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I: THE PREPARATION AND OPTICAL RESOLUTION OF dl–2 $\beta$–ACETOXY–8 $\alpha$–METHYLPODOCARPANE–7,9–DIONE. II: EXPLORATORY STUDIES IN THE TOTAL SYNTHESIS OF AJMALINE.

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RICE UNIVERSITY

I: The Preparation and Optical Resolution of dl-2$\beta$-Acetoxy-8$\alpha$-methylpodocarpane-7,9-dione.

II: Exploratory Studies in the Total Synthesis of Ajmaline.

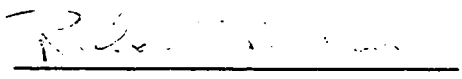
by

James Milton Sanders

A THESIS SUBMITTED
IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF

Doctor of Philosophy

Thesis Director's signature:



Houston, Texas

June 1966

To my parents.

## ACKNOWLEDGMENTS

I wish to express my sincere appreciation to Professor Richard B. Turner for his guidance and inspiration.

The financial support for this investigation which was provided by William Marsh Rice University and by the National Aeronautics and Space Administration is gratefully acknowledged.

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# PART I

## I. INTRODUCTION

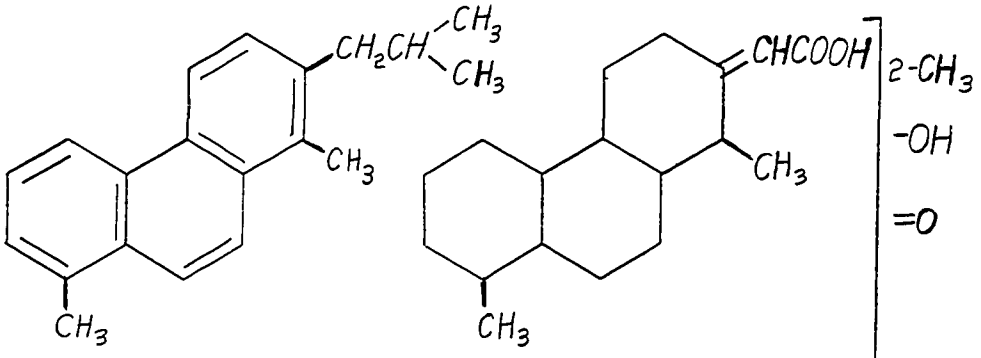
# INTRODUCTION

Cassaine, $C_{24}H_{39}O_4N$, an alkaloid present in the bark of Erythrophleum Guineense, G. Don, and other Erythrophleum species, was first obtained in a crystalline, well characterized form by Dalma[1,2] in 1935. Hydrolysis of cassaine with dilute mineral acid afforded dimethylaminoethanol and cassaic acid,[3] $C_{20}H_{28}O_4$, from which cassaine could be regenerated by treatment of the sodium salt with dimethylaminoethyl chloride.[4]

Cassaine and cassaic acid were each shown to possess one hydroxyl group and one keto group.[3] The ultraviolet absorption spectra of these compounds (cassaic acid, $\lambda_{max}$ 215 m$\mu$, log $\epsilon$ 4.3; cassaine, $\lambda_{max}$ 223 m$\mu$, log $\epsilon$ 4.26) suggested that the acid function in cassaic acid and the ester function in cassaine were $\alpha,\beta$-unsaturated.[5] Confirmation of this conclusion was found in the fact that the dihydro derivatives obtained upon catalytic hydrogenation of cassaine and cassaic acid showed no discrete absorption in the ultraviolet.[4,5] From this evidence, these compounds were inferred to be tricyclic.

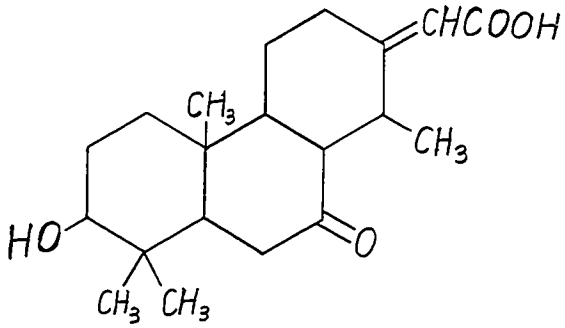
The isolation of 1,2,8-trimethylphenanthrene from the selenium dehydrogenation of various derivatives of dihydrocassaic acid[5,6,7] provided evidence for the nuclear structure. Further information was obtained by removal of the hydroxyl and keto groups present in dihydrocassaic acid and reaction of the corresponding methyl ester (cassanic acid methyl ester) with methylmagnesium bromide to label the carboxyl group. Successive dehydration and dehydrogenation of this Grignard product afforded a crystalline hydrocarbon, $C_{20}H_{22}$,[8]

ultimately identified as 1,8-dimethyl-2-isobutylphenanthrene (1).[9] If no rearrangement had taken place in the steps leading to (1), cassaic acid could be assigned the part structure (2).




