300 g silica gel (Grace, 100-200 mesh). Elution with 2.5 l. petroleum ether-benzene (1:1) gave 1.51 g (15%) di-bromide B-1 as yellow crystals, homogeneous by vpc (oven temp 140-300° @ 20°/min, rt 4.9 min). Recrystallization of a portion of these crystals from acetone-n-hexane afforded the analytical sample (47) as white needles, mp 93.5-94.0°. ir ($CHCl_3$) 1599, 1410, 1150, 830 $cm^{-1}$; nmr ($CDCl_3$) δ 7.02 (s, 1, C-3-$CHBr_2$), 7.45 (m, 2, aromatic hydrogens), 7.85 (m, 1, aromatic H), and 8.47 (m, 1, aromatic H).

Anal. Calcd for $C_8H_5Br_2NS$: C, 31.28; H, 1.64; Br, 52.07. Found: C, 31.45; H, 1.66; Br, 52.16.

Further elution with 300 ml petroleum ether-benzene (1:1) and 1.3 l. benzene gave 5.40 g (71%) mono-bromide Ia as a pale yellow oil homogeneous by vpc (oven temp 140-300° @ 20°/min, rt 3.8 min), which crystallized slowly upon standing. Distillation of a portion of this material, bp 93-96° (0.1 mm), provided the analytical sample (47) as a colorless oil which crystallized as long needles, mp 55-56°. ir ($CHCl_3$) 1595, 1480,

1425, 1410, 1365, 1325, 1115 $cm^{-1}$; nmr ($CDCl_3$) δ 4.82 (s, 2, C-3-$CH_2Br$), 7.44 (m, 2, aromatic hydrogens), and 8.00 (m, 2, aromatic hydrogens).

Anal. Calcd for $C_8H_6BrNS$: C, 42.12; H, 2.66; Br, 35.52. Found: C, 42.15; H, 2.62; Br, 35.63.

Continued elution with 500 ml benzene-ether (1:1) afforded 0.64 g (13%) starting benzisothiazole II as a yellow oil, homogeneous by vpc (oven temp 140-300° @ 20°/min, rt 2.0 min) and identified by its infrared spectrum.

Treatment of 3-methyl-1,2-benzisothiazole (II) with Raney nickel in ethanol.—In a 50 ml three-necked flask equipped with a magnetic spinbar and reflux condenser was placed 3 g (5 ml catalyst sludge) of W-2 Raney nickel (48). The catalyst was transferred as a slurry in absolute ethanol. The supernatant ethanol was then drawn off with a pipette and immediately replaced by a solution of 1.00 g (6.70 mmoles) benzisothiazole II, in 10 ml absolute ethanol. The mixture was placed under a nitrogen atmosphere and vigorously stirred at reflux for 24 hr. The mixture was then cooled and filtered through Celite to remove the catalyst. The filter pad was washed thoroughly with 100 ml hot methanol, and the combined alcohol solutions, acidified by addition of 0.5 ml concentrated hydrochloric acid to insure against loss of any volatile amines that could be present in the product,

were concentrated at reduced pressure on a rotary evaporator at 25°. The crude material was taken up in chloroform and basic-nitrogen containing products were extracted with aqueous acid (water acidified with hydrochloric acid). The chloroform solution, washed with water and brine, dried ($Na_2SO_4$) and concentrated, yielded 558 mg (70%) acetophenone B-2 as a pale yellow oil, homogeneous by vpc (oven temp 150°, rt 0.6 min), identified by a comparison of its ir spectrum with that of authentic material.

The aqueous acid solution from above, basified with 10% aqueous sodium hydroxide, was extracted with chloroform. Workup as before afforded 199 mg (17%) yellow oil, identified as N,N-diethyl-1-phenylethyl amine B-3 by virtue of its nmr spectrum. nmr ($CDCl_3$) $\delta$ 0.98 (t, 6, J 7.5 Hz, $-N-CH_2-\underline{CH_3}$), 1.32 (d, 3, J 7.0 Hz, $CH-\underline{CH_3}$), 2.53 (q, 4, J 7.5 Hz, $N-CH_2-$), 3.79 (q, 1, J 7.0 Hz, Ph-CH-Me), and 7.30 (m, 5, phenyl hydrogens). ir (film) 2810 $cm^{-1}$ ($N-CH_2-CH_3$).

This experiment was repeated exactly as described above, using nickel catalyst from the same batch as before, and the yields were 62% acetophenone B-2, 28% diethyl amine B-3. A third experiment using the quantities above and catalyst which was prepared at the same time as that used previously, but from a portion of that batch which had not previously been opened, afforded acetophenone B-2 in 30% yield and the diethyl amine B-3 in 52% yield.

N-Ethyl-3-methyl-1,2-benzisothiazolium fluoroborate (B-4).— The general procedure of Kemp and Woodward (31c) was followed in the preparation of this compound. To a solution of 1.495 g (10.0 mmoles) benzisothiazole II in 10 ml dry dichloromethane was added 1.90 g (10.0 mmoles) triethyloxonium fluoroborate, prepared by the procedure of Meerwein (49). The solution was cooled in ice and crystallization began within 30 min. Crystallization was allowed to proceed for 12 hr at room temperature, and then the crystalline mass was transferred to a centifuge tube. Centrifugation followed by separation of the supernatant liquid and washing of the crystalline portion with iced dichloromethane afforded 2.12 g white crystals, mp 137.5-138°. Crystallization of the combined mother liquor and washings from acetone-n-hexane provided 205 mg white crystals, which when added to the material from the initial crystallization gave 2.32 g (88%) of the fluoroborate salt B-4. Recrystallization of a portion of this material from acetone-n-hexane afforded the analytical sample as white needles, mp 138-140°. ir (Nujol) 1595 (C=N), 1100-1000 ($BF_4^-$), 770 $cm^{-1}$ (aromatic C-C); nmr ($CH_3CN$) δ 1.64 (t, 3, J 7.5 Hz, -N-$CH_2$-$CH_3$), 2.99 (s, 3, C-3-$CH_3$), 4.62 (q, 2, J 7.5 Hz, -N-$CH_2$-Me), and 7.64-8.46 (m, 4, aromatic hydrogens).

Anal. Calcd for $C_{10}H_{12}BF_4NS$: C, 45.29; H, 4.57. Found: C, 45.33; H, 4.52.

2-[3'-(1,2-benzisothiazolyl)]-methylcyclohexanone (D-2).— The general procedure of Ritchie and Taylor (32) was followed in the preparation of this compound. To a flask equipped with a magnetic spinbar and reflux condenser was added 325 mg (13.5 mmoles) sodium hydride (550 mg of a 59.4% dispersion in mineral oil). The flask was flushed with nitrogen, and 15 ml dry benzene and 10 ml dry dimethylformamide were added. Then 2.16 g (13.2 mmoles of available β-keto ester) of a 1:2 mixture of methyl and ethyl 2-cyclohexanone carboxylate D-1 (50) was added to the stirred mixture as a solution in 5 ml dry benzene. The solution was heated to 70° and 2.90 g (12.7 mmoles) bromide Ia was added resulting in immediate formation of a precipitate, presumably sodium bromide. The reaction mixture was heated at reflux for 22 hr, then cooled to room temperature and poured into 10% aqueous hydrochloric acid. The aqueous acid mixture was extracted several times with ether and the combined extracts were washed with brine until neutral to litmus paper. Concentration of the undried ethereal solution afforded 5 g of dark oil which was immediately taken up in 8 ml glacial acetic acid. To this solution was added 8 ml concentrated hydrochloric acid, and the resulting solution was heated at reflux for 30 hr. The mixture was then cooled and poured into saturated aqueous sodium chloride. The salt

solution was extracted with ether several times and the combined extracts were washed with saturated aqueous bicarbonate and brine. Drying ($Na_2SO_4$) and concentration afforded 3.6 g of an oil which was filtered through 40 g Merck alumina. Elution with 50 ml petroleum ether returned 290 mg mineral oil and further elution with 200 ml ether-petroleum ether afforded 2.28 g (73%) ketone D-2 as a yellow oil, homogeneous by vpc (oven temp 200-300° @ 30°/min, rt 3.5 min). The analytical sample was obtained from a portion of this material by evaporative distillation. It distilled as a colorless oil, oven temperature 140° (0.02 mm), which darkened upon exposure to air. ir (film) 3050 (aromatic C-H), 1715 (C=O), 1595, 760, 735 $cm^{-1}$ (aromatic); nmr ($CDCl_3$) δ 7.21-7.57 (m, 2, aromatic hydrogens), and 7.73-8.07 (m, 2, aromatic hydrogens).

Anal. Calcd for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16; N, 5.71; S, 13.07. Found: C, 68.74; H, 6.25; N, 5.55; S, 12.91.

2-[3'-(1,2-benzisothiazolyl)]-methyl-1,1-ethylenedioxycyclohexane (D-3).—To a 100 ml flask equipped with a magnetic spinbar was added 0.70 g (2.86 mmoles) ketone D-2, 50 mg (0.26 mmole) p-toluenesulfonic acid monohydrate, 1.5 ml ethylene glycol, and 40 ml reagent benzene. This mixture was stirred at reflux for 17 hr and the water formed

during this time was removed by means of a Dean-Stark water separator. The mixture was cooled and poured into ether-saturated aqueous bicarbonate (2:1). The ethereal solution was separated and washed in succession with 5% aqueous bicarbonate and water. After drying ($Na_2SO_4$) and concentration there remained 0.79 g (96%) ketal D-3 as a yellow oil which exhibited a single peak by vpc (oven temp 230-300° @ 30°/min, rt 3.0 min). The analytical sample, obtained by evaporative distillation of a portion of this oil, was a pale yellow oil, oven temperature 155° (0.02 mm). ir (thin film) 1585 (aromatic), 1150-1010, 940, 920 (ketal), 755, 730 $cm^{-1}$ (aromatic); nmr ($CDCl_3$) δ 4.03 (m, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{16}H_{19}NO_2S$: C, 66.41; H, 6.62; N, 4.84; S, 11.08. Found: C, 66.56; H, 6.66; N, 4.90; S, 11.15.

Treatment of D-3 with Raney nickel in ethanol.—To a flask equipped with a magnetic spinbar and a water condenser was added 0.18 g (0.3 ml catalyst sludge) W-2 Raney nickel as a slurry in absolute ethanol. The supernatant ethanol was drawn off with a pipette and immediately replaced with a solution of 98 mg (0.339 mmoles) ketal benzisothiazole D-3 in 3 ml absolute ethanol. The system was then placed under a positive nitrogen atmosphere and stirred vigorously at reflux for 24 hr. The reaction mixture was cooled below reflux; the catalyst was removed by filtration through

Celite, and the filter pad was washed with 25 ml hot methanol. The alcoholic solution, concentrated at reduced pressure on a rotary evaporator, provided 87 mg oil. This oil was purified by ptlc (aluminum oxide, benzene) and appeared as one major band accompanied by two minor bands. The major band ($R_f$ 0.37) afforded 40 mg (37%) of the diethylamino ketal D-4 as a pale yellow oil, greater than 95% pure by vpc analysis (oven temp 200-300° @ 30°/min, rt 3.2 min). The oil was identified by its ir and nmr spectra. ir (film) 2800 (N-Et), 1595, 1490, 760, 730, 695 (phenyl), 1150, 1080, 1045, 940, 920 $cm^{-1}$ (ketal); nmr ($CDCl_3$) δ 0.98 (t, 6, J 7 Hz, N-$CH_2$-$CH_3$), 3.75, 3.93 [m, 5, PhCH($NEt_2$)- and ketal], and 7.28 (m, 5, phenyl hydrogens).

One of the minor bands from the ptlc ($R_f$ 0.28) provided 13 mg yellow oil which appeared as two peaks in the vpc (oven temp 200-300° @ 30°/min; rt 3.0, 3.25 min) in the ratio of 1:4 in order of increasing retention time. The major peak in the vpc was identified as additional diethylamino ketal D-4 when the vpc of a mixture containing amine D-4 from above showed an enhancement of the peak with a retention time of 3.25 min.

The minor component, rt 3.0 min, was tentatively identified as the corresponding benzylic ketone ketal based on the presence of a medium strength absorption at 1685 $cm^{-1}$ in the

ir spectrum of the 1:4 mixture.

The remaining minor band ($R_f$ 0.75) afforded 5 mg oil, homogeneous by vpc (oven temp 200-300° @ 30°/min, rt 2.4 min). The ir spectrum of this oil was devoid of absorption in the carbonyl region and lacked the 2800 $cm^{-1}$ band characteristic of the diethylamine D-4. On this basis, plus its relatively high $R_f$, this product was tentatively identified as phenylethyl ketal IX. ir ($CHCl_3$) 1605, 1495, 695 (phenyl), 1155, 1085, 945, 920 $cm^{-1}$ (ketal).

This experiment was repeated on a larger scale using 600 mg (2.08 mmoles) ketal isothiazole D-3 and 1 g (1.8 ml catalyst sludge) W-2 Raney nickel in 10 ml absolute ethanol. After a reflux time of 23 hr, workup afforded 490 mg yellow oil, which as before exhibited two peaks in the vpc (oven temp 200-300° @ 30°/min; rt 2.5, 3.4 min) in the approximate ratio of 1:9 in order of increasing retention time. These peaks were assigned to phenylethyl ketal IX and diethylamino ketal D-4 respectively, by the method of peak enhancement.

2-(2'-Phenylethyl)cyclohexanone (D-5) from ketal benzisothiazole (D-3).—Following the procedure described above for the Raney nickel treatment of D-3, a solution of 589 mg (2.04 mmoles) D-3 in 10 ml absolute ethanol was vigorously

stirred at reflux under an atmosphere of nitrogen in the presence of 1 g (1.8 ml catalyst sludge) W-2 Raney nickel for 24 hr. The catalyst was removed by filtration through Celite, and the filter cake was washed with 100 ml hot methanol. After concentration of the alcoholic solution at reduced pressure on a rotary evaporator, there remained 577 mg yellow oil, 95% of which consisted of a 1:9 mixture of phenylethyl ketal IX and diethylamino ketal D-4, as determined by vpc analysis (oven temp 200-300° @ 30°/min; rt 2.5, 3.5 min). This oil, without additional purification, was dissolved in 70 ml acetone, and the resulting solution was diluted to 100 ml with 10% aqueous hydrochloric acid. The mixture was heated on a steam bath for 1 hr, cooled, and the bulk of the acetone removed at reduced pressure on a rotary evaporator. The residue was partitioned between ether-benzene (100 ml, 4:1) and water (100 ml) in a separatory funnel. The aqueous layer was made alkaline with 10% aqueous sodium hydroxide, drawn off, and extracted a second time with ether-benzene (4:1). The combined extracts were washed with brine until neutral, dried ($Na_2SO_4$), and concentrated to afford 450 mg yellow oil, 90% of which consisted of a 1:9 mixture of two products by vpc (oven temp 200-300° @ 30°/min; rt 1.9, 2.9 min). The minor product, rt 1.9 min, was identified as the desired phenylethyl ketone D-5 by

peak enhancement with an authentic sample of D-5. The major product, rt 2.9 min, was assumed to be the expected diethylamino ketone X, and this assumption was supported by the ir and nmr spectra of the crude product. ir (film) 2800 (N-Et), 1710 $cm^{-1}$ (C=O); nmr ($CDCl_3$) $\delta$ 0.87 (t, J 7.0 Hz, $N-CH_2-CH_3$), and 3.60 [q, $PhCH(NEt_2)-$].

The crude mixture of ketones, without further purification, was taken up in 30 ml absolute ethanol containing 0.2 ml concentrated hydrochloric acid and stirred at 75° in the presence of 75 mg of 10% palladium-on-charcoal under one atmosphere of hydrogen for 12 hr. The catalyst was removed by filtration and the alcoholic solution was concentrated at reduced pressure on a rotary evaporator. The residue was taken up in ether-benzene (4:1) and washed in succession with water and brine. Drying ($Na_2SO_4$) and concentration afforded 348 mg yellow oil, homogeneous by vpc (oven temp 200-300° @ 30°/min; rt 1.9 min) and identified as the phenylethyl ketone D-5 by peak enhancement on vpc and by the fact that both its ir and nmr spectra were superimposable on those obtained from an authentic sample of D-5 prepared by another route. The 348 mg of D-5 obtained in this three-step process represents an overall yield of 85%.

2-[3'-(1,2-benzisothiazoyl)]-methyl-1-hydroxycyclohexane (D-6).—To a solution of 0.54 g (2.2 mmoles) ketone D-2 in

100 ml methanol was added 0.40 g (10.5 mmoles) sodium borohydride in several portions. The mixture was stirred at room temperature for 12 hr, and then poured into a solution of water-saturated aqueous sodium chloride (5:1). The aqueous mixture was extracted twice with ether-benzene (4:1), and the combined extracts were washed in succession with water and brine. Drying ($Na_2SO_4$) and concentration afforded 0.54 g (100%) of a yellow oil, homogeneous by vpc (oven temp 200-300° @ 30°/min, rt 3.6 min) but showing two components by tlc. [ether-benzene (1:1), $R_f$ 0.21, 0.28]. The two components were assumed to be the two epimeric alcohols and no attempt was made to separate them. Evaporative distillation of a portion of this material afforded the analytical sample as a pale yellow oil, oven temperature 155-160° (0.02 mm). ir (thin film) 3370 (-OH), 3050 (aromatic C-H), 1595, 1485, 760, 735 (aromatic), 975 $cm^{-1}$ (C-O); nmr ($CDCl_3$) δ 7.22-7.56 (m, 2, aromatic hydrogens), and 7.75-8.15 (m, 2, aromatic hydrogens).

Anal. Calcd for $C_{14}H_{17}NOS$: C, 67.98; H, 6.93; N, 5.66; S, 12.96. Found: C, 67.79; H, 7.06; N, 5.61; S, 12.90.

1-Hydroxy-2-(2'-phenylethyl)cyclohexane (D-7) from hydroxy benzisothiazole D-6.—A 1 g portion of W-2 Raney nickel,

which had been stored under ethanol, was washed by decantation with three 10 ml portions of methanol. Then 600 mg (1 ml catalyst sludge) of this catalyst was transferred (as a slurry in methanol) to a three-necked 25 ml flask equipped with a magnetic spinbar and a reflux condenser. The system was placed under an atmosphere of nitrogen, the supernatant methanol was drawn off with a pipette, and a solution of hydroxy benzisothiazole D-6 in 10 ml methanol was added. The resulting mixture was stirred vigorously at reflux for 23 hr, and then the catalyst was washed by decantation with three 10 ml portions of hot methanol. The combined alcoholic solutions were concentrated at reduced pressure on a rotary evaporator to provide 284 mg oil which was taken up in 20 ml absolute ethanol containing 0.3 ml concentrated hydrochloric acid and stirred at reflux in the presence of 25 mg of 10% palladium-on-charcoal under one atmosphere of hydrogen. Reaction was complete after 36 hr as determined by the presence of a single peak in the vpc (oven temp 200-300° @ 30°/min, rt 1.9 min). The catalyst was removed by filtration through Celite and the alcoholic solution was concentrated on a rotary evaporator at reduced pressure. The residue was taken up in chloroform and washed with water and brine. After drying ($Na_2SO_4$) and concentration there remained 148 mg (61%) phenylethyl alcohol D-7

as a pale yellow oil. The ir spectrum and vpc record of this oil were identical to those of an authentic sample of D-7 prepared by another route.

2-(2'-Phenylethyl)-cyclohexanone (D-5).—A mixture of 1.5 g (6.95 mmoles) α-(2'-cyclohexanonyl)-acetophenone (D-8) (51, 52), mp 45-46°, 0.3 ml of 60% aqueous perchloric acid, and 150 mg of 10% palladium-on-charcoal in 100 ml of absolute ethanol was shaken in a Parr hydrogenation apparatus under two atmospheres of hydrogen for 12 hr. The catalyst was removed by filtration, the filter pad was washed with hot ethanol, and the ethanol was removed at reduced pressure on a rotary evaporator. The residue was taken up in chloroform and washed with water. Drying ($Na_2SO_4$) and concentration afforded 1.35 g (96%) ketone D-5 as a yellow oil that exhibited a single peak by vpc (oven temp 200-250° @ 30°/min, rt 1.8 min). The ir spectrum of this oil displayed a strong carbonyl absorption at 1715 $cm^{-1}$ (six-membered ring ketone) and lacked the benzylic ketone absorption at 1680 $cm^{-1}$ present in the starting diketone. ir (film) 1715 (C=O), 1600, 1125, 750, 700 $cm^{-1}$ (phenyl).

The semicarbazone prepared from a portion of this oil and recrystallized from 95% ethanol melted in the range 166-169° [lit (53), mp 157°; (1b), mp 179-180°].

1-Hydroxy-2-(2'-phenylethyl)-cyclohexane (D-7).—A solution of 200 mg (0.99 mmoles) phenylethyl ketone D-5, prepared directly above, in 50 ml methanol was treated portionwise with 200 mg (5.26 mmoles) sodium borohydride. After 16 hr, the mixture was diluted with water and the aqueous mixture was extracted with ether-benzene (4:1). The organic solution was washed with brine, dried ($Na_2SO_4$) and concentrated to give a quantitative yield of cyclohexanol D-7. The ir spectrum of this material showed a broad absorption at 3360 $cm^{-1}$ (-OH) and no absorption in the carbonyl region. The oil was homogeneous by vpc (oven temp 200-300° @ 30°/min, rt 2.1 min) but was deduced to be a 1:1 mixture of epimeric alcohols by virtue of its nmr spectrum. Assuming the phenylethyl side-chain is in the equatorial configuration, two types of C-1 protons were discernible, each integrating for one-half of a proton, as follows: nmr ($CDCl_3$) δ 3.08 (m, ½, w/2 ∽ 14 Hz, C-1-$H_{axial}$), 3.77 (m, ½, w/2 ∽ 7 Hz, C-1-$H_{equatorial}$), and 7.13 (s, 5, phenyl hydrogens); ir (film) 3360 (OH), 1605, 1495, 745, 695 (phenyl), 1450 $cm^{-1}$ (C-C).

