THE TOTAL SYNTHESIS OF
(±) 1-DEAZA- 1-THIA-RESERPINE

Thesis for the Degree of M. S.
MICHIGAN STATE UNIVERSITY
George Peter Nilles
1967

THESIS

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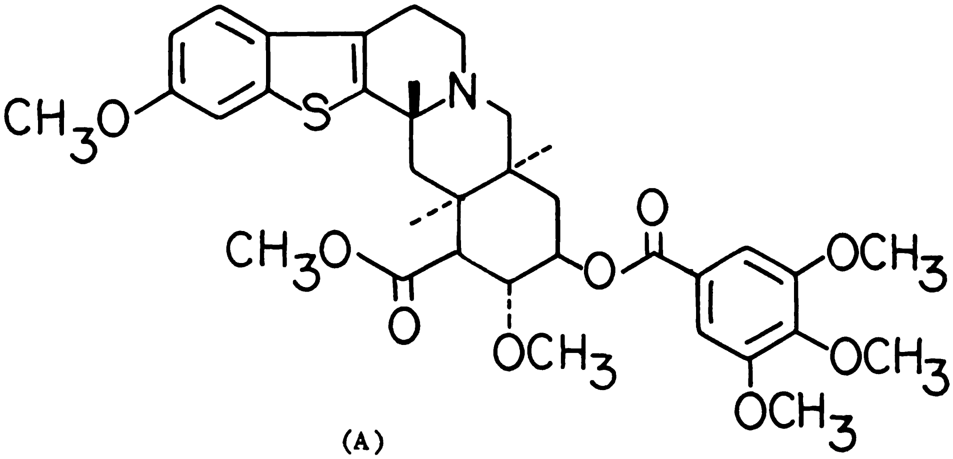
ABSTRACT

THE TOTAL SYNTHESIS OF
(±) 1-DEAZA-1-THIA-RESERPINE

By

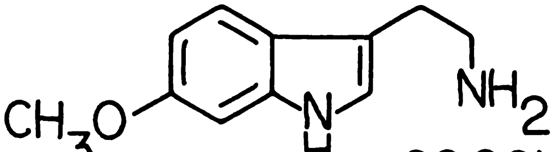
George Peter Nilles

Reserpine, isolated from Rauwolfia Serpentina Benth., has widespread use in modern pharmacology as an anti-hypertensive. The goal of this investigation was to carry out the initial synthesis of a compound in which the basic ring skeleton of reserpine was modified while retaining all other functional groups intact (viz. 1-deaza-1-thia reserpine (A)).



(A)

The original total synthesis of reserpine (13,14) called for the condensation of three molecular fragments (B, C, D).



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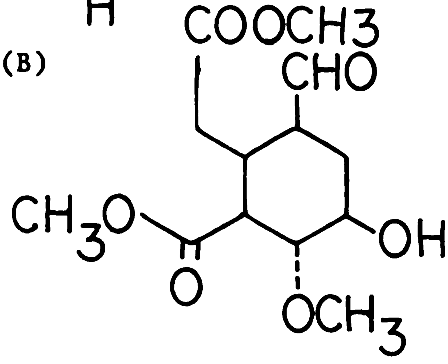

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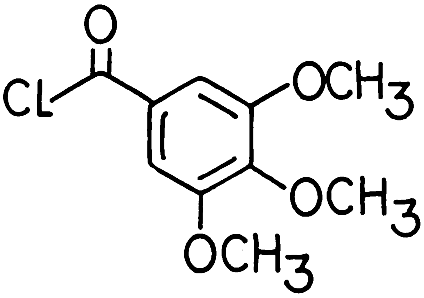
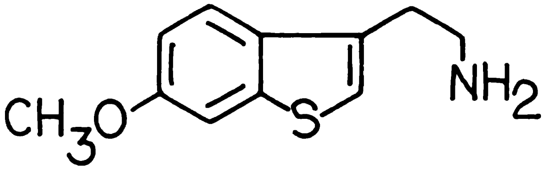


(D)

Molecules (C) and (D) have been previously described by this synthesis. Thus attention was directed toward the synthesis of the sulfur analog of (B); the thianapthyl derivative (E) of the indole molecule, having sulfur in place of the indole nitrogen.



(E)

Titus (10) in these laboratories had already synthesized the amide from which the amine (E) could be obtained by simple reduction. He was unable to effect such a reduction with any of the common reducing agents.

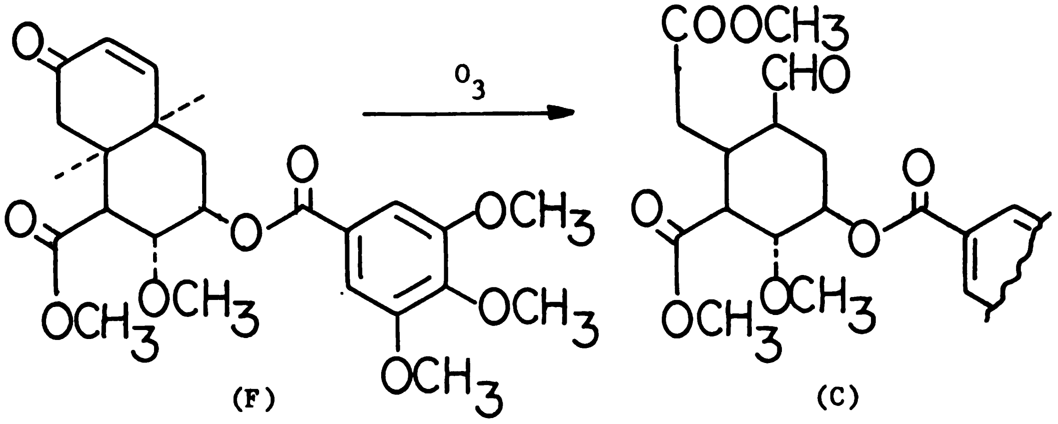
Application of a new reductive process (19) in the present work, utilizing diborane lead to the formation of (E) in good yield.

Molecule (C) was synthesized by a procedure which involved some original work and incorporating the findings of other investigators (12, 13, 14). In the final stage of the synthesis of (A) the sequence of the reactions necessary to effect condensation of the molecules (C, D, E) was changed from those reported to take advantage of favorable steric factors.

The 3,4,5-trimethoxybenzoyl function was attached to molecule (C) before molecule (E) was added to obtain (A). The effect of this proceedure was to isolate exclusively the desired "thiareserpine" molecule having the proper stereochemistry at the C-3 carbon thus obviating the necessity to separate the thiareserpine from its C-3 epimer.

Advantage was taken of other newer developments since the advent of the original reserpine synthesis to shorten the number of steps required and to improve the overall yields of intermediates.

These included the conversion of the precursor of (C) i.e. compound (F) by ozonolysis, to obtain directly the 18β ester function eliminating the need for a laborious acid catalyzed epimerization of the C-3 hydrogen.



(F) (C)

This and other minor changes in reaction conditions improved the yields in some specific steps in the initial synthetic sequence of reactions to obtain (A). As a result the desired compound was synthesized in an overall yield of 0.2% from its simplest starting materials.

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A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirments
for the degree of

MASTER OF SCIENCE

Department of Chemistry

1967

G45715
8/25/67

ACKNOWLEDGEMENT

The author wishes to express his sincere appreciation to Professor Robert D. Schuetz for his guidance and encouragement throughout the course of this investigation.

Special thanks are also extended to those individuals of the Department of Chemistry who made available the necessary instruments used in the experimental portion of this work.

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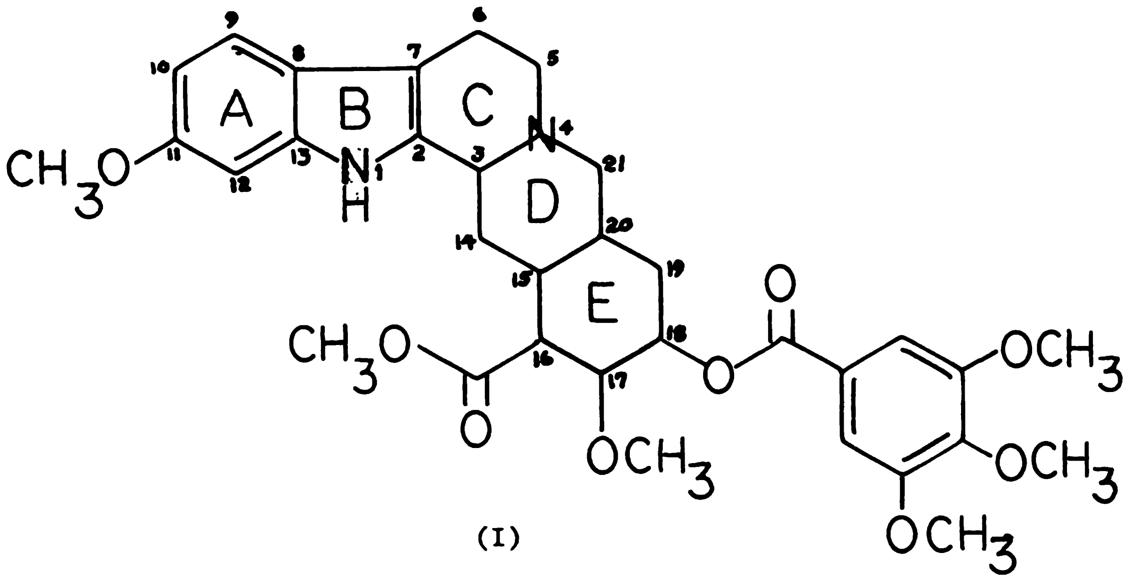
INTRODUCTION AND HISTORICAL

Totally unaware of its chemical constitution, reserpine was initially brought to the attention of western civilzation by Leonhart Rauwolf some 400 years ago (1). Extracted from the root of the Indian shrub <u>Rauwolfia</u> <u>Serpentina</u> <u>Benth.</u> (named in honor of this sixteenth century explorer) it has stimulated the imagination of countless men of chemistry and medicine.

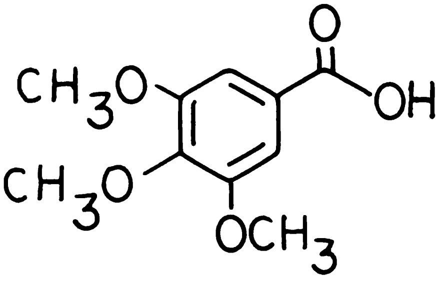
Originally the entire ground root was used in the treatment of hypertension. In 1952 a team of Swiss researchers (2) succeeded in isolating the physiologically active principle, reserpine (I). Although other compounds similar in structure, both natural and artificial, have been discovered, none have an activity greater than reserpine, which is effective at a dosage of 0.5 mg./day (3).



(I)

Investigations directed towards its structural elucidation were initiated independently both here and abroad. Dorfman and his colaborators (4,5) showed the overall structure to be (I).

Infrared analysis of reserpine indicated the presence of an N-H bond, two carbonyls probably as esters, and an ortho disubstituted benzene. Elemental analysis gave an empirical formula, $C_{33}H_{40}O_9N_2$. Alkaline hydrolysis yielded 3,4,5-trimethoxy benzoic acid (II) and reserpic acid. The reserpic acid was reconvertable to reserpine on treatment with 3,4,5-trimethoxy benzoyl chloride. The ultraviolet spectrum of reserpic acid was almost identical to a tetrahydro-β-carboline system (III, R=H) and suggested a relationship to the Harmala alkaloid skeleton (III, $R=OCH_3$).



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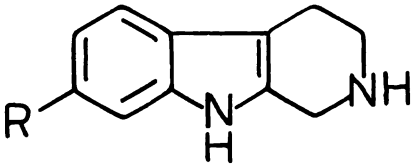
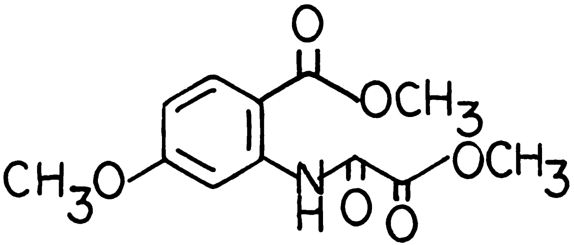


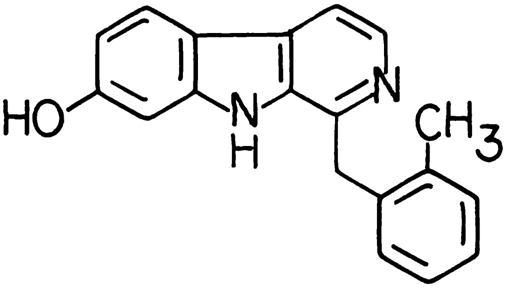
(III)

Reduction of reserpine with lithium aluminum hydride afforded 3,4,5-trimethoxy benzyl alcohol and reserpic alcohol ($C_{22}H_{30}O_4N_2$). This diol contained only two methoxy groups. The 11-methoxy group was confirmed on the basis of permanganate oxidation followed by treatment with diazomethane to obtain the dimethyl ester of 4-methoxy-N-oxalyl anthranilic acid (IV).

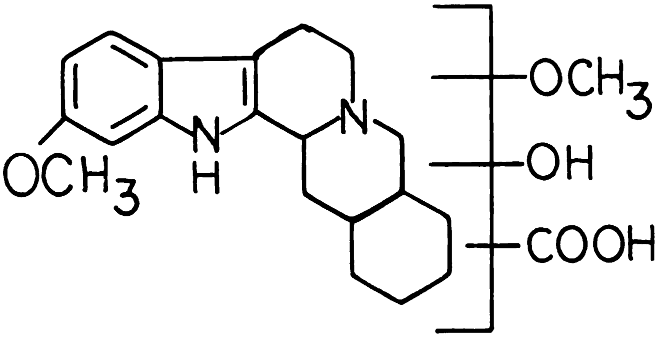


(IV)

A yohimbane type nucleus was evident upon selenium dehydrogenation of reserpic acid, which yielded structure (V) which was confirmed by synthesis. Dorfman (4,5) then postulated structure (VI) for reserpic acid, which had to contain a methoxy group, a non phenolic hydroxyl, and a carboxyl function in then unknown positions.

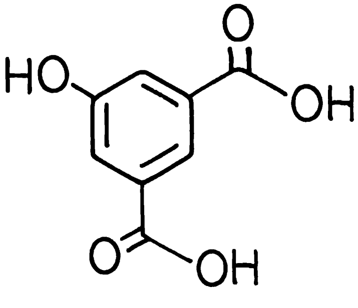


(V)

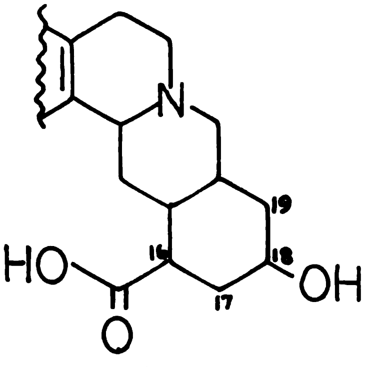


(VI)

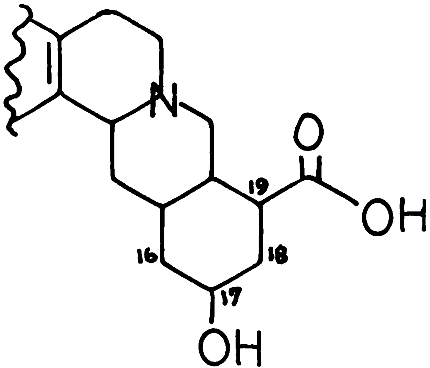
Potassium hydroxide fusion of reserpic acid led to 3-hydroxy isophthalic acid (VII). Carbon atom number 14 (C-14) should have been lost as carbon dioxide. This assumption was based on the prior report of the analogous reaction of the previously established rauwolscine. This fact placed two of the groups named above as in structure (VIII). An alternate structure (IX) was given less probability on biogenetic grounds. The C-16 carboxyl being considered more probable on comparison to the Strychnos alkaloids (6).



(VII)



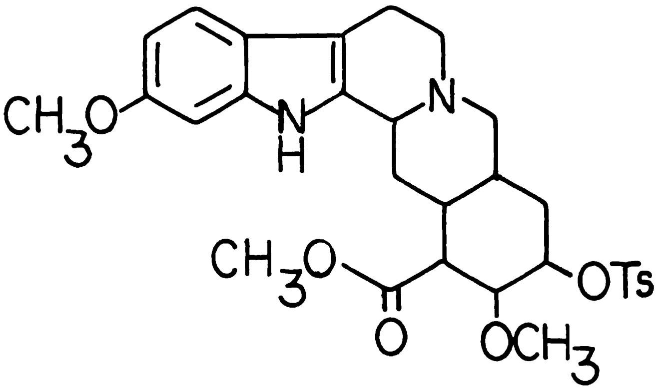
(VIII)



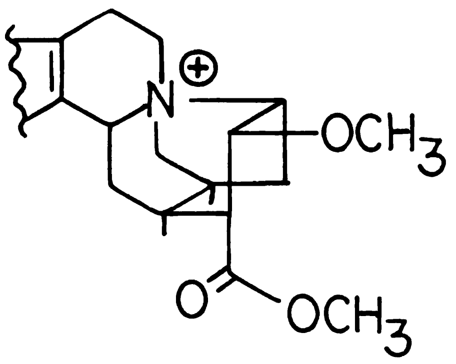
(IX)

On heating the methyl ester tosylate of reserpic acid in collidine Dorfman obtained a compound $C_{23}H_{28}O_4N_2$ whose infrared and ultraviolet spectra suggested the presence of an ether substituted α,β unsaturated ester. On this basis they assigned reserpine structure (I).

This work only partially established the complete structure since a task of equal dimension still remained, namely the determination of absolute configuration of reserpine. "Stereochemical abandon" as phrased by Woodward, predominates among the members of the yohimbane family. Reserpine itself contains six asymmetric carbons. The first clue to their orientations came from the fact that the methyl ester tosylate of reserpic acid (X) easily formed a quaternary salt in collidine, and this was postulated to have structure (XI) (7).

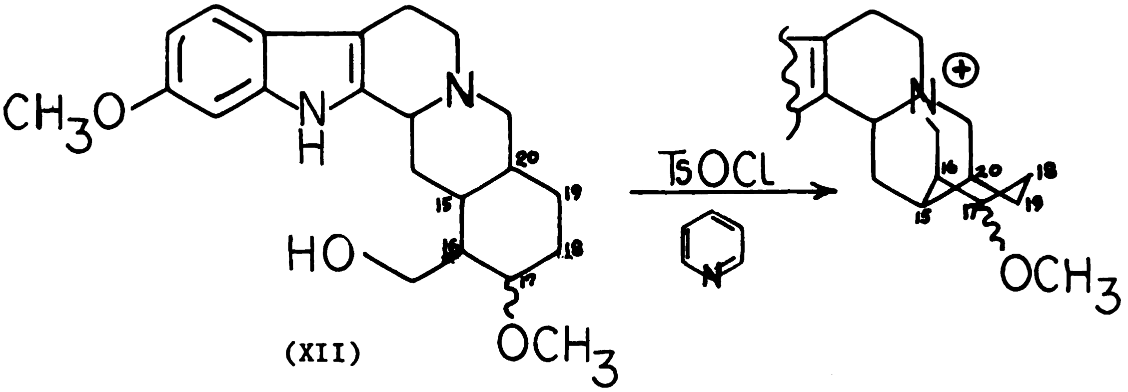


(X)



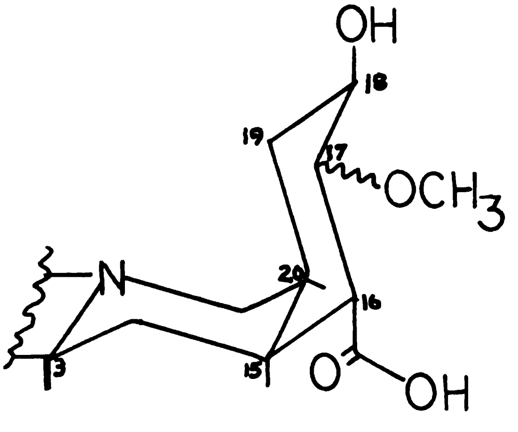
(XI)

Structure (XI) for the quaternary salt demands a cis fusion of rings D and E. Huebner and Wenkert (8) found a quaternary salt readily formed in pyridine at room temperature upon the detosylation of 3-isoreserpinol (XII) which requires a cis axial placement of the C-16 carbon function, and shows that the C-16 group and the C-20 hydrogen are trans. Since reserpic acid readily forms a lactone (9) this places the C-18 hydroxyl cis axial to the C-16 carboxyl (XIII).

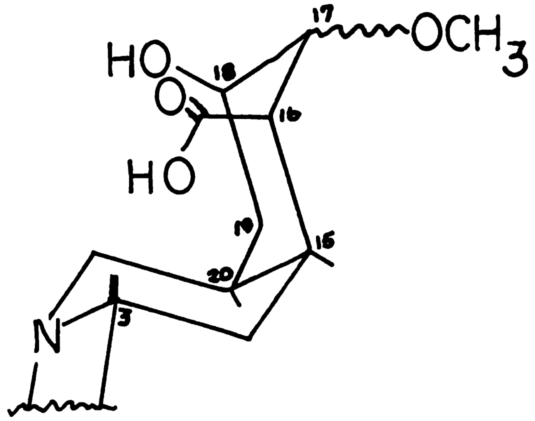


(XII)

That reserpine possesses the epi allo configuration for the C-3 hydrogen (the less thermodynamically stable form) is shown by this facile lactone formation. In the allo case (XIV) the carboxyl and the hydroxyl functions are to far apart to form a lactone while the epi allo case has these groups cis 1,3 diaxial. (XIII).