5α-[3'-(1,2-Benzisothiazoyl)]methyl-1β-hydroxy-8aβ-methyl-1,2,3,4,4aα,7,8,8a-octahydro-6(5H)-naphthalenone (E-2).—To a vigorously stirred mixture of 27 mg (3.90 mmoles)

lithium wire in 50 ml liquid ammonia (distilled from sodium) and 10 ml dry 1,2-dimethoxyethane was added a solution of 0.50 g (1.90 mmoles) tetrahydropyranyl ether enone viii (54) in 10 ml dry 1,2-dimethoxyethane. The blue solution was stirred for 10 min and then a solution of 0.18 ml (0.14 g, 1.90 mmoles) dry tert.-butyl alcohol in 2 ml dry 1,2-dimethoxyethane was added in one lot. Stirring was continued for an additional 15 min and then a solution of 0.865 g (3.80 mmoles) bromide Ia in 10 ml dry 1,2-dimethoxyethane was added to the vigorously stirred reaction mixture through a dropping funnel. The ammonia was allowed to evaporate over 4 hr and the organic residue was taken up in 200 ml ether-benzene (3:2) and washed several times with water and brine. After drying ($Na_2SO_4$) and concentration there remained 1.0 g of a yellow gum. This gum was purified by chromatography on 100 g of a neutral alumina (Woelm, activity II). Elution with 150 ml ether-petroleum ether (3:7) afforded 265 mg acetal ketone E-1 as a colorless gum. ir ($CHCl_3$) 1705 (saturated C=O), 1590 (aromatic), 1160, 1125, 1115, 1070, 1020, 985 $cm^{-1}$ (tetrahydropyranyl ether); nmr ($CDCl_3$) $\delta$ 1.20 (s, 3, C-8a$\beta$-$CH_3$).

Continued elution with 300 ml ether-petroleum ether (3:7) provided an additional 205 mg colorless gum whose ir spectrum contained two absorptions in the carbonyl region

at 1705 and 1665 $cm^{-1}$ in the ratio of 3:2, respectively.

The material recovered from the chromatography was treated separately as follows. A solution of the 265 mg (0.63 mmoles) acetal ketone E-1, ir ($CHCl_3$) 1705 $cm^{-1}$ (saturated C=O), in 15 ml of a solution prepared by mixing 5 ml of 10% aqueous hydrochloric acid with 45 ml methanol was stirred at room temperature for 3 hr. The acid was neutralized with saturated aqueous sodium bicarbonate and the methanol was removed at reduced pressure on a rotary evaporator. The organic residue was taken up in ether-benzene (5:1) and washed with brine. Drying and concentration afforded 190 mg colorless oil which, upon crystallization from ether-n-hexane deposited 145 mg hydroxy ketone E-2 as white crystals, mp 134-138°.

The impure material recovered from the chromatography, which amounted to 205 mg, ir ($CHCl_3$) 1705, 1665 $cm^{-1}$ (saturated and unsaturated C=O), was likewise hyrdrolyzed with hydrochloric acid in methanol. After a similar workup, there was obtained 133 mg colorless oil which was purified by ptlc (ether) to give two major bands. The band with $R_f$ 0.31 returned 17 mg colorless oil whose ir spectrum ($CHCl_3$) possessed the following principal bands: 3600, 3415 (OH), 1660 (unsaturated C=O), 1620 $cm^{-1}$ (aromatic). The major band, $R_f$ 0.54, returned 95 mg hydroxy ketone, E-2, ir ($CHCl_3$)

3600, 3420 (OH), 1705 (saturated C=O), 1590 $cm^{-1}$ (aromatic).

The overall yield of E-2 for this two step sequence was 240 mg (39%). The analytical sample was obtained from acetone-n-hexane as white prisms, mp 137-139°. ir ($CHCl_3$) 3600, 3430 (OH), 1705 (C=O), 1590 (aromatic), 975 $cm^{-1}$ (C-O); nmr ($CDCl_3$) δ 1.13 (s, 3, C-8aβ-$CH_3$), 7.42 (m, 2, aromatic hydrogens), and 7.95 (m, 2, aromatic hydrogens).

Anal. Calcd for $C_{19}H_{23}NO_2S$: C, 69.27; H, 7.04. Found: C, 69.17; H, 7.01.

5α-[3'-(1,2-Benzisothiazoyl)]methyl-1,2,3,4,4aα,5,6,7,8,8a-decahydro-6,6-ethylenedioxy-1β-hydroxy-8aβ-methylnaphthalene (E-3).—A mixture of 116 mg (0.365 mmole) keto alcohol E-2, mp 134-138°, 17 mg (0.09 mmole) p-toluenesulfonic acid monohydrate, 1 ml ethylene glycol and 15 ml benzene was stirred vigorously at reflux for 2 hr. The water formed during this time was removed by means of a Dean-Stark water trap containing Drierite. The reaction mixture was taken up in ether and the ethereal solution was washed successively with saturated aqueous sodium bicarbonate, water, and brine. Drying ($Na_2SO_4$) and concentration gave 155 mg yellow oil which, although homogeneous by vpc (oven temp 265°, rt 3.0 min), was purified further by ptlc (ether). This chromatography produced a single colorless

band, $R_f$ 0.2-0.35, which provided 123 mg colorless oil whose ir spectrum possessed a weak absorption at 1700 $cm^{-1}$ (vestigial ketone). An attempt to crystallize this oil from ether-n-hexane resulted in the deposition of 8 mg white solid and returned a mother liquor, which when concentrated, afforded 110 mg (83%) hydroxy ketal E-3 as a white foam. This foam appeared as a single peak by vpc (oven temp 265°, rt 2.8 min) and its ir spectrum showed no absorption in the carbonyl region. Further attempts to induce this oil to crystallize were unsuccessful as it was highly soluble in ether, acetone, benzene, ethyl acetate, and methanol, and insoluble in petroleum ether and n-hexane.

The analytical sample was obtained by a further purification of a portion of this foam by a second ptlc. The product was washed from the silica gel with dry ether and concentrated. The oil thus obtained was taken up in 2 ml dry ether, filtered through glass wool and the ether removed under a stream of nitrogen. The residue was dried for 12 hr at high vacuum to afford the analytical sample as a white foam. ir ($CHCl_3$) 3600, 3430 (OH), 1590 (aromatic), 1110, 1035, 1010, 945, 900 (ketal), 980 $cm^{-1}$ (C-OH); nmr ($CDCl_3$) $\delta$ 0.90 (s, 3, C-8a$\beta$-$CH_3$), 4.0 (m, 4, -$OCH_2CH_2O$-), 7.49 (m, 2, aromatic hydrogens), and 8.05 (m, 2, aromatic hydrogens).

Anal. Calcd for $C_{21}H_{27}NO_3S$: C, 67.53; H, 7.29. Found: C, 67.75; H, 7.41.

1β-Hydroxy-8aβ-methyl-1,2,3,4,4aα,7,8,8a-octahydro-5α-(2'-phenylethyl)-6(5H)-naphthalenone (E-4).—To a flask equipped with a magnetic spinbar and reflux condenser was added 0.3 g (0.5 ml catalyst sludge) W-2 Raney nickel as a slurry in 5 ml absolute ethanol. The catalyst was allowed to settle and the supernatant ethanol was drawn off with a pipette. Immediately, a solution of 100 mg (0.268 mmole) hydroxyketal E-3 in 10 ml absolute ethanol was added to the reaction flask and the system was placed under a nitrogen atmosphere. The heterogeneous mixture was stirred vigorously at reflux for a total of 44 hr and monitored by vpc (oven temp 220-280° @ 20°/min; major products with rt 2.5, 2.9, and 3.2 min). An additional 0.1 ml W-2 Raney nickel was added after 31 hr and ethanol was added periodically as necessary to maintain the original volume. After 44 hr, analysis by vpc indicated that the product composition was changing only slightly, so the reaction was terminated. The final ratio of the three major products, as determined by vpc (conditions as stated above) was approximately 2:1:7 in order of increasing retention time. The catalyst was removed by filtration and washed with 100 ml hot methanol.

The alcoholic solution was concentrated at reduced pressure on a rotary evaporator to afford 90 mg oil which was immediately taken up in 20 ml acetone. To this solution was added 5 ml of 10% aqueous hydrochloric acid and the resulting mixture was heated gently at reflux for 1 hr. The bulk of the acetone was removed at reduced pressure on a rotary evaporator, and the residue was partitioned between ether (150 ml) and water (50 ml) in a separatory funnel. The aqueous layer was basified by the addition of 10% aqueous sodium hydroxide, drawn off, and extracted a second time with ether. The combined ethereal solutions were washed with brine, dried over $Na_2SO_4$, and concentrated to provide 85 mg yellow oil which exhibited three major peaks in the vpc (oven temp 220-280° @ 20°/min; rt 1.7, 2.4, 2.6 min). The ir spectrum of this oil exhibited the expected carbonyl absorption at 1705 $cm^{-1}$, and the nmr spectrum lacked the previous ketal resonance at $\delta$ 4.0.

The 85 mg oil, without additional purification, was taken up in 10 ml absolute ethanol containing 0.2 ml concentrated hydrochloric acid. This solution was stirred at gentle reflux in the presence of 50 mg of 10% palladium-on-charcoal under one atmosphere of hydrogen for 18 hr. The catalyst was removed by filtration through a pad of Celite and the alcoholic solution was concentrated on a rotary evaporator at reduced pressure. The residue was taken up

in ether-benzene (9:1) and washed in succession with water and brine. After drying ($Na_2SO_4$) and concentration there remained 39 mg oil. Re-extraction of the washings provided an additional 12 mg oil which was combined with that recovered earlier. The 51 mg oil appeared largely as two components upon analysis by vpc (oven temp 220-290° @ 20°/min; rt 1.65, 1.8 min). This oil was purified by ptlc (ether) to give two bands. From the band with $R_f$ 0.3 was recovered 5 mg oil which by vpc analysis contained no less than six components. The major band with $R_f$ 0.42 returned 16 mg oil which, from ether-n-hexane, deposited 14 mg (18%) hydroxy ketone E-4 as small white plates, mp 114-115°. This material was the component with a vpc retention time of 1.8 min. A portion of this solid was recrystallized from ether-n-hexane to provide the analytical sample as white prisms, mp 114-115°. ir ($CHCl_3$) 3610, 3460 (OH), 1705 (C=O), 1600, 1490 $cm^{-1}$ (phenyl); nmr ($CDCl_3$) (55) δ 1.05 (s, 3, C-8aβ-$CH_3$), 3.26 (m, 1, C-1α-H), and 7.24 (s, 5, phenyl hydrogens).

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.47; H, 9.10.

3,4,4aα,7,8,8a-Hexahydro-8aβ-methyl-5α-(2'-phenylethyl)-1(2H), 6(5H)-naphthalenedione (E-5).—To a solution of

10.7 mg (0.0374 mmole) hydroxy ketone E-4 in 1.2 ml acetone at 0° was added 0.01 ml (0.08 meq) Jones' reagent (56) with a micro syringe. The mixture was stirred at 0° for 30 min, and then 3 drops of iso-propyl alcohol were added and stirring was continued for an additional 5 min to dispose of excess oxidizing agent. The reaction mixture was basified with 1 ml saturated aqueous sodium bicarbonate, diluted with 5 ml water, and extracted several times with ether. The combined ethereal solutions were washed with brine and dried over $Na_2SO_4$. Concentration afforded a semi-crystalline solid which was crystallized from ether-n-hexane to give 7.5 mg (71%) dione E-5 as small white plates, mp 103-105°. ir ($CHCl_3$) 1705 (C=O), 1600, 1490 $cm^{-1}$ (phenyl). A portion of these crystals were recrystallized from 95% ethanol to again give small white plates, mp 103-105° [lit (9a) mp 96-98° from ethanol].

4-[3'-(1,2-Benzisothiazoyl)]methyl-1β-hydroxy-7aβ-methyl-2,3,7,7a-tetrahydro-5(6H)-indenone (F-3).—To a flask that had been flushed with nitrogen was added 72 mg (3.00 mmoles) sodium hydride (125 mg of a 58.6% dispersion in mineral oil) followed by a solution of 500 mg (2.00 mmoles) tetrahydropyranyl ether enone vii (26) in 15 ml of dry 1,2-dimethoxyethane. The mixture was heated at reflux under nitrogen

for 5 hr to give a dark brown solution. The reaction mixture was then cooled to room temperature, and a solution of 460 mg (2.02 mmoles) bromide Ia in 10 ml of dry 1,2-dimethoxyethane was added dropwise over 0.5 hr by means of a pressure-equalizing dropping funnel. The resulting mixture was stirred for 21 hr and then excess sodium hydride was decomposed by the addition of 15 ml saturated aqueous sodium chloride. The mixture was diluted with additional brine and extracted with several portions of benzene. The combined extracts were washed with brine and dried ($Na_2SO_4$). Concentration afforded 930 mg yellow oil which was chromatographed on 150 g of neutral alumina (Woelm, activity III). Elution with 300 ml of ether-petroleum ether (2:3) returned 395 mg benzisothiazoyl indenone F-1 as a colorless oil. ir ($CHCl_3$) 1655 (unsaturated C=O), 1635 (conjugated C=C), 1130, 1120, 1070, 1030, 1015, 970 $cm^{-1}$ (acetal); nmr ($CDCl_3$) $\delta$ 1.13 (s, 3, C-7a$\beta$-$CH_3$), 4.03 (s, 2, C-4-$CH_2$-), and 4.68 (m, 1, acetal methine H). Further elution with 150 ml of ether-petroleum ether (1:1) provided 300 mg of a colorless oil whose ir spectrum possessed significant absorptions at 1700 and 1660 $cm^{-1}$ (saturated and unsaturated C=O moieties, respectively), as well as the characteristic absorptions of the acetal functionality.

The two oils isolated from the chromatography were

treated separately as follows. A solution of the 395 mg (0.995 mmole) acetal enone F-1 in 75 ml methanol and 5.5 ml 10% aqueous hydrochloric acid was heated at reflux for 2.5 hr. The bulk of the methanol was removed at reduced pressure on a rotary evaporator. The residue was taken up in ether-benzene (1:1) and washed successively with water, saturated aqueous bicarbonate, and brine. Drying ($Na_2SO_4$) and concentration afforded 310 mg pale yellow oil which deposited 230 mg white crystals from ether-n-hexane. These crystals represented the desired hydroxy enone F-3, obtained in overall yield of 37%. The analytical sample was recrystallized from ether-n-hexane and existed as white crystals, mp 163.5-166°. ir ($CHCl_3$) 3600, 3400 (-OH), 1655 (C=O), 1635 (C=C), 1015 $cm^{-1}$ (C-OH); nmr ($CDCl_3$) δ 1.10 (s, 3, C-7aβ-$CH_3$), and 4.03 (s, 2, C-4-$CH_2$-).

Anal. Calcd for $C_{18}H_{19}NO_2S$: C, 68.96; H, 6.11; N, 4.47; S, 10.24. Found: C, 68.97; H, 6.17; N, 4.42; S, 10.26.

The 300 mg of unidentified oil from the chromatography was hydrolyzed in similar fashion to give a colorless oil which was purified by ptlc (ether). The major band had $R_f$ 0.5 and returned a colorless oil which was crystallized from ether-n-hexane to give the dibenzisothiazoyl indenone F-2b as white crystals of analytical purity, mp 169.5-171°.

ir ($CHCl_3$) 3600, 3410, (-OH), 1700 (C=O), 1590 $cm^{-1}$ (aromatic); nmr ($CDCl_3$) δ 0.80 (s, 3, C-7aβ-$CH_3$), 2.62 (m, 2, C-6-H), 3.63, 3.87 (d and d, 4, C-4α-$CH_2$- and C-4β-$CH_2$-), and 5.00 (t, 1, C-3-vinyl H).

Anal. Calcd for $C_{26}H_{24}N_2O_2S_2$: C, 67.78; H, 5.26; N, 6.09; S, 13.93. Found: C, 67.59; H, 5.26; N, 5.98; S, 13.89.

Attempted ketalization of enone F-3.—A solution of 100 mg (0.320 mmole) hydroxy enone F-3 in 25 ml benzene containing 3 ml ethylene glycol and 10 mg p-toluenesulfonic acid monohydrate was stirred at reflux for 20 hr. The water formed during this time was remcved by a Dean-Stark water separator containing calcium chloride. The mixture was cooled to room temperature, diluted with 50 ml ether-benzene (5:1) and washed in succession with saturated aqueous sodium bicarbonate and brine. After drying ($Na_2SO_4$) and concentration there remained 129 mg of semi-crystalline material which upon analysis by vpc (oven temp 270°) appeared as two components: 20% starting enone (rt 1.7 min) and 80% product (rt 2.1 min). Indeed, the ir spectrum of this material possessed an absorption of medium intensity at 1650 $cm^{-1}$ (unsaturated C=O) and a series of characteristic ketal bands in the region 1120-950 $cm^{-1}$. The nmr spectrum of this crude mixture

exhibited three resonances in the region occupied by the C-7aβ-$CH_3$ group: the resonance at δ 1.10 was assigned to the starting enone while the resonances at δ 0.95 and 1.02, of approximately equal intensity, indicated the presence of at least two products. The spectrum included a multiple resonance in the region about δ 4.0 attributable to ethylene ketal as well as a resonance at δ 5.35 (one-third proton by integration) characteristic of a C-3-vinyl hydrogen.

An attempt to separate these three components by ptlc was unsuccessful: while two bands were obtained, each contained (nmr analysis) significant amounts of starting enone F-3.

1α-[3'-(1,2-Benzisothiazoyl)]methyl-1β, 4aβ-dimethyl-7-methoxy-3,4,4a,9-tetrahydro-2(1H)-phenanthrone (H-1).—The general procedure of D. A. Evans (36) was followed in the preparation of this compound. To a flask that had been purged with nitrogen was added 20 ml of dry 1,2-dimethoxyethane followed by 112 mg (4.68 mmoles, 191 mg of a 58.6% dispersion in mineral oil) sodium hydride and 1.00 g (3.91 mmoles) of the tricyclic enone ix (57), mp 87-91°. The resulting mixture was heated at reflux under nitrogen for 5 hr, and then cooled to 0°, at which time a solution of 1.025 g (4.50 mmoles) bromide Ia in 6 ml of dry 1,2-dimeth-

oxyethane was added dropwise to the stirred solution over a period of 10 min. After the addition was complete, the mixture was stirred at 0-5° for 1 hr, allowed to warm gradually to room temperature, and then stirred for 14 hr. Excess sodium hydride was quenched with several drops of concentrated hydrochloric acid. The reaction mixture was diluted with 200 ml of ether-benzene (1:1) and the organic solution was washed with water until neutral (litmus paper) and with brine. After drying ($Na_2SO_4$) and concentration there remained 1.975 g of a yellow gum whose infrared spectrum possessed carbonyl absorptions at 1715 and 1660 $cm^{-1}$ in the approximate ratio of 4:1, respectively. This crude product was immediately chromatographed on 200 g of neutral alumina (Woelm, activity II). Elution with 500 ml ether-petroleum ether (1:3) afforded 85 mg of starting enone ix, identified by its infrared spectrum ($CHCl_3$): 1660 (unsaturated C=O), 1620, 1610 $cm^{-1}$ (C=C and aromatic). Further elution with 1500 ml of ether-petroleum ether (3:7) returned 1.32 g (84%) keto benzisothiazole H-1 as a pale yellow gum that resisted all efforts to crystallize it. This gum decomposed noticeably when exposed to air and was always stored under nitrogen in a refrigerator. ir ($CHCl_3$) 1707 (C=O), 1610, 1595, 1580, 1498 (aromatic), 1020 $cm^{-1}$ ($-OCH_3$); nmr ($CDCl_3$) $\delta$ 1.20 (s, 3, C-1$\beta$-$CH_3$), 1.47 (s, 3, C-4a$\beta$-$CH_3$), 3.22 (m, 2, C-9-methylene hydrogens), 3.55

(s, 2, C-1α-$CH_2$-), 3.72 (s, 3, -$OCH_3$), 5.85 (d of d, 1, C-10-vinyl H), 6.86 (m, 2, aromatic hydrogens), 7.30 (m, 3, aromatic hydrogens), and 7.70 (m, 2, aromatic hydrogens).

The semicarbazone prepared from a portion of this material and recrystallized from hot 95% ethanol existed as minute white crystals, mp 205-207° (decomposed upon melting). ir ($CHCl_3$) 3525, 3410, 3375 (NH), 1687 (C=O), 1560 (amide type II band), 1620, 1495 $cm^{-1}$ (aromatic).

Anal. Calcd for $C_{26}H_{28}N_4O_2S$: C, 67.80; H, 6.13. Found: C, 67.73; H, 6.12.

Reduction of ketone H-1 with sodium borohydride.—A solution of 516 mg (1.28 mmoles) ketone H-1 in 50 ml methanol was treated portionwise with 236 mg (6.21 mmoles) sodium borohydride. The resulting solution was stirred at room temperature for 17 hr and then poured into 250 ml of a 1:1 mixture of water-saturated aqueous sodium chloride. The aqueous mixture was extracted several times with ether-benzene (3:1) and the combined extracts were washed with brine and dried ($Na_2SO_4$). Concentration afforded 460 mg (89%) of a colorless gum whose ir spectrum possessed no absorption in the carbonyl region. The nmr of this gum exhibited two pairs of resonances, δ 1.20, 1.28 and δ 1.25, 1.32, in the approximate ratio of 1:2 which were tentatively

assigned to the angular methyl groups of the two possible epimeric alcohols. Indeed, this material appeared as two spots on tlc (15% ether in benzene) with $R_f$ 0.5 and 0.55. This gum yellowed noticeably on exposure to air; and in subsequent work with this material, only deoxygenated solvents were used.