(XIV)

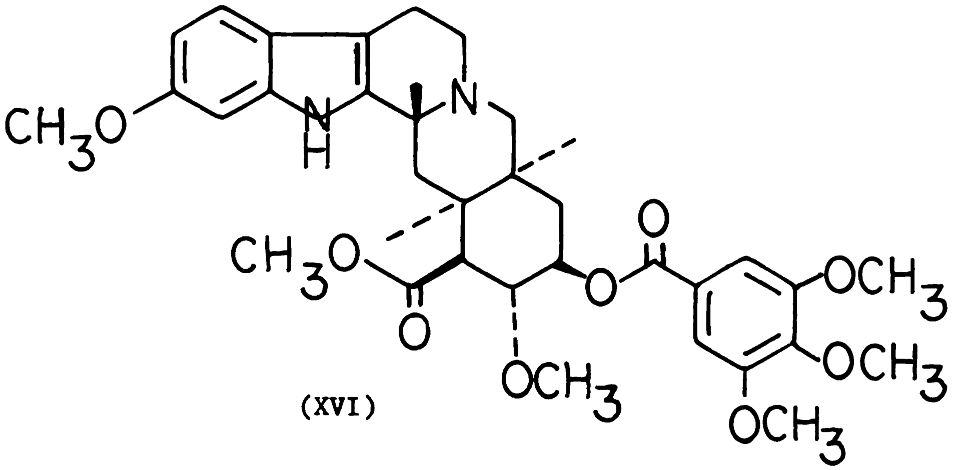


(XIII)

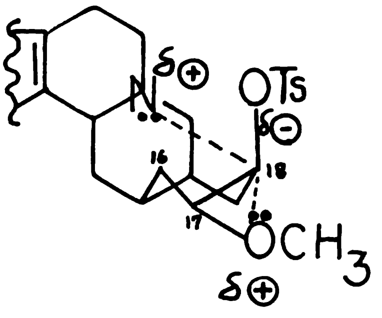
The allo case can not be reoriented to the epi allo structure without serious C-2, C-16 group interactions (10). By molecular rotation studies (10) the C-18 carbon was related to D-glyceraldehyde to give the absolute configuration as in structure (XIII).

Further evidence of the β-oriented C-3 hydrogen came from infra studies (11,12). It was found that a β-oriented C-3 hydrogen provides only a single C-H absorption at 2780 cm^{-1}, while the α-oriented C-3 hydrogen shows an absorption at 2740 cm^{-1} as well. Since reserpine shows only the 2780 cm^{-1} absorption, the C-3 hydrogen must be β-oriented.

The remaining asymmetric carbon at C-17 was shown to be α by a closer look at Dorfmans' work (9). Since the C-18 carbon group is β, the formation of the quaternary salt (XV) should occur easily only if the methoxy group at C-17 could give anchimeric assistance to the back side displacement of the C-18 tosylate. Therefore the C-17 methoxy group must be α-oriented, thereby giving the absolute configuration shown in structure (XVI).



(XVI)



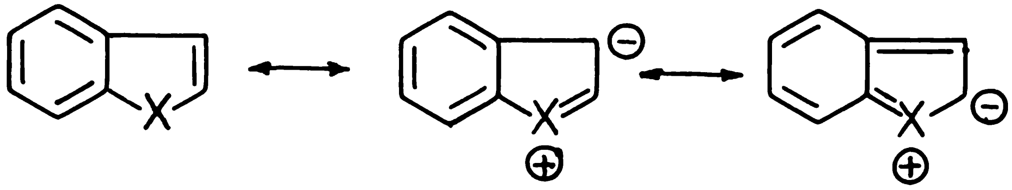
(XV)

That structure (XVI) is correct for natural reserpine was shown by the brilliant total synthesis by Woodward (13,14).

Although numerous modifications of the basic reserpine skeleton have been reported (1,15) these have involved only peripheral changes. Of these the most effective from a phramacological point of view have been the substitution of various ester functions at C-18.

Accordingly work was initiated in these laboratories to modify the reserpine skeleton internally, namely replacement of ring B (pyrrole) by thiophene.

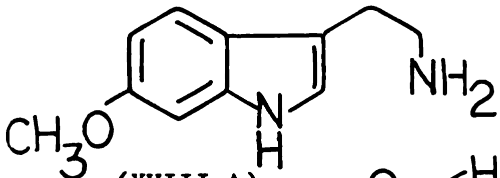
Huckel molecular orbital calculations of bond orders in indole (16) and benzothiophene (17) indicate a greater resonance contribution to structure (XVII-A) than (XVII-B) in both benzothiophene and indole.



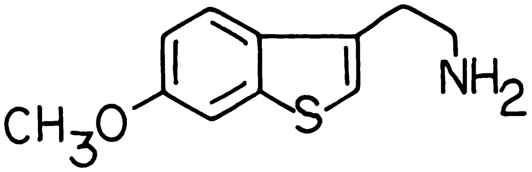
(XVII-A) (XVII-B)

Calculations from average value bond lengths reveal the thiophene ring to be only 0.3 Å^2 larger than pyrrole, 3.9 Å^2 for thiophene vs. 3.6 Å^2 for pyrrole. These two facts tend to substantiate the postulate that substitution of ptrrole by thiophene should not adversely affect the phramacologic response of the molecule if this part is engaged at either an active or locking enzymic site. Further support of this postulate stems from the already established procedure of substitution of thiophene for pyrrole in some phramaceuticals, albeit with some decrease in activity (30). Hopefully this thia analog of reserpine will overcome many of the adverse side effects of the natural compound. This desire along with the want to establish and extend some fundamental chemistry in the field of sulfur heterocyclic compounds motivated this undertaking.

Woodwards' synthesis of reserpine involved the condensation of three large molecules (XVIII-A), (XVIII-B), (XVIII-C) with five of the six asymmetric carbons properly oriented in (XVIII-B).



(XVIII-A)



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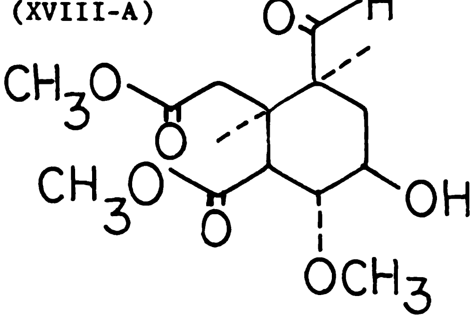
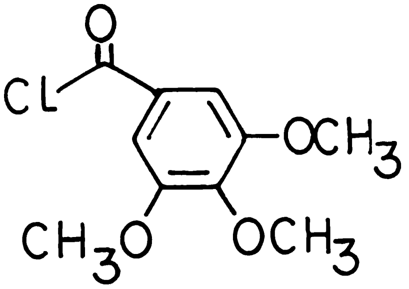


(XVIII-B)



(XVIII-C)

Therefore, attention was directed to the synthesis of the previously unknown 6-methoxy-3-(2-aminoethyl) benzothiophene (XIX).

Titus (18) in previous work in these laboratories had synthesized 6-methoxy-3-acetamidobenzothiophene. Unfortunately he was unable to reduce the amide to the desired amine. However, a recent paper by Brown (19) late in 1964 showed a facile reduction of all types of amides to the corresponding amines in high yield by borane in tetrahydrofuran. With this new reductive procedure available, the total synthesis of 1-deaza-1-thia-reserpine was undertaken.

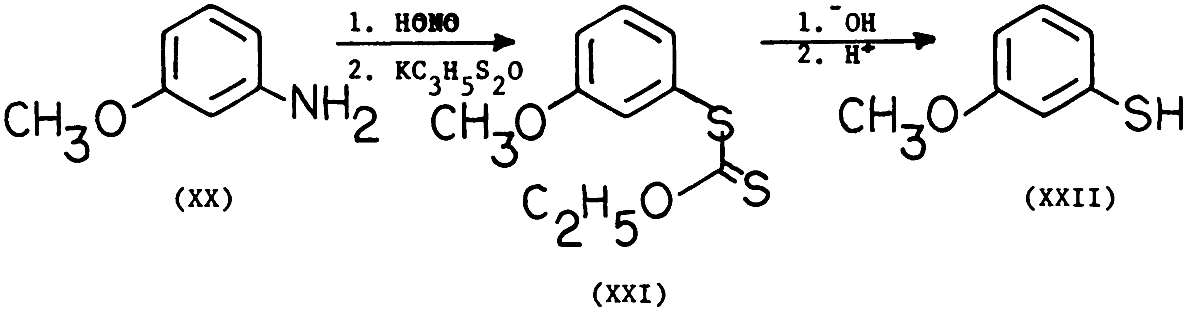
DISCUSSION

PART I Preparation of 6-methoxy-3-(2-aminoethyl) benzothiophene

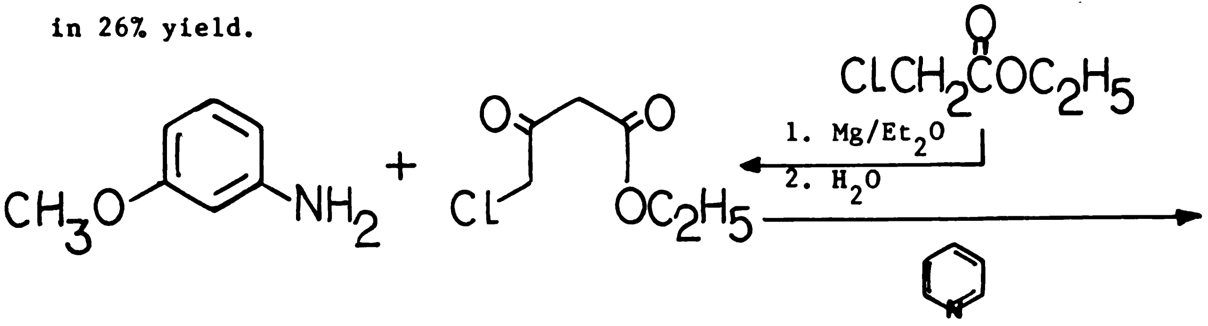
Since Woodward had already described a stereospecific synthesis of the E ring of reserpine (14) attention was first directed toward the synthesis of the sulfur heterocyclic amine necessary to form rings A,B and part of C in the "thiareserpine" molecule.

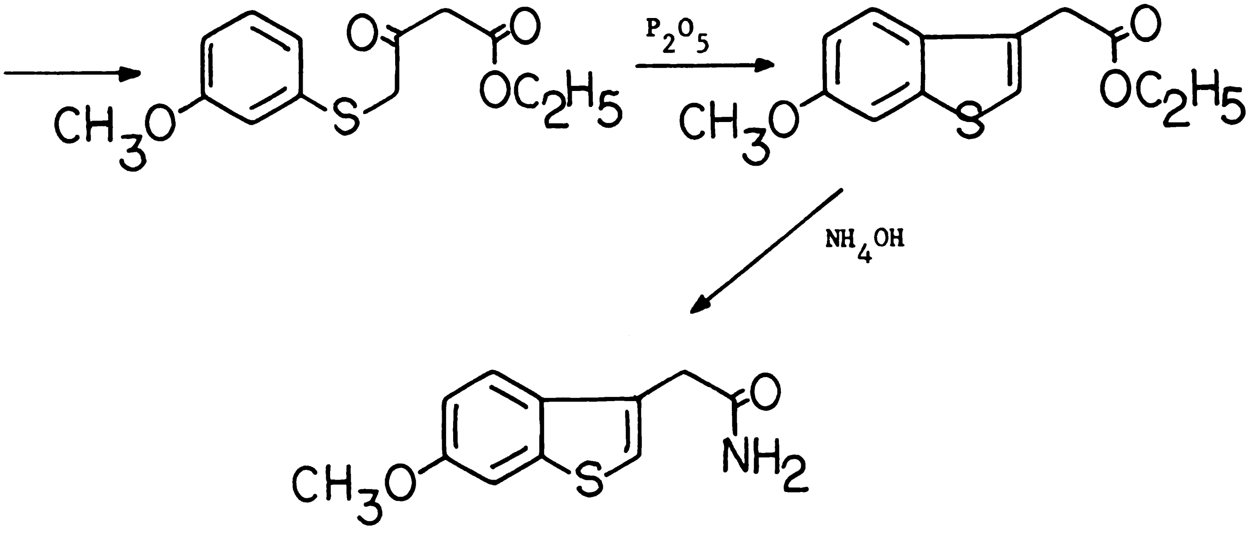
Placement of the 6-methoxy group (i.e. 11-methoxy in thiareserpine) was the initial consideration. Titus' original procedure (18) called for starting with meta-methoxy phenyl mercaptan (XXII) which he prepared in a six step procedure from the sodium salt of metanilic acid. It was decided the overall procedure could be considerably shortened by taking advantage of a procedure described by Godt and Wann (20).

Accordingly, meta-anisidine (XX) was diazotized and treated with potassium ethyl xanthate to give meta-methoxy phenyl xanthate (XXI) which was isolated but not purified. The crude xanthate upon alkaline hydrolysis gave the desired mercaptan (XXII) in a 31.6% overall yield.



Using the mercaptan (XXII) Titus' procedure was followed as outlined below to obtain the desired 6-methoxy-3-acetamido benzothiophene (XXIII) in 26% yield.





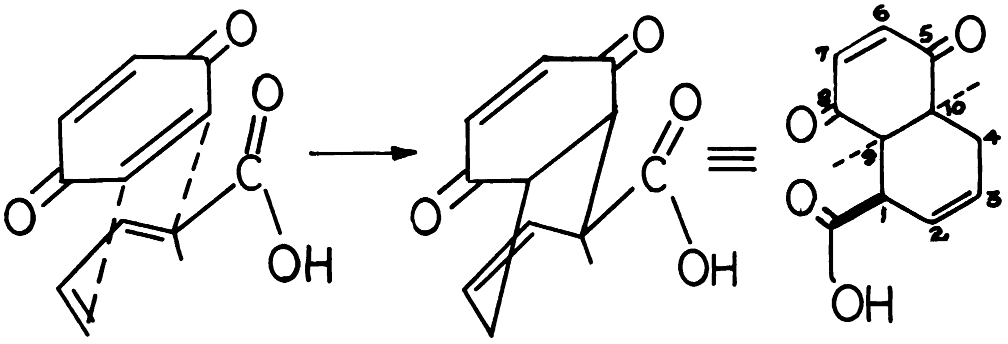
(XXIII)

Titus' attempt to reduce the amide to the amine with lithium aluminum hydride under a wide variety of experimental conditions gave only a trace of the desired amine (18). Browns' general procedure (19) for the reduction of amides to amines using "diborane" (actually borane-tetrahydrofuranate) readily gave the required amine (XIX) in 61.4% yield. The amine was found to rapidly absorb carbon dioxide from the atmosphere, and consequently had to be stored under nitrogen until needed. Herz (21) reported similar behavior for 3-(2-aminoethyl) benzothiophene. The melting point of the picrate derivative of the amine differed by only a few degrees from that of Herz' desmethoxy compound. With the amine in hand, work was directed toward preparing the sterically complicated E ring (XVIII-B).

Considerable work has been exerted toward finding new routes capable of effecting the synthesis of this reserpine intermediate in greater overall yield and/or fewer steps in the experimental proceedure (15). A number of these were utilized in the present work and will be described in detail at the appropriate junctures.

PART II The Bicyclic Series

The initial step involved the Diels-Alder condensation of quinone with vinylacrylic acid to form cis-5,8-diketo-1,4,5,8,9,10-hexahydronapthalene 1-carboxylic acid (XXIV). The stereochemical consequence of the reaction is as shown.



(XXIV)

The stereochemistry of the adduct may be rationalized by invoking two principles. Maximum molecular overlap favors a transition state in which the carboxyl group is oriented to a β position. The formation of a cis $\alpha\beta$ ring fusion may be explained on the basis of the Woodward-Hoffman rules (22) which state that an endo product should be expected for a concerted cycloaddition reaction. involving 2 + 4 π electrons.

The resultant product now has all three asymmetric carbons with the proper stereochemistry for ring E of the thiareserpine molecule. The reaction has, however, resulted in a racemic mixture of the two adducts.*

Advantage was now taken of the cis fusion of the rings to bring about selective reduction of the 5-keto group, using sodium borohydride in a slightly basic medium. As Woodward (14) pointed out, sodium borohydride is not particularly selective in its reducing capacity. However, from structure (XXV) it may be seen that interaction of the 1-carboxyl function with the 8-keto group can lead to steric repulsion of the borohydride ion.

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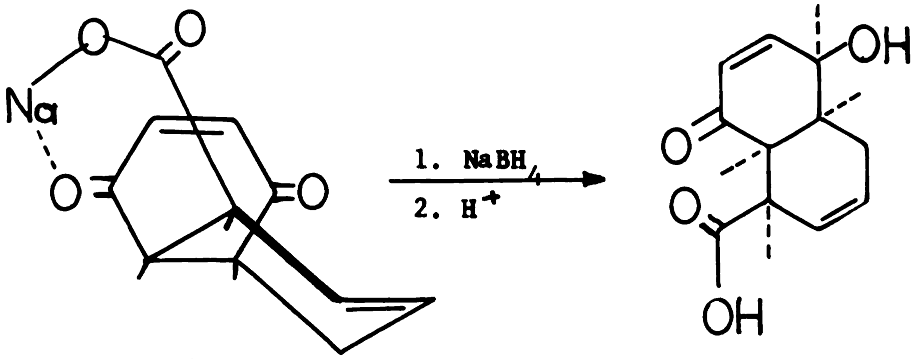
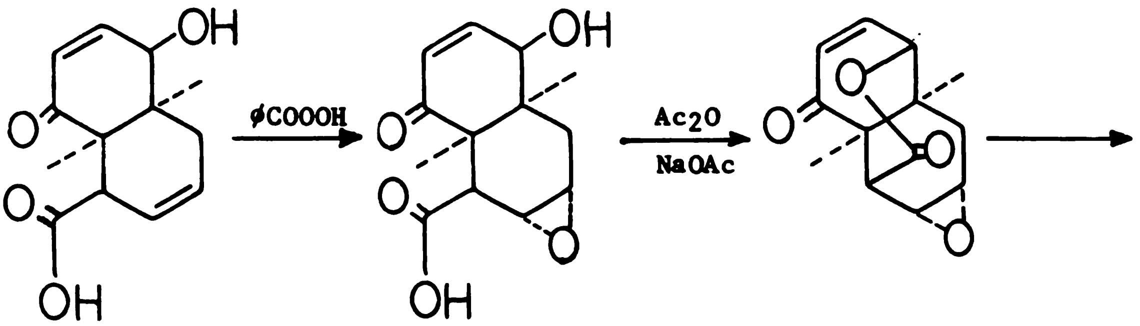
*Resolution has been carried out at this stage (12) but in view of the of the large quantities of material involved in the present work, this operation would have been rather cumbersome.



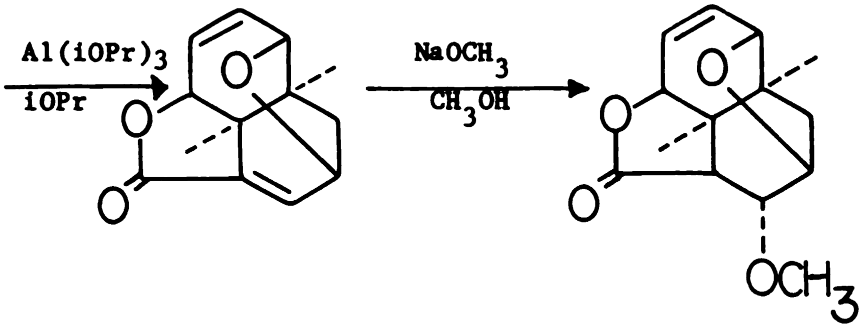
(XXV) (XXVI)

As a result the reduction proceeded smoothly to give the 5-hydroxy compound (XXVI). The keto-carboxyl interaction also aids in bringing about an even greater steric consequence. It serves to "freeze" into position the normal cage like structure of the cis decalin system. As a result attack by the borohydride ion must occur (for steric reasons) only from the rear or "convex" side of the molecule, thereby obtaining the α configuration of the C-5 hydrogen. Hinderence to attack at the concave side of the system was employed extensively throughout the entire (XVIII-B) synthesis.

Compound (XXVI) may be regarded as a point of juncture for two different routes directed toward obtaining an intermediate with the proper substituent at C-2 (C-17 in thiareserpine). This intermediate (XXVII) may be synthesized by the following route (14).

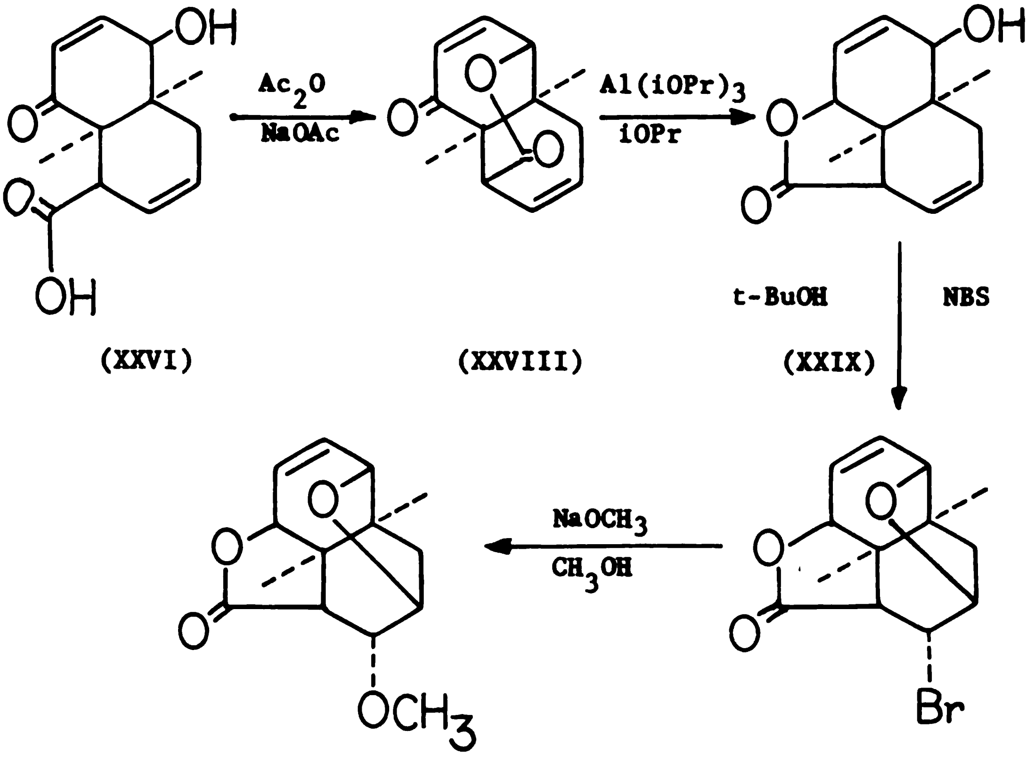


(XXVI)



(XXVII)

A significant increase in yield was obtained (22.2% vs. 13.9% for the former route) by employing a synthesis through the five member lactone as follows:



(XXVI)

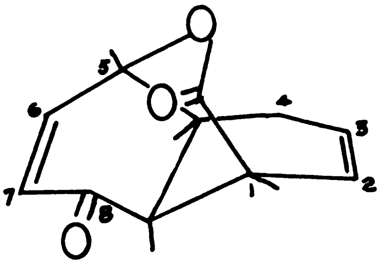
(XXVIII)

(XXIX)

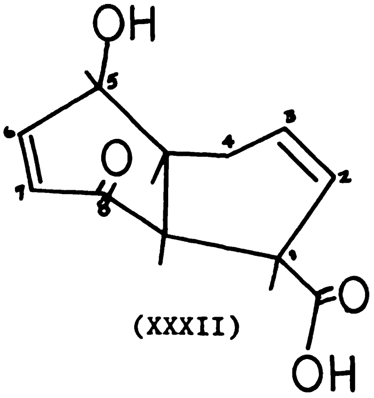
(XXVII)

(XXX)

Dehydration of the hydroxy ketone (XXVI) by heating a solution of it in benzene under reflux with acetic anhydride produced the 1,5 lactone in a 60% yield. It should be noted here that this fixes the geometry of the decalin ring system in one of the two alternate conformations, i.e. the C-1 carboxyl is oriented cis axial to the C-5 hydroxyl (XXXI) compared to the alternate structure (XXXII) where the carboxyl is oriented cis equitorial.

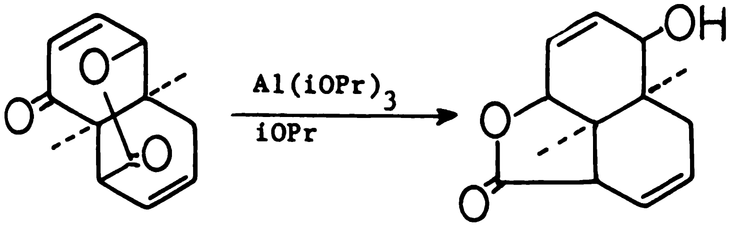


(XXXI)



(XXXII)

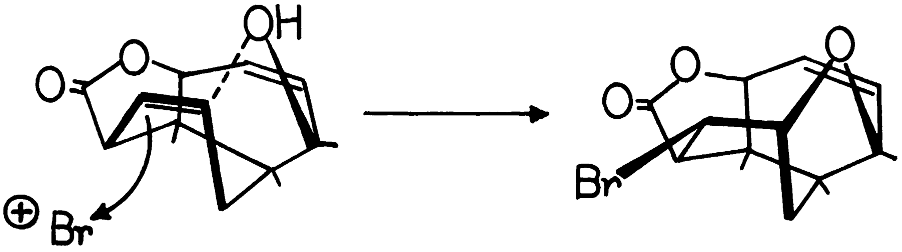
That the 1,5 lactone is thermodynamically less stable than the 1,8 lactone (XXIX) is readily shown by its facile formation from (XXVIII) upon a Meerwein-Verley-Pondorff reduction of the 8-ketone.



(XXVIII) (XXIX)

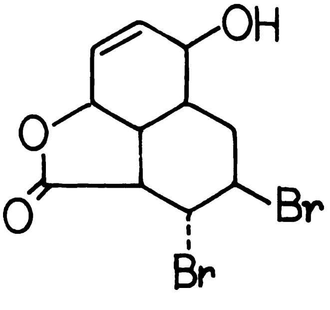
Thus, when the 1,5 lactone was heated in isopropanol containing a slight excess of aluminum isopropoxide, the 1,8 lactone resulted in a 53% yield. Woodward claimed a 90% yield for this translactonization and although this procedure was repeated several times in the present work (even using isopropanol dried over sodium and freshly distilled, together with freshly distilled aluminum isopropoxide) no improvement in yield could be realized.

Having obtained compound (XXIX) its structure was ready for introduction of the desired substituent at C-2. From structure (XXIX-A) it may be easily seen that the C-5 hydroxyl is readily disposed to aid in electrophilic attack upon a bromonium ion through theelectron rich $\Delta 2$ system, with concomitant formation of a 3,5 epoxide bridge. This leads directly to structure (XXX) since again the attacking species (in this case the bromonium ion) must occur from the convex side of the molecule.



(XXIX-A) (XXX)

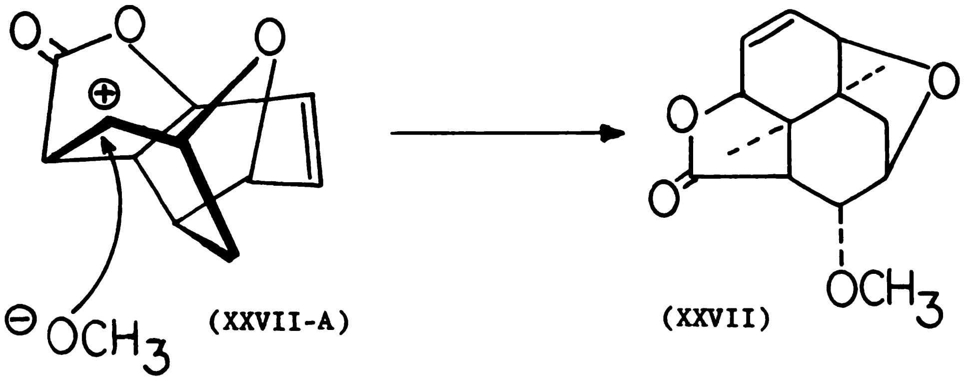
By treating compound (XXIX) with bromine in methylene chloride following Woodwards' procedure (14) the bromo-epoxide was indeed obtained. However, considerable bromination by addition also occured. Presumably the dibromo material would have structure (XXXIII).



(XXXIII)

In spite of the lack of experimental detail the procedure described by Velluz (12) for the preparation of compound (XXX). was utilized. This involved the bromination of (XXIX) with N-bromo succinimide in tert-butanol. Compound (XXX) was obtained in an 87% yield (compared with Woodwards' proceedure which gave a 47% yield). No detectable amount of the dibromo compound was produced. The increased yield of the product via the N-bromo succinimide route may be attributed to two factors. One, the increased polarity of the protic solvent, tert-butanol, leads more readily to the formation of a bromonium ion (23) and secondly the total bromine concentration is lower than in the case where elemental bromine is utilized directly.

The introduction of the thiareserpine C-17 α methoxy group was readily accomplished by treatment of the bromolactone (XXX) with sodium methoxide in methanol at room temperature. That the entering methoxy group has the same configuration as its bromo predecessor may be explained on the basis of an S_N1 reaction mechanism.



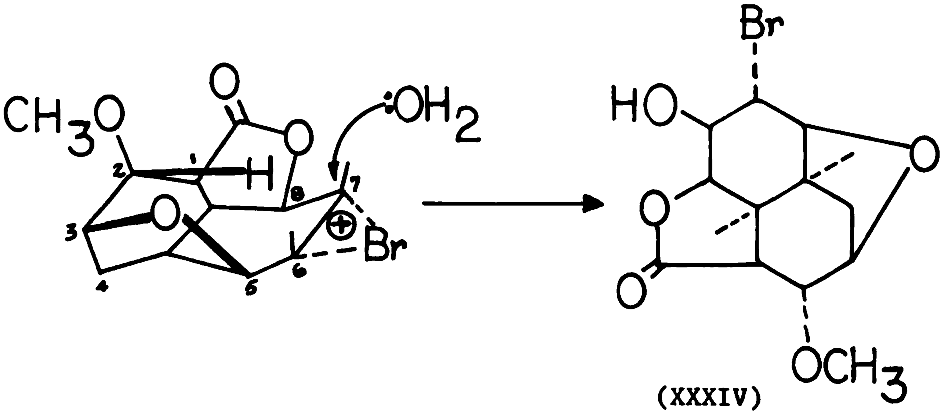
(XXVII-A)

(XXVII)

Dreiding models of the intermediate carbonium ion (XXVII-A) indicate the structure must remain in the same locked configuration despite the formation of an sp^2 C-2 carbon. Attack of the methoxy ion then occurs from the sterically accessible convex side to yield the methoxy lactone (XXVII).

Work was now advanced to place substituents in the upper ring which would allow subsequent conversion to the aldehyde (XVIII-B).

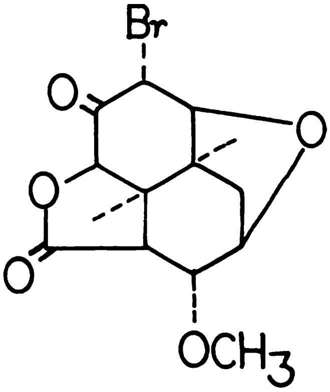
Addition of hypobromous acid to the Δ^{6-7} system was accomplished using N-bromo succinimide in dilute sulfuric acid. At first glance it may be difficult to visualize why the prefered bromohydrin is 6-bromo-7-hydroxy rather than 7-bromo-6-hydroxy. The structure may be assigned on the following basis. The initial attack is by the $\Delta^{6-7}\pi$ electron system on the bromonium ion to give structure (XXXIV).



(XXXIV)

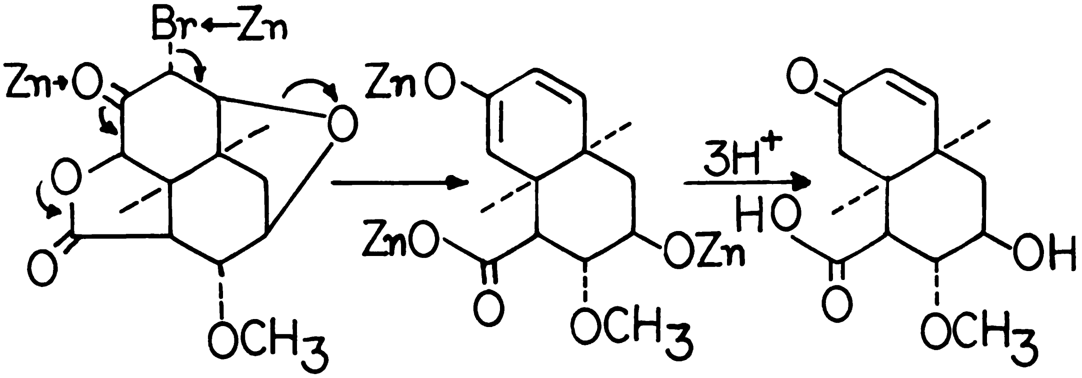
Inspection of carefully constructed Dreiding models reveals just slightly less steric interference at the C-7 carbon than the C-6 carbon (which suffers from steric hinderence by the methine hydrogen at C-2). Consequently attack by water proceeds to give the trans diaxial bromohydrin.

The oxidation of the bromohydrin was carried out using either Woodwards' (14) or Velluz' (12) procedure . Essentially both involve the use of chromium trioxide in a weak acidic medium. In the present work it was possible to obtain only a 33% yield of the bromo ketone (XXXVI) using Woodwards procedure with an aqueous acetic acid solvent. However, by using a mixture of acetic acid, water, and phosphoric acid employing a repetitive addition of the oxidizing medium in accord with Velluz' method, a 56% yield of the bromo ketone resulted.



(XXXVI)

A brilliantly fortuitous reductive process described by Woodward (14) was now carried out. By using zinc dust in glacial acetic acid, three objectives were met in one step, namely, a dehydrohalogenation to form a $\Delta^{5-6}\alpha,\beta$ unsaturated ketone, the opening of the 3,5 epoxy bridge to yield the 3β hydroxy function, and opening of the 1,8 lactone to form the 1β carboxylic acid (XXXVII). Mechanistically, Woodward portrays this process as follows:

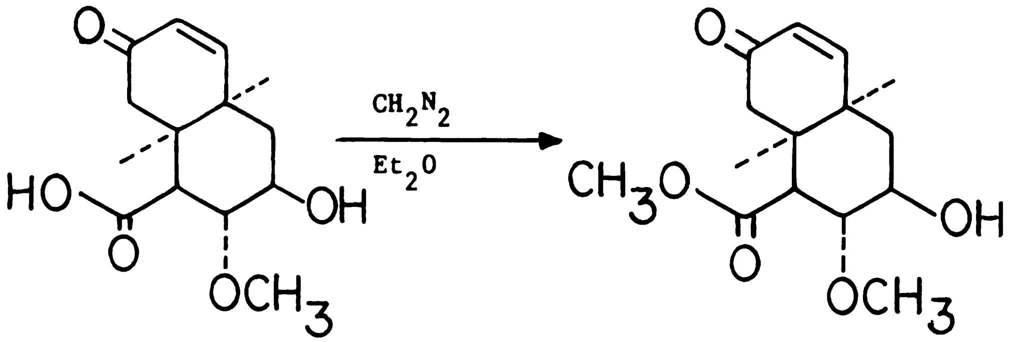


(XXXVII)

The sucess of this reaction depends on two factors. The period of reduction was very short (90 sec. in the present work). Furthermore, when acetic acid only slightly wet with water, was used, an over reduction of the system occurred.

However, by using a solvent of sufficiently low water content, prepared by distilling a mixture of glacial acetic acid containing 2% acetic anhydride, the reduction could be carried out in 78% yield. The product was readily identified on the basis of its ultraviolet spectrum, a maximum occuring at 227μm , (ϵ = 10,100) compared to Woodwards' (14) values of 228 mμ, (ϵ=10,000). When over reduction of the Δ^{5-6} system occured the λ_{max} frequently appeared in the neighborhood of 4000-6000.

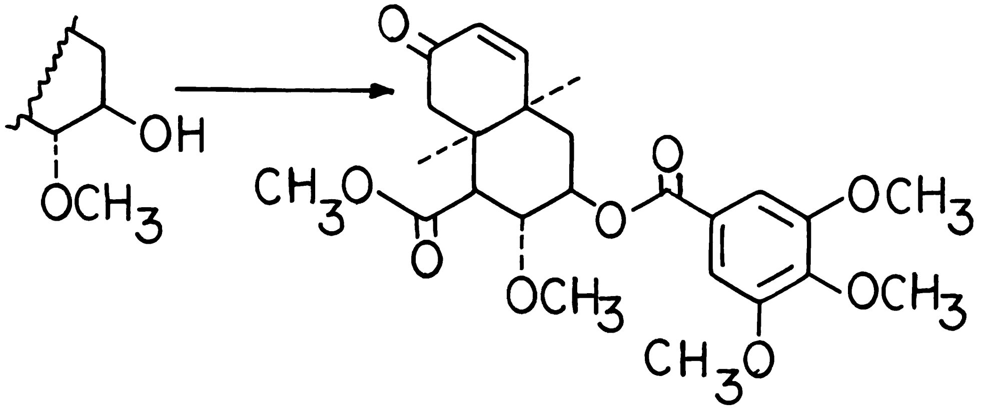
The acid was now esterified with a slight excess of ethereal diazomethane to obtain the 1β methoxy carbonyl (16β in thiareserpine) compound (XXXVIII) in a 98% yield.



(XXXVII) (XXXVIII)

At this juncture it was decided to introduce the 3,4,5-trimethoxy benzoyl group (XVIII-C) for two reasons. It markedly increased the total amount of material available, and it was felt that the introduction of this bulky substituent at this stage (Woodward introduced it only in the last stage of his work) would exert a favorable steric guidance effect on the later orientation of the hydrogen at the thiareserpine C-3 carbon. As evidence for support of this approach, Protiva (24,25) found that in his synthesis of 1-deaza-1-thiadeserpidine, the product was a 50/50 mixture of the C-3 epimers, when this group was introduced prior to the C/D ring closure.

Accordingly this ester (XXXIX) was prepared in a carefully dried mixture of pyridine and benzene by treating the alcohol (XXXVIII) with 3,4,5-trimethoxy benzoyl chloride.

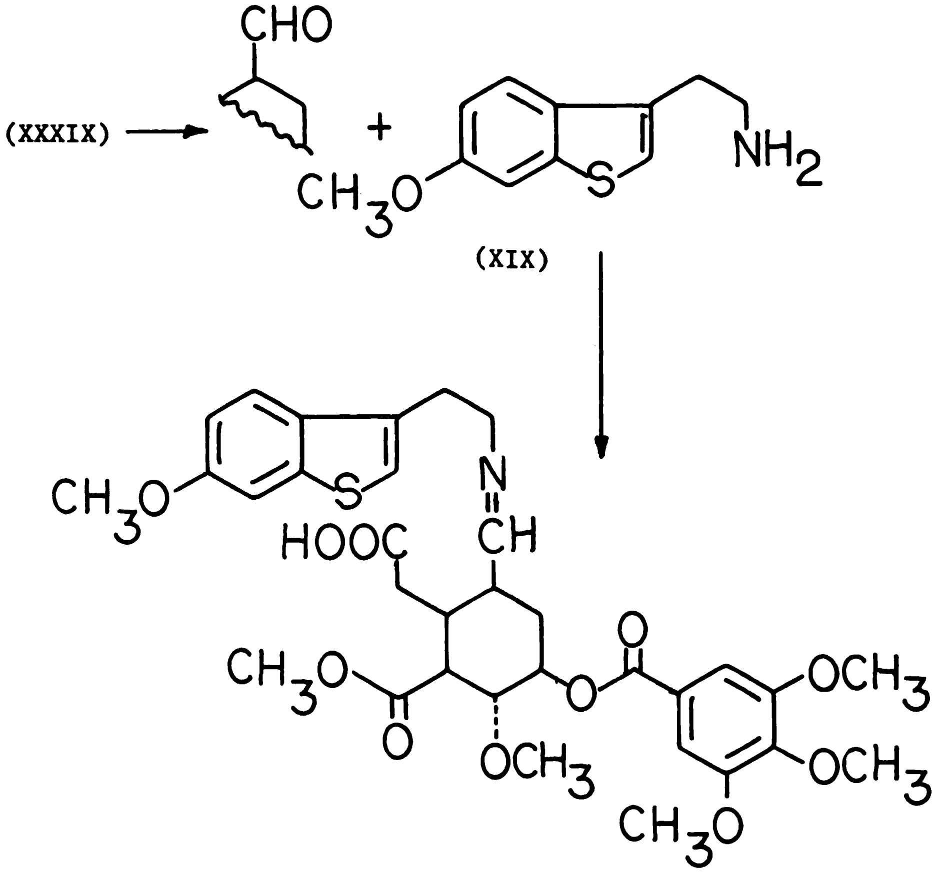


(XXXVIII) (XXXIX)

With the preparation of this compound (accomplished in 7.6% overall yield from XXIV) work could be directed towards its condensation with the thianapthyl amine system (XIX).

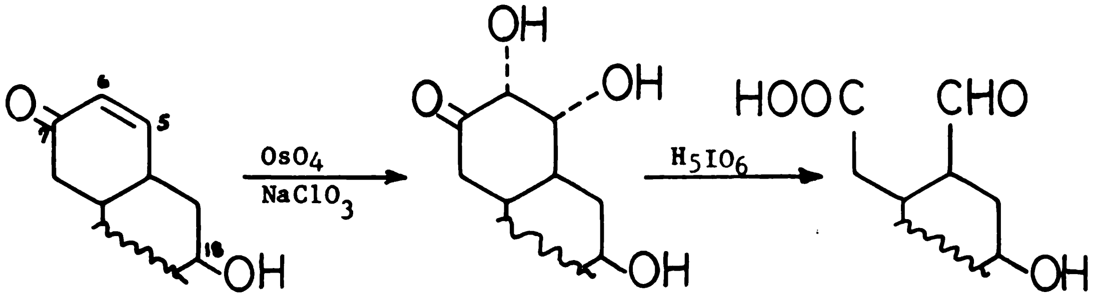
PART III The Tetracyclic and Pentacyclic Series

It was now desired to modify the upper ring of (XXXIX) by conversion of carbon 5 to a formyl group. This would allow condensation with the thianapthylamine (XIX) to form an aldimine (XXXXIV-A).



(XXXXIV-A)

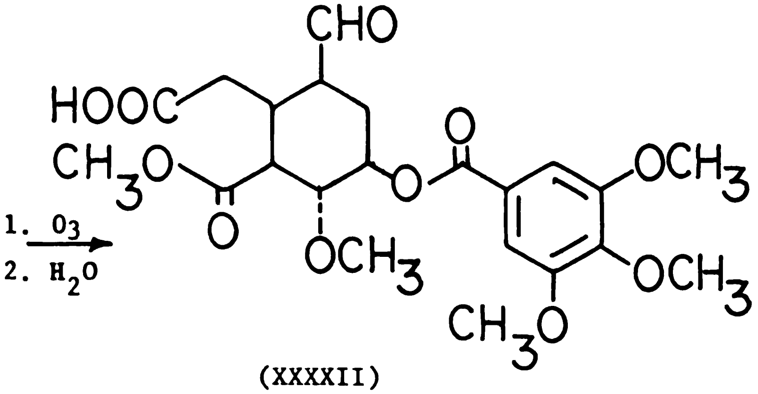
To effect this conversion, essentially two routes were open. Woodwards' procedure (14) called for the formation of the 5α,6α-dihydroxy-7-ketone (XXXX) from the 18β-hydroxy-Δ5-ene-7-one via osmium tetroxide and cleavage of the diol to the formyl acid (XXXXI) by means of periodic acid.