The two components of this gum were separated by ptlc (15% ether in benzene). The chromatography was conducted in a nitrogen atmosphere using solvents that had been deoxygenated by bubbling nitrogen through them for 15 min prior to use. After development, two major bands were evident with $R_f$ 0.44 and 0.59. The band of lower $R_f$ returned 221 mg (43%) of a colorless gum. ir ($CHCl_3$) 3600, 3400 (-OH), 1610, 1590, 1575, 1495 (aromatic), 1035 $cm^{-1}$ (ArO-$CH_3$), 1005 $cm^{-1}$ (C-OH); nmr ($CDCl_3$) $\delta$ 1.27 (s, 3, C-1$\beta$-$CH_3$ or C-4a$\beta$-$CH_3$), 1.32 (s, 3, C-1$\beta$-$CH_3$ or C-4a$\beta$-$CH_3$), 3.70 (s, 3, C-7-$OCH_3$), 4.05 (m, 1, w/2 $\sim$12 Hz, C-2$\alpha$-$H_{axial}$), and 6.32 (m, 1, C-10-vinyl H). Because of its relatively low $R_f$ on tlc and the breadth of the resonance assigned to the C-2-hydrogen in the nmr, this component was tentatively identified as the equatorial alcohol H-2a.

The band of higher $R_f$ afforded 108 mg (21%) of a colorless gum. ir ($CHCl_3$) 3410 (-OH), 1610, 1590, 1580, 1495 (aromatic), 1030 (ArO-$CH_3$), 1005 $cm^{-1}$ (C-OH); nmr ($CDCl_3$) $\delta$ 1.22 (s, 3, C-1$\beta$-$CH_3$ or C-4a$\beta$-$CH_3$), 1.28 (s, 3,

C-1β-$CH_3$ or C-4aβ-$CH_3$), 3.75 (s, 3, C-7-$OCH_3$), and 6.13 (t, 1, C-10-vinyl H). This component was tentatively identified as the axial alcohol H-2b on the basis of its relatively greater $R_f$ on tlc. The C-2-hydrogen did not appear as an isolated resonance in the nmr.

Attempted degradation of benzisothiazoyl hydroxy olefin H-2.—(a) W-2 Raney nickel, stored under absolute ethanol, was washed with methanol several times by decantation. Then 1.5 g (2.5 ml catalyst sludge) of it was transferred to a reaction flask as a slurry in methanol. The catalyst was allowed to settle and the supernatant methanol was drawn off with a pipette. Immediately, a solution of 0.55 g (1.36 mmoles) of alcohols H-2 (as an epimeric mixture of alcohols direct from sodium borohydride reduction of ketone H-1) in 35 ml methanol was added. The heterogeneous mixture was stirred at gentle reflux for 23 hr, cooled, and the catalyst washed with four 20 ml portions of hot ethanol by alternate centrifugation and decantation. The combined alcoholic solution was concentrated at reduced pressure on a rotary evaporator and the residue taken up in ether-benzene (9:1). After a routine workup, concentration afforded 290 mg yellow oil. This low recovery prompted a re-extraction of the combined aqueous washings with

several portions of chloroform, which after a normal workup provided an additional 120 mg colorless oil for a total recovery of 410 mg.

The crude product from above was dissolved in 50 ml absolute ethanol containing 0.5 ml concentrated hydrochloric acid. The resulting solution was stirred at reflux in the presence of 200 mg of 10% palladium-on-charcoal under one atmosphere of hydrogen for 25 hr. The catalyst was removed by filtration and washed thoroughly with absolute ethanol. The acidic solution was neutralized with aqueous sodium bicarbonate, the ethanol removed at reduced pressure on a rotary evaporator, and the residue worked up with chloroform as usual. After concentration there remained 359 mg of a yellow oil. ir ($CHCl_3$) 3600, 3500 weak (OH), 1610, 1500 (aromatic), 1250, 1040 ($ArOCH_3$), 1000 $cm^{-1}$ (C-OH). The nmr spectrum of this material exhibited at least five resonances in the region δ 1.16-1.25, and three nearly equal resonances in the region δ 3.67-3.70, the former attributed to angular methyl groups and the latter to aromatic methyl ethers. Analysis of this crude mixture by sodium fusion gave a positive test for nitrogen.

(b) Following the procedure described above, a solution of 106 mg (0.262 mmole) β-alcohol H-2a in 5 ml methanol was stirred at reflux in presence of 0.2 g (0.35 ml catalyst sludge) W-2 Raney nickel for 24 hr. A similar workup

afforded 84 mg of semi-crystalline material which was taken up in 10 ml absolute ethanol containing 0.5 ml concentrated hydrochloric acid. This solution was stirred at reflux in the presence of 40 mg of 10% palladium-on-charcoal under one atmosphere of hydrogen for 40 hr. Filtration to remove the catalyst and workup with chloroform as before provided 64 mg pale yellow oil. ir ($CHCl_3$) 3600, 3510 (OH), 1610, 1495 (aromatic), 1035 ($-OCH_3$) 1000 $cm^{-1}$ (C-OH); nmr ($CDCl_3$) $\delta$ 1.20, 1.27 (two singlets, C-1$\beta$-$CH_3$, C-4a$\beta$-$CH_3$), and 3.39 (d, J 4 Hz, C-10-vinyl H). Although the general features of the nmr spectrum are consistent with a compound such as the phenylethyl hydroxy olefin H-3a, the spectrum does not integrate correctly for this compound.

(c) When the $\alpha$-alcohol H-2b was treated in succession with Raney nickel and palladium-on-charcoal/hydrogen as described above, similar inconclusive results were obtained.

3-Methyl-7-nitro-1,2-benzisothiazole (I-1) and 3-methyl-5-nitro-1,2-benzisothiazole (I-2).—A mixture of 2.0 g (13.4 mmoles) benzisothiazole II and 2.5 g (24.7 mmoles) potassium nitrate was cooled to -5° in an ice-salt bath. To this mixture was added 20 ml cold, concentrated sulfuric acid (pre-cooled to -5°) in one lot. The resulting mixture was stirred at -5° for 2 hr, and then poured onto crushed ice,

at which time a yellow precipitate formed. The precipitate was taken up in 200 ml chloroform and the chloroform solution washed with water and 5% aqueous potassium hydroxide followed by further washing with water until neutral (litmus paper). Drying ($Na_2SO_4$) and concentration gave 2.5 g yellow crystals which were chromatographed on 125 g silica gel (Grace, 100-200 mesh). Elution with 1.3 l. petroleum ether-benzene (1:4) gave 950 mg (37%) 5-nitrobenzisothiazole I-2 as white crystals, homogeneous by vpc (oven temp 150-300° @ 30°/min, rt 3.1 min). Recrystallization of a portion of this material from acetone-ethanol provided the analytical sample (47) as white needles, mp 116-117°. ir ($CHCl_3$) 1600 (aromatic), 1520, 1315 $cm^{-1}$ (C-$NO_2$); nmr ($CDCl_3$) $\delta$ 2.80 (s, 3, C-3-$CH_3$), 8.06 (d of d, 1, $J_{4,7}$ 0.6 Hz, $J_{6,7}$ 8.6 Hz, C-7-H), 8.36 (d of d, 1, $J_{4,6}$ 1.9 Hz, $J_{6,7}$ 8.6 Hz, C-6-H), and 8.82 (d of d, 1, $J_{4,7}$ 0.6 Hz, $J_{4,6}$ 1.9 Hz, C-4-H).

Anal. Calcd for $C_8H_6NO_2S$: C, 49.45; H, 3.12. Found: C, 49.52; H, 3.18.

Further elution with 500 ml of 2% ether in benzene gave 250 ml yellow crystals which were identified by vpc as a mixture of the two nitrated products. Continued elution with 400 ml ether-benzene (1:9) afforded 940 mg (36%) 7-nitrobenzisothiazole I-1 as yellow crystals, greater than

98% pure by vpc (oven temp 150-300° @ 20°/min, rt 3.4 min). Recrystallization of a portion of this material from acetone-ethanol provided the analytical sample (47) as yellow needles, mp 177-178°. ir ($CHCl_3$) 1610 (aromatic), 1525, 1315 $cm^{-1}$ (C-$NO_2$); nmr ($CDCl_2$) δ 2.81 (s, 3, C-3-$CH_3$), 7.66 (t, 1, $J_{4,5}$, $J_{5,6}$ 7.6 Hz, C-5-H), 8.30 (d of d, 1, $J_{4,6}$ 1.0 Hz, $J_{4,5}$ 7.6 Hz, C-4-H), and 8.48 (d of d, 1, $J_{4,6}$ 1.0 Hz, $J_{5,6}$ 7.6 Hz, C-6-H).

Anal. Calcd for $C_8H_6NO_2S$: C, 49.45; H, 3.12. Found: c, 49.34; H, 3.25.

7-Amino-3-methyl-1,2-benzisothiazole (I-3).—This compound was prepared by an aluminum amalgam reduction following a general procedure suggested by E. J. Corey (40).

Preparation of the aluminum amalgam.—Commercial aluminum foil (2.0 g), in a loose ball of 1 inch strips, was washed successively in absolute ethanol and ether (Mallinckrodt, anhydrous) with several repeated dippings. The foil was then dipped in 2% aqueous mercury(II) chloride for 15-20 sec, rinsed by momentary dipping in absolute ethanol, and finally submerged in ether (avoid excessive exposure to air) where it was cut into smaller pieces.

A solution of 250 mg (1.29) 7-nitrobenzisothiazole I-1 in 125 ml reagent ether containing 12 ml methanol and

6 ml water was mechanically stirred while the aluminum amalgam, prepared above, was added as quickly as possible. The mixture was initially cooled in ice as necessary to maintain the temperature at 25-30°. The mixture was stirred for 6 hr, at which time analysis by vpc (oven temp 150-300° @ 30°/min, rt 2.6 min) indicated 95% conversion to a single component. The mixture was filtered through Celite and the filtercake was washed thoroughly with 200 ml ether-methanol (1:1). The filtrate was concentrated on a rotary evaporator and the organic residue was partitioned between ether-benzene (4:1) and water made alkaline by the addition of 10% aqueous sodium hydroxide. The organic solution was separated, washed with brine, dried ($Na_2SO_4$), and concentrated to afford 181 mg (86%) amine I-3 as yellow crystals, homogeneous by vpc (oven temp 150-300° @ 30°/min, rt 2.6 min). Recrystallization of a portion of the above material from ether gave the analytical sample as light yellow crystals, mp 110-111°. ir ($CHCl_3$) 3450, 3380 ($ArNH_2$), 1620, 1570, 1490 (aromatic), 1380, 1350, 1330, 1285 $cm^{-1}$ (C-N); nmr ($CDCl_3$) δ 2.65 (s, 3, C-3-$CH_3$), 4.03 (s, 2, C-7-$NH_2$), 6.75 (d of d, 1, $J_{4,6}$ 2.4 Hz, $J_{5,6}$ 6.1 Hz, C-6-H), and 7.22 (m, 2, C-4-H and C-5-H).

Anal. Calcd for $C_8H_8N_2S$: C, 58.51; H, 4.91; N, 17.05; S, 19.52. Found: C, 58.61; H, 4.88; N, 17.00; S, 19.56.

5-Amino-3-methyl-1,2-benzisothiazole (I-4).—This compound was prepared by an aluminum amalgam reduction following the procedure described above for preparation of the 7-amino isomer I-3. A solution of 250 mg (1.29 mmoles) 5-nitrobenzisothiazole I-2 in 125 ml reagent ether containing 12 ml methanol and 6 ml water was mechanically stirred while aluminum amalgam, prepared as above from 2 g aluminum foil, was added. The reaction was allowed to continue for 20 hr at 25-30°, and worked up as before to give 166 mg yellow crystals. Purification by ptlc [ether-petroleum ether (2:1)] afforded 87 mg (41%) amine I-4 as pale yellow crystals, mp 130-133°. The analytical sample was recrystallized from ether-petroleum ether to give white crystals, mp 127.5-130.5°. ir ($CHCl_3$) 3450, 3380 ($ArNH_2$), 1620, 1495 (aromatic), 1380, 1350, 1320, 1265 $cm^{-1}$ (C-N); nmr ($CDCl_3$) δ 2.60 (s, 3, C-3-$CH_3$), 6.98 (d of d, 1, $J_{4,6}$ 2.2 Hz, $J_{6,7}$ 8.8 Hz, C-6-H), 7.17 (d of d, 1, $J_{4,7}$ 0.8 Hz, $J_{4,6}$ 2.2 Hz, C-4-H), and 7.72 (d of d, 1, $J_{4,7}$ 0.8 Hz, $J_{6,7}$ 8.8 Hz, C-7-H).

Anal. Calcd for $C_8H_8N_2S$: C, 58.51; H, 4.91; N, 17.05; S, 19.52. Found: C, 58.43; H, 4.97; N, 17.00; S, 19.45.

7-Amino-3-methyl-1,2-benzisothiazole (I-3) and 5-amino-3-methyl-1,2-benzisothiazole (I-4).—To a slush consisting

of 12.0 g (80.6 mmoles) benzisothiazole II and 20.0 g (198 mmoles) potassium nitrate cooled in an ice bath was added 100 ml concentrated sulfuric acid in a steady stream. After an incubation period of several minutes, there was a sudden evolution of brown gas which lasted only momentarily. The mixture was cooled in ice for 15 min and then stirred at room temperature for 4 hr. The reaction was quenched by pouring the mixture into 1.5 l. crushed ice, at which time a yellow precipitate settled out. The entire mixture was transferred to a separatory funnel and extracted several times with chloroform. The combined extracts (500 ml) were washed six times with 40 ml portions of 5% aqueous potassium hydroxide and then with brine. After drying ($Na_2SO_4$) and concentration there remained 14.2 g yellow crystals. These crystals were dissolved in chloroform and filtered through 500 g neutral alumina (Woelm, activity I). The two isomeric nitro benzisothiazoles I-1 and I-2 were eluted with 1 l. of chloroform and a red residue remained on the column. The yellow crystalline solid thus obtained weighed 13.2 g (85%) and consisted of an approximate 3:2 mixture of I-2:I-1 as determined by vpc [oven temp 150-250° @ 30°/min; rt 3.0 (I-2), 3.2 min (I-1)].

The 13.2 g from above, without further purification, was reduced in three batches following the procedure describ-

ed earlier for the preparation of amine I-3. The three reductions were conducted with 4.0 g (20.6 mmoles), 5.0 g (25.8 mmoles), and 4.2 g (21.6 mmoles) of the 2:3 mixture of I-1:I-2. For each reduction, a solution of the I-1:I-2 mixture in 1200 ml reagent ether containing 60 ml methanol and 30 ml water was stirred mechanically while aluminum amalgam, prepared as before from 13 g aluminum foil, was added over a period of 10-15 min. Each reduction was allowed to continue for 20 hr at room temperature, and then worked up as before with particular attention paid to a thorough washing of the aluminum filtercake [1-l. of methanol-ether (1:1) was used in each instance]. Respectively, the three batches gave 2.7 g (80%), 3.3 g (78%), and 2.7 g (76%) of a mixture of amines I-3 and I-4, greater than 95% pure by vpc [¼" column, oven temp 150-300° @ 30°/min, rt 5.1 (I-3), 5.6 min (I-4)]. In each case, the 7-aminobenziso-thiazole I-3 was the predominant product in the 3:2 mixtures that were obtained.

The importance of the chromatographic filtration of the crude product from the nitration prior to using that material in the reduction reaction is emphasized by the fact that when 6.37 g of a 3:2 mixture of I-2 and I-1 was reduced without the preliminary chromatographic filtration, the yield of mixed amines I-3 and I-4 was only 2.36 g (44%).

The amines from the four sources above were chromatographed in one lot on 500 g of silica gel (Merck, 0.05-0.2 mm). Elution with 1500 ml ether-petroleum ether (3:2) provided 4.938 g of amine I-3 as yellow crystals, mp 106-110°. Continued elution with 1000 ml ether-petroleum ether (3:2) and 500 ml ether-petroleum ether (3:1) gave 260 mg of a mixture of I-3 and I-4 as oily crystals. The amine I-4 was then eluted with 1500 ml of ether and was obtained as dark yellow crystals weighing 3.858 g with mp 125-129°.

7-Methoxy-3-methyl-1,2-benzisothiazole (I-5).—This compound was prepared by the procedure described below for the synthesis of the related 5-methoxybenzisothiazole I-6. To a solution of 1.660 g (10.1 mmoles) amine I-3 and 4.0 ml (48 mmoles) concentrated hydrochloric acid in 500 ml methanol at 0° and under an atmosphere of oxygen was added 7.0 ml (6.1 g, 52.0 mmoles) iso-amyl nitrite. The reaction was conducted as before except only 19 hr heating at 50-55° was necessary to decompose the diazonium salt. Workup afforded 1.90 g of a red oil which was chromatographed on 100 g neutral alumina (Woelm, activity II). Elution with 2% ether in petroleum ether gave 420 mg of a colorless oil which was a 1:2 mixture of benzisothiazole II and methyl

ether I-5 as determined by vpc (oven temp 150-300° @ 30°/min; rt 1.4, 2.2 min). This oil was crystallized from n-hexane to afford 205 mg methyl ether I-5 as pale yellow crystals, mp 57-59°. Further elution with 300 ml of 5% ether in petroleum ether provided 1.02 g I-5 as a colorless oil which crystallized upon standing. It was homogeneous by vpc (oven temp 150-300° @ 30°/min, rt 2.2 min) and melted at 59-60°. The total yield of methyl ether I-5 was 1.225 g (68%).

Two recrystallizations of a portion of this material from n-hexane provided the analytical sample as pale yellow prisms, mp 60.0-60.5°. ir ($CHCl_3$) 2840 ($-OCH_3$), 1570, 1494 (aromatic), 1260, 1045 $cm^{-1}$ ($ArOCH_3$); nmr ($CDCl_3$) δ 2.68 (s, 3, C-3-$CH_3$), 3.95 (s, 3, C-7-$OCH_3$), 6.83 (d of d, 1, $J_{4,6}$ 1.8 Hz, $J_{4,5}$ 6.8 Hz, C-4-H), and 7.20-7.55 (m, 2, C-5-H and C-6-H).

Anal. Calcd for $C_9H_9NOS$: C, 60.29; H, 5.06; N, 7.82; S, 17.90. Found: C, 60.10; H, 5.08; N, 7.72; S, 17.88.

5-Methoxy-3-methyl-1,2-benzisothiazole (I-6).—To a solution of 1.68 g (10.2 mmoles) amine I-4 and 4.0 ml (48 mmoles) concentrated hydrochloric acid in 500 ml methanol at 0° and under an atmosphere of oxygen was added 7.0 ml (6.1 g, 52.0 mmoles) iso-amyl nitrite (Matheson, Coleman, and Bell,

USP grade). The mixture was stirred at -10° to +5° for 12 hr. The solution was stirred at room temperature for 25 hr and then heated at 50-55° for 70 hr. The methanol was removed at reduced pressure on a rotary evaporator and the residue partitioned between chloroform and water. The aqueous layer was made alkaline by the addition of aqueous bicarbonate. The chloroform layer was separated and the aqueous solution was extracted several times with chloroform. The combined chloroform extracts were washed with brine, dried ($Na_2SO_4$), and concentrated to afford 1.97 g red oil which was chromatographed on 100 g neutral alumina (Woelm, activity III). Elution with 300 ml petroleum ether gave 119 mg of a colorless oil which was identified by vpc (oven temp 150-300° @ 30°/min; rt 1.5, 2.2 min) as a 3:2 mixture of benzisothiazole II (arising from reduction) and the desired methyl ether I-6. Elution with 150 ml of 2% ether in petroleum ether provided 330 mg of a colorless oil which, when crystallized from n-hexane, deposited 260 mg of methyl ether I-6 as pale yellow crystals, mp 49-53°, 97% pure by vpc analysis (conditions as stated below). Continued elution with 450 ml of 2% ether in petroleum ether gave 1.31 g methyl ether I-6 as white crystals, homogeneous by vpc (oven temp 150-300° @ 30°/min, rt 2.3 min) and melting at 55-57°. The total yield of I-6 was 1.57 g (86%).

The analytical sample was crystallized from n-hexane as colorless plates, mp 57.0-57.5°. ir ($CHCl_3$) 2830 ($-OCH_3$), 1610, 1495 (aromatic), 1265, 1050 $cm^{-1}$ ($ArOCH_3$); nmr ($CDCl_3$) δ 2.63 (s, 3, C-3-$CH_3$), 3.58 (s, 3, C-5-$OCH_3$), 7.04-7.22 (m, 2, C-4-H and C-6-H), and 7.72 (d of d, 1, $J_{4,7}$ 1.2 Hz, $J_{6,7}$ 8.6 Hz, C-7-H).

Anal. Calcd for $C_9H_9NOS$: C, 60.29; H, 5.06; N, 7.82; S, 17.90. Found: C, 60.37; H, 5.07; N, 7.82; S, 17.80.

3-Bromomethyl-7-methoxy-1,2-benzisothiazole (Ib).—To a solution of 800 mg (4.47 mmoles) methyl ether I-5 in 80 ml carbon tetrachloride was added 800 mg (4.50 mmoles) N-bromosuccinimide (recrystallized from acetone-water, mp 180-182°). The resulting mixture, heated with an oil bath, was stirred at reflux in the presence of a 150 W tungsten light for 1.5 hr, at which time vpc analysis (oven temp 150-300° @ 30°/min) indicated the presence of three major components: 15% starting material (rt 3.1 min), 70% of the desired bromide Ib (rt 4.4 min), and 10% of dibromide I-7 (rt 5.2 min). The mixture was cooled and the bulk of the carbon tetrachloride was removed at reduced pressure on a rotary evaporator. The organic residue was taken up in chloroform and the chloroform solution was washed in succession with 5% aqueous sodium hydroxide (to remove succinimide), water,

and brine. Drying ($Na_2SO_4$) and concentration afforded 1.25 g yellow crystalline material, greater than 70% monobromide Ib by vpc analysis (conditions as above). This material was twice recrystallized from ether-n-hexane to give 265 mg monobromide Ib, mp 101-105°, greater than 99% pure by vpc (oven temp 150-300° @ 30°/min, rt 4.4 min). Recrystallization of a portion of this material from ether-n-hexane (1:1) provided the analytical sample as light yellow needles, mp 104.5-106.0°. ir ($CHCl_3$) 2840 ($-OCH_3$), 1570, 1490 (aromatic), 1265 (-OAr), 1040 $cm^{-1}$ ($-OCH_3$); nmr ($CDCl_3$) δ 4.00 (s, 3, C-7-$OCH_3$), 4.82 (s, 2, C-3-$CH_2Br$), 6.89 (d of d, 1, $J_{4,6}$ 1.2 Hz, $J_{5,6}$ 7.5 Hz, C-6-H), 7.39 (d of d, 1, $J_{5,6}$ 7.5 Hz, $J_{4,5}$ 8.3 Hz, C-5-H), and 7.70 (d of d, 1, $J_{4,6}$ 1.2 Hz, $J_{4,5}$ 8.3 Hz, C-4-H).

Anal. Calcd for $C_9H_8BrNOS$: C, 41.85; H, 3.13; Br, 30.97; N, 5.43; S, 12.43. Found: C, 41.97; H, 3.07; Br, 31.12; N, 5.47; S, 12.30.

The mother liquors obtained in the above crystallizations were purified by ptlc on silica gel [ether-petroleum ether (1:4)]. Isolation of the slower moving of the two bands boosted the yield of Ib to 560 mg (49%). The faster moving component, recovered in poor yield as white crystals, was identified as di-bromide I-7. Recrystallization of this material from n-hexane afforded the

analytical sample as white needles, mp 113.5-114.0°. ir ($CHCl_3$) 2840 ($-OCH_3$), 1565, 1485 (aromatic), 1265 (-OAr), 1040 $cm^{-1}$ ($-OCH_3$); nmr ($CDCl_3$) δ 4.02 (s, 3, C-7-$OCH_3$), 6.91 (d, 1, $J_{5,6}$ 7.9 Hz, C-6-H), 7.10 (s, 1, C-3-$CHBr_2$), 7.50 (d of d, 1, $J_{5,6}$ 7.9 Hz, $J_{4,5}$ 8.4 Hz, C-5-H), and 8.09 (d of d, 1, $J_{4,6}$ 1.0 Hz, $J_{4,5}$ 8.4 Hz, C-4-H).

Anal. Calcd for $C_9H_7Br_2NOS$: C, 32.05; H, 2.09; Br, 47.43; N, 4.16; S, 9.52. Found: C, 32.21; H, 2.10; Br, 47.30; N, 4.22; S, 9.61.

A study of the method herein employed to separate the components in the crude product, namely repeated crystallization, indicates that during this process considerable decomposition of mono-bromide Ib to starting material I-5 occurred. This conclusion is based on a comparison of the vpc analyses of crystalline fractions and mother liquors obtained during this process. It is likely that chromatography of the crude product on silica gel would be the preferred method of purification, as was the case in the isolation of the related bromides Ia and Ic.

3-Bromomethyl-5-methoxy-1,2-benzisothiazole (Ic).—To a solution of 1.30 g (7.27 mmoles) methyl ether I-6 in 120 ml carbon tetrachloride was added 1.30 g (7.30 mmoles) N-bromosuccinimide (NBS) (recrystallized from acetone-

water, mp 180-182°). The heterogeneous mixture, heated with an oil bath, was stirred at reflux in the presence of a 150 W tungsten light. After 1.5 hr, visual inspection indicated that no NBS remained and vpc analysis (oven temp 170°; rt 0.7, 1.8 min) of a portion of the reaction mixture showed a 1:3 mixture of starting material I-6 to bromide Ic. An additional 130 mg (0.73 mmoles) NBS was added and the reaction was allowed to continue for 0.5 hr, at which time analysis by vpc showed only a trace of I-6 remaining. The mixture was cooled, the bulk of the carbon tetrachloride was removed on a rotary evaporator at reduced pressure, and the organic residue was taken up in chloroform. The chloroform solution was washed in succession with 5% aqueous potassium hydroxide (to remove succinimide), water, and brine. Drying ($Na_2SO_4$) and concentration gave 2.02 g of a yellow oil that provided an irreproducible record when analyzed by vpc. However, the nmr of this crude product indicated the presence of monobromide Ic, dibromide I-8, and starting material I-6 in the ratio of 72:16:10 as determined by integration of the C-3-methylene, -methine, and -methyl hydrogens, respectively.

This crude oil was chromatographed on 120 g silica gel (Grace, 100-200 mesh). Elution with 900 ml petroleum ether-benzene (1:4) afforded 300 mg (12%) dibromide I-8 as pale

yellow crystals, homogeneous by vpc (oven temp 170°, rt 3.1 min). Further purification of a portion of this material by ptlc on silica gel [ether-petroleum ether (1:1)] followed by crystallization from ether-n-hexane provided the analytical sample as white prisms, mp 109-112°. ir ($CHCl_3$) 1610, 1480 (aromatic), 1270 (-OAr), 1040 $cm^{-1}$ ($-OCH_3$); nmr ($CDCl_3$) δ 3.96 (s, 3, C-5-$OCH_3$), 7.02 (s, 1, C-3-$CHBr_2$), 7.22 (d of d, 1, $J_{4,6}$ 2.8 Hz, $J_{6,7}$ 9.2 Hz, C-6-H), and 7.72, 7.87 (m, 2, C-4-H and C-7-H).

Anal. Calcd for $C_9H_7Br_2NOS$: C, 32.05; H, 2.09; Br, 47.43; N, 4.16; S, 9.52. Found: C, 32.20; H, 2.16; Br, 47.50; N, 4.12; S, 9.50.

Continued elution of the silica gel column with 450 ml benzene-ether (5:1) yielded 1.28 g (68%) monobromide Ic as white needles, homogeneous by vpc (oven temp 170°, rt 1.8 min). Further purification of a portion of this material by ptlc on silica gel [ether-petroleum ether (1:1)] provided white crystals which were recrystallized from ether-n-hexane to give the analytical sample as long white needles, mp 84-86.5°. ir ($CHCl_3$) 2830 ($-OCH_3$), 1610, 1485 (aromatic), 1265 (-OAr), 1040 $cm^{-1}$ ($-OCH_3$); nmr ($CDCl_3$) δ 3.93 (s, 3, C-5-$OCH_3$), 4.83 (s, 2, C-3-$CH_2Br$), 7.21 (d of d, 1, $J_{4,6}$ 1.2 Hz, $J_{6,7}$ 8.8 Hz, C-6-H), 7.45 (d, 1, $J_{4,6}$ 1.2 Hz, C-4-H), and 7.80 (d of d, 1, $J_{4,7}$ 0.8 Hz, $J_{6,7}$ 8.8 Hz,

C-7-H).

Anal. Calcd for $C_9H_8BrNOS$: C, 41.85; H, 3.13; Br, 30.97; N, 5.43; S, 12.43. Found: C, 42.05; H, 3.16; Br, 31.00; N, 5.39; S, 12.50.

Continued elution with benzene-ether (1:1) afforded only trace amounts of unreacted starting material I-6.

Treatment of I-6 with Raney nickel in ethanol.—To a flask equipped with a magnetic spinbar was transferred 1.5 g (2.5 ml catalyst sludge) of W-2 Raney nickel as a slurry in absolute ethanol. The catalyst was allowed to settle and the supernatant ethanol, drawn off with a pipette, was replaced by a solution of 300 mg (1.68 mmoles) methoxy benzisothiazole I-6 in 5 ml absolute ethanol. The mixture was stirred vigorously at room temperature for 12 hr. After filtration through Celite to remove the catalyst, the filtercake was thoroughly washed with 75 ml absolute ethanol. The alcoholic solution was concentrated at reduced pressure on a rotary evaporator at 20-25°, and the residue was diluted with 60 ml water that had been acidified with 1 ml of concentrated hydrochloric acid. The aqueous acid solution was extracted with two 30 ml portions of chloroform. The combined extracts were washed with brine, dried ($Na_2SO_4$) and concentrated to afford 86 mg yellow oil homogeneous by

vpc (oven temp 125°, rt 1.0 min; oven temp 100°, rt 2.2 min). ir ($CHCl_3$) 1680 (benzylic C=O), 1595, 1585, 1485 (aromatic), 1270, 1035 $cm^{-1}$ ($ArOCH_3$). This oil was identified as m-methoxyacetophenone (XVI) by a comparison of its ir spectrum with that of authentic material (59). Further, a portion of the product enriched with authentic material exhibited a single peak in the vpc (conditions as above).

The aqueous acid solution from above was basified with 10% aqueous sodium hydroxide and extracted with chloroform. Workup, conducted as before, yielded 118 mg yellow oil whose ir spectrum possessed a band of medium intensity at 1680 $cm^{-1}$ and a weaker band at 1630-1635 $cm^{-1}$. The vpc of this oil indicated the presence of considerable m-methoxyacetophenone as well as several products with much longer retention times. This oil was taken up in 20 ml of 95% ethanol; and after the addition of 5 ml of 10% aqueous hydrochloric acid, the mixture was stirred at room temperature for 5 hr. After removal of the alcohol on a rotary evaporator, the residue was diluted with water and basified with 7 ml of 10% aqueous sodium hydroxide. The usual chloroform workup provided a yellow oil exhibiting a single peak in the vpc (oven temp 100°, rt 2.4 min) and possessing an ir spectrum identical with that of authentic m-methoxyacetophenone.

The total yield of m-methoxyacetophenone was 131 mg (52%).

2-[3'-(7-Methoxy-1,2-benzisothiazoyl)]methylcyclohexanone (J-2).—This compound was prepared by the general alkylation procedure of Stork and Hudrlik (60). To a solution of 204 mg (1.20 mmoles) trimethylsilyl enol ether J-1 (58), bp 71-72° (18 mm), in 2 ml of dry 1,2-dimethoxyethane was added 0.58 ml of a solution of methyl lithium in ether (2.05 M, 1.19 mmoles). The solution was stirred at room temperature under an atmosphere of nitrogen for 15 min, and then a solution of 339 mg (1.31 mmoles) bromide Ic in 2.5 ml of dry 1,2-dimethoxyethane was added radidly in one lot to the vigorously stirred mixture. Stirring was continued for 12 hr, after which time the reaction mixture was diluted with 50 ml of ether-benzene (1:1). The organic solution was washed with three 10 ml portions of water and the combined aqueous solutions were back extracted with 10 ml of ether. The combined ethereal solutions were washed with brine, dried ($Na_2SO_4$), and concentrated to afford 362 mg of semi-crystalline material. An attempt to dissolve this crude product in ether resulted in the precipitation of a white solid which was collected by filtration, washed with ether, and air dried to provide 51 mg (19%) of bis-alkylated ketone J-3, mp 179-183°. Recrystallization of a portion of this material from acetone gave the analytical sample as white prisms, mp 184-186°.

ir ($CHCl_3$) 1705 (C=O), 1605, 1480 (aromatic), 1035, 1015, $cm^{-1}$ ($ArOCH_3$); nmr ($CDCl_3$) δ 2.75 (m, 2, C-6-methylene hydrogens), 3.49 (s, 4, C-2-α-$CH_2$- and β-$CH_2$-), 3.65 (s, 6, C-5'-$OCH_3$ of α and β side chains), 7.03 (m, 4, C-4'-H and C-6'-H of α and β side chains), and 7.55 (m, 2, C-7'-H of α and β side chains).

Anal. Calcd for $C_{24}H_{24}N_2O_3S_2$: C, 63.72; H, 5.31. Found: C, 63.72; H, 5.31.

Concentration of the filtrate from above returned 300 mg yellow oil which was purified by ptlc [ether-petroleum ether (2:3), double development] to give three bands with $R_f$ 0.11, 0.21, and 0.42. The band of $R_f$ 0.11 provided 88 mg of yellow oil which contained no less than four components by vpc (oven temp 130-300° @ 40°/min, then isothermal at 300°; rt 4.1, 5.6, 8.1, 9.5 min). The peak with rt 4.1 min corresponds to ketone J-2 and that at rt 8.1 min to ketone J-3. The band with $R_f$ 0.21 returned 124 mg (38%) ketone J-2 as a colorless oil, homogeneous by vpc (oven temp 130-300° @ 40°/min, rt 4.1 min). ir ($CHCl_3$) 1710 (C=O), 1605, 1485 (aromatic), 1270, 1035 $cm^{-1}$ ($ArOCH_3$); nmr ($CDCl_3$) δ 3.82 (s, 3, C-5'-$OCH_3$), 7.02 (d of d, 1, $J_{4,6}$ 2.4 Hz, $J_{6,7}$ 8.8 Hz, C-6'-H), 7.23 (d, 1, $J_{4,6}$ 2.4 Hz, C-4'-H), and 7.63 (d of d, 1, $J_{4,7}$ 0.7 Hz, $J_{6,7}$ 8.8 Hz, C-7'-H).

The semicarbazone prepared from a portion of this oil and recrystallized from ethanol-water (2:1) existed as fine white needles, mp 173-175.5°. ir ($CHCl_3$) 3520, 3390 (NH), 1685 (C=O), 1565 (amide type II band), 1605, 1485 $cm^{-1}$ (aromatic).

Anal. Calcd for $C_{16}H_{20}N_4O_2S$: C, 57.81; H, 6.06. Found: C, 57.75; H, 6.00.

The band with $R_f$ 0.42 returned 19 mg bromide Ic.

1,1-Ethylenedioxy-2-[3'-(7-methoxy-1,2-benzisothiazoyl)] methyl-cyclohexane (J-4).—A mixture of 153 mg (0.557 mmole) ketone J-2, 1 ml ethylene glycol, 16 mg p-toluene-sulfonic acid monohydrate, and 15 ml benzene was stirred at reflux for 2 hr. Water formed during this time was removed by a Dean-Stark water trap. The reaction mixture was cooled, diluted with ether, and washed with saturated aqueous bicarbonate. The aqueous bicarbonate solution was back-extracted with ether and the combined ethereal solutions were washed successively with water and brine. After drying ($Na_2SO_4$) and concentration there remained 195 mg color-less oil. This oil was purified by ptlc [ether-petroleum ether (3:2)] to give a single band with $R_f$ 0.38-0.56 which returned 171 mg (97%) ketal J-4 as a colorless oil which slowly crystallized to a white solid, mp 97-100°. The analytical sample was obtained by recrystallization of a

portion of this material from n-hexane. The large white prisms had mp 100-101.5°. ir ($CHCl_3$) 1605, 1485 (aromatic), 1270, 1040 ($ArOCH_3$), 1150, 1085, 1020, 940, 920 $cm^{-1}$ (ketal); nmr ($CDCl_3$) δ 2.78 [m, 1, C-2-C<u>H</u>(H)-], 3.33 [m, 1, C-2-CH(<u>H</u>)-], 3.83 (s, 3, C-5'-$OCH_3$), 3.97 (s, 4, $-OCH_2CH_2O-$), 7.04 (d of d, 1, C-6'-H), 7.32 (d, 1, C-4'-H), and 7.65 (d, 1, C-7'-H).

<u>Anal.</u> Calcd for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63. Found: C, 64.04; H, 6.66.

<u>Degradation of J-4.</u>—To a flask equipped with a magnetic spinbar and containing 0.5 g (0.8 ml catalyst sludge) W-2 Raney nickel was added 98 mg (0.307 mmoles) ketal methoxybenzisothiazole <u>J-4</u>, mp 98-101°, as a solution in 3 ml absolute ethanol. The heterogeneous mixture was stirred vigorously at room temperature for 12 hr; the catalyst was removed by filtration through Celite and washed thoroughly with 40 ml absolute ethanol. After 10 ml of 10% aqueous hydrochloric acid had been added to the alcoholic solution, it was stirred at room temperature for 10 hr. The bulk of the ethanol was removed at reduced pressure on a rotary evaporator at room temperature. The acidic residue, after a standard ether workup, provided 78 mg yellow oil. This oil was purified by ptlc [ether-petroleum ether (1:1)].

The major band, $R_f$ 0.32 - 0.43, returned 25 mg (33%) diketone J-5 as a colorless oil homogeneous by vpc (oven temp 180°, rt 3.8 min). ir ($CHCl_3$) 2860 ($OCH_3$), 1710 (saturated C=O), 1680 (benzylic C=O), 1600, 1585 (aromatic), 1255 $cm^{-1}$ (-OAr); nmr ($CDCl_3$) δ 3.63 (s, 3, $-OCH_3$).

The aqueous acid solution from above was basified with saturated aqueous sodium bicarbonate and worked up as usual with ether to afford 40 mg yellow oil greater than 90% one component by vpc (oven temp 200°, rt 1.3 min). The ir spectrum of this oil lacked absorption in the carbonyl region. It exhibited a strong band at 1650 $cm^{-1}$ as well as aromatic-type bands at 1615, 1600, and 1585 $cm^{-1}$. The nmr spectrum of this material was inconclusive and an attempt to purify it further by ptlc resulted in the appearance of no less than four significant bands.

1β-Hydroxy-4-[3'-(7-methoxy-1,2-benzisothiazoyl)]methyl-7aβ-methyl-2,3,7,7a-tetrahydro-5(6H)-indenone (K-3).—To a flask that had been flushed with nitrogen was added 27 mg (1.12 mmoles) sodium hydride (46 mg of a 58.6% dispersion in mineral oil) and a solution of 256 mg (1.02 mmoles) tetrahydropyranyl ether enone vii (61) in 15 ml of dry 1,2-dimethoxyethane. The mixture was heated at reflux under a nitrogen atmosphere for 4.5 hr and then cooled to

room temperature, at which time a solution of 200 mg (0.775 mmole) methoxy bromide Ib in 15 ml dry 1,2-dimethoxyethane was added dropwise over 0.5 hr. The resulting mixture was stirred for 17 hr and then diluted with 75 ml of saturated aqueous sodium chloride. The mixture was extracted with three 30 ml portions of benzene. The combined extracts were washed with brine, dried ($Na_2SO_4$), and concentrated to afford 425 mg of an orange oil which was chromatographed on 50 g of neutral alumina (Woelm, activity III). Elution with 150 ml ether-petroleum ether (2:3) returned 204 mg colorless oil, tentatively identified as acetal enone K-1 by virtue of its ir spectrum in chloroform: 1655 (unsaturated C=O), 1570, 1490 (aromatic), 1265 (Ar-$OCH_3$), 1130, 1120, 1075, 1030, 1015, 975 $cm^{-1}$ (acetal). Continued elution with 75 ml ether-petroleum ether (2:3) gave 74 mg oil whose ir spectrum possessed absorptions at 1700 (saturated C=O) and 1655 $cm^{-1}$ (unsaturated C=O) in the ratio of 1:3, respectively. Further elution with 75 ml of the same solvent system afforded 52 mg white gum, ir ($CHCl_3$) 1700 (saturated C=O), 1565, 1485 (aromatic), 1265 (Ar-$OCH_3$), 6 bands from 1130-975 $cm^{-1}$ (acetal). This gum was tentatively identified as the dibenzisothiazoyl indenone K-2a.

The 204 mg (0.477 mmole) K-1 isolated by the chromatography was dissolved in 40 ml methanol. After 4.5 ml of

10% aqueous hydrochloric acid had been added to this solution, it was heated at reflux for 2 hr. The workup procedure was the same as that described for the isolation of the hydroxy indenone F-3 and afforded 141 mg pale yellow oil which crystallized when triturated with ether. Recrystallization of this solid from ether-n-hexane gave 105 mg K-3 as white plates, mp 150-152°. This quantity represents a 40% yield for the two-reaction sequence. The analytical sample was obtained by recrystallization of a portion of this material from ether-n-hexane (2:1). It existed as white needles, mp 151.5-153.5°. ir ($CHCl_3$) 3600, 3400 (-OH), 1570, 1490 (aromatic), 1265, 1035 $cm^{-1}$ ($ArOCH_3$); nmr ($CDCl_3$) δ 1.10 (s, 3, C-7aβ-$CH_3$), 3.98 (s, 3, C-7'-$OCH_3$), 6.87 (m, 1, C-6'-H), 7.38 (m, 1, C-5'-H), and 7.70 (m, 1, C-4'-H).

Anal. Calcd for $C_{19}H_{21}NO_3S$: C, 66.43; H, 6.17; N, 4.08; S, 9.34. Found: C, 66.43; H, 6.06; N, 4.05; S, 9.26.

The 52 mg (0.087 mmole) K-2a obtained from the chromatography was likewise hydrolyzed with hydrochloric acid in methanol. After a similar workup, 27 mg of semi-crystalline solid was obtained. This material was crystallized from ether-n-hexane to afford 23 mg of dibenzisothiazoyl hydroxy indenone K-2b as white amorphous crystals, mp 195-199°. The

analytical sample was obtained from acetone-n-hexane as white plates, mp 196-199°. ir ($CHCl_3$) 3400 (w) (-OH), 2840 ($-OCH_3$), 1700 (C=O), 1565, 1485 (aromatic), 1265, 1035 $cm^{-1}$ ($ArOCH_3$); nmr ($CDCl_3$) δ 0.80 (s, 3, C-7aβ-$CH_3$), 2.67 (m, 2, C-6-methylene hydrogens), 3.60, 3.84 (two doublets, 4, C-4α-$CH_2$- and C-4β-$CH_2$-), 3.96, 4.00 (two singlets, 6, C-7'-$OCH_3$ in α and β side chains), and 4.95 (m, 1, C-3-vinyl H).

Anal. Calcd for $C_{28}H_{28}N_2O_4S_2$: C, 64.57; H, 5.42; N, 5.38; S, 12.32. Found: C, 64.53; H, 5.45; N, 5.33; S, 12.38.