(XXXX) (XXXXI)

However, Velluz (12) prepared the intermediate (XXXXI) directly from the eneone by ozonolysis. In each case the C-6 carbon is lost as carbon dioxide. Blaha and his coworkers (26) prepared the aldehyde (XXXXII) from (XXXIX) by ozonolysis, although they did not purify it.

(XXXIX)

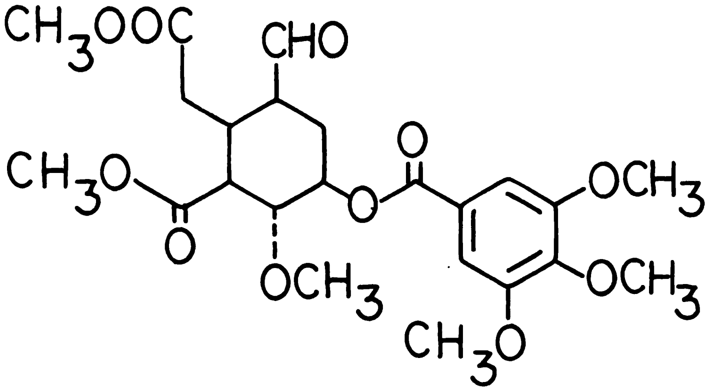


(XXXXII)

Since the ozonolysis procedure is one step shorter, more economically feasible, and less time consuming, it was adopted in the present work.

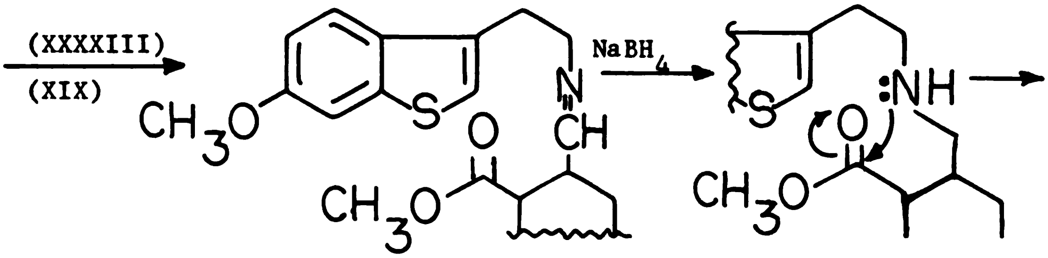
However, Blahas procedure gave very poor yields of the desired aldehyde as shown by the poor overall yield of the lactam (XXXXVI). Improved yields were obtained using a highly modified proceedure. Here the ozonolysis was carried out in methylene chloride at -30° using a solution of potassium iodide as an external indicator. Use of even a slight excess of ozone was found to decrease markedly the overall yield of the desired lactam (XXXXVI).

The aldehyde was characterized as its previously unknown 2,4-dinitrophenylhydrazone. Treatment of the aldehyde with ethereal diazomethane gave the triester (XXXXIII).

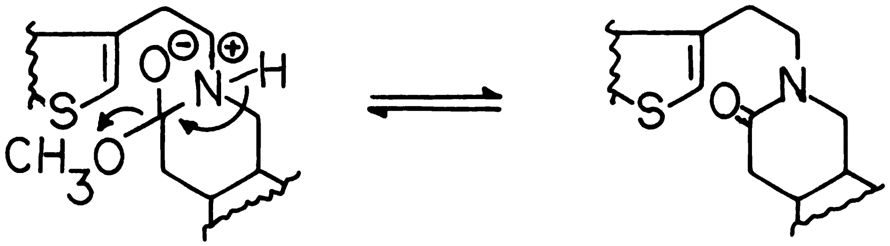


(XXXXIII)

Condensation of the triester (XXXXIII) with the thianapthylamine (XIX) would be expected to produce the aldimine (XXXXIV-B) which upon reduction with sodium borohydride would yield the amine (XXXXV). The amine nitrogen could then attack the acetate function to give the lactam (XXXXVI) by internal ammonolysis. The entire scheme being anologous to that described by other authors (12, 13, 14, 15, 24, 26) for the formation of such a system.



(XXXXIV-B) (XXXXV)



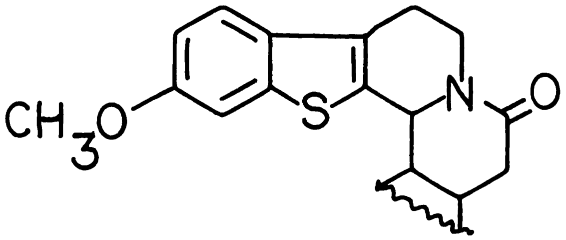
(XXXXVI)

These expectations were born out in the experimental procedures employed. In order to minimize the losses of the labile intermediates, they were not isolated but rather all operations were carried out in the original methylene chloride solvent used in the ozonolysis step.

Frequently the sodium borohydride reduction reduced not only the aldimine but also the 18β ester to the 18β alcohol as shown by the loss of absorption at 1330 cm^{-1} (assigned to C-C bending of the carbonyl carbon and the phenyl ring of the trimethoxy benzoyl function). In support of this assumption, Blaha and his coworkers (26) also found this hydrolysis to occur especially when the reaction mixture was heated to reflux with the sodium borohydride.

Therefore, in the present work the reduction was carried out at 0°. Even at this temperature the yellow orange color of the reaction mixture (due to the C-N double bond) was rapidly discharged upon treatment with the borohydride. The ammonolysis step proceeded rapidly merely by allowing the reaction mixture to stand a few minutes at room temperature.

It should be noted in passing that the formation of a 1,2,3,4-tetrahydro benzothieno[2,3-c]pyridine system via a Pictet-Spengler type ring closure, i.e. structure (XXXXVII) may be precluded on the basis of two points of experimental evidence.

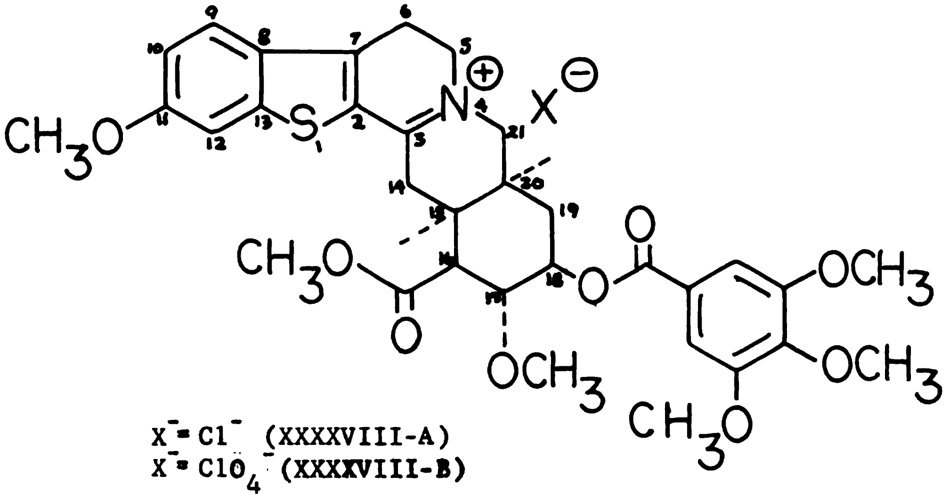


(XXXXVII)

The yellow orange color of the aldimine solution was stable at 0°, whereas if the ring closure had occured, the color would have been rapidly destroyed without the use of the reducing agent or it would have not developed at all. Secondly, the elemental analysis supports structure (XXXXVI) although structure (XXXXVII) can not be ruled out purely on the basis of the percentage values found. Structure (XXXXVI) $C_{33}H_{39}O_{10}NS$ demands C= 61.76%, H= 6.12%. Structure (XXXXVII) $C_{33}H_{37}O_{10}NS$ demands C= 61.95%, H= 5.83%. The analysis found C= 61.51%, H= 6.07%. However, considering the carbon/hydrogen ratio, compound (XXXXVI) has a C/H ratio of 10.091:1, whereas compound (XXXXVII) has a C/H ratio of 10.626:1. The ratio was found to be 10.133:1.

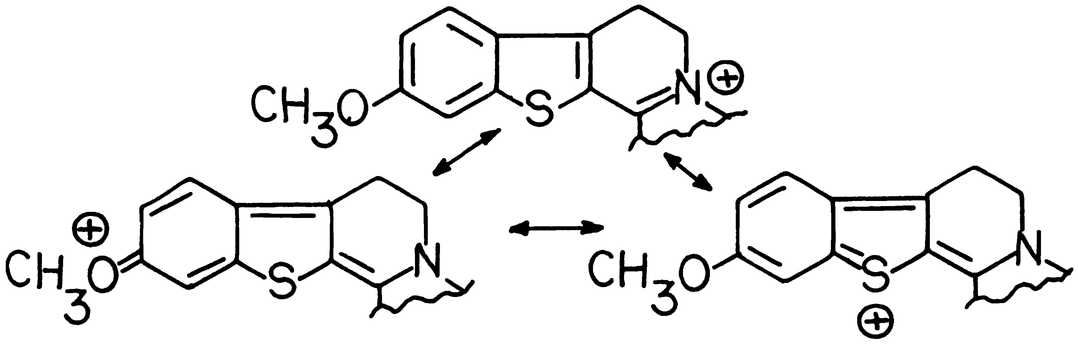
With the obtaining of the lactam (XXXXVI) in an overall yield of 75% from the aldehyde (XXXIX) an intermediate was now at hand to allow a condensation to form the complete ring skeleton of thiareserpine. To effect this ring closure a modified Bischler-Napieralski reaction was carried out.

The lactam (XXXXVI) was heated at 65° for 45 minutes with freshly distilled phosphorous oxychloride to obtain 1-deaza-1-thia-3,4-dehydro-reserpine chloride (XXXXVIII-A).



$X^- = Cl^-$ (XXXXVIII-A)
$X^- = ClO_4^-$ (XXXXVIII-B)

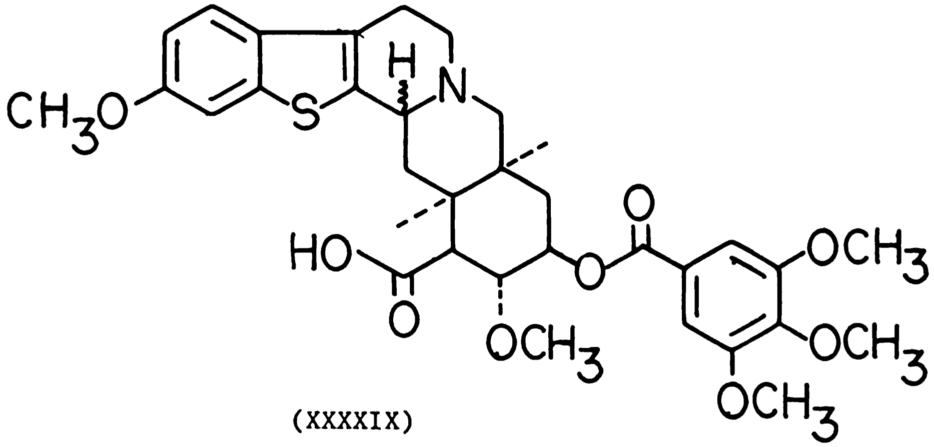
This rapid and facile ring closure is undoubtably aided by the presence of the electron donating 11-methoxy substituent which increases the nucleophilic character of the C-2 carbon. Thus, Protiva and his coworkers (24) found the 11-desmethoxy compound formed in good yield only after heating the corresponding lactam for two hours in phosphorous oxychloride in the presence of phosphorous pentoxide. This amorphous immonium chloride was converted to the perchlorate salt (XXXXVIII-B) for purification and subsequent reduction. The bright orange immonium perchlorate was found to have a pale orange fluorescence in the solid phase, a very intense blue-green-white fluorescence in a wide variety of solvents, and a strong absorption at 366mμ (log ε = 3.99) tailing off into the visible region. The fluorescent effect which further supports structure (XXXXVIII-B) is undoubtably the consequence of the highly conjugated charge delocalized aromatic system in which the positive charge of the N-4 nitrogen may be supported by the 11-methoxy oxygen and the thiophene sulfur as shown in the contributing resonance structures.



Advantage was taken of this fluorescent effect in the following reduction of the immonium salt to the desired 1-deaza-1-thia-reserpine.

The immonium perchlorate was heated under nitrogen with zinc dust in an acetone-water-tetrahydrofuran-perchloric acid system. The reaction mixture was illuminated at intervals with a long wave ultra violet light. The reduction was assumed complete when the fluorescence had fallen to only slightly perceptable levels.

On the neutralization of the acidic reaction mixture with ammonium hydroxide, two solid products were found. They were readily separated by extraction with boiling ethanol. The non soluble material (m.p. 340°) showed a strong broad absorption at 3450 cm^{-1} (KI) indicating the presence of a hydroxyl function. Since the absorption at 1330 cm^{-1} remained, this material was assumed to be the 16β carboxylate. (XXXXIX).

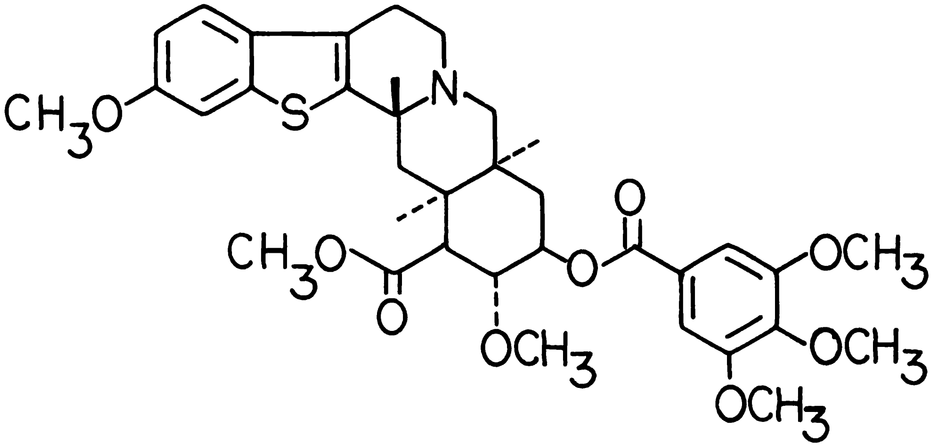


(XXXXIX)

The ethanol soluble portion of the reaction products did not possess this 3450 cm^{-1} absorption whereas the band at 1330 cm^{-1} remained, indicating that both ester functions had survived the reduction process.

The reduction introduced a new asymmetric center at C-3, and this material was shown to be homogeneous by thin layer chromatography ($R_f = 0.65$). Consequently it remained to be determined whether the C-3 hydrogen conformation was α or β.

Wenkert and Roychaudhuri (11) had determined that allo systems possess an absorption at 2740 cm^{-1} in the infrared, while epiallo systems (i.e. those having a C-3β hydrogen, such as reserpine) do not have this absorption. The validity of extending this point in the present study has its basis in the work of Protiva and Jirkovsky (24) which established that 1-deaza-1-thia-isodeserpidine (i.e. 11-desmethoxy isothiareserpine) does have an absorption at 2760 cm^{-1} in the infrared. The infrared spectrum of the ethanol soluble reduction product does not possess this absorption, p.29 and as a consequence must belong to the epiallo system. Therefore the compound synthesized is the desired 1-deaza-1-thia-reserpine (L).



(L)

For comparison the infrared spectrum, p29 of the synthesized thiareserpine is shown superimposed on the spectrum of an equimolar mixture of 6-methoxy 3-2(piperidinoethyl) benzothiophene, methyl cyclohexane carboxylate, and methyl 3,4,5-trimethoxy benzoate. The ultraviolet spectrum of the thiareserpine is compared in a similar manner, p.30.

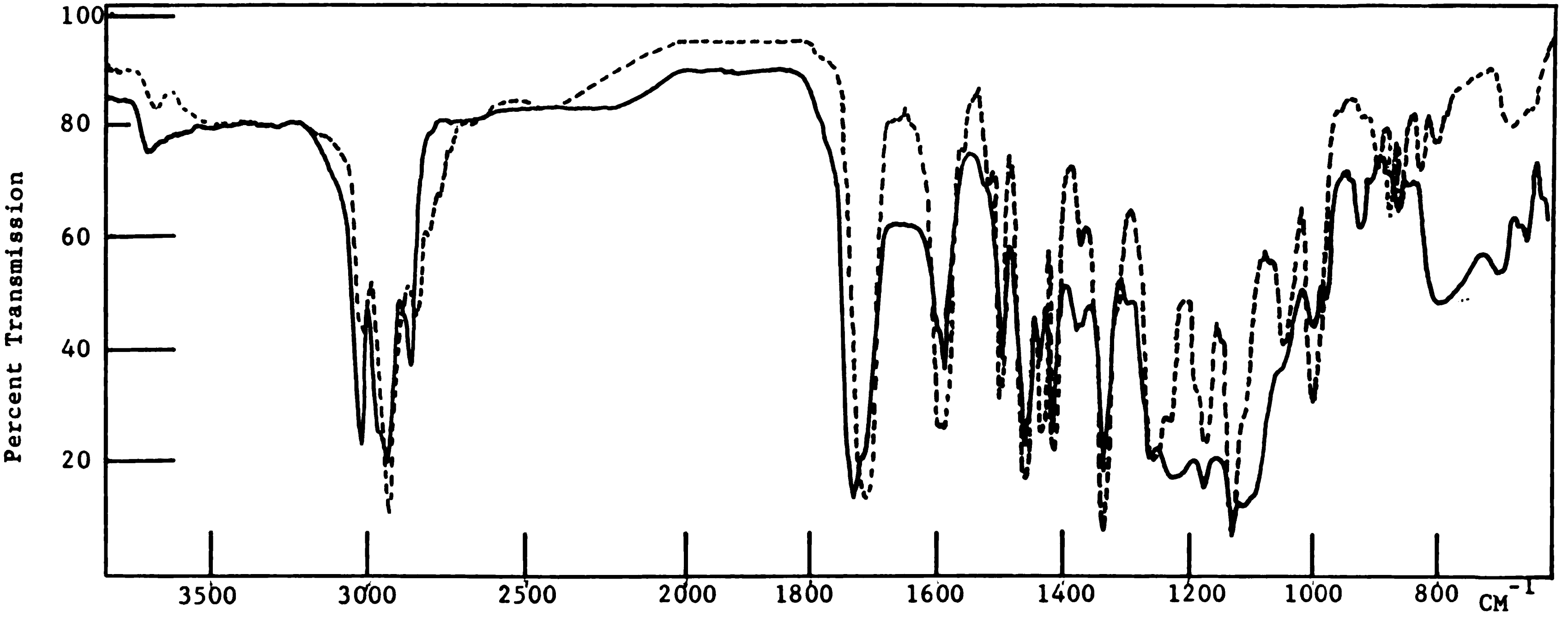


Fig. 1. The Infrared Spectrum of 1-Deaza-1-Thia-Reserpine ——— and a 0.100 M Mixture of Methyl Cyclohexaxne Carboxylate, Methyl 3,4,5-Trimethoxy Benzoate and 6-Methoxy-3-2(Piperidinoethyl) Benzothiophene ------ in Chloroform.

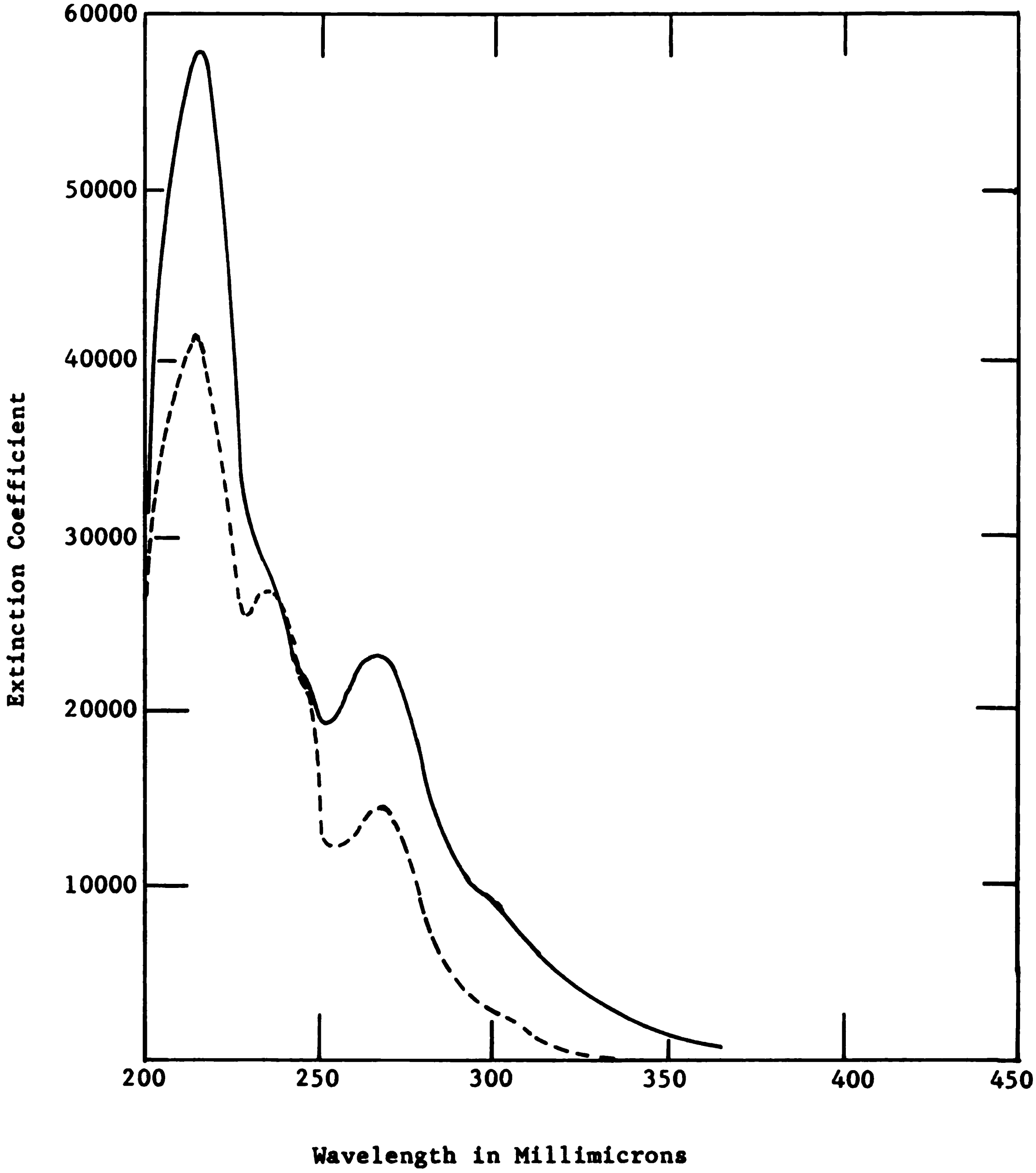
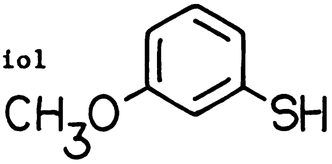


Fig. 2. The Ultraviolet Spectrum of 1-Deaza-1-Thia-Reserpine ——— and a 0.100 X 10^{-4} M Mixture of Methyl Cyclohexane Carboxylate, Methyl 3,4,5-Trimethoxy Benzoate and 6-Methoxy-3-2(Piperidinoethyl) Benzothiophene - - - - - - - - - in 95% Ethanol.