4-[3'-(7-Methoxy-1,2-benzisothiazoyl)]methyl-7aβ-methyl-1-oxo-2,3,7,7a-tetrahydro-5(6H)-indenone (K-4).—This compound was prepared using the dipyridine—chromium(VI) oxide complex described by Collins (44). To a solution of 92 mg (0.268 mmole) hydroxy enone K-3, mp 150-152°, in 12 ml dichloromethane was added 550 mg (2.25 mmoles) Collins' reagent in one lot. The heterogeneous reaction mixture was stirred at room temperature for 15 min protected from moisture by a calcium chloride drying tube. The mixture was filtered through 10 g of alumina (Merck, acid washed) and the dione was eluted with 160 ml of dichloromethane. The oil thus obtained was crystallized from ether-n-hexane to

afford 72 mg (78%) dione K-4 as white plates, mp 163-165.5°. ir ($CHCl_3$) 1745 (five-membered ring C=O), 1660 (unsaturated C=O), 1570, 1485 (aromatic), 1265, 1040 $cm^{-1}$ ($ArOCH_3$); nmr ($CDCl_3$) δ 1.28 (s, 3, C-7aβ-$CH_3$), 3.98 (s, 3, C-7'-$OCH_3$), 4.12 (s, 2, C-4-$CH_2$-), 6.86 (m, 1, C-6'-H), 7.38 (m, 1, C-5'-H), and 7.72 (m, 1, C-4'-H).

Anal. Calcd for $C_{19}H_{19}NO_3S$: C, 66.82; H, 5.61; N, 4.10; S, 9.40. Found: C, 66.72; H, 5.57; N, 4.08; S, 9.49.

Attempted cyclization of K-4 with polyphosphoric acid.—Into a test tube reaction flask equipped with a nitrogen inlet and a screw-type mechanical stirrer was placed 30 mg (0.088 mmole) ene dione K-4, mp 163-165.5°. The flask was flushed with nitrogen and then 10 ml of polyphosphoric acid prepared from a solution of 18.8 g phosphorus pentoxide in 16.5 ml of 85% phosphoric acid was added. The thick solution was stirred vigorously at 120-125° for 30 min, poured onto 50 ml crushed ice and extracted several times with ether. The combined extracts were washed successively with saturated aqueous sodium bicarbonate, water, and brine. Drying ($Na_2SO_4$) and concentration afforded 30 mg of an orange gum identified as a 2:1 mixture of starting material and a single product by vpc (oven temp 270°;

rt 1.6 min for starting material, 2.2 min for product). This gum was purified by ptlc [ether-petroleum ether (4:1)]. Two bands were observed after double development. The major band with $R_f$ 0.3 afforded 6 mg of a pale yellow solid with the following spectral characteristics: ir ($CHCl_3$) 1700 (C=O), 1600, 1585, 1575, 1475 (aromatic), 1265, 1065 $cm^{-1}$ ($ArOCH_3$); nmr ($CDCl_3$) (62) $\delta$ 1.25 (s, 3), 3.80 (s, 1), 3.91 (s, 3), 6.03 (m, 1), 6.60 (s, 1), 6.71 (m, 1), and 7.65 (m, 1).

When the cyclodehydration of ketone K-4 was conducted in polyphosphoric acid at 120° for 75 min, starting material was totally consumed and two products resulted. While the major product was that mentioned above, an attempt to separate the two products by ptlc afforded a single broad band containing both components.

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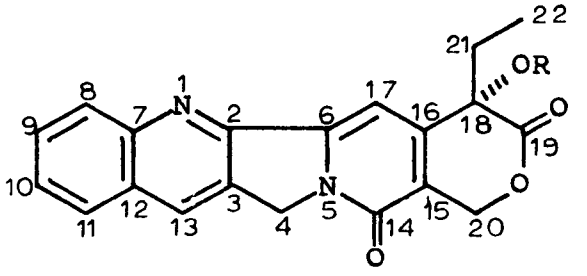
## Proposition 1

**PROPOSED:** A biosynthetic scheme and partial degradation for camptothecin (I), a recently discovered alkaloid with a novel ring system.

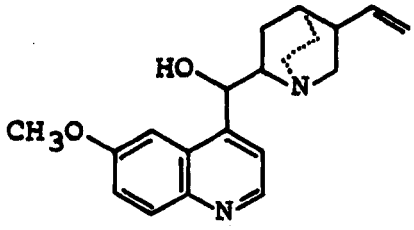
Camptothecin (I), an alkaloid having potent anti-leukemic and antitumor activities in animals, was isolated from the tree Camptotheca acuminata, Nyssaceae by Wall and co-workers (1). This same group determined the structure of this new alkaloid by x-ray crystallographic analysis of its iodoacetate II.




I: R=H

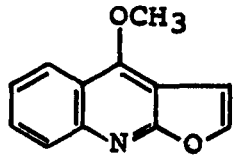
II: R=-$COCH_2I$

Although camptothecin possess a unique ring system, the fact that it does contain a quinoline system justifies including it in the quinoline family of alkaloids, representative members of which are shown on the next page:



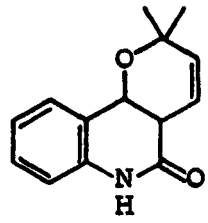

quinine

III




dictamine

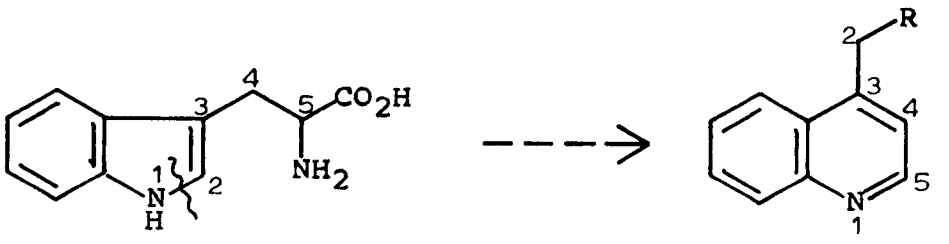
IV




flindersine

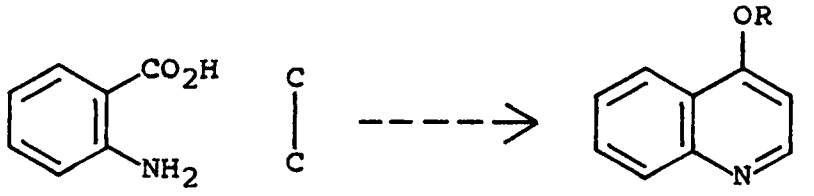
V

When considering the quinoline alkaloids, it is common practice to divide them into two groups: the Cinchona alkaloids and the non-Cinchona alkaloids. While members of each group do contain a basic quinoline ring system, much evidence is presently available which indicates that the two groups derive the quinoline portion of their skeleton from different biosynthetic precursors. Tracer studies with the Cinchona alkaloids, such a quinine (III), show that their quinoline moiety is derived from tryptophane (VI) in the manner illustrated in Figure 1a (2). Other quinoline alkaloids, such as dictamine (IV), incorporate anthranilic acid (VIII) and acetate to synthesize their quinoline portion, as depicted in Figure 1b (3).




VI VII

(a)




VIII IX

(b)

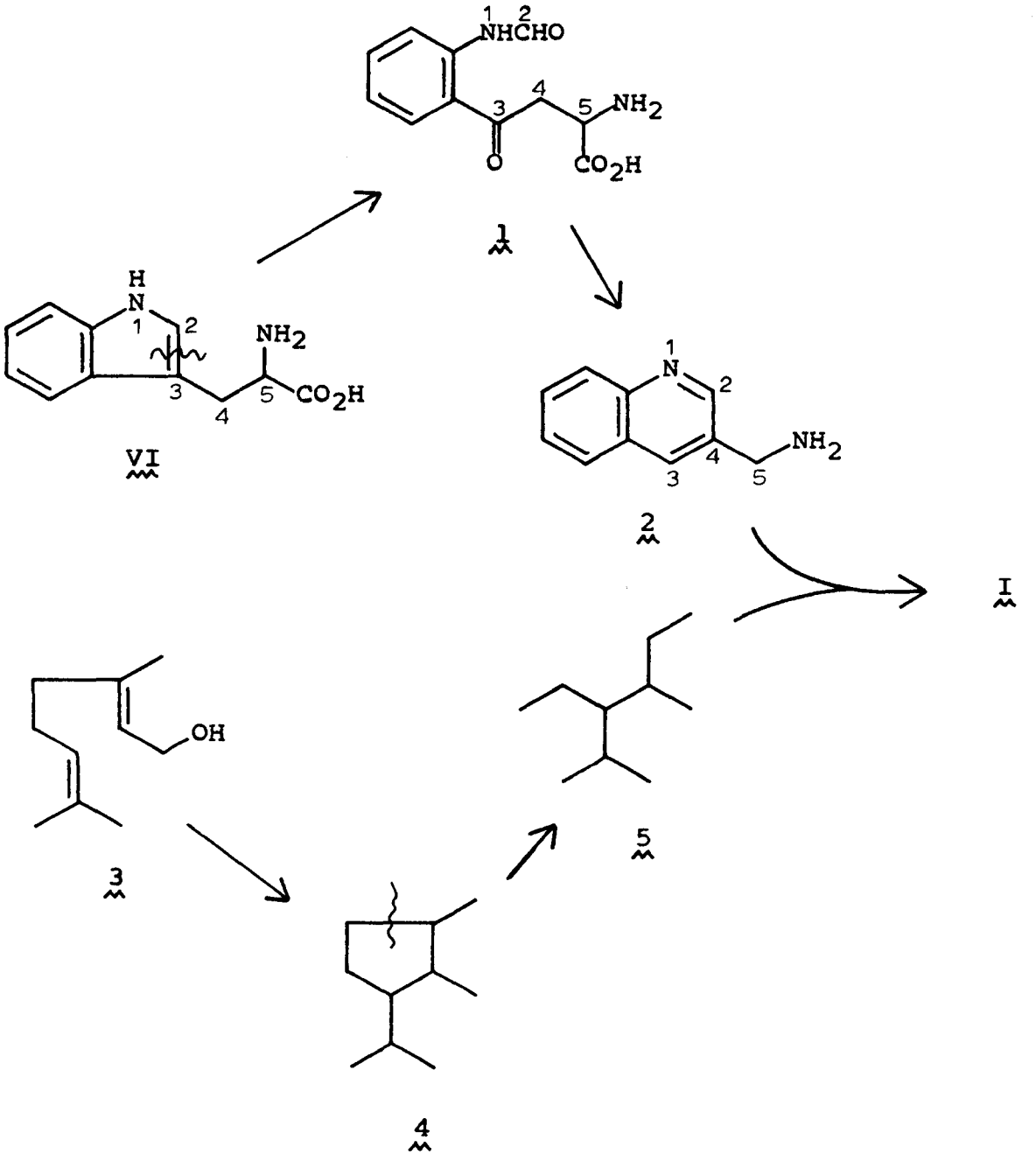
Figure 1

It is proposed that camptothecin (I) is formed by an unspecified condensation of two biosynthetic intermediates, a quinoline moiety A-2 derived from tryptophane (VI) and a monoterpenoid fragment A-5 derived from geraniol (A-3). The basic pattern of bond cleavage and bond formation necessary to arrive at the appropriate

intermediate is illustrated in Chart A. In following common practice for the presentation of an elementary biosynthetic scheme, the sequence in which transformations are listed is not meant to imply that such transformations necessarily occur in that order. Also, oxidation states of the various carbon atoms are usually not indicated.

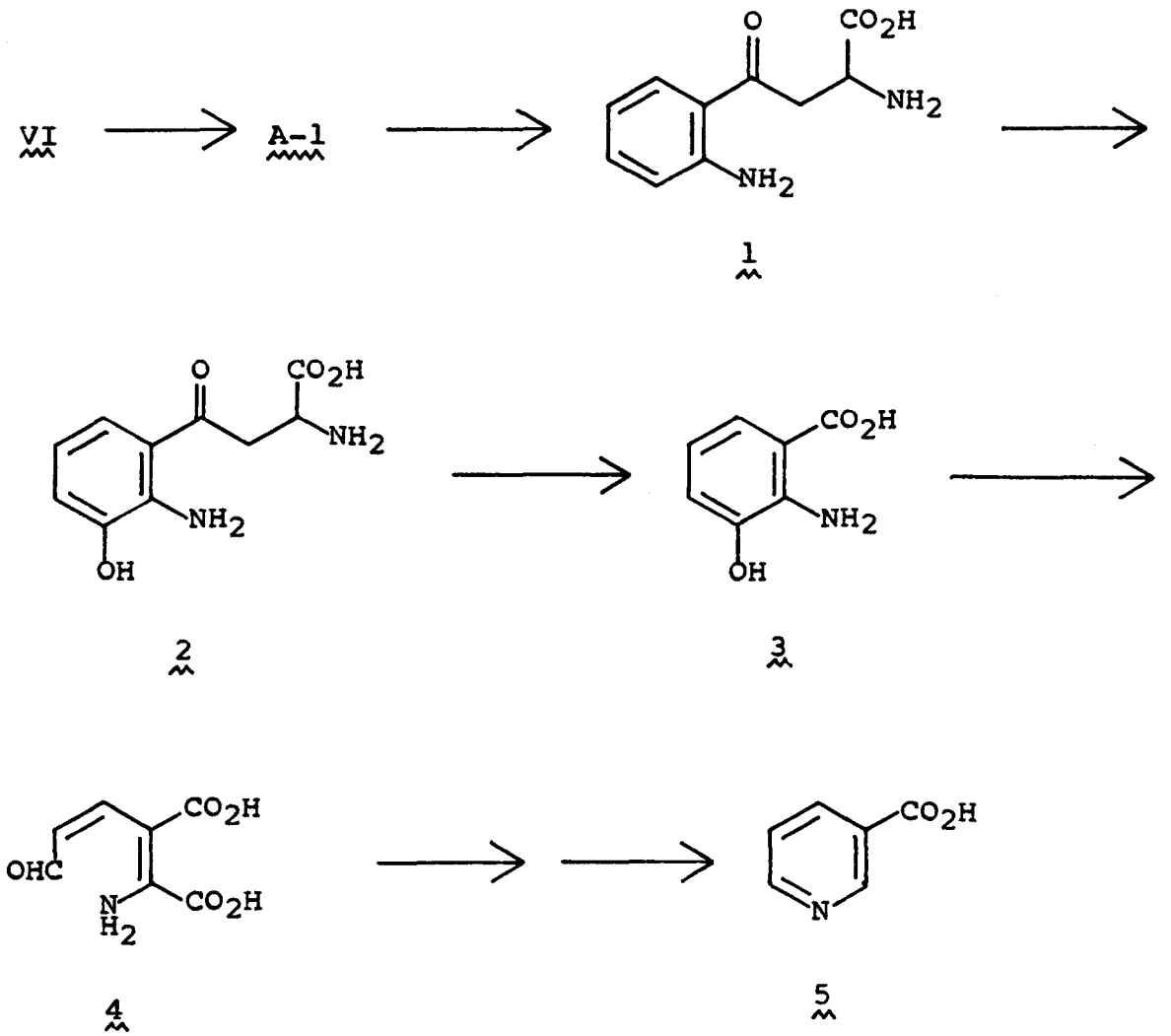
That an alkaloid containing a quinoline system could derive that moiety from tryptophane (VI) is not a new idea, as it has already been shown that the major Cinchona alkaloids do indeed incorporate tryptophane (VI) (2). However, a comparison of Figure 1a and Chart A discloses that the incorporation of tryptophane (VI) into a Cinchona alkaloid differs from its proposed incorporation into camptothecin (I). Using quinine (III) as an example of a Cinchona alkaloid (Figure 1a), it can be seen that both the carboxylate carbon and the amine nitrogen have been lost from the original tryptophane molecule. Furthermore, rearrangement of the indole system to the quinoline system involves cleavage of the $N_1$-$C_2$ bond with subsequent formation of a new bond between $N_1$ and $C_5$. However, in the case of camptothecin (I) (Chart A), the proposed intermediate A-2 is derived from tryptophane (VI) by a quite different route involving the following transformations: oxidative cleavage of the $C_2$-$C_3$ bond of the indole system, decarboxylation, and formation of a new carbon-carbon bond between $C_2$ and $C_4$.

CHART A

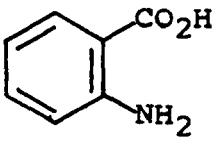

1 2
NHCHO
3
4
5
NH2
O
CO2H
1
H
N
1
2
NH2
3
5
CO2H
4
VI
1
N
2
NH2
4
3
5
2
I
OH
3
5
4

There is indirect evidence which indicates that the proposed $C_2$-$C_3$ bond cleavage of tryptophane (VI) or tryptamine is within the capability of higher plants. Such an oxidative cleavage leading to N-formylkynurenine (A-1) is known to occur in animals and fungi in the metabolic conversion of tryptophane (VI) to nicotinic acid (B-5) (4) as summarized in Chart B. Although it is generally accepted

CHART B



that tryptophane (VI) is not the precursor of nicotinic acid (B-5) in plants, Teas and Anderson (5) found a maise mutant which can convert tryptophane (VI) to anthranilic acid (X). Thus it would appear that this plant can convert



X

tryptophane (VI) to kynurenine (B-1) via N-formylkyrurenine (A-1); but that, being unable to hydroxylate kynurenine (B-1), the metabolic process produces anthranilic acid (X) rather than nicotinic acid (B-5) (6).

There seems to be no precedent for forming a quinoline system from N-formylkynurenine (A-1), but then that is much the same as saying that no previously known alkaloid has a structure like that of camptothecin (I). Indeed, camptothecin (I) is the first alkaloid with a structure that suggests that its quinoline moiety could be derived from tryptophane (VI) by way of N-formylkynurenine (A-1).

That geraniol (A-3) is the precursor of the monoterpenoid portion of camptothecin (I) seems quite reasonable

in view of much recent tracer work with the terpenoid moieties of the indole alkaloids (7). For example, it has been found that ajmalicine, catharanthine, and vindoline incorporate labeled geraniol pyrophosphate (7a). In each case, the existence of the cyclopentanoid intermediate A-4 has been substantiated by extensive labeling experiments. Specific bond cleavages and rearrangements of A-4 then lead to the different terpenoid units of each alkaloid. Quinine has also been shown to incorporate geraniol (7a). The proposed fragmentation of A-4 to give the monoterpenoid unit A-5 for incorporation into camptothecin (I) is the same as that shown to apply to ajmalicine (7a). As shown in Chart A, coupling fragment A-5 with the quinoline moiety A-2 accounts for the complete skeleton of camptothecin (I).

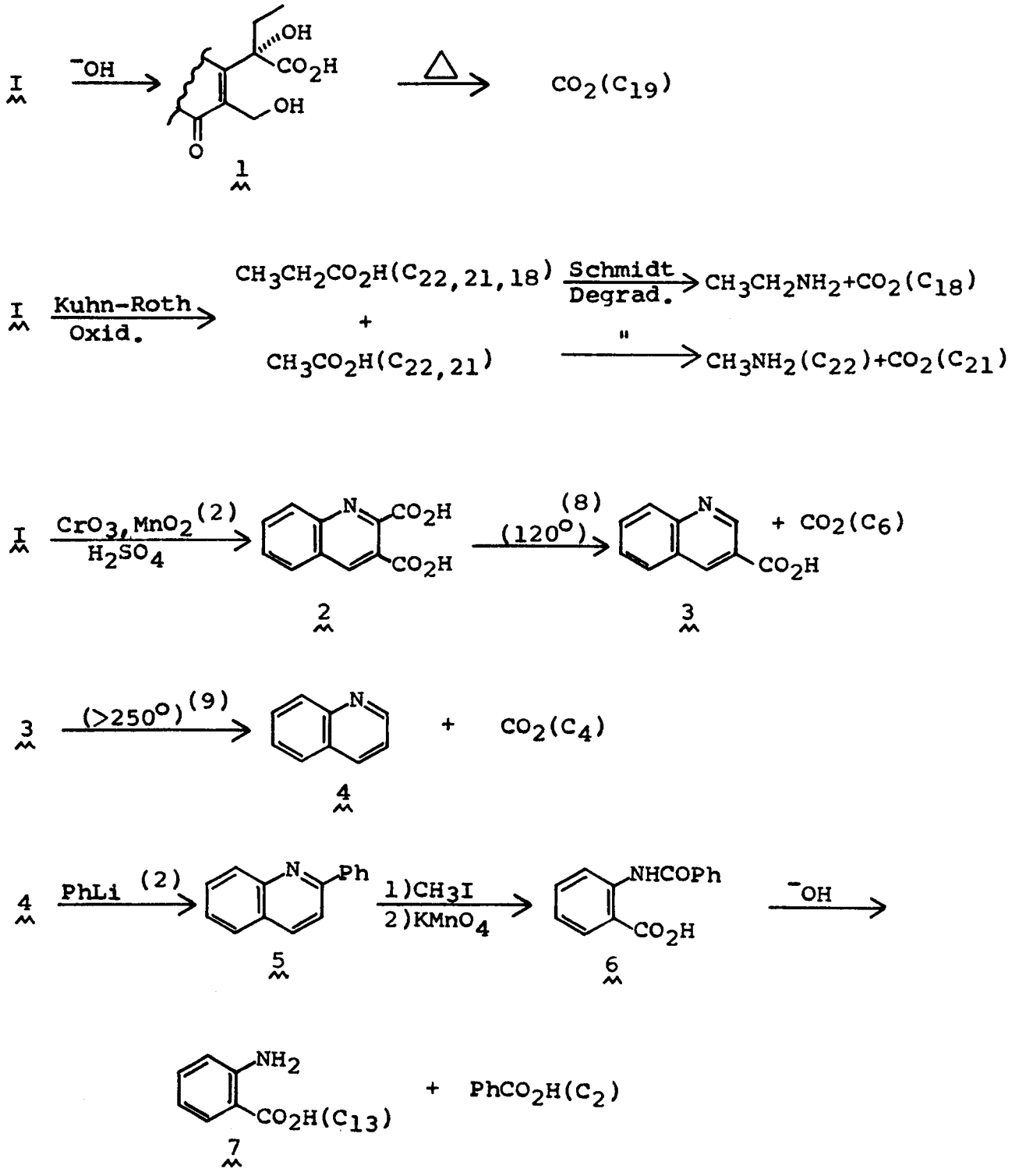
Since the structure of camptothecin (I) was determined solely by x-ray techniques, a partial degradative scheme is herewith presented which would allow one to substantiate the incorporation of both tryptophane (VI) and geraniol (A-3) into this alkaloid. The degradative steps presented in Chart C illustrate how one may selectively isolate $C_6$, $C_{18}$, $C_{19}$, $C_{21}$, and $C_{22}$ which, according to the hypothesis, are derived from geraniol. It also includes methods for isolating $C_2$, $C_4$, and $C_{13}$ which

are believed to originate in tryptophane. Table I lists the theoretical incorporation expected at each of these carbons by use of appropriately labeled tryptophane, geraniol, or mevalonic acid. Tryptophane and geraniol tracer studies predict 100% incorporation at the carbons of interest, while mevalonic acid tracer studies predict 50% incorporation at the carbons of interest.

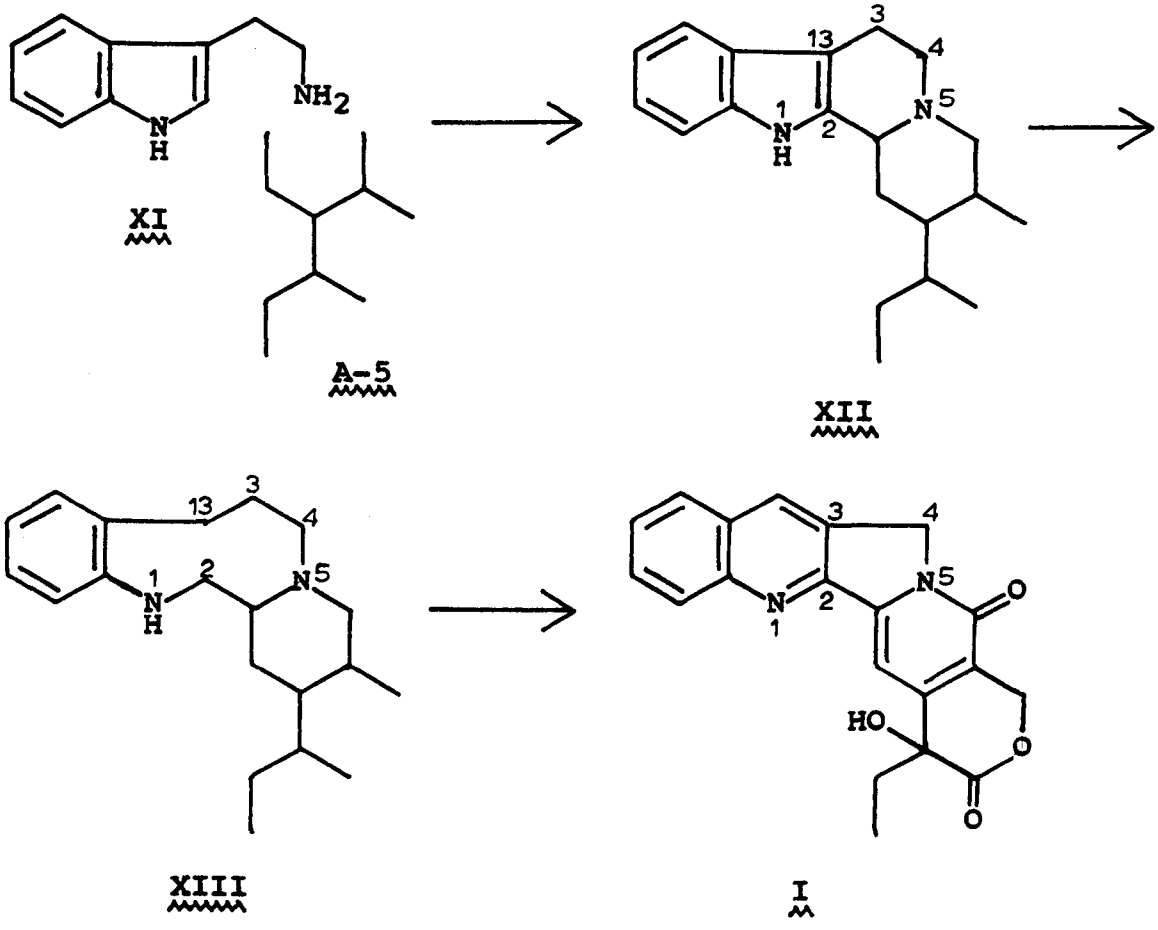
Table I: Camptothecin Tracer Studies.

| Position of Carbon in Camptothecin | Position of $^{14}C$ label in Tryptophane | Position of $^{14}C$ label in geraniol | Position of $^{14}C$ label in mevalonate |
|---|---|---|---|
| 2 | 2 | - | - |
| 4 | 5 | - | - |
| 6 | - | 4 | 2 |
| 13 | 3 | - | - |
| 18 | - | 2 | 4 |
| 19 | - | 1 | 5 |
| 21 | - | 3 | 3 |
| 22 | - | 10 | 6 |

CHART C


I
⁻OH
OH
CO2H
OH
O
1
CO2(C19)
I
Kuhn-Roth Oxid.
CH3CH2CO2H(C22,21,18)
+
CH3CO2H(C22,21)
Schmidt Degrad.
CH3CH2NH2+CO2(C18)
"
CH3NH2(C22)+CO2(C21)
I
CrO3,MnO2 H2SO4 (2)
CO2H
CO2H
2
(120°) (8)
+ CO2(C6)
CO2H
3
3
(>250°) (9)
+ CO2(C4)
4
4
PhLi (2)
Ph
5
1)CH3I
2)KMnO4
NHCOPh
CO2H
6
⁻OH
NH2
CO2H(C13)
7
+ PhCO2H(C2)

A more plausible biosynthetic route utilizing tryptophane (VI) or tryptamine (XI) with the geraniol derivative A-5 is outlined below. This scheme involves cleavage of the $C_2$-$C_{13}$ bond in intermediate XII followed by internal cyclization of XIII to give the desired skeleton of camptothecin (I).



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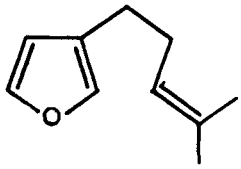
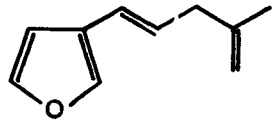
## Proposition 2

PROPOSED: A general synthesis of 3-alkylfurans.

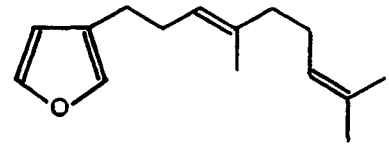
There are a variety of compounds of plant origin that contain a 3-monosubstituted furan nucleus (1), and more recently this structural unit has been found in dendrolasin, an odorous substance isolated from ants (2). However, while nature has supplied ample proof of her ability to



Perillene



Clausenane



Dendrolasin

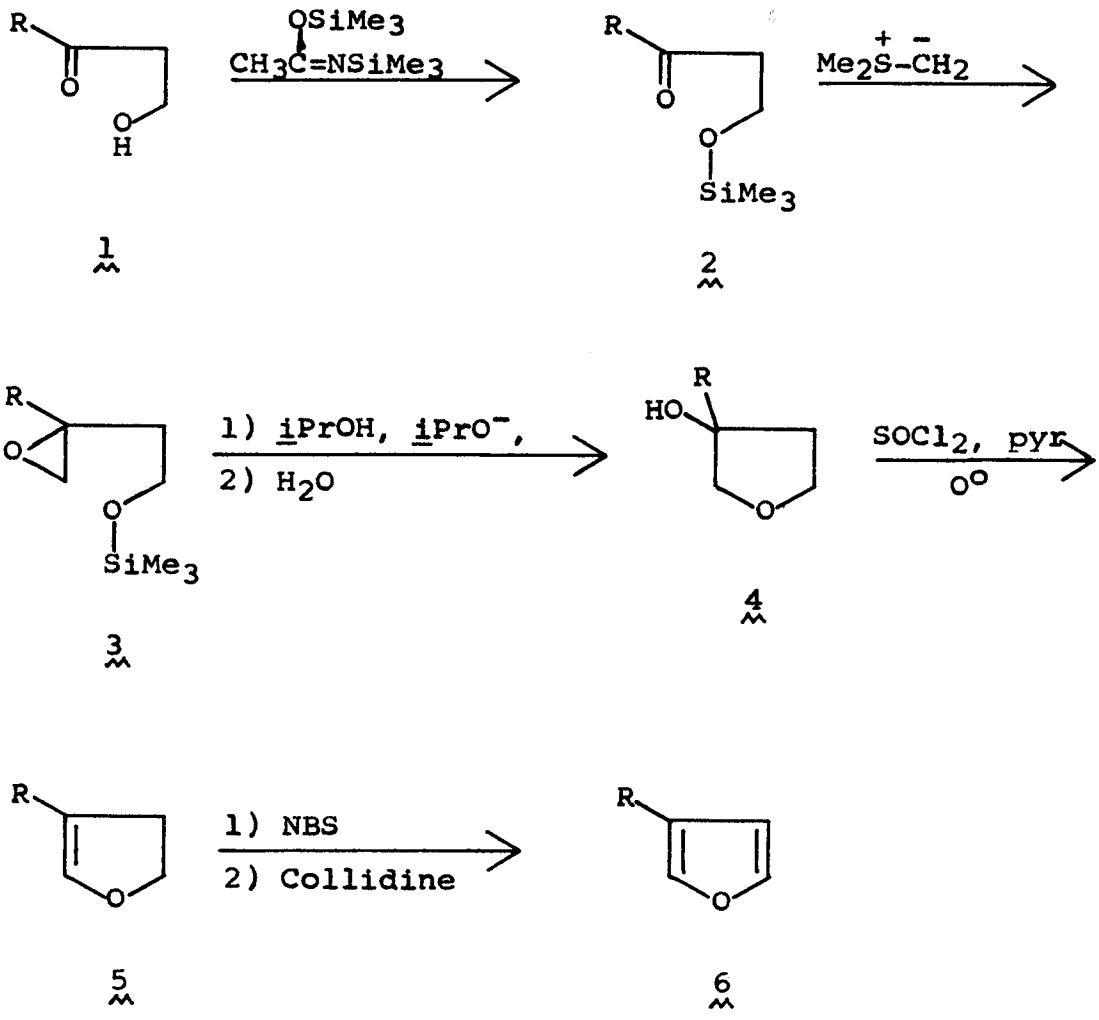
create these outwardly simple systems, the laboratory chemist is still quite restricted in his choice of methods available for constructing 3-alkylfurans. Other than two specific syntheses of 3-methylfuran (3), the literature contains only one report of an efficient route to 3-alkylfurans. Recently, Gianturco and Friedel (4) prepared several 3-alkylfurans in approximately 50% overall yield by application of the Bamford-Stevens reaction to the tosylhydrazones of some 3-alkyl-tetrahydrofuran-4-ones.

As is well known, 3-alkylfurans unsubstituted at the 2- and 5-positions are exceedingly difficult to synthesize because substitution of the furan nucleus always occurs preferentially at C-2 and C-5 (5). This order of reactivity implies that an efficient synthesis of a 3-alkylfuran must involve an indirect route in which the future 3-alkyl group is properly situated prior to formation of the furan ring. Such a synthesis is proposed and is outlined in Chart A. Besides providing an efficient route to a variety of 3-alkylfurans, this scheme has added value in that one of the intermediates is the 3-alkyl-4,5-dihydrofuran A-5. Dihydrofurans have found commercial value in the production of polymers, pharmaceuticals, and pesticides (6).

The starting material for the proposed synthesis, the β-hydroxyketone A-1, can be obtained from any terminal alkyne by the route outlined in Chart B (7). Compounds such as A-1 could also be synthesized by a base catalyzed aldol condensation between a methyl ketone and formaldehyde, however the efficiency of such a process is doubtful as much dehydrated product would be expected. In the conversion of B-3 to A-1 with potassium carbonate in methanol, only trace amounts of vinyl ketone are observed, even for the lower yields of 75-80%.

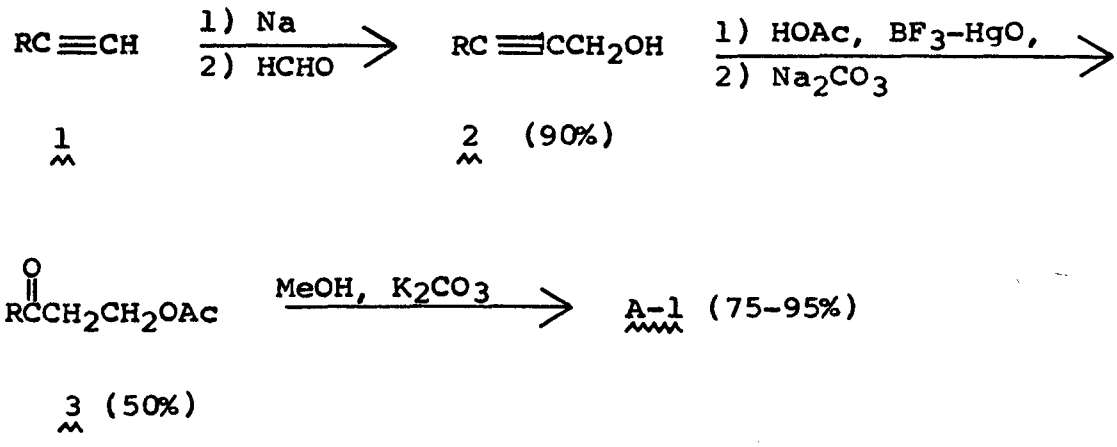
While it may be satisfactory to form oxirane C-1 by allowing two equivalents of dimethylsulfonium methylide

CHART A




to react directly with hydroxy ketone A-1, there is a good chance that the initially formed alkoxide would undergo a retroaldol reaction before the second equivalent of ylide could add to the carbonyl group. Use

CHART B



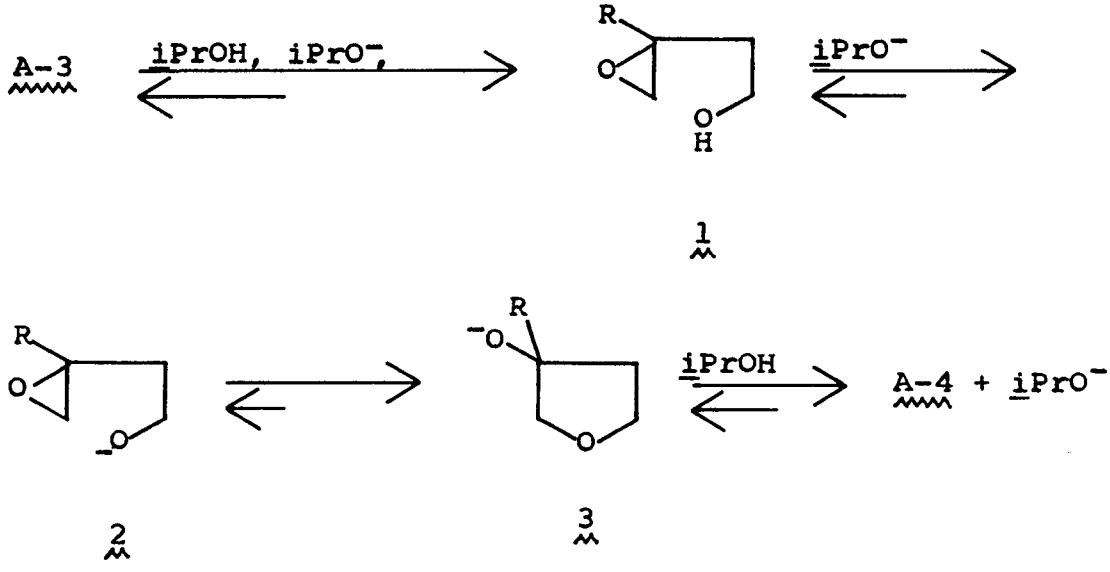

of the trimethylsilyl group to protect the alcohol function will preclude the possibility of a retroaldol reaction. Bis(trimethylsilyl)acetamide should quantitatively silylate hydroxy ketone A-1 under extremely mild conditions (i.e. room temperature, several minutes) (8, 9) to provide siloxy ketone A-2. While the silyl group can be hydrolyzed easily in the presence of alcohol or water, it is expected to be quite stable under the anhydrous conditions employed in the subsequent oxirane formation (9, 10).

The conversion of siloxy ketone A-2 to siloxy oxirane A-3 is to be accomplished with dimethylsulfonium methylide. This ylide, initially described by Corey and Chaykovsky (11), has been used to selectively add methylene to the carbonyl group of cycloheptanone (97%), carvone (89%),

and eucarvone (93%). The aqueous workup procedure used to isolate A-3 may result in some hydrolysis of the silyl group, although it should be minor (10, 12, 13, 14). In any event, partial hydrolysis at this time poses no problem as the silyl group is to be hydrolyzed in the next step.

The crux of the proposed synthesis, the conversion of siloxy oxirane A-3 to hydroxy tetrahydrofuran A-4, is to be effected in one step by refluxing a solution of A-3 in iso-propyl alcohol containing 1% sodium iso-propoxide as catalyst. These reaction conditions are expected to bring about the desired hydrolysis and ring closure as illustrated in Chart C. Alcoholysis of

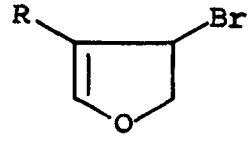
CHART C



compounds of the type $Me_3SiOR$ is an equilibrium process normally slow in the absence of catalysts; however, this equilibrium is rapidly established in the presence of acids or bases (13). Using iso-propyl alcohol as solvent favors formation of hydroxy oxirane C-1, and the hydrolysis should be complete within a half-hour (10, 12, 13). In this brief time, the oxirane should easily remain intact. Opening of epoxides by alcohols in the presence of basic catalysts requires on the order of five to six hours; however when iso-propyl alcohol is employed for this purpose, the time for complete reaction is increased to fifteen to twenty hours (15). The equilibrium between C-1 and iso-propoxide is an equilibrium between a primary and secondary alcohol and would favor the formation of alkoxide C-2. This alkoxide is made to order for an intramolecular $S_N2$ attack on the oxirane moiety to generate the tetrahydrofuran system C-3. This intramolecular process to form the five-membered ring is expected to occur much faster than intermolecular attack of iso-propoxide on the epoxide (15, 16). As the tertiary alkoxide C-3 is generated, it would abstract a hydrogen from the solvent, a secondary alcohol (17). Thus, the differences in acidity among primary, secondary, and tertiary alcohols favor the overall process in converting A-3 to hydroxytetrahydrofuran A-4.

The tertiary alcohol A-4 can dehydrate in three different directions; however, by employing mild conditions (i.e. thionyl chloride in pyridine at 0°), it is expected that the two possible dihydrofurans would be formed in high yield. Between the two dihydrofurans, the 4,5-dihydrofuran A-5 should be the dominate one as the relatively acidic C-2 hydrogens, being adjacent to the ether oxygen, are more easily removed than the non-activated C-4 hydrogens. Actually, either dihydrofuran can be converted to the same furan by the bromination—dehydrobromination sequence described below.

Bromination of dihydrofuran A-5 with N-bromosuccinimide should give the allylic bromide I, which can be dehydrobrominated with collidine to afford the desired 3-alkylfuran




I

A-6. With this procedure, 3,5-dialkylisoxazoles have been prepared in high yield from their 4,5-dihydro derivatives (75-95%) (18), which indicates that side chain bromination is not an important side reaction in this process. Actually,

it is not anticipated that the allylic bromide I need be isolated, as elimination of hydrogen bromide is often a spontaneous process when increased conjugation or aromatization results (19).

With this proposed synthetic route it should be possible to obtain 3-alkylfurans in better than 50% overall yield with no stringent limitation on the identity of the alkyl group.

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## Proposition 3

PROPOSED: A synthesis of 3-bromomethyl-5-methoxy-1,2-benzisothiazole (A-7), an alkylating agent which can be used with strongly basic enolates to introduce a functionalized β-phenylethyl group (1).

As outlined in Chart A, the previously reported synthesis (1) of methoxy bromide A-7, based on the concept of functionalizing the C-5 position of benzisothiazole A-2, suffered from the almost total lack of discrimination between positions C-5 and C-7 during the initial nitration reaction. The proposed synthesis of A-7, depicted in Chart B, avoids this shortcoming by introducing the necessary functionality prior to formation of the 1,2-benzisothiazole ring system. The heart of the synthetic scheme involves the efficient, step-wise conversion of thiocyano acetate B-3 to keto thioether B-6 under mild conditions.

The hydroxy ether B-2 can be obtained quite routinely by sodium borohydride reduction of the commercially available ketone B-1 (2). The subsequent transformation of B-2 to the thiocyano acetate B-3 makes use of the fact that aryl ethers, which are unreactive to thiocyanogen, react readily with thiocyanogen chloride in acetic acid to give para-substituted thiocyano derivatives in high yield (3, 4).