EXPERIMENTAL

All melting points are uncorrected and were determined on an Electrothermal melting point apparatus. Infrared spectra were determined with a Beckman model IR5-A prism spectrophotometer or a Perkin-Elmer model 237B grating infrared spectrophotometer, in either chloroform solution or as potassium iodide pellets. Ultra violet spectra were determined with a Beckman model DB, a Beckman model DK2-A instrument, or a Unicam SP800 recording spectrophotometer. All ultraviolet spectra were determined in 95% ethanol. Ozone was generated employing a Wellsbach model T-23 ozonator.

Preparation of Meta-Methoxy Benzene Thiol
C_7H_8OS M.W. 140



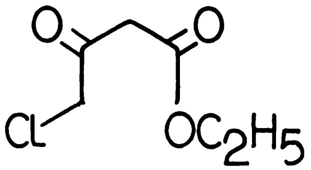
(XXII)

This compound was prepared by a slight modification of the procedure described by Godt and Wann (20). With constant stirring, 113 g. (0.810 mole) of meta-anisidine was slowly added to a mixture of 150 g. of crushed ice and 150 ml. of conc. hydrochloric acid. The solution of the amine hydrochloride was cooled in an ice bath and an ice cold solution of 59.4 g. (0.860 mole) of sodium nitrite in 140 ml. of water was added at such a rate that the reaction temperature was maintained below 5°. The diazonium solution was stored in an ice bath and added in small portions with constant stirring during a three hour period to a solution of 152 g. (0.947 mole) of potassium ethyl xanthate in 200 ml. of water heated to 40-45°. The reaction solution was stirred an additional half hour following the addition of diazonium solution. The red oily layer of crude product was separated and the aqueous layer was extracted with ether (2X200 ml.). The oil and ether extracts were combined, washed with water (2X100 ml.) and dried over calcium chloride. The ether was removed in a rotary evaporator at water pump pressure to leave the meta-methoxy phenyl xanthate as a red brown liquid.

The xanthate was dissolved in 500 ml. of 95% ethanol and heated to reflux with stirring. External heating was discontinued and the solution was maintained at its reflux temperature by the careful addition of 177 g. (3.00 moles) of potassium hydroxide pellets through the condenser. The stirred solution was refluxed ten hours, cooled to room temperature, and then poured cautiously into a beaker containing 350 ml. of conc. hydrochloric acid and 500 g. of ice. The resulting oily suspension was extracted with benzene (5X100 ml.). The combined extracts were dried over magnesium sulfate and the solvent removed in vacuo. The residue was vacuum distilled and the fraction boiling from 70-75° $^{2\text{ torr.}}$ was collected. The yield was 35.7 g. (0.255 mole, 31.6%). Literature values (20) b.p. 74.5° $^{2\text{ torr.}}$, in 29% yield.

Preparation of Ethyl (3-keto-4-chloro) Butanoate

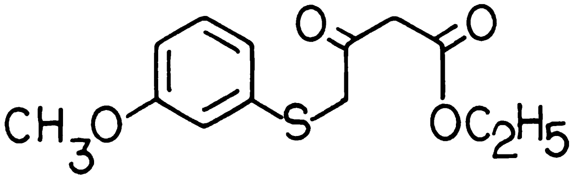
$C_6H_9ClO_3$ M.W. 164



The procedure employed in obtaining this material is essentially that of Titus (18). A 2 liter, 3 neck flask fitted with dropping funnel, overhead stirrer, and condenser topped with a drying tube was charged with 24.0 g. (1.00 mole) of magnesium chips, and 1. g. of mercuric chloride. By means of the dropping funnel, 50 ml. of a solution of 245 g. (2.00 moles) of ethyl chloroacetate in 200 ml. of anhydrous ether was added to the flask. The flask was gently heated by immersion in a water bath until the reaction had been initiated as evidenced by the formation of a milky suspension. The water bath was removed and the remainder of the ester solution was added at a rate sufficient to maintain the reaction mixture under reflux. When the magnesium had been nearly consumed, external heat was applied and the reaction mixture allowed to reflux four hours. Finally it was hydrolyzed by pouring it onto crushed ice with stirring. The precipitate of magnesium salts was dissolved by slowly adding 4 N sulfuric acid until the aqueous solution reached a pH of 5 (Hydrion B). The ethereal layer was separated and the aqueous layer was extracted with ether (3X200 ml.). The ethereal solutions were combined,dried over magnesium sulfate, and filtered. The ether was removed by flash distillation. The oily residue was vacuum distilled and the material boiling $80-90^{\circ}$ $^{9\ \mathrm{torr.}}$ was collected. The yield was 78.3 g. (0.476 mole, 47.6%) $n_D^{24^{\circ}}$ 1.4460. Literature values (27) $100-103^{\circ}$ $^{12\ \mathrm{torr.}}$, $n_D^{17^{\circ}}$ 1.4545.

Preparation of Ethyl 4-(meta-methoxy phenyl mercapto)-3-Keto Butanoate

$C_{13}H_{16}O_4S$ M.W. 268

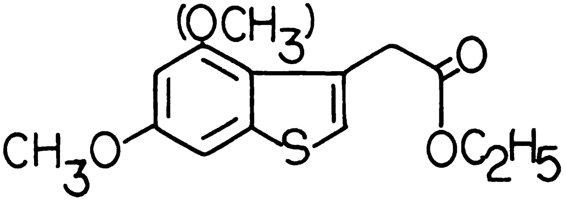


The experimental procedure described by Titus (18) was slightly modified to prepare this ester.

A 500 ml. 3 neck flask equipped with an overhead stirrer, dropping funnel, and a thermometer extending below 180 ml. of pyridine in the flask was supported in an ice bath. With constant stirring, 35.8 g. (0.256 mole) of meta-methoxy benzene thiol was added in one portion. This was followed by the dropwise addition of 41.9 g. (0.256 mole) of ethyl (3-keto-4-chloro) butanoate at such a rate that the reaction temperature was maintained between 25-30°. The ice bath was removed and the solution was heated to 70-80° for ten minutes on a steam bath after which it was allowed to cool to room temperature. The pH of the solution was adjusted to 5 (Hydrion B) by the slow addition of 6 N hydrochloric acid, approxiametly 400 ml. being required. The resulting oil which separated was removed and the aqueous layer was extracted with ether (2X50 ml.). The ether extract was dried over magnesium sulfate, filtered, and the ether was removed in a rotary evaporator to yield a yellow odoriferous residue. Since Titus reported decomposition upon attempting to distill this material, it was used without further purification in the suceeding ring closure step. The yield of the crude material was 62.4 g. (0.233 mole 91.0%).

Preparation of Ethyl [6-(and -4-) Methoxythianapthyl-3-] Acetate

$C_{13}H_{14}O_3S$ M.W. 250

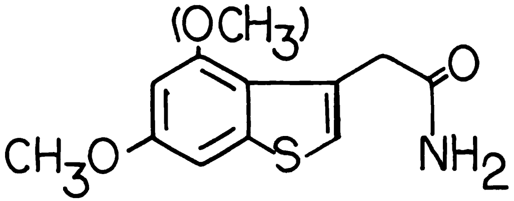


Titus' experimental procedure (18) was slightly modified for the preparation of this material. A solution of 30.6 g. (0.114 mole) of ethyl 4-(meta-methoxy phenyl mercapto)-3-keto butanoate in 200 ml. of chlorobenzene was treated with 50 ml. of 85% ortho phosphoric acid and 100 g. of phosphorous pentoxide. After heating the reaction mixture at its reflux temperature for three hours, the chlorobenzene was decanted and replaced with 200 ml. of dry benzene, and the reaction mixture was again heated under reflux for three hours.

The benzene was decanted and combined with the previous chlorobenzene solution. The aromatic solution was washed succusively with 10% sodium bicarbonate solution (50 ml.) and water (2X50 ml.). The solvents were removed in a rotary evaporator at 80° 20 torr.. The reddish orange oil was used without further purification to prepare the corresponding amide. The crude yield was 25.6 g. (0.102 mole, 90.5%).

Preparation of 6-(and-4-)-Methoxy Thianapthyl 3-Acetamide

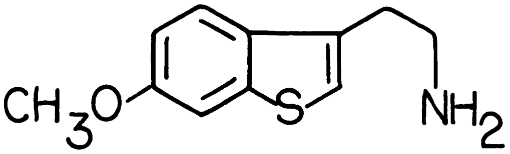
$C_{11}H_{11}NO_2S$ M.W. 221



(XXIII)

Titus' laboratory procedure (18) was used with some modification to obtain this amide. A 4 liter resin kettle equipped with an air driven overhead stirrer was charged with 400 ml. of conc. ammonium hydroxide. To this, 17.0 g. (0.0692 mole) of ethyl 6-(and-4-) methoxythianapthyl-3-) acetate was added. The mixture was stirred for seven days at room temperature. The resulting crude gummy amide was dissolved in 100 ml. of boiling ethanol. Upon cooling, the amide crystallized. It was collected by vacuum filtration and recrystallized from 70 ml. of hot ethanol to yield 4.82 g. (0.0218 mole, 31.7%) of pale yellow plates m.p. 192-193°. The 4-methoxy isomer was recovered from the mother liquor of the 6-methoxy compound as follows. The alcohol filtrate was reduced to near dryness by evaporation in vacuo. The residue was dissolved in a minimum amount of chloroform and placed on an alumina column (Matheson Activated Alumina, 80-200 mesh, dried at 200° for 18 hours) measuring 3X45 cm. The column was eluted with chloroform which was collected in 50 ml. fractions. Fractions 10 through 13 inclusive contained the 4-methoxy thianapthyl-3- acetamide. The melting point for the 4-isomer was 199-200°. Literature values (18) for the 4 isomer 200-200.5°, for the 6 isomer 192.8-193.3°.

Preparation of 6-Methoxy-3-(2-Aminoethyl) Benzothiophene
$C_{11}H_{13}NOS$ M.W. 207



(XIX)

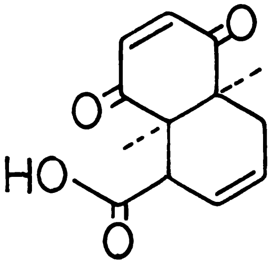
A solution of 40 ml. of borane tetrahydrofuranate (Metal Hydrides Inc., Beverly, Mass.) was cooled to 0° under nitrogen. With constant stirring, 1.10 g. (5.00 mmoles.) of 6-methoxy-3-thianapthyl acetamide was added in one portion. The tetrahydrofuran insoluable amide rapidly went into solution with the evolution of gas. The reaction solution was allowed to warm to room temperature and was then heated under reflux for eight hours, after which it was set aside at room temperature for sixteen hours. The solution was carefully acidified with 20 ml. of 6 N hydrochloric acid. The tetrahydrofuran was removed in a rotary evaporator at water pump pressure under nitrogen. The aqueous residue was cooled in an ice bath. The solution was adjusted to a pH of 10 (Hydrion B) with 5 M sodium hydroxide and extracted with ether (5X30 ml.). The ether extracts were combined, dried over magnesium sulfate, and flash distilled. The oily yellow liquid remaining was vacuum distilled to yield 0.636 g. (3.08 mmoles., 61.4%) of the desired amine boiling from 130-140° $^{0.3 \text{ torr.}}$, n_D^{25} 1.5964.
The rapid reaction of the amine with atmospheric carbon dioxide made it necessary to store it under nitrogen. A picrate derivative of the thianapthylamine was prepared in benzene in the usual manner and recrystallized three times from ethanol for analysis, melting point 177-178°.

Analysis: Calculated for $C_{17}H_{16}N_4SO_8$:C, 46.78; H, 3.69; N, 12.84; S, 7.35; O, 29.34. Found:C, 46.60; H, 4.26; N, 12.77; S, 7.31; O, (by difference) 29.06.

THE BICYCLIC SERIES

Preparation of cis-5,8-Diketo-1,4,5,8,9α,10α-Hexahydronapthalene-1β-Carboxylic Acid

$C_{11}H_{10}O_4$ M.W. 206



(XXIV)

I Vinylacrylic Acid

A sufficient quantity of this material was prepared by a slight modification of Woodwards' procedure (14) and combining such preparations. A typical synthesis follows. With vigorous stirring, 240 g. (2.73 moles) of malonic acid was dissolved in 520 ml. of anhydrous pyridine. After precooling the solution to 5° by immersion in an ice bath, 160 g. (3.50 moles) of acrolein (Matheson practical grade, stabilized with hydroquinone) was added dropwise during a half hour while maintaining the reaction temperature below 12°. Following the addition of the acrolein, the reaction mixture was stirred at 0-5° for three hours, then heated to 35-40° in a water bath with stirring for an additional five hours. The reaction mixture was then quickly poured into 520 ml. Of 50% aqueous sulfuric acid (1:1 conc.) previously cooled to -10°. The temperature of the acid solution was maintained below 20° by immersing it in an isopropanol-dry ice bath. The acid (litmus) reaction mixture, which now contained considerable precipitate, was extracted six times with ether (3X500 ml., 3X300 ml.). The ethereal extracts were combined and ca. 2000 ml. of ether was removed by distillation. The residue in the distillation flask was stoppered and set aside overnight at -78°.

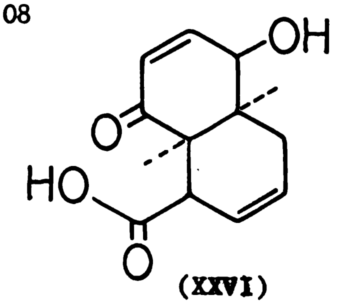
II The Quinone Adduct

A 3 liter, 3 neck flask equipped with condenser, overhead stirrer, thermometer, and Dean-Stark trap was charged with 140 g. (1.30 moles) of quinone (Eastman Yellow Label) and 600 ml. of benzene. The vinylacrylic acid solution, prepared as described above was added in one portion, and the reaction mixture was heated at its reflux temperature with vigorous stirring. The solvent was slowly removed by distillation through the Dean-Stark trap until a still head temperature of 60° was reached, after which the reaction mixture was heated under reflux for two hours. During this time the adduct product separated as a gray precipitate.

The solvent was then distilled until the reaction mixture had been reduced to half of its initial volume. The reaction temperature was reduced to 50° and the precipitated adduct was collected by vacuum filtration. The mother liquor was returned to the reaction vessel and again concentrated to half of its volume by distillation and then filtered hot. The combined product material was washed with two liters of pentane containing 100 ml. of acetone. The crude adduct was dissolved in 800 ml. of acetone and 1000 ml. of pentane was added. The material was allowed to crystallize slowly overnight in the ice box and was then recovered by vacuum filtration. The yield was 92.4 g. (0.402 mole, 31.0% overall) of the adduct in the form of pale yellow plates. The melting point of 215-225° was identical to that of Woodwards' as was the infrared spectrum (as a KI pellet) (14).

Preparation of cis-5β-Hydroxy-8-Keto-1,4,5,8,9α,10α-Hexahydronapthalene-1β-Carboxylic Acid

$C_{11}H_{12}O_4$ M.W. 208

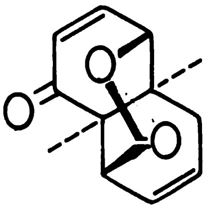


(XXVI)

This material was prepared as described by Woodward (14) using a slightly different product isolation procedure.

A 4 liter resin kettle immersed in an ice bath and equipped with overhead stirrer was charged with 700 ml. of water and 107 g. (0.522 mole) of the diketo adduct (XXIV). A thin layer of ethyl acetate was maintained over the vigorously stirred slurry to control foaming while a solution of 43.8 g. (0.522 mole) of sodium bicarbonate in 700 ml. of water was slowly added. When the adduct had dissolved, 12.5 g. (0.330 mole) of sodium borohydride dissolved in 40 ml. of water was added in small portions during a period of 15 minutes. The reaction mixture was stirred an additional 15 minutes, then acidified (congo red) with 20% (4:1 conc.) of aqueous sulfuric acid. The acidic solution was allowed to stir an additional 30 minutes at 0°. The product was separated by vacuum filtration and air dried to yield 87.0 g. (0.418 mole, 79.8%) of material melting at 175-178°. Reported melting point (14) 179-180°. This hydroxy ketone was identical to that reported by Woodward by infra red spectrum in a KI pellet.

Preparation of 8-Keto-1,4,5,8,9α,10α-Hexahydronapthalene-1β-
Carboxylic acid 1,5-Lactone
$C_{11}H_{10}O_3$ M.W. 190



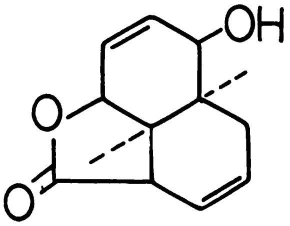
(XXVIII)

This compound was prepared following the procedure of Woodward (14). A vigorously stirred mixture of 20.0 g. (0.0960 mole) of the hydroxy ketone (XXVI), 20 ml. of acetic anhydride, 4 g. of anhydrous sodium acetate, and 400 ml. of anhydrous benzene was heated at its reflux temperature for one hour. Heating was discontinued and the reaction mixture was cooled by immersion in an ice bath. Approxiametly 200 ml. of ethyl acetate along with 50 ml. of ice cold water was added.

The organic layer was separated and extracted with 50 ml. of 10% sodium bicarbonate solution. The aqueous phases were combined and washed with ethyl acetate (3X30 ml.). The ethyl acetate solutions were combined, washed with saturated sodium chloride solution (2X25 ml.) and dried over 10 g. of anhydrous sodium sulfate. The filtrate was concentrated to 20 ml., 10 ml. of ether was added, and the mixture was set aside for several hours in the cold. The crystalline lactone which separated was recovered by filtration, washed with ether and air dried to obtain a pale yellow solid weighing 11.0 g. (0.0579 mole, 60.4%) which melted at 121°. The melting point was not reported by Woodward but the infrared spectrum in KI was identical to that reported (14).

Preparation of 5β-Hydroxy-1,4,5,8,9α,10α-Hexahydro-1β-Napthoic acid 1,8-Lactone

$C_{11}H_{12}O_3$ M.W. 192

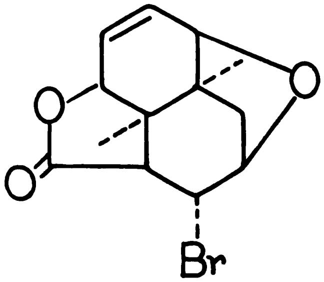


(XXIX)

The material was prepared by a slight modification of Woodwards' method (14). To 30.7 g. (0.162 mole) of the 1,5 lactone (XXVIII) suspended in 400 ml. of anhydrous isopropanol, 37.0 g. (0.181 mole) of aluminum isopropoxide (Eastman Yellow Label) was added. The reaction mixture was stirred and heated to remove the isopropanol by distillation which was checked for its acetone content with aqueous 2,4-dinitro phenylhydrazine hydrochloride solution (28). From time to time fresh isopropanol was added to maintain the reaction level approxiametly constant. After two hours the distillate failed to give a positive acetone reaction.

The reaction solution was heated at its reflux temperature for an additional 45 minutes. The solvent was removed in a rotary evaporator. The residue was dissolved in 400 ml. of ethyl acetate and cooled to 0°. It was added to 600 ml. of a solution of 500 g. of potassium sodium tartrate and 37 g. of sodium bicarbonate in water. The milky aqueous phase was separated and extracted with ethyl acetate (3X100 ml.). The ethyl acetate solutions were combined and washed with saturated sodium bicarbonate solution (3X50 ml.). Finally the solution was dried with 50 g. of anhydrous sodium sulfate and filtered. The solvent was removed in a rotary evaporator, leaving a viscous yellow colored residual oil which solidified when set aside. It was triturated with ether to give a nearly pure white solid lactone, melting point 116-118°, reported (14) 120-122°. The yield was 16.4 g. (0.0863 mole, 53.4%). The infrared spectrum (in chloroform) was identical to that reported by Woodward(14).