Chart A

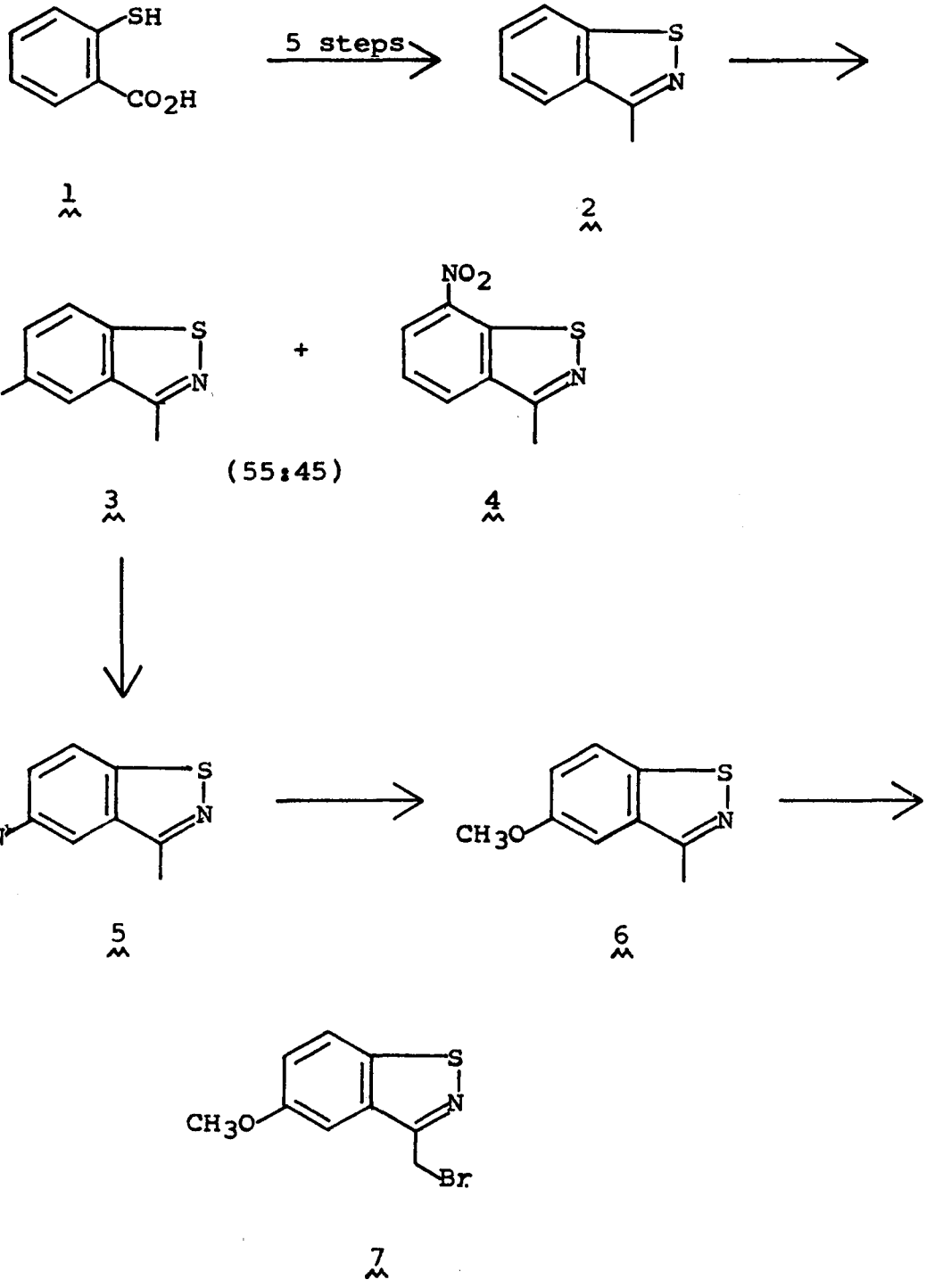
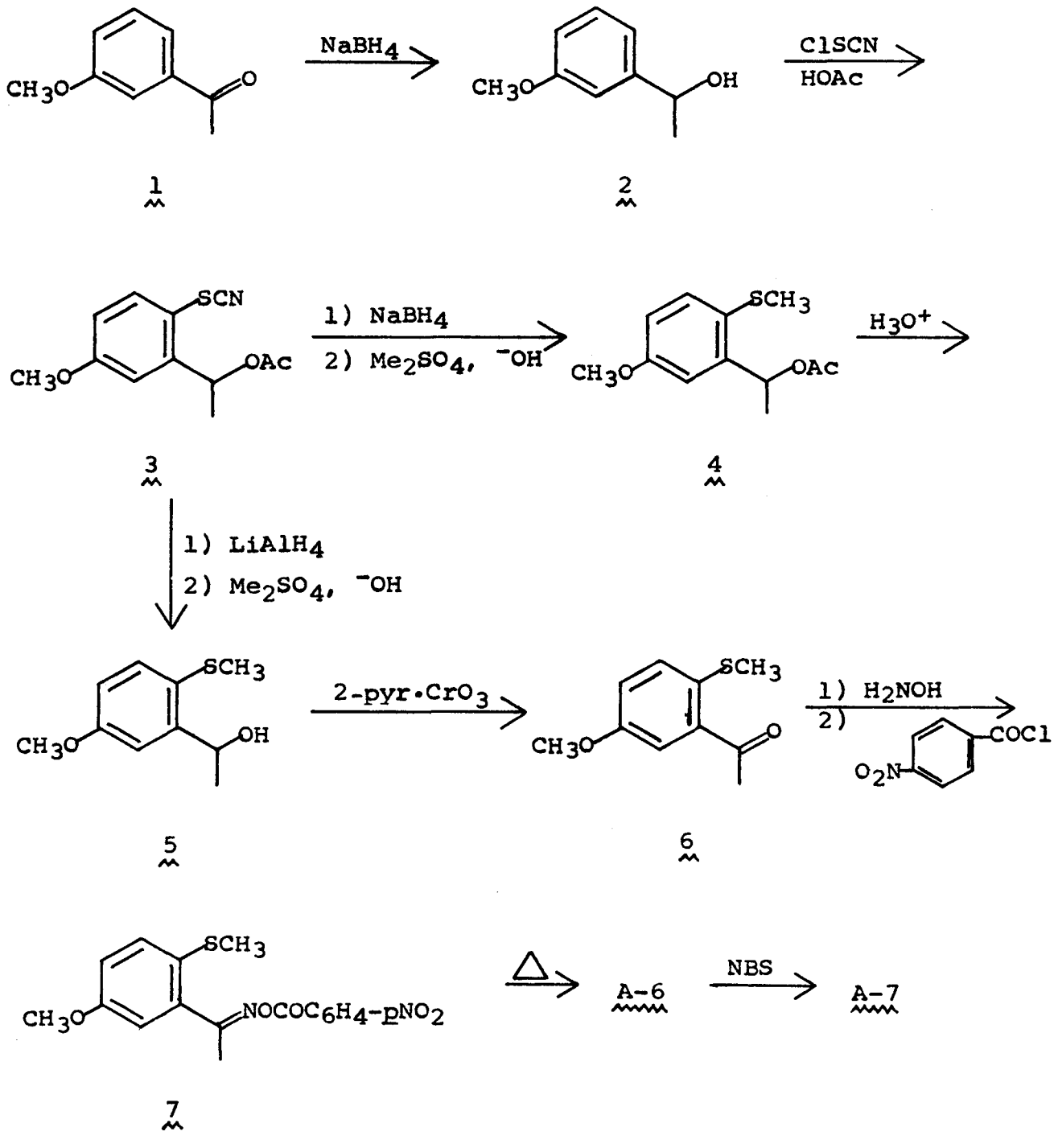


CHART B

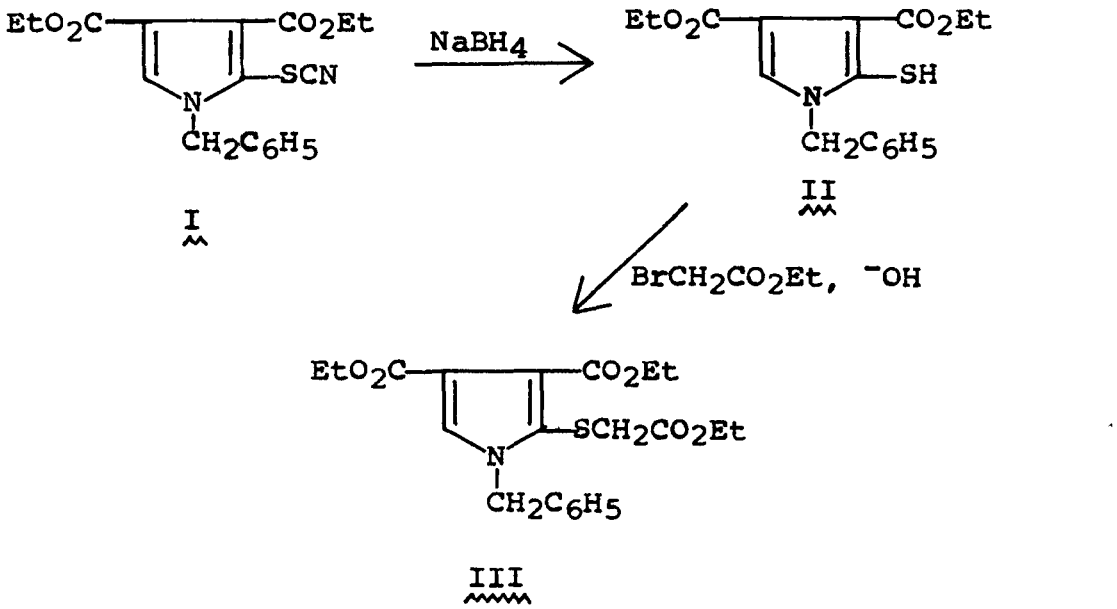

NaBH4
ClSCN
HOAc
1
2
SCN
OAc
1) NaBH4
2) Me2SO4, -OH
SCH3
H3O+
3
4
1) LiAlH4
2) Me2SO4, -OH
2-pyr•CrO3
1) H2NOH
2)
COCl
O2N
5
6
NOCOC6H4-pNO2
A-6
NBS
A-7
7

The reactivity of thiocyanogen chloride was first reported by Bacon and Guy (4), who found that nuclear aromatic thiocyanations resembled the corresponding substitutions by molecular halogen in that the rate of reaction was affected by both solvent polarity and the nature of the activating group. The order of reactivity for thiocyanation in acetic acid was found to parallel that observed in electrophilic aromatic halogenation reactions in that anisole was more reactive than benzanilide but less reactive than phenol. In all cases, thiocyanation of simple benzene derivatives afforded only para-substituted products and no concomitant chlorination was observed. In general, the reactions were conducted at room temperature using one to two equivalents of thiocyanogen chloride, which was generated *in situ* from lead thiocyanate and chlorine. Because of the great reactivity of thiocyanogen chloride in polar solvents, acetic acid was the solvent of choice; however, chloroform was also used with success.

The thiocyano acetate B-3 was actually prepared in these laboratories in the course of some related work (5). It was obtained as the sole product in 75% yield from alcohol B-2 by the general procedure described above and was identified by its characteristic nmr spectrum plus the presence of a strong band at 2150 $cm^{-1}$ (-S-C≡N) in the

infrared. In this earlier work, the use of the amino or hydroxy analogue of ketone B-1 was necessary in order to introduce the thiocyanate group on the aromatic ring, as direct thiocyanation of ketone B-1 afforded only the product arising from dithiocyanation of the methyl ketone sidechain.

The conversion of thiocyano acetate B-3 to hydroxy thioether B-5 either directly or by way of acetoxy thioether B-4 should present no problems as the required transformations have precedent. Olsen and Snyder (6) successfully reduced thiocyano pyrrole I with sodium




borohydride in ethanol to give thiol II in 60-80% yield. However, the overall conversion of I to III was found to

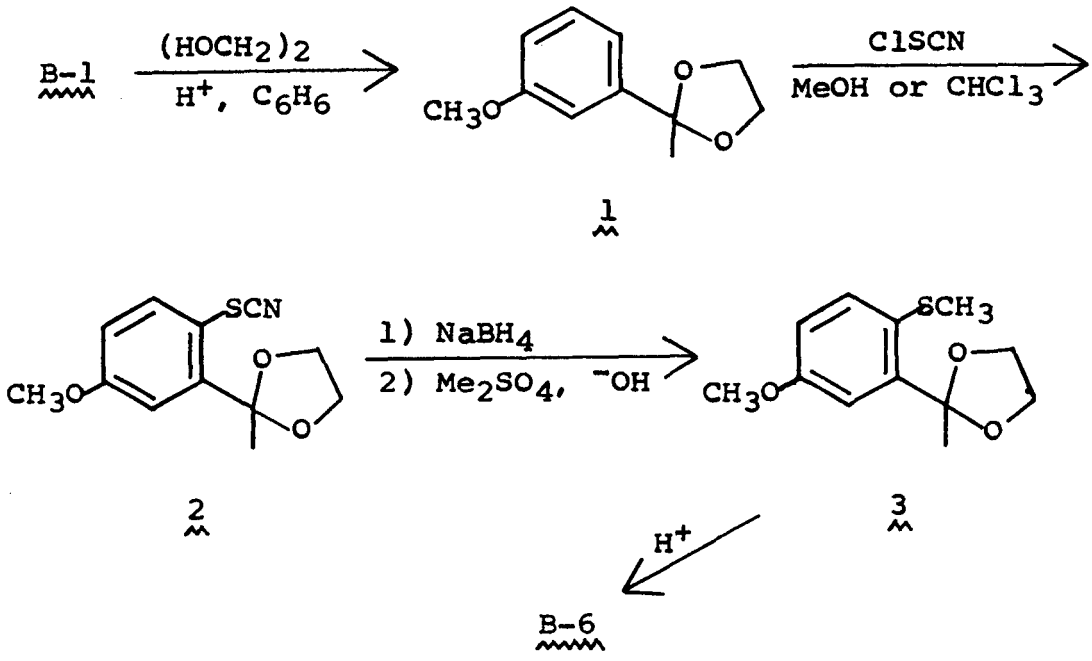
be much more efficient if the thiol II was not isolated. When thiol II, generated by reduction of thiocyanate I, was alkylated *in situ* with ethyl bromoacetate, the two step sequence leading to III was accomplished in excellent 94% yield.

In our case, sodium borohydride reduction of thiocyano acetate B-3 followed by methylation of the intermediate thiol with dimethyl sulfate or methyl iodide would give acetoxy thioether B-4. This in turn could be hydrolyzed with acid or base to provide hydroxy thioether B-5. As thiocyanates can also be reduced to thiols with lithium aluminum hydride (7), reduction of both the thiocyanate and acetate moieties of B-3 with lithium aluminum hydride followed by alkylation would provide yet another route to B-5.

Subsequent oxidation of alcohol B-5 with chromium trioxide—dipyridine complex by the procedure of Collins (8) should provide the keto diether B-6 in high yield. The Collins' procedure, a modification of the standard Sarett oxidation (9), has been used to convert alcohols to aldehydes or ketones in consistently good yields. The oxidation conditions, a five-fold excess of oxidizing agent in dichloromethane at room temperature, are expected to be much too mild to affect the thioether group (9).

An alternate route to the important keto diether B-6, starting from acetophenone B-1, is outlined in Chart C. Thiocyanation of ketal C-1 in a non-acidic

Chart C




solvent such as methanol or chloroform should provide thiocyano ketal C-2. Applying the previously described reduction and alkylation sequence to this ketal would give the diether ketal C-3, which could be hydrolyzed to the desired keto diether B-6. Although thiocyanations

with thiocyanogen chloride have not previously been conducted in methanol, chloroform has been used with success (4). Furthermore, analogous reactions with thiocyanogen have been carried out in methanol (10).

Benzisothiazole A-6 can be obtained from ketone B-6 by employing the procedure reported by Crawford and Woo (11) for the similar conversion of o-methylthioacetophenone to benzisothiazole A-2. Treatment of ketone B-6 with hydroxylamine hydrochloride in ethanol-pyridine followed by p-nitrobenzoyl chloride in pyridine should provide oxime ester B-7. The oxime ester is expected to decompose smoothly in refluxing tetrachloroethane to afford methoxy benzisothiazole A-6 and methyl p-nitrobenzoate. The desired bromide A-7 can then be obtained by treating A-6 with N-bromosuccinimide in the presence of light, as previously reported (1).

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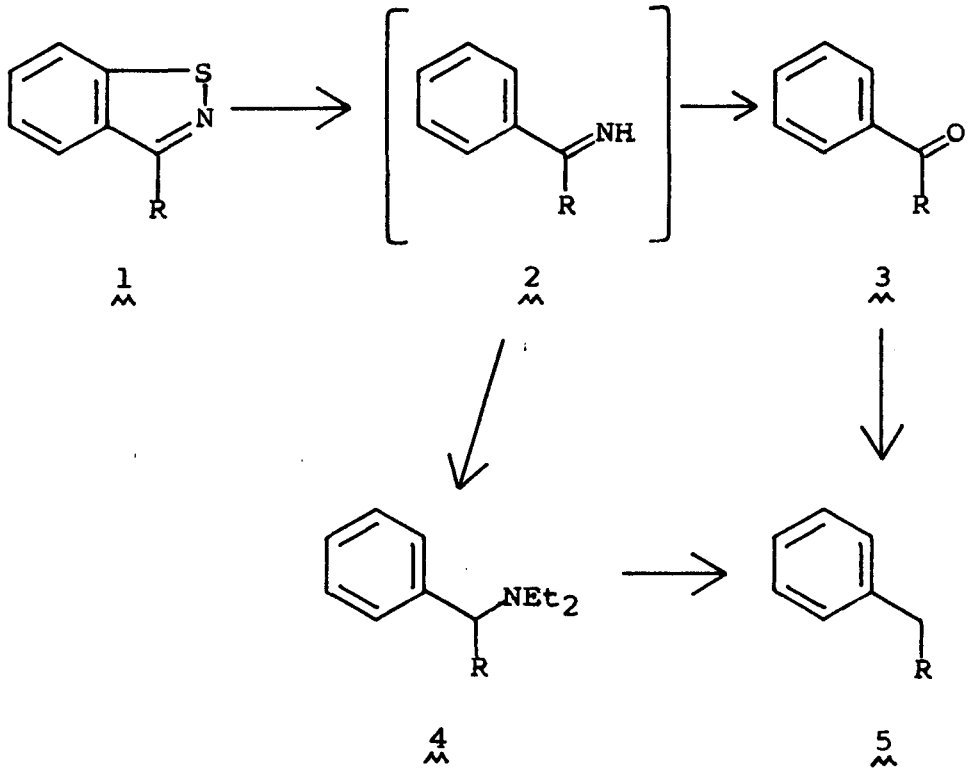
## Proposition 4

**PROPOSED:** A mild procedure for degrading 3-alkyl-1,2-benzisothiazoles to alkylbenzenes.

Previous workers have found the 5-membered heteroaromatic ring of 1,2-benzisothiazole systems to be quite stable to a wide range of degradation procedures (1, 2, 3). Nevertheless, in these laboratories (1) we have been able to develop two methods for removing the heteroatoms from several 3-alkyl-1,2-benzisothiazoles A-1, as outlined in Chart A. In both degradations, the aromatic character of the 5-membered ring was initially destroyed by extracting the sulfur atom with Raney nickel. In one instance, the resulting imine A-2 was hydrolyzed to afford ketone A-3; and in the other case it was reduced and alkylated to give amine A-4. Both the ketone and the tertiary amine, being benzylic, could then be converted to alkylbenzene A-5 by catalytic hydrogenolysis procedures.

We now propose yet a third method for dismantling the benzisothiazole ring. As presented in Chart B, this degradative process can be tested on the readily available 3-methyl-1,2-benzisothiazole (B-1) (4). As was true in the previous degradations, the success of this method rests on the generation of a useful intermediate during

CHART A

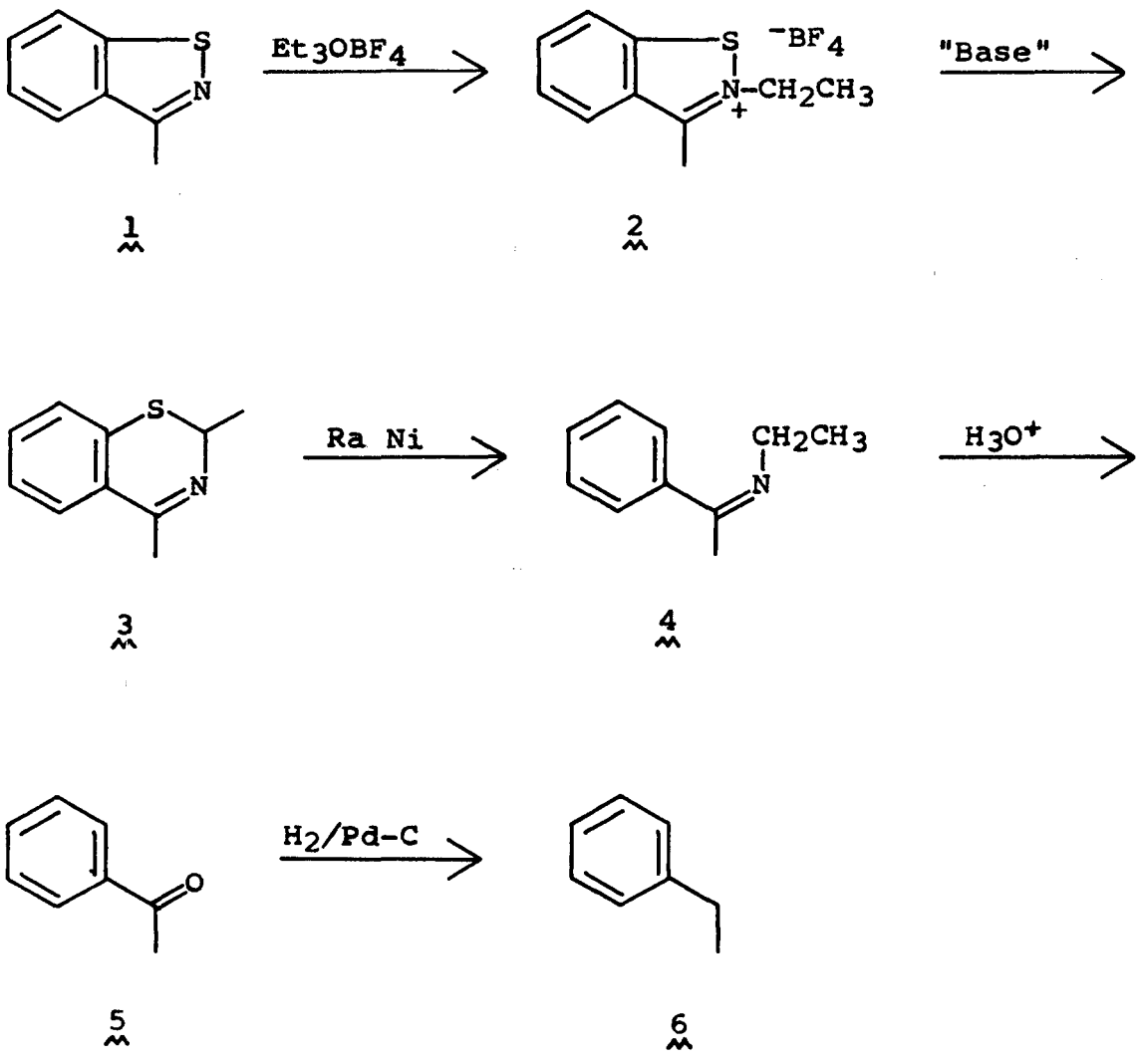



1 2 3 4 5

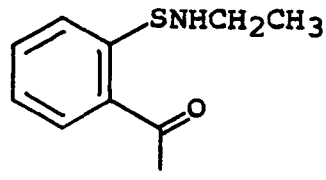
the step in which the aromaticity of the isothiazole moiety is destroyed. In the proposed sequence, the key step involves the conversion of fluoroborate salt B-2 to benzothiazine B-3, a compound which, because of the non-aromatic character of the 2H-1,3-thiazine ring, can then be further degraded to ethylbenzene (B-6) by conventional methods.

The fluoroborate salt B-2 has actually been prepared in these laboratories (1) by combining benzisothiazole B-1 with triethyloxonium fluoroborate in dichloromethane at room temperature (5, 6). Alkylation was assumed to

Chart B



have occurred on nitrogen rather than sulfur by analogy to the previous work of Chaplan and co-workers (7), who report having prepared several N-alkylisothiazolium salts by an equivalent method. At the time of its preparation, a cursory attempt was made to decompose B-2 with aqueous hydroxide with the intention of generating keto sulfenamide I.

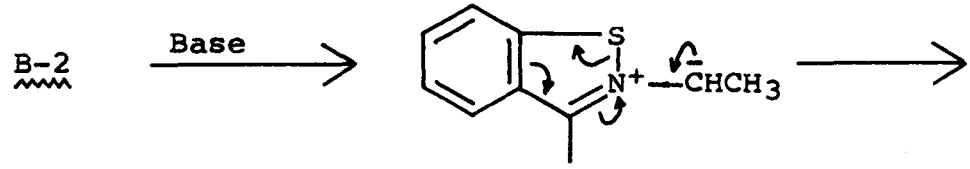



I

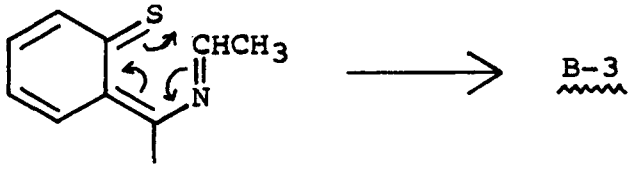
However, when the intractable product, very likely polymeric, exhibited no benzylic ketone absorption in the infrared, the reactivity of B-2 was not further investigated.

In the proposed degradation scheme, fluoroborate salt B-2 is to be decomposed under less basic conditions than those which exist in aqueous hydroxide solutions, as milder conditions are expected to favor the controlled rearrangement of B-2 to B-3 (6) as shown in Chart C. Earlier workers (8, 9) have reported that indoxazenium salt II undergoes a similar rearrangement when shaken with dilute aqueous alkali. Since in strongly basic solutions

Chart C




1

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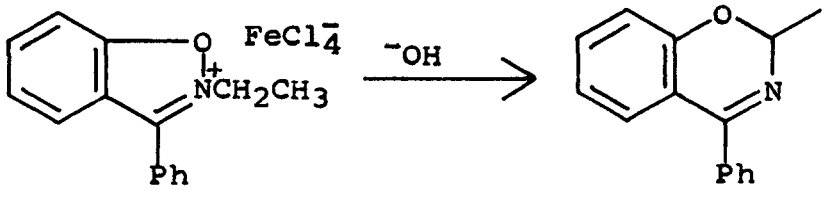
fluoroborate salt B-2 decomposes to a highly colored, intractable product, it is proposed that aqueous solutions




II III

of weak bases, such as sodium bicarbonate, triethylamine, pyridine, or sodium acetate, be employed to initiate the crucial transformation of B-2 to B-3.

Once benzothiazine B-3 has been obtained, its subsequent degradation to ethylbenzene (B-6) should present no problems. By stirring an alcoholic solution of B-3 in the presence of W-2 Raney nickel for several hours at room temperature, a high yield of imine B-4 is expected (10). This imine could be hydrolyzed quite easily with dilute mineral acid (11) to afford benzylic ketone B-5, which in turn could be further degraded to ethylbenzene (B-6) by standard hydrogenolysis methods (12).

If the overall degradation process could be accomplished in 60-70% yield, then this new procedure would constitute a useful addition to the methods already available for degrading 1,2-benzisothiazole systems (1).

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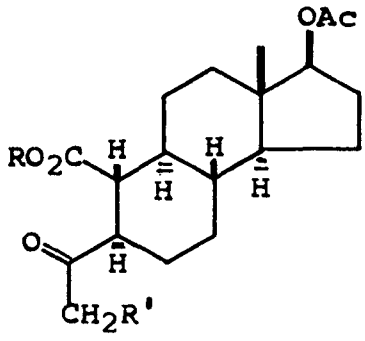
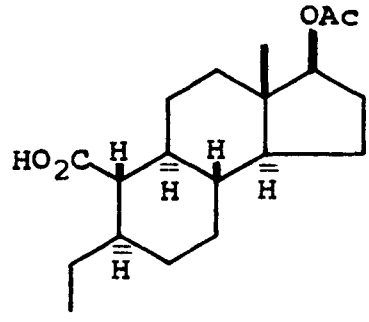
## Proposition 5

**PROPOSED:** A mechanism for a novel lead tetraacetate reaction.

While investigating approaches to the partial synthesis of heterocyclic steroids, Piatek and Caspi (1,2) attempted to functionalize the acetyl moiety of keto acid Ia by employing the method of Cocker and co-workers (3)




I




II

a: R=R'=H

b: R=Me, R'=H

c: R=Me, R'=OAc

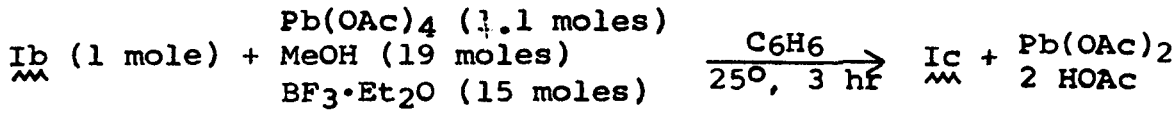
d: R=H, R'=OMe

e: R=H, R'=OAc

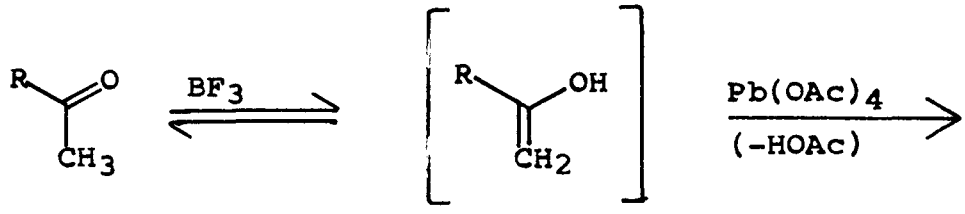
for the α-acetoxylation of ketones. This oxidation procedure, which employs lead tetraacetate in benzene-methanol with boron trifluoride etherate as catalyst,

allows one to α-acetoxylate ketones in high yield at room temperature within two to three hours. Under these conditions, the keto ester Ib gave the anticipated α-acetoxyketo ester Ic. However, under the same conditions it was found that keto acid Ia gave the unexpected α-methoxyketo acid Id in 80% yield, but none of the desired α-acetoxyketo acid Ie. This novel reaction is not peculiar to methanol. The corresponding alkoxyketo acids were obtained with ethanol (60%), 1-butanol (25%), and 2-propanol (low yield). As Piatek and Caspi were not interested in the unexpected α-methoxyketo acid Id, they did not venture a mechanism to rationalize its formation. However, they did establish certain requirements for this reaction: 1) in the absence of either lead tetraacetate or boron trifluoride, no reaction took place; 2) when the acid II was treated under the same conditions used to effect the formation of Id, only starting material was recovered. Based on both direct and indirect analogies to other established reactions of lead tetraacetate, a rational mechanism will be proposed to explain the formation of α-methoxyketo acid Id. Included with the mechanism is a set of experiments which would allow one to deduce its validity.

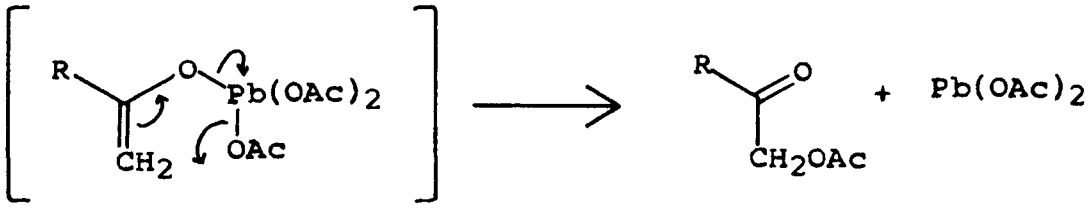
Before presenting a mechanism for the unexpected conversion of Ia to Id, it is worthwhile to consider certain features of a normal α-acetoxylation reaction, such as the formation of Ic from Ib. The chemical equation for this reaction, including relative quantities of the participants, appears below:




The α-acetoxylation is believed to involve a mechanism in which enolization of the ketone is the rate determining step (4,5):




III IV




V VI

In the absence of boron trifluoride, longer reaction times and temperatures above 80° are required; and usually the yields are substantially lower. With boron trifluoride the reaction is complete within several hours at room temperature (1, 3, 6). In its capacity as a Lewis acid, boron trifluoride is thought to accelerate dissociation of the ketone; but it could also accelerate dissociation of lead tetraacetate into $^{+}Pb(OAc)_3$ and $^{-}OAc$. Actually, with methanol also present, the most probable acid catalyst is the coordination compound $BF_3 \cdot MeOH$, which is more properly represented as $(MeOBF_3)^{-}H^{+}$. The acidity of this species rivals that of the strong mineral acids (7). The ester function in Ib probably does not enter into the mechanism, as esters are known to be quite stable to a wide range of lead tetraacetate oxidation conditions (8).

Since the above requirements for normal α-acetoxylation have been fairly well established, the proposed mechanism must satisfactorily explain both the failure of keto acid Ia to give the anticipated acetoxylated product Ie and the unexpected formation of methoxylated product Id. With regard to the formation of Id, the mechanism must take cognizance of the required presence of lead tetraacetate, methanol, and boron trifluoride, as well as the presence of both the ketone and acid moieties in the substrate. If any one

of these groups is absent, no methoxylated product is observed (1). As presented in Chart A, the proposed mechanism does indeed utilize the five required components. The relative amounts of the reagents used in this reaction are the same as those listed earlier for the conversion of Ib to Ic.

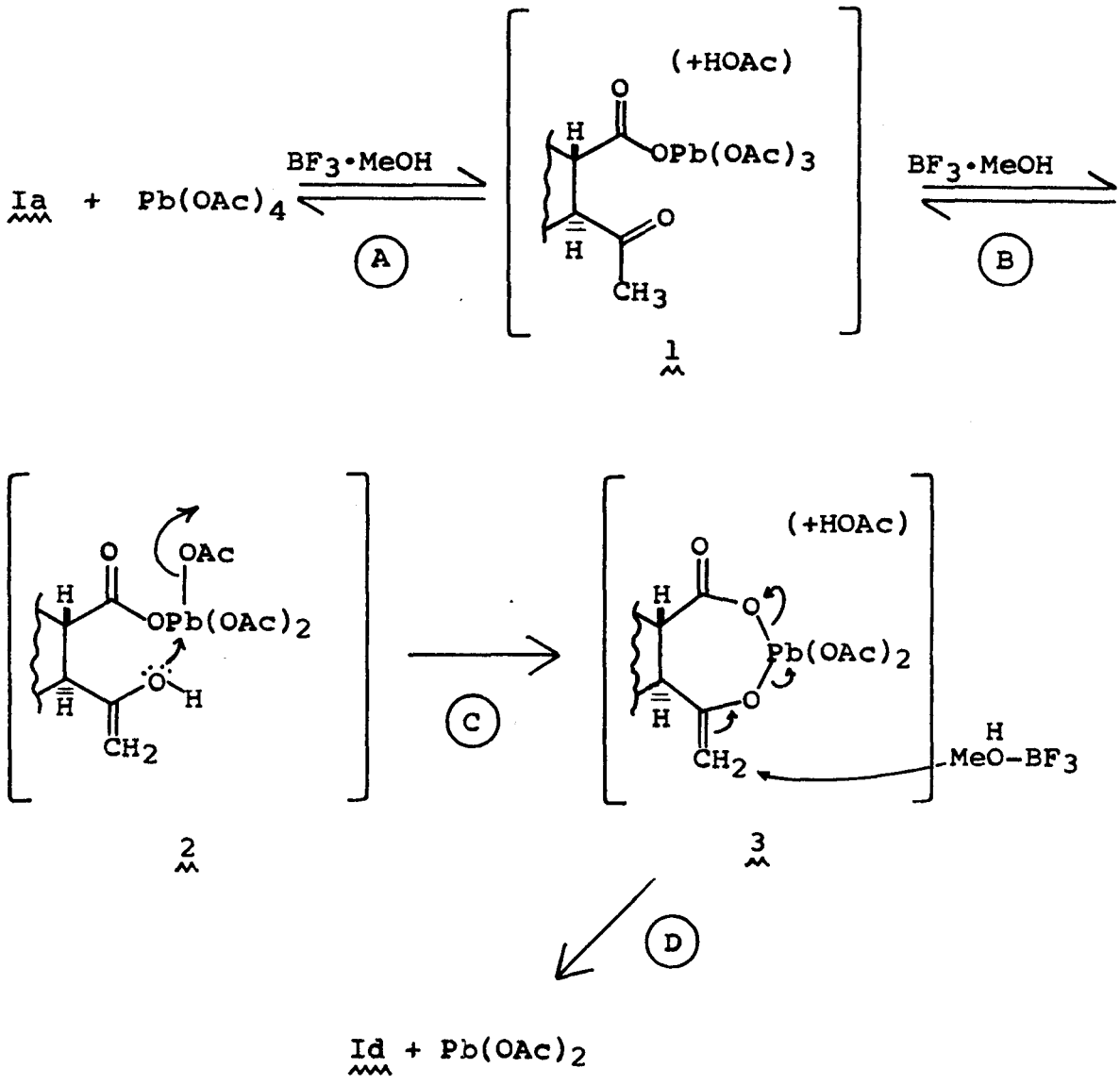
Step A—Formation of lead ester A-1.

Hidden within this equilibrium are several rapid exchange processes, all of which can be catalyzed by boron trifluoride, a reagent which is quite indiscriminate in its preference for non-bonded electrons (7). The exchange of the acetate groups of lead tetraacetate with other carboxylate groups is rapid, and the equilibrium position is determined by the relative acidity of the acids and by the mass law (9). As the only source of acetic acid is from dissociation of lead tetraacetate, the existence of some lead ester A-1 is likely. It is also possible to have exchange between lead tetraacetate and methanol (9), however it is not necessary to invoke intermediates such as $MeOPb(OAc)_3$ to explain the proposed mechanism.

Step B—Enolization.

For keto acid Ia or keto ester A-1, the least substituted enol is also the thermodynamic enol. The

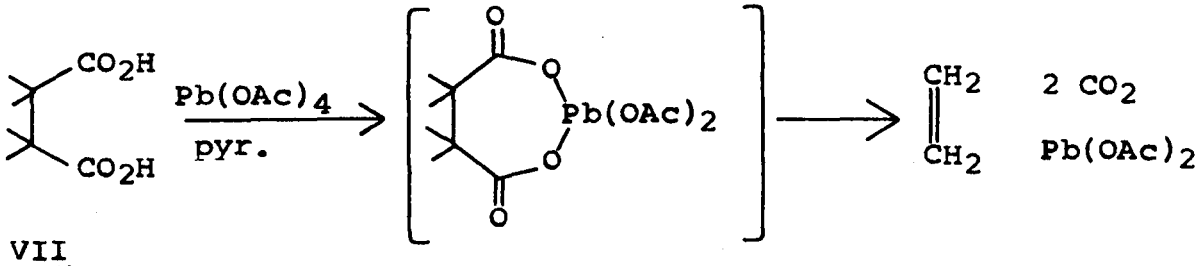
CHART A


Ia + Pb(OAc)4
BF3•MeOH
A
(+HOAc)
OPb(OAc)3
CH3
1
BF3•MeOH
B
OAc
OPb(OAc)2
CH2
2
C
(+HOAc)
Pb(OAc)2
CH2
H
MeO-BF3
3
D
Id + Pb(OAc)2

ketone functionality in either molecule would be expected to enolize toward the terminal methyl group rather than into the ring junction, as the formation of either of the two possible tetra-substituted enols would introduce a significant interaction between the α-carboxylate group and the syn exo-substituent.

Step C—Ring formation.

Support for formation of the seven-membered ring in A-3 can be obtained by analogy to the postulated intermediate in the Grob degradation of succinic acids (10, 11):




VII

VIII

Note that in the formation of A-3, an acetate is ejected. At this point, the lead atom no longer has an acetate fragment readily available for intramolecular transfer to the terminal methylene group, as is the case in normal α-acetoxylations. Furthermore, ring formation removes the remaining lead-bound acetates from the vicinity of the methylene group.

Studies with molecular models indicate that the ring intermediate A-3 can be formed and exist without undue strain on the molecule. The preferred conformation is expected to be one in which the carboxyl carbonyl is below the plane of the molecule and the terminal methylene group is above the plane. This conformation exposes the methylene group for easy attack by methanol, and it is this attack that initiates the decomposition of A-3.

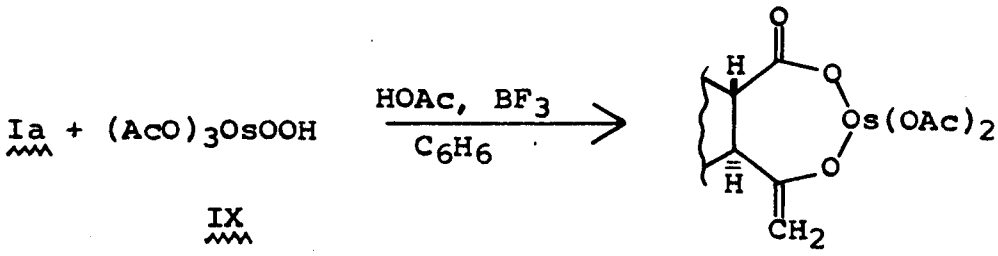
Step D—Product formation.

Decomposition of A-3 involves the actual oxidation step, the transfer of an electron pair from oxygen to lead. Bond heterolysis is made possible because the electron pair lost by oxygen is simultaneously replaced with the electron pair that had formerly constituted the olefinic bond. This movement of electrons is in agreement with Levitt's general mechanism of oxidation (12).

The crux of the proposed mechanism is the existence of the seven-membered ring intermediate A-3. By altering the relative positions of the ketone and acid moieties, one could prohibit the possibility that such an intermediate could form. In such an instance, one would expect to observe α-acetoxylation in the normal manner by attack of free lead tetraacetate on the enolized ketone. For example, the oxidation of cyclohexanone-3-carboxylic acid (13), which also has a 1,3-relationship between ketone

and acid functions, would be expected to give normal α-acetoxylated product, as molecular models indicate that it could not form a cyclic intermediate with lead tetraacetate.

More direct evidence for the existence of A-3 would be its isolation or the isolation of a closely analogous cyclic ester; for example, the corresponding osmate ester. By reducing the acidity of the reaction medium, one might be able to isolate the cyclic osmate ester X by allowing keto acid Ia to react with $(AcO)_3OsOOH$. With this osmate,




X

Criegee and co-workers (14) have been able to isolate cyclic esters derived from 1,2-diols.

Indirect evidence for the formation of A-3 can be obtained by determining the overall rate of the reaction. If for a series of runs in which the initial concentrations of keto acid Ia and lead tetraacetate are varied, the rate of reaction exhibits a first order dependence on

the concentration of lead tetraacetate, then one cannot exclude the possibility that A-3 is formed. [The rates of normal α-acetoxylations are independent of lead tetraacetate concentration (4).] On the other hand, if the rate is second order or higher with respect to the lead tetraacetate concentration, then the proposed mechanism is incorrect. If the rate of reaction is independent of the lead tetraacetate concentration, then all that can be said is that if A-3 does form, its formation occurs after the rate determining step.

The above presentation is not meant to provide conclusive proof of the proposed mechanism; however, it should provide insight into the workings of a rather complicated lead tetraacetate oxidation. Since very little definite is known about the intricacies of oxidations with lead tetraacetate, mechanistic evidence obtained from these studies might also prove applicable to related reactions within the field, several of which were mentioned in the process of developing the proposed mechanism.

## References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