Preparation of 2α-Bromo-1,2,3,4,5,8-cis-9α,10α-Octahydro-6-ene-1β-
(3,5-epoxy)-Napthoic Acid 1,8-Lactone
$C_{11}H_{11}O_3Br$ M.W. 271



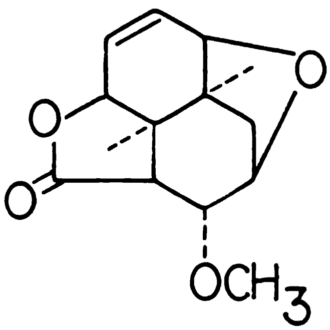
(XXX)

The preparation described by Velluz (12) was modified slightly for the preparation of this compound. An 11.5 g. (0.600 mole) quantity of the previously prepared 1,8 lactone (XXIX) was dissolved by heating it in 120 ml. of tert-butanol, on the steam bath. The steam bath was removed and the hot solution was allowed to cool to room temperature, in one portion 11.1 g. (0.0623 mole) of N-bromo succinimide was added to the solution.

The reaction solution was stirred for ten minutes during which most of the N-bromo succinimide had dissolved. The mixture was then evaporated to dryness in vacuo. The residue was suspended in 100 ml. of water and filtered. The solid bromo compound remaining was dried to obtain 14.2 g. (0.0522 mole, 87.2%) of pale tan colored crystalline material melting at 120-122°. Reported (14) 120-124°. This material was identical by infrared spectrum (in chloroform) to that reported by Woodward for the bromo lactone (XXX) (14).

Preparation of 2α-Methoxy-1,2,3,4,5,8-cis-9α,10α-6-ene-Octahydro-1β-(3,5-epoxy)-Napthoic Acid 1,8-Lactone

$C_{12}H_{14}O_4$ M.W. 222

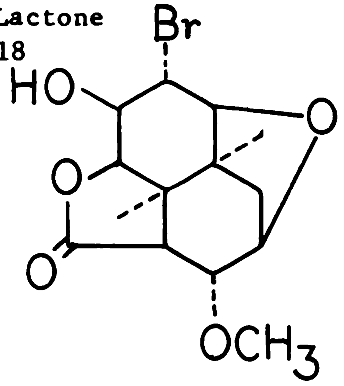


(XXVII)

This material was prepared as described by Woodward (14). A 5.59 g. (0.0206 mole) quantity of the bromo lactone (XXX) was dissolved in 80 ml. of anhydrous methanol, previously dried over magnesium and freshly distilled. A 50 ml. volume of sodium methoxide solution, prepared by dissolving 0.49 g. (0.021 mole) of sodium in 50 ml. of anhydrous methanol, was added in one portion. The reaction mixture was set aside at room temperature for two hours and thirty minutes. The basic solution was neutralized with glacial acetic acid and concentrated in vacuo to ca. 10 ml.. The reaction mixture was diluted with 50 ml. of methylene chloride and 20 ml. of ice cold water. The aqueous layer was separated and the organic layer was washed sucessively with 15 ml. of 10% aqueous sodium bicarbonate, 10 ml. of saturated sodium chloride, and dried over 3 g. of anhydrous sodium sulfate.

The salt was removed by filtration and the filtrate was concentrated to approxiametely 5 ml. in vacuo. The methoxy lactone (XXVII) crystallized from the solution when it was set aside at room temperature to yield 4.48 g. (0.0202 mole, 98.0%). The melting point was 98-100°. The reported melting point was 100-102° (14). The infrared spectrum was identical to that reported by Woodward as a KI pellet (14).

Preparation of 2α-Methoxy-6α-Bromo-7β-Hydroxy-cis-Perhydro-(3,5-epoxy)-1βNapthoic Acid 1,8-Lactone
$C_{12}H_{15}O_5Br$ M.W. 318



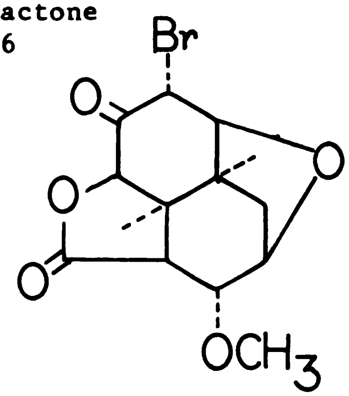
(XXXIV)

Woodwards' procedure (14) was used with slight modification for the preparation of this bromohydrin. A 4.00 g. (0.0180 mole) quantity of the methoxy lactone (XXVII) was dissolved by heating it to 80° in 30 ml. of water containing 8 ml. of 1 N sulfuric acid. After cooling to room temperature, the acidic solution was reheated to 60-70° by immersion in an oil bath and 3.21 g. (0.0180 mole) of N-bromo succinimide (freshly recrystallized from glacial acetic acid) was added with constant stirring during a perion of ten minutes. The reaction temperature was then increased to 80-90° and held there for 90 minutes. Heating was discontinued and the reaction was allowed to cool to room temperature. Approxiametely 1.g. of sodium bisulfite was added to the aqueous reaction mixture and it was continuously extracted with chloroform for four hours. The chloroform was removed in vacuo.

The residual yellow colored oil (identical to Woodwards' bromohydrin as determined by infra red spectrum in chloroform) was utilized in the next step of the synthetic sequence without further purification. The yield of the crude bromohydrin was 7.32 g. (0.0234 mole, 130%). Woodward by a similar proceedure reports (14) a 129% yield of this compound. Infrared analysis showed the crude bromohydrin was contaminated with succinimide.

Preparation of 2α-Methoxy-6α-Bromo-7 -Keto-cis-Perhydro-(3,5-epoxy)-1-Napthoic Acid 1,8-Lactone

$C_{12}H_{13}O_5Br$ M.W. 316



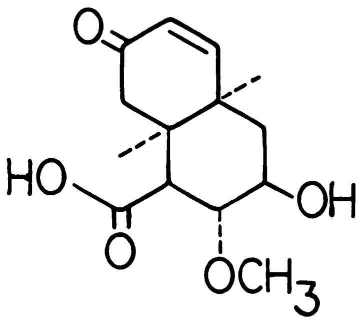
(XXXVI)

The method reported by Velluz (12) was used without modification. A suspension of 15.5 g. (0.0488 mole) of the previuosly prepared bromohydrin (XXXIV) in 200 ml. of 1,2-dichloroethane was treated with 35 ml. of glacial acetic acid. An oxidizing medium consisting of 14 g. of chromium trioxide, 14 ml. of water, 12 ml. of orthophophoric acid and 25 ml. of acetic acid was prepared. A 30 ml. quantity of this oxidizing medium was added to the bromohydrin contained in a flask immersed in an ice bath at such a rate that the reaction temperature was held below 30^{o} during the addition of the oxidizing agent. With occasional swirling of the reaction flask 10 ml. of fresh oxidizing agent was added in ten minutes. The remainder of the oxidizing agent was added after another 30 minutes. The reaction flask was then removed from the ice bath, and stored in the cold until frozen. After thawing, the reaction mixture was filtered. The collected material was washed on the filter with acetic acid followed by ether.

The nearly pure white crystalline mass of the bromo ketone, weighing 8.74 g. (0.0296 mole, 56.5%) had a melting point of 172-173°. It was reported as 166-167° (14). This bromo ketone was shown to be identical to the material prepared by Woodward by infrared spectrum in KI.

Preparation of 2α-Methoxy-3β-Hydroxy-5-ene-7-Keto-1,2,3,4,7,8-cis-9α-10α-Octahydro-1βNapthoic Acid

$C_{12}H_{15}O_6$ M.W. 240

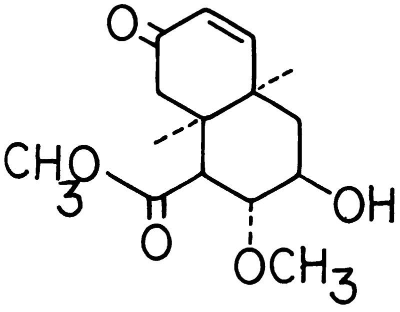


(XXXVII)

This compound was prepared exactly as described by Woodward (14). A 1 liter, 3 neck flask equipped with an overhead stirrer, a widebore funnel, and a thermometer extending to the solvent, was charged with 1.87 g. (5.92 mmoles) of the bromo ketone (XXXVI) and 500 ml. of freshly distilled glacial acetic acid. The ketone was dissolved by heating the solvent to 70°. External heating was discontinued and the acetic acid solution chilled to 18° by immersion in an ice bath. The ice bath was removed and 7.5 g. of zinc dust (200 mesh) previously cooled to 0°, was added rapidly in one portion. The acid solution was stirred very vigorously for 90 seconds and immediately filtered through a medium porosity sintered glass funnel. The filtrate was concentrated to dryness by distillation at water pump pressure, heat being supplied by a water bath heated to 80°. The residue was dissolved in 25 ml. of water and made basic (Hydrion B) with solid sodium bicarbonate. The basic solution was extracted continuously with ether for three hours.

The ether extract was discarded, and the aqueous phase was acidified (congo red) with conc. hydrochloric acid, saturated with solid sodium chloride, and re-extracted with ether for 36 hours. Concentration of the extract in vacuo produced a white crystalline solid which was triturated with a small amount of acetone to yield the acid (XXXVII) as a pure white solid weighing 1.12 g. (4.67 mmoles, 79.0%). This material had a melting point of 204-206°, while the reported melting point was 204-206° (14). This material was shown to be identical to that prepared by Woodward by infrared spectrum in KI. The ultraviolet spectrum showed a λ_{max} 227 mμ, ε=10,100, the reported λ_{max} at 228 mμ, ε=10,000 (14).

Preparation of 2α-Methoxy-3β-Hydroxy-5-ene-7-Keto-1,2,3,4,7,8-cis-9α-10α-Octahydro-1-Napthoic Acid Methyl Ester
$C_{13}H_{17}O_6$ M.W. 254



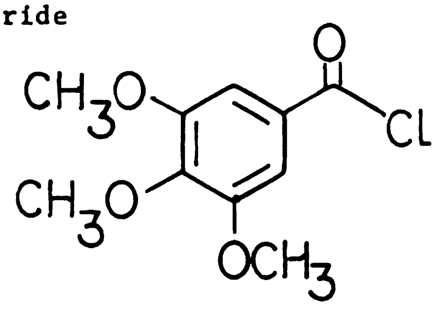
(XXXVIII)

The procedure given by Woodward (14) was slightly modified for the preparation of this ester. A 60 ml. volume of hot anhydrous dioxane was used to dissolve 1.20 g. (5.00 mmoles) of the previously prepared acid (XXXVII). The dioxane solution was cooled to 13° by immersion in an ice bath and 55 ml. of an ethereal solution of diazomethane (0.136 mmoles./ml., 7.47 mmoles. total) was added to the acid solution in one portion. The ice bath was removed and the reaction mixture was allowed to warm to room temperature. The solvent was immediately removed in a rotary evaporator, holding the bath temperature at 40°. The oily residue was triturated with 5 ml. of ether containing a few drops of acetone, whereupon the ester crystallized. The crystalline ester was collected by filtration and washed with ether. The ester was recrystallized from a small volume of ether/acetone (~90/10) to yield the colorless ester weighing 1.25 g. (4.92 mmoles., 98.5%).

This material melted at 130-131° compared to the reported melting point of 134-136°(14). The ester had an identical infrared spectrum compared to that reported by Woodward (14).

Preparation of 3,4,5-Trimethoxy Benzoyl Chloride

$C_{10}H_{11}O_4Cl$ M.W. 230



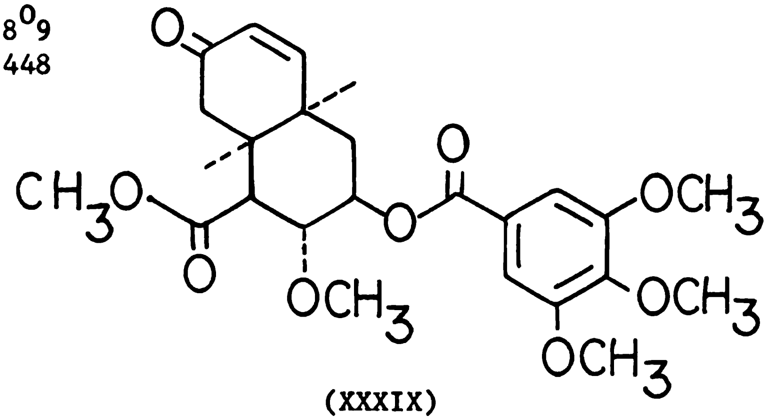
(XVIII-C)

A mixture of 21.2 g. (0.100 mole) of 3,4,5-trimethoxy benzoic acid and 20.8 g. (0.100 mole) of phosphorous pentachloride was metathesized and set aside until the vigorous evolution of hydrogen chloride had ceased. The reaction mixture was heated on a steam bath for 1 hour. The phosphorous oxychloride was removed at water pump pressure. The resulting violet colored acid chloride was recrystallized from 300 ml. of 60-90° petroleum ether/pentane/benzene (8/1/1) to give 21.5 g. (0.0934 mole, 93.4%) of colorless needles of the title compound, melting at 81-82°. Literature value (29) 81-82°.

Preparation of 2α-Methoxy-3β-(3',4',5'-Trimethoxybenzyloxy)-5-ene-7-Keto-1,2,3,4,7,8-cis-9α-10α-Octahydro-1β-Napthoic Acid Methyl Ester

$C_{23}H_{28}O_9$

M.W. 448



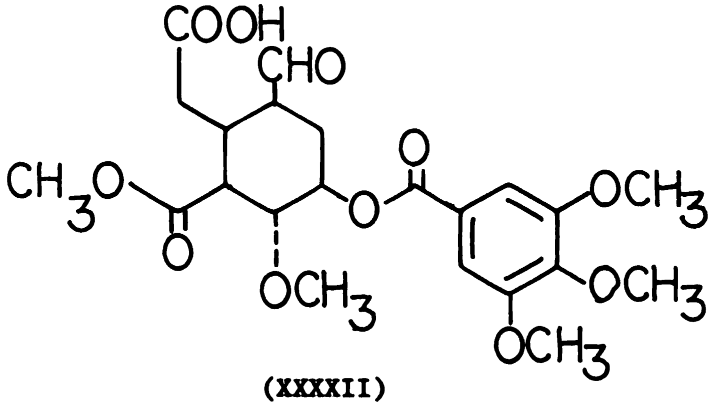
(XXXIX)

The method of Weichet, Pelz, and Blaha (26) was employed with minor differences to obtain this ester. A solution of 0.500 g. (1.98 mmoles.) of the previously prepared ester (XXXVIII) was formed in 15 ml. of anhydrous pyridine (dried over barium oxide and distilled from barium oxide). The pyridine solution was cooled to 5° by immersion in an ice bath and added to a chilled solution of 0.685 g, (2.96 mmoles.) of 3,4,5-trimethoxy benzoyl chloride in 12 ml. of benzene (previously dried over sodium wire and distilled). The solution was allowed to warm to room temperature and was then set aside undisturbed for 20 hours. The reaction mixture was hydrolyzed with 8 ml. of water and stirred for a half hour. A 20 g. quantity of ice was added and the pH of the reaction mixture was adjusted to 5 (Hydroin B) with conc. hydrochloric acid. The acidic solution was extracted with chloroform (3X40 ml.). The chloroform solution of the diester was washed with saturated sodium bicarbonate solution (2X20 ml.) and saturated sodium chloride (2X10 ml.). The combined chloroform extracts were taken to dryness in a rotary evaporator at reduced pressure. The residue was suspended in 10 ml. of methanol and filtered. The methanol filtrate was treated with 5 ml. of ether and set aside in the cold for a day to allow crystallization of the product. This was collected to yield 0.701 g. (1.56 mmoles., 79.0%) of pale tan colored crystalline material melting at 110-114°. The reported melting point was 107-115° (26). The ultraviolet spectrum showed absorbtion maxima at 268 mμ ϵ=10,900; 217 mμ,ϵ=38,300. The infrared spectrum is shown on page 57.

THE TETRACYCLIC AND PENTACYCLIC SERIES

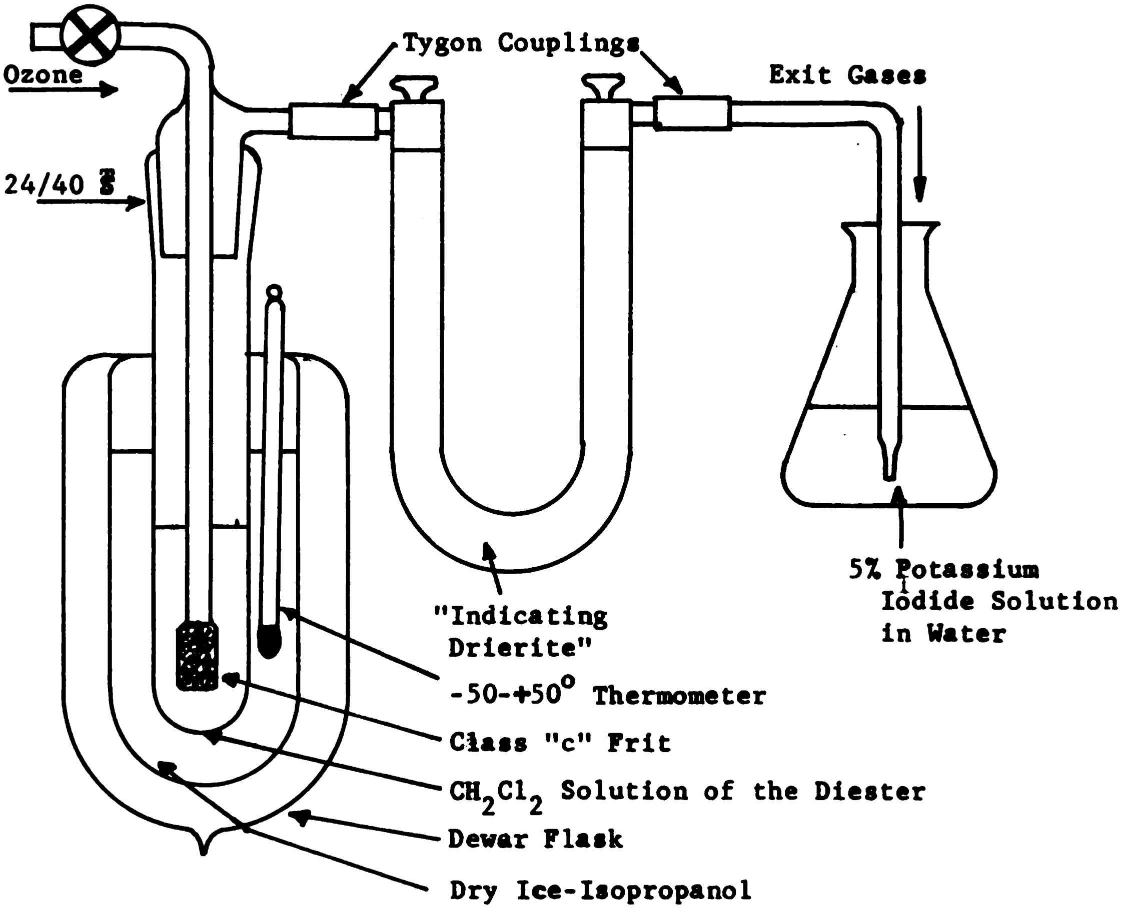
Preparation of (±) 1β-Methoxycarbonyl-2α-Methoxy-3β-(3',4',5'-Trimethoxybenzyloxy)-5β-Formyl-6β-Cyclohexyl Acetic Acid

$C_{22}H_{28}O_{11}$ M.W. 468



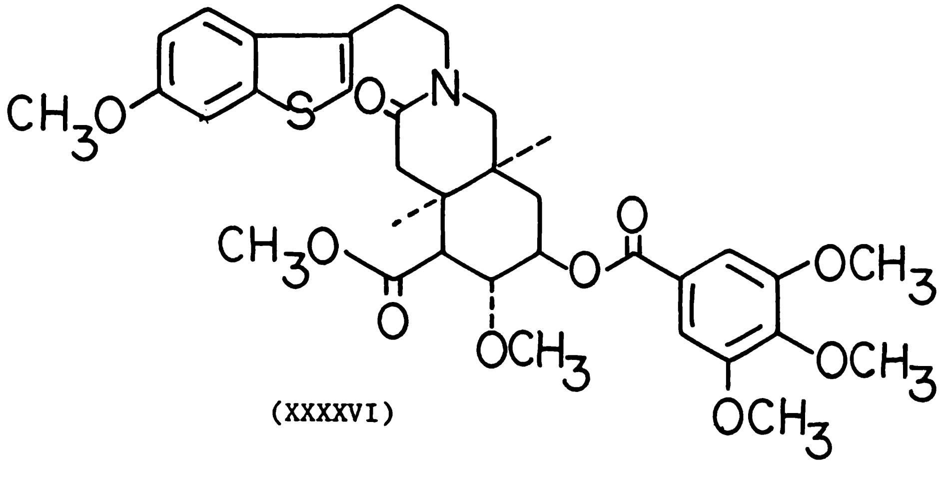
(XXXXII)

A 224 mg. (0.500 mmole.) quantity of the diester (XXXIX) was dissolved in 10 ml. of anhydrous methylene chloride contained in the reaction vessel attached to the apparatus shown.



The isopropanol bath temperature was lowered to -30° by adding small pieces of dry ice to the bath. Ozone (~1% V/V concentration of O_3 in O_2; flow rate ~ 0.002 ft^3/min.) was passed into the methylene chloride solution, the exit gases being passed into 30 ml. of a 5% aqueous potassium iodide solution. After five min. and twenty sec. the iodide solution changed rapidly from colorless to yellow brown and the flow of O_3-O_2 gas was terminated. This corresponds, on the basis of gas flow time, to an uptake of ~ 470 μmoles. of O_3. The solution of ozonide at -30° was purged of ozone by passing a stream of dry nitrogen through it for ten min.. The solution was then heated, under reflux, for 45 min. in an atmosphere of nitrogen with 2 ml. of water containing 0.01 g. of hydroquinone. After cooling the solution to room temperature, the aqueous layer was separated, washed with methylene chloride (2X5 ml.) and the combined methylene chloride solutions were dried by filtering them through a bed of anhydrous sodium sulfate. The aldehyde solution was treated with a slight excess of 2,4-dinitro phenylhydrazine in 20 ml. of isopropanol. After standing several hours at room temperature the solid material was collected by vacuum filtration and recrystallized three times from ethanol to obtain brilliant red colored needles melting at 128-131°. Analysis: Calculated for $C_{28}H_{32}O_{14}N_4$: C, 51.88; H, 4.97; NO, 43.18 Found: C, 51.60; H, 5.10; NO, (by difference) 43.30.

Preparation of (±) 1-Deaza-1-Thia-2,3-seco-3-Oxo Reserpine
$C_{33}H_{39}O_{10}NS$ M.W. 642



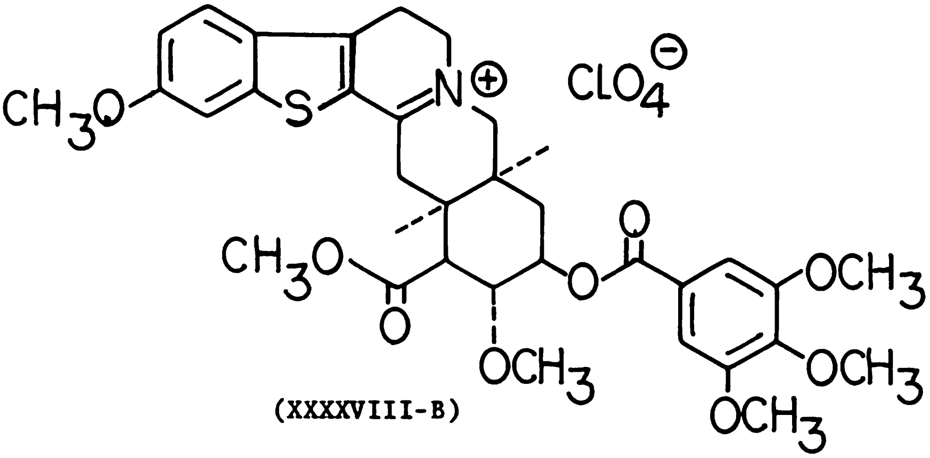
(XXXXVI)

The aldehyde described above and obtained from 224 mg. (0.500 mmoles.) of the diester (XXXXIX) in the original methylene chloride solution was immediately cooled to 0^{o} by immersion in an ice bath and treated with a slight excess of ethereal diazomethane. The ice bath was removed and the reaction mixture was set aside for 10 min. at room temperature, and then concentrated to ½ its initial volume in an atmosphere of nitrogen in a rotary evaporator. The concentrated solution of the triester was chilled to 0^{o} in an ice bath and a solution of 104 mg. (0.503 mmole.) of 6-methoxy-3-(2-aminoethyl) benzothiophene (XIX) in 1.4 ml. of anhydrous benzene was added in one portion. The reaction solution which took on a yellow orange coloration was set aside for ten min. and 20 ml. of anhydrous methanol was added. After recooling the reaction mixture to 0^{o}, a solution of 19.0 mg. (0.500 mmole.) of sodium borohydride in 2 ml. of anhydrous methanol was added to the mixture, during a period of five minutes. Acetic acid (2 drops) was added to the mixture and all solvents were removed, first in an atmosphere of nitrogen in a rotary evaporator and finally with an oil pump at 0.01 torr.. The dry residue was triturated with ether, collected by vacuum filtration and washed well with ether. In order to re-esterify and alcohol which may have formed during the reduction with sodium borohydride, the throughly dry lactam was dissolved in 15 ml. of anhydrous pyridine and treated with 115 mg. (0.500 mmole.) of solid 3,4,5-trimethoxy benzoyl chloride. After being set aside at room temperature in an atmosphere of nitrogen for four days, the pyridine was removed in a rotary evaporator under nitrogen. The residue was dissolved in 10 ml. of chloroform and the chloroform solution was extracted with 5 ml. of 5% aqueous sodium bicarbonate. After drying over anhydrous sodium sulfate, the chloroform solution was heated with a small amount of Norit-A and filtered. Ether was added to precipitate the lactam which was collected by vacuum filtration and dried over anhydrous calcium sulfate in a vacuum desiccator.

The yield of pale tan powder product was 240 mg. (0.374 mmole., 74.8%) The melting point was 145-148° dec. (sealed capillary). For analysis the material was purified by repitative precipitation from ethyl acetate by adding ether.

Analysis Calculated for $C_{33}H_{39}O_{10}NS$: C, 61.76; H, 6.12; N, 2.18 S, 5.00: Found: C, 61.51; H, 6.07; N, 3.00; S,4.67.

Preparation of (±) 1-Deaza-1-Thia-3,4-Dehydro-Reserpine Perchlorate
$C_{33}H_{38}O_{13}NSCl$ M.W. 723



(XXXXVIII-B)

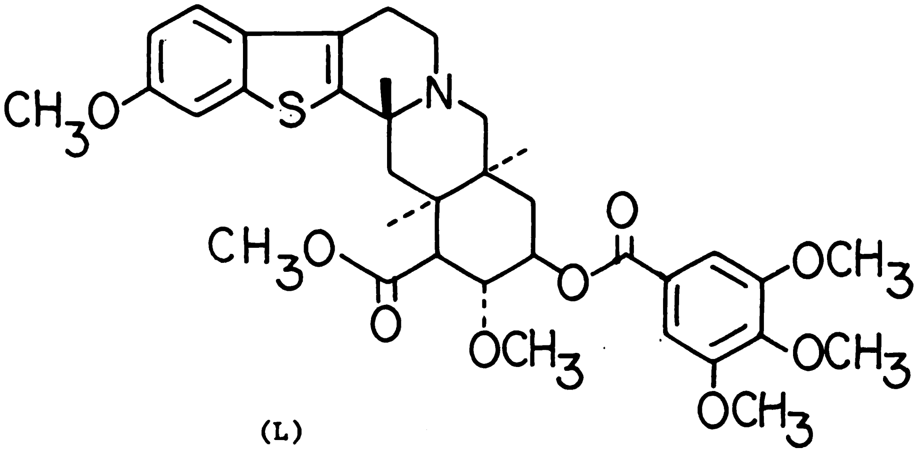
A 100 mg. quantity of the lactam (XXXXVI) was dissolved in 2 ml. of freshly distilled phosphorous oxychloride. The reaction mixture was heated in an atmosphere of nitrogen by immersion in an oil bath previously heated to 65°. After 45 min. the phosphorous oxychloride was distilled at water aspirator pressure. Finally the reaction mixture was evaporated to dryness at 0.01 torr. using an oil pump. The oil bath was removed and the glassy residue in the reaction vessel was dissolved in 4 ml. of acetone. The acetone solution of the florescent immonium chloride was treated with 3.5 ml. of 0.1 N perchloric acid. The semi solid which formed was not removed but rather the entire suspension was concentrated in a rotary evaporator under nitrogen to remove the acetone. The aqueous suspension of the immonium perchlorate was extracted (3X5 ml.) with chloroform. The combined chloroform extracts were dried over anhydrous sodium sulfate and taken to dryness in a rotary evaporator under nitrogen.

The residue was triturated with ether, collected by vacuum filtration and washed with ether to obtain 101 mg. (0.140 mmole., 89.8%) of the immonium perchlorate melting at 178-186° dec. (sealed capillary). For analysis the crude product was recrystallized from ethanol/acetone 5/1 to obtain an analytical sample in the form of fine orange colored needles melting at 203-205° dec. (sealed capillary).

Analysis Calculated for $C_{33}H_{38}O_{13}NSCl$: C, 54.80; H, 5.29; N, 1.94; S, 4.43; ClO, 33.52; Found: C, 54.28; H, 5.53; N, 2.07; S, 4.64: ClO, (by difference) 33.58.

Preparation of (±) 1-Deaza-1-Thia-Reserpine

$C_{33}H_{39}O_9NS$ M.W. 626



(L)

A solution of 111 mg. (0.153 mmole.) of the immonium perchlorate (XXXXVIII-B) in 5 ml. of acetone was placed in a 25 ml. 3 neck flask fitted with nitrogen inlet, reflux condenser and mercury trap. To the acetone solution of the perchlorate, 1.5 ml. of 0.7 N perchloric acid was added. Sufficient tetrahydrofuran was added to the mixture to effect a clear solution. The reaction vessel was purged with nitrogen and placed in an oil bath previously heated to 70°. When the reaction mixture commenced refluxing, it was stirred vigorously by means of a magnetic stirrer and 0.15 g. of zinc dust was added to the mixture.

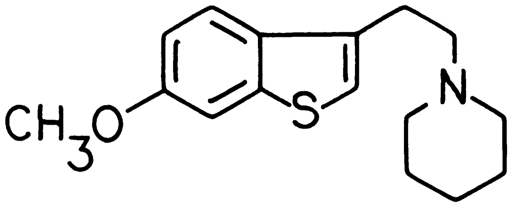
After 10 min., a second 0.15 g. portion of zinc dust was added to the mixture followed by a third similar quantity after another 10 minute interval. The reaction was considered complete after stirring the mixture an additional 10 min.. At this point the reaction mixture showed only a very slight fluorescence.The oil bath was removed and the reaction mixture was allowed to cool to room temperature, and the zinc was removed by filtration. The filtrate was made basic (pH 9, Hydrion B) with concentrated ammonium hydroxide and 10 ml. of chloroform was added to the basic filtrate. The layers were separated and the aqueous layer was extracted (2X5 ml.) with chloroform. The combined chloroform extracts were filtered through anhydrous sodium sulfate. The solvents were removed in a rotary evaporator under nitrogen. The residue (71 mg.) was triturated with 10 ml. of boiling ethanol and filtered while hot. The residue collected on the filter (17 mg., m.p. 340^{o} dec., sealed capillary) was recrystallized from acetone/ether (1/5) and showed a broad absorption at 3450 cm^{-1}(KI). This material was assumed to be the 16β carboxylic acid, although no further characterization, was carried out.

The ethanol filtrate obtained above was concentrated to 3 ml. in a rotary evaporator under nitrogen and 15 ml. of ether was added dropwise with constant stirring. The precipitate(54 mg., 0.086 mmole. 56%) of 1-deaza-1-thia reserpine had a melting point of 182-189^{o} dec. (sealed capillary). It was shown to homogeneous by thin layer chromatography on Woelm activity II alumina eluting with chloroform-methanol-benzene (10:3:1), R_f= 0.65. For analysis the product was recrystallized three times from a minimum amount of ethanol/ether (9/1) to obtain 21 mg. of pure thiareserpine melting at 188-191^{o} (sealed capillary). <u>Analysis</u> Calculated for $C_{33}H_{39}O_9NS$: C, 63.34; H, 6.28; N, 2.24; SO, 28.13 Found: C, 63.08; H, 6.75; N, 2.53; SO (by difference) 27.64.

The Synthetic Spectrum

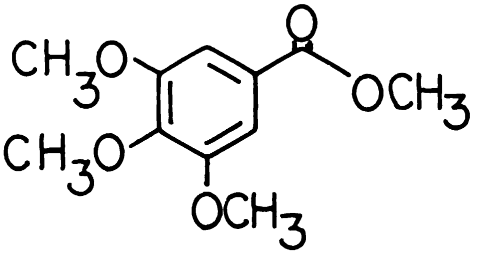
The materials used in the synthetic spectrum, p. 29 were prepared in the following manner.

Preparation of 6-Methoxy-3-(2-Piperidinoethyl) Benzothiophene
$C_{16}H_{21}ONS$ M.W. 275

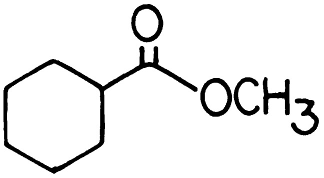


A 0.298 g. (1.00 mmole.) quantity of the hydrochloride salt of this compound as prepared by Titus (18) was dissolved in 5 ml. of water in a separatory funnel. To this 10 ml. of ether was added and then 5 ml. of 1 N sodium hydroxide. The ether layer was separated and the aqueous layer was extracted (2X5 ml.) with ether. The ethereal solutions were combined, dried over anhydrous soudium sulfate and filtered. The filtrate was evaporated first in a rotary evaporator and finally with an oil pump at 0.01 torr. to obtain the pure amine as a pale yellow colored oil.

Preparation of Methyl 3,4,5-Trimethoxy Benzoate and Methyl Cyclohexane Carboxylate



$C_{11}H_{14}O_5$ M.W. 216



$C_8H_{14}O_2$ M.W. 142

The individual acids (1.00 mmole. each in anhydrous ether) of the corresponding esters were treated with a 10% excess of ethereal diazomethane.

The ether was initially removed in a rotary evaporator under nitrogen and finally with an oil pump at 0.01 torr. to obtain the methyl cyclohexane carboxylate and the methyl 3,4,5-trimethoxy benzoate as pure colorless materials.

These three reagents were combined in chloroform and diluted to 0.100 M. for the determination of the infrared spectrum. The ultraviolet spectrum was determined by diluting 10 μl. of the chloroform solution to give a concentration of all species of 10^{-5} M in 95% ethanol. These spectra are reported on pp 29-30 and shown superimposed on the spectra of the thiareserpine.

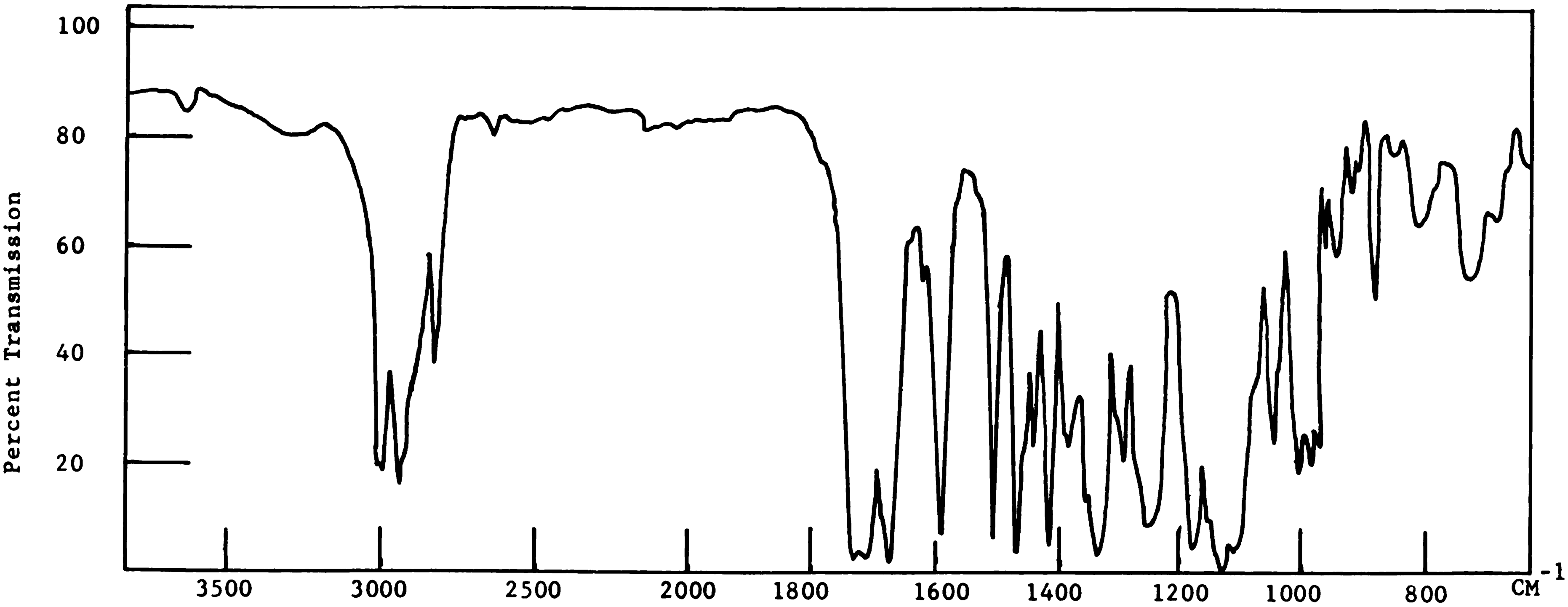


Fig. 3. The Infrared Spectrum of 2α-Methoxy-3β-(3', 4', 5'-Trimethoxybenzyloxy)-5-ene-7-Keto-1,2,3,4, 7,8-cis-9α,10α-Octahydro-1β-Napthoic Acid Methyl Ester in Chloroform.

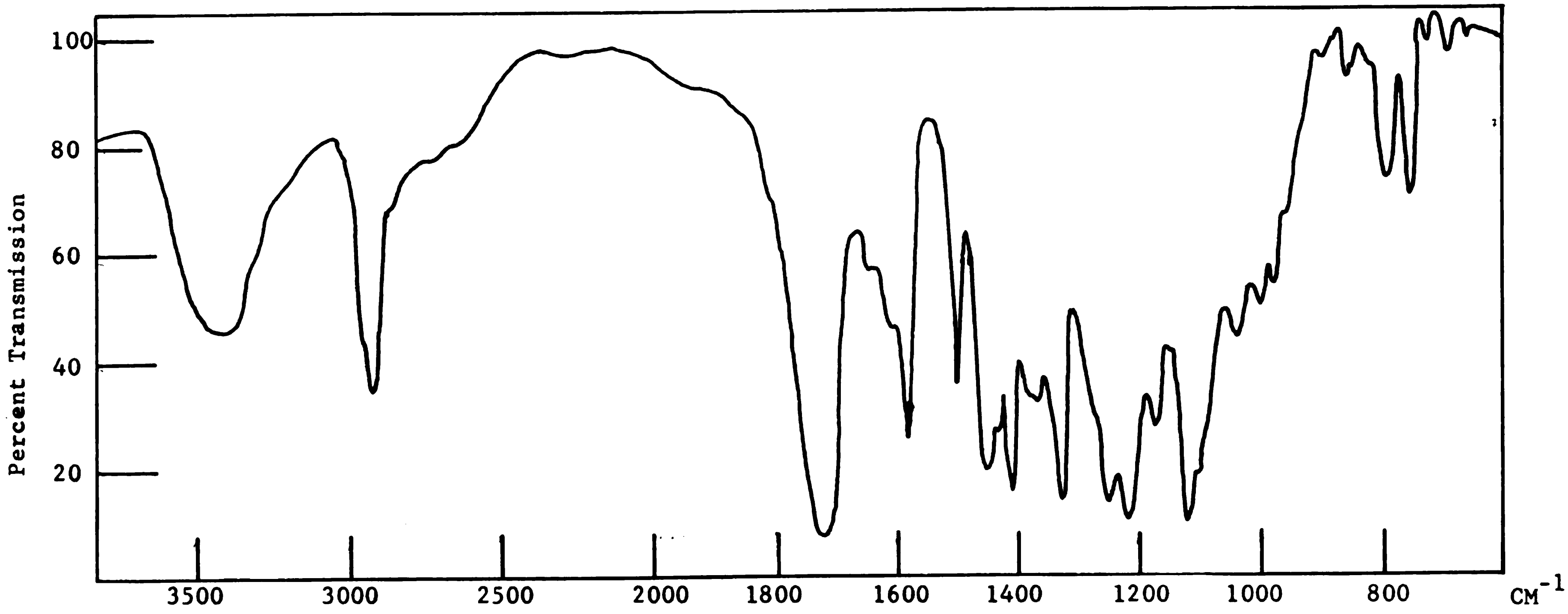


Fig. 4. The Infrared Spectrum of (±) 1β-Methoxycarbonyl-2α-Methoxy-3β-(3', 4', 5'-Trimethoxybenzyloxy)-5β-Formyl-6β-Cyclohexyl Acetic Acid in Chloroform

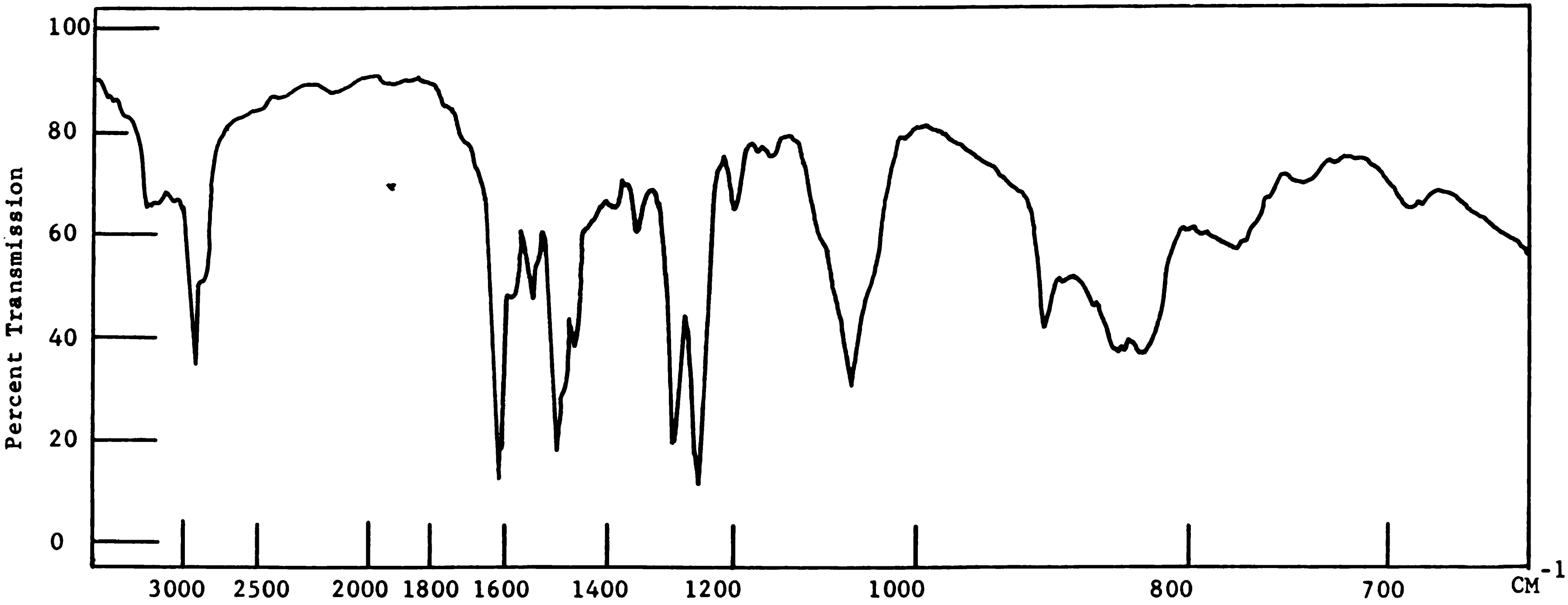


Fig. 5. The Infrared Spectrum of 6-Methoxy-3-2(Aminoethyl) Benzothiophene Between Salts

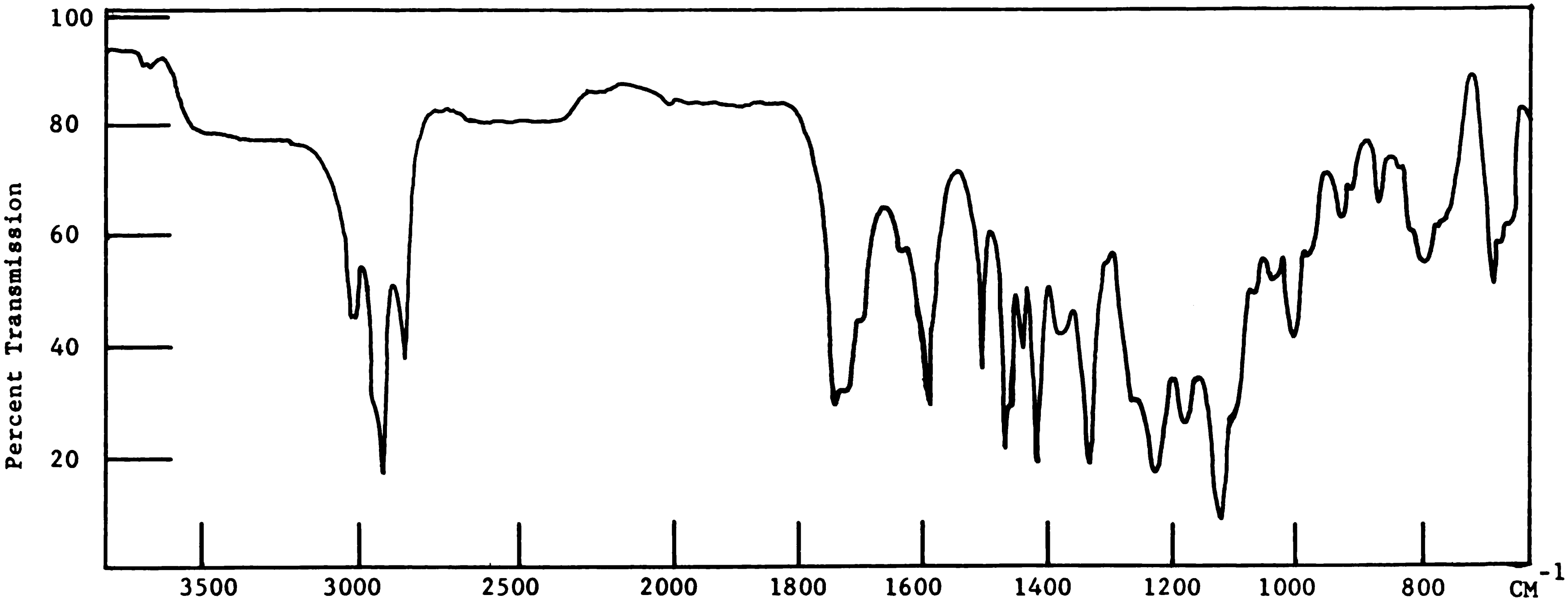


Fig. 6. The Infrared Spectrum of (±) 1-Deaza-1-Thia-2,3-seco-3-Oxo-Reserpine in Chloroform

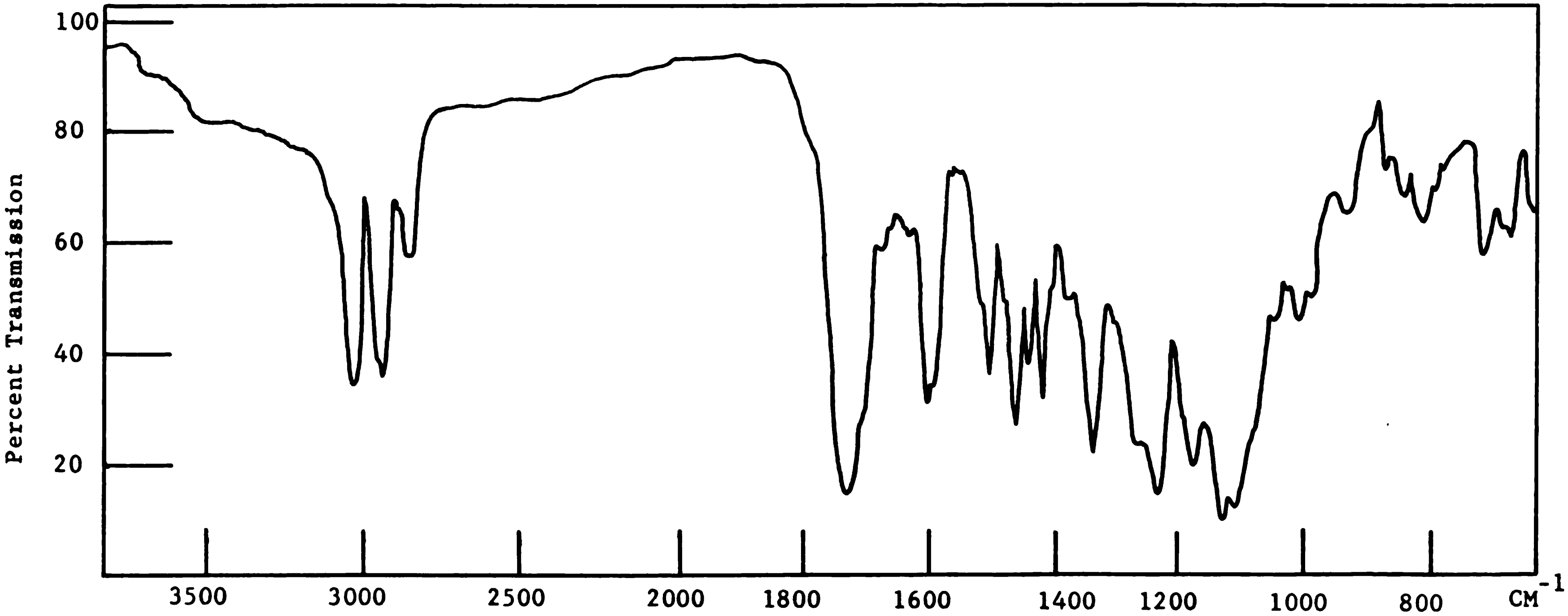


Fig. 7. The Infrared Spectrum of (±) 1-Deaza-1-Thia-3,4-Dehydro-Reserpine Perchlorate in Chloroform

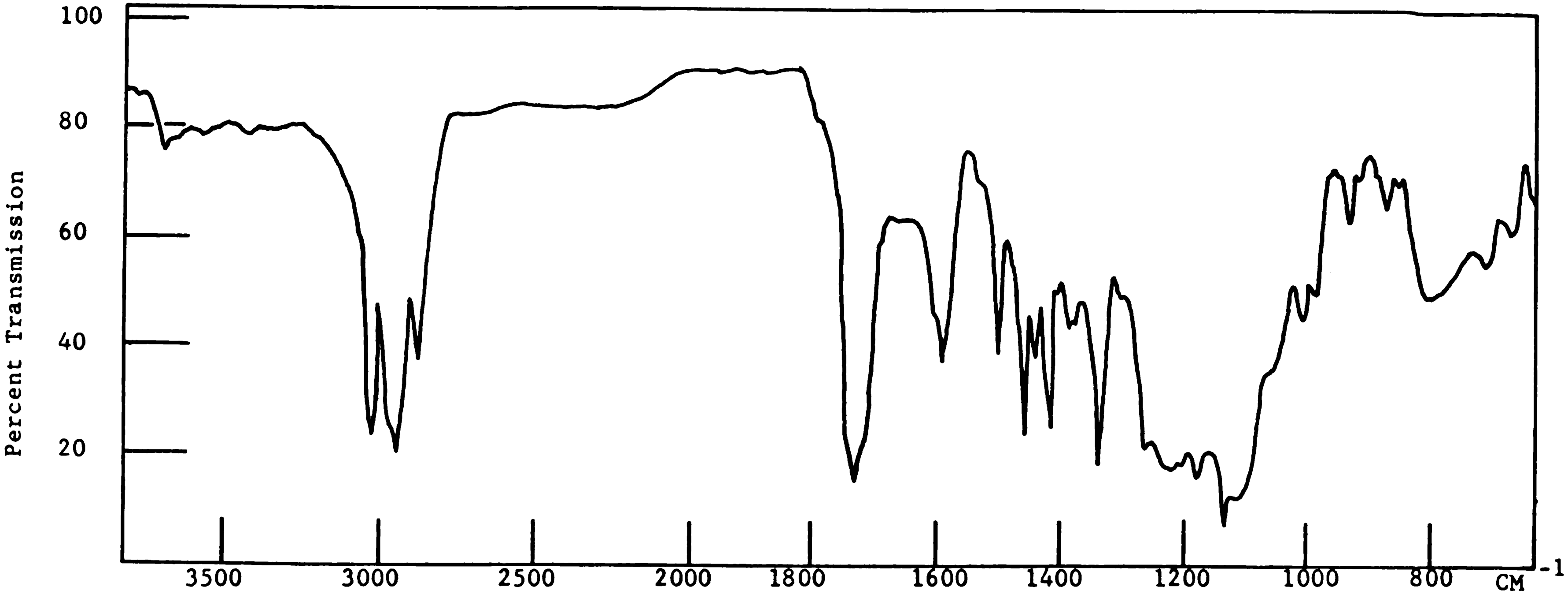


Fig. 8. The Infrared Spectrum of 1-Deaza-1-Thia-Reserpine in Chloroform

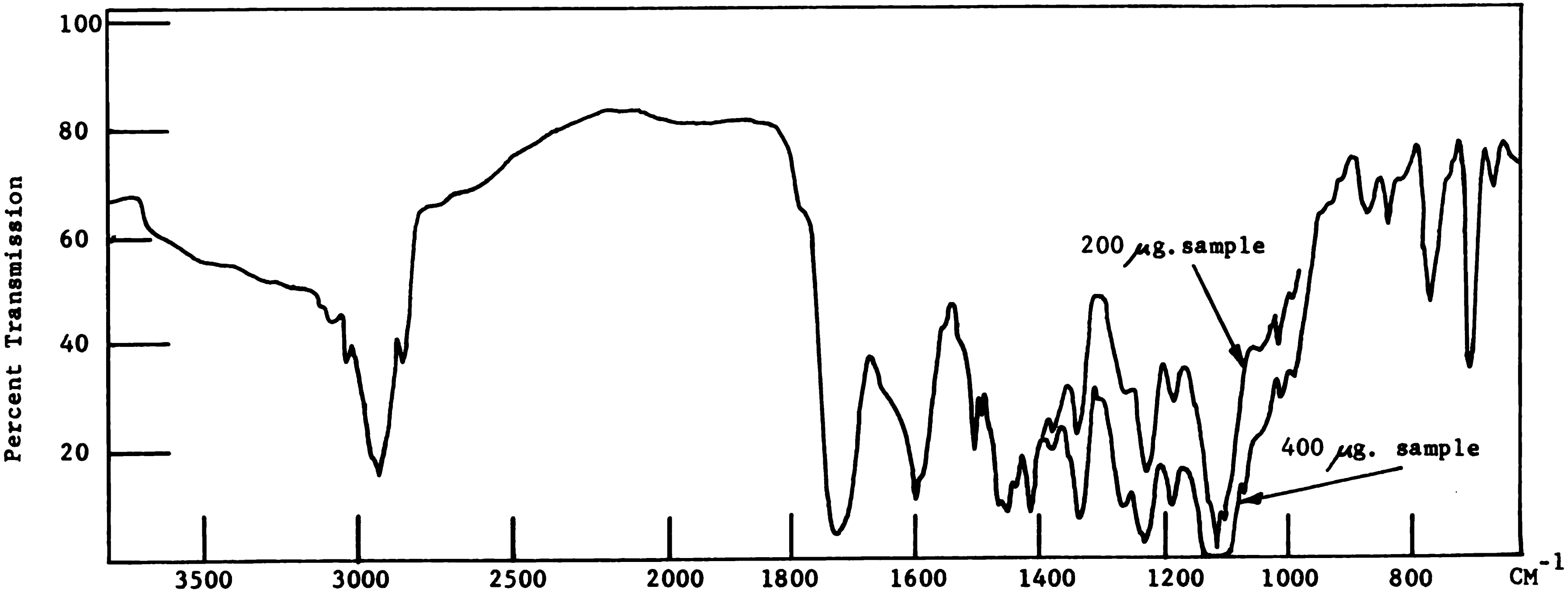


Fig. 9. The Infrared Spectrum of 1-Deaza-1-Thia-Reserpine in KI

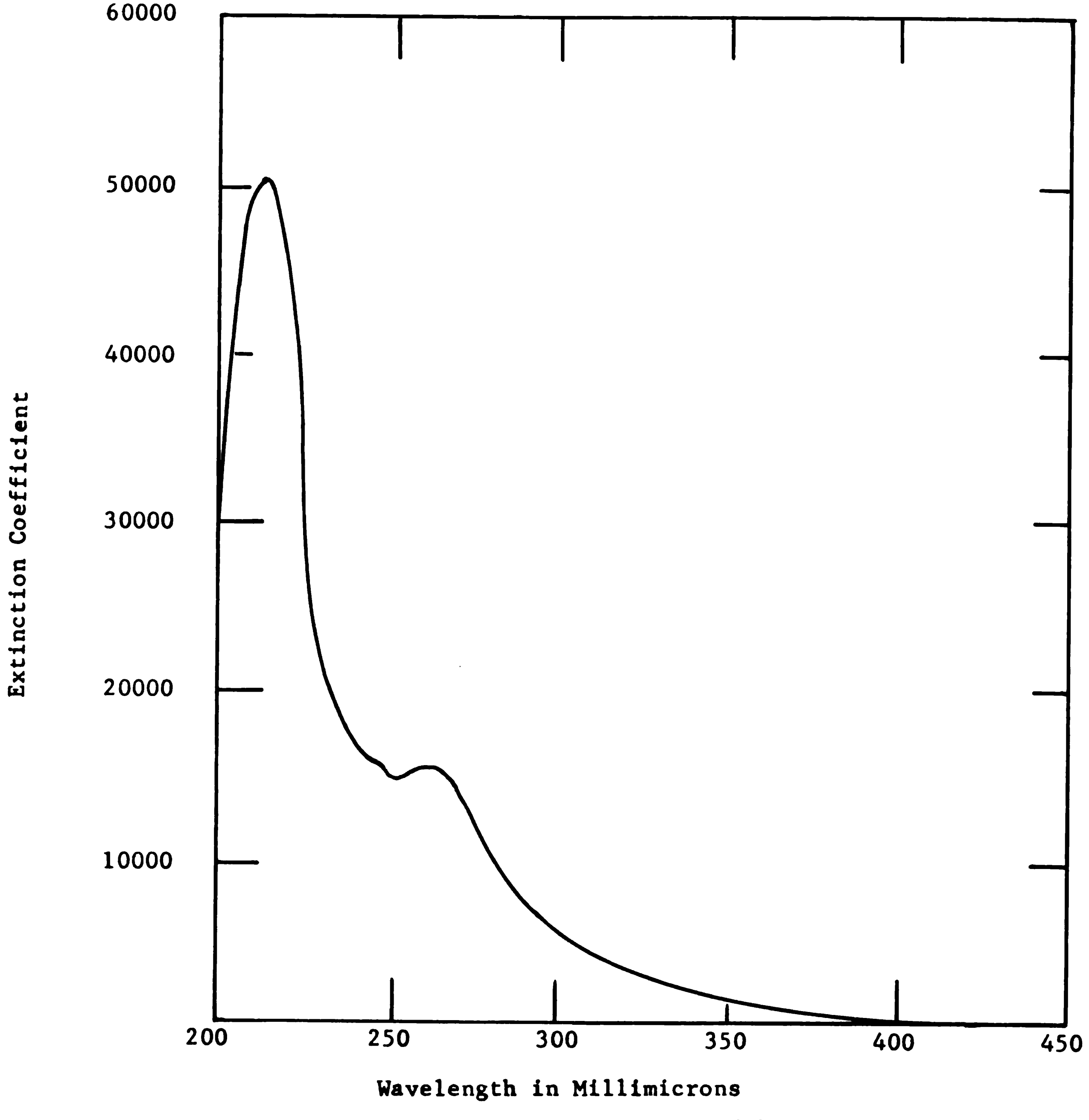


Fig. 10 The Ultraviolet Spectrum of (±) 1-Deaza-1-Thia-2,3-seco-3-Oxo Reserpine in 95% Ethanol

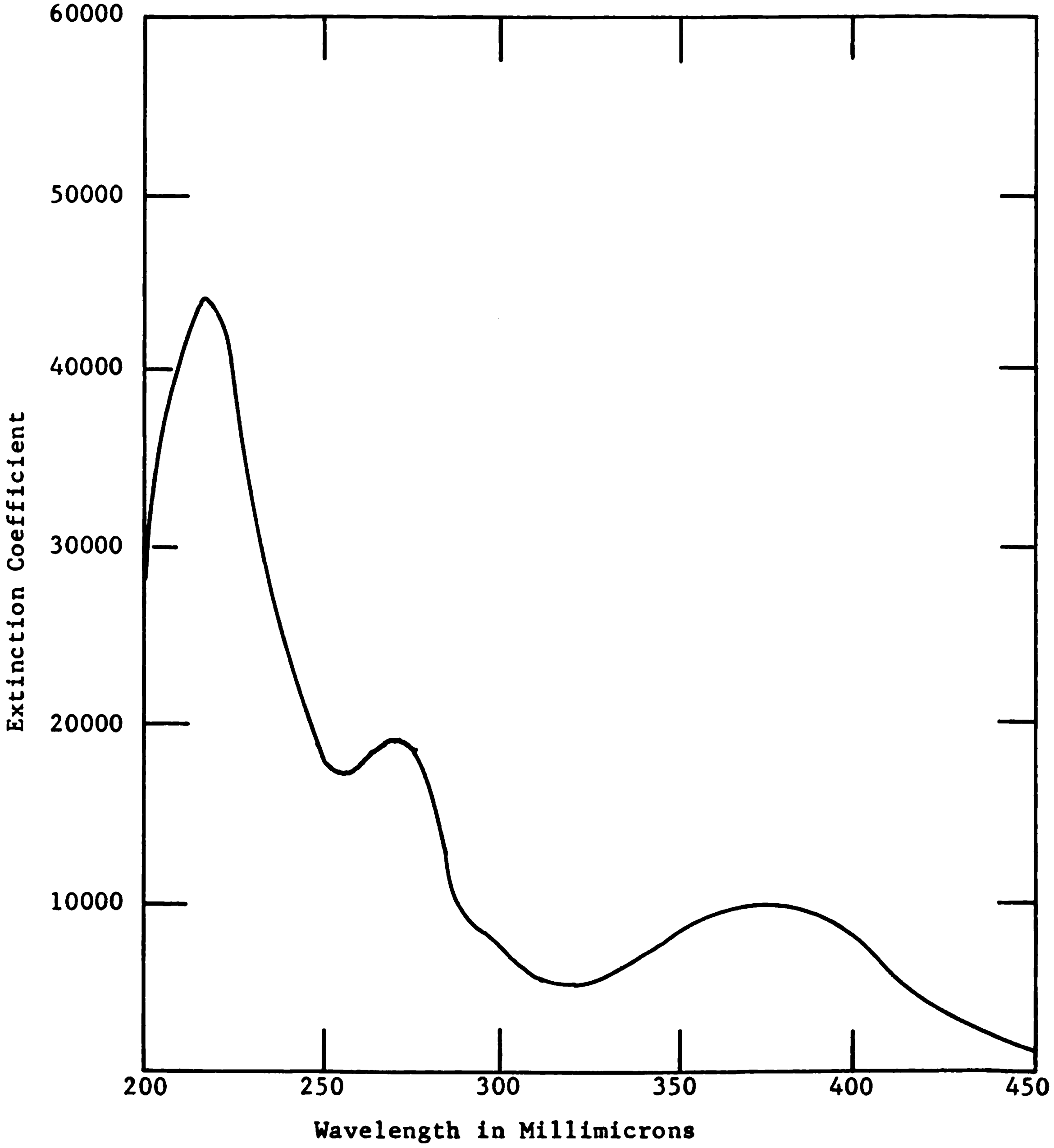


Fig. 11. The Ultraviolet Spectrum of (±) 1-Deaza-1-Thia-3,4-Dehydro Reserpine Perchlorate

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