(1) (2)

From considerations of the general behavior of the keto group and of an assumed analogy to other deterpenes, Humber and Taylor[9] expanded this structure to the non-isoprenoid formulation (3).

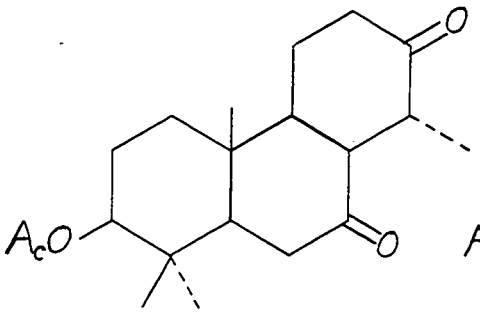



(3)

Work in this laboratory[10,11,12] showed that (3) was, in fact, the correct structure for cassaic acid. If the Humber and Taylor suggestion

for the ring A structure were tentatively accepted as correct, the keto group could only be assigned to C.9 or C.10. This followed from the observations that cassaic acid was neither an $\alpha$- nor a $\beta$-hydroxy-ketone, did not possess the properties of a vinylogous $\beta$-keto ester, and did not show conjugated ketonic absorption in the ultraviolet. This argument was further strengthened by the observation of Engel[13] that the diketone, dehydrocassaic acid, afforded on ozonolysis oxalic acid and a triketone, $C_{18}H_{26}O_3$, in which the carbonyl groups were isolated and, hence, presumably in different rings.

An unequivocal proof of the correctness of the C.9 assignment of the keto group in cassaic acid was obtained as follows.[10,11] Ozonization of cassaic acid acetate methyl ester afforded an acetoxydiketone to which structure (4) was assigned. Treatment of this diketone with base or chromatography over certain types of alumina converted it into an isomeric diketone (5). These assignments of structure were based

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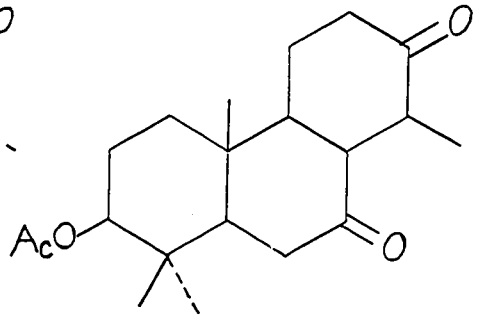
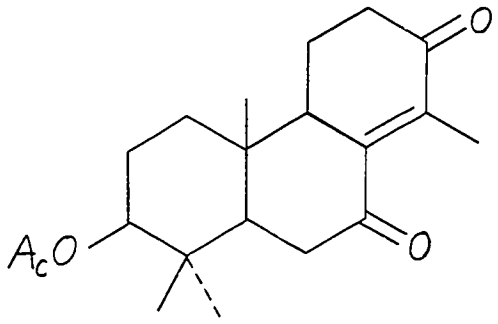



(5)

on the assumption that the transformation (4)⟶(5) involved conversion of the C.8 methyl group from an axial configuration in (4) into the presumably more favorable equatorial configuration in (5).

Bromination of (5) followed by dehydrobromination of the product in refluxing collidine afforded material to which the enedione structure (6) was assigned on the basis of its ultraviolet absorption spectrum ($\lambda_{max}$ 266.5 mμ, ε 10,800).[14,15] The presence of the enedione system was confirmed by the very smooth reduction of compound (6)




(6)

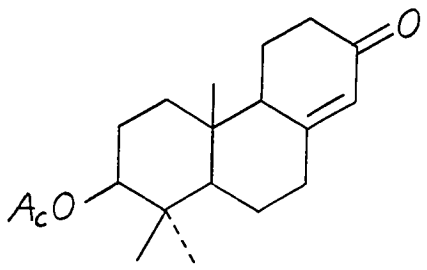
with zinc and acetic acid[16,17] to give material reported to be identical with the diketone (5).[10,11] The formation of the enedione established a 1,4— relationship for the two carbonyl groups. As one of these groups resulted from an oxidative cleavage of the unsaturated side chain known to be attached at C.7, the only position available for the second keto group, originally present in cassaic acid, was C.9.

With the general features of the B/C ring system of cassaic acid firmly established, the elucidation of the ring A constitution was

undertaken. This was done through a synthetic approach because only very limited supplies of the natural material were available for degradative work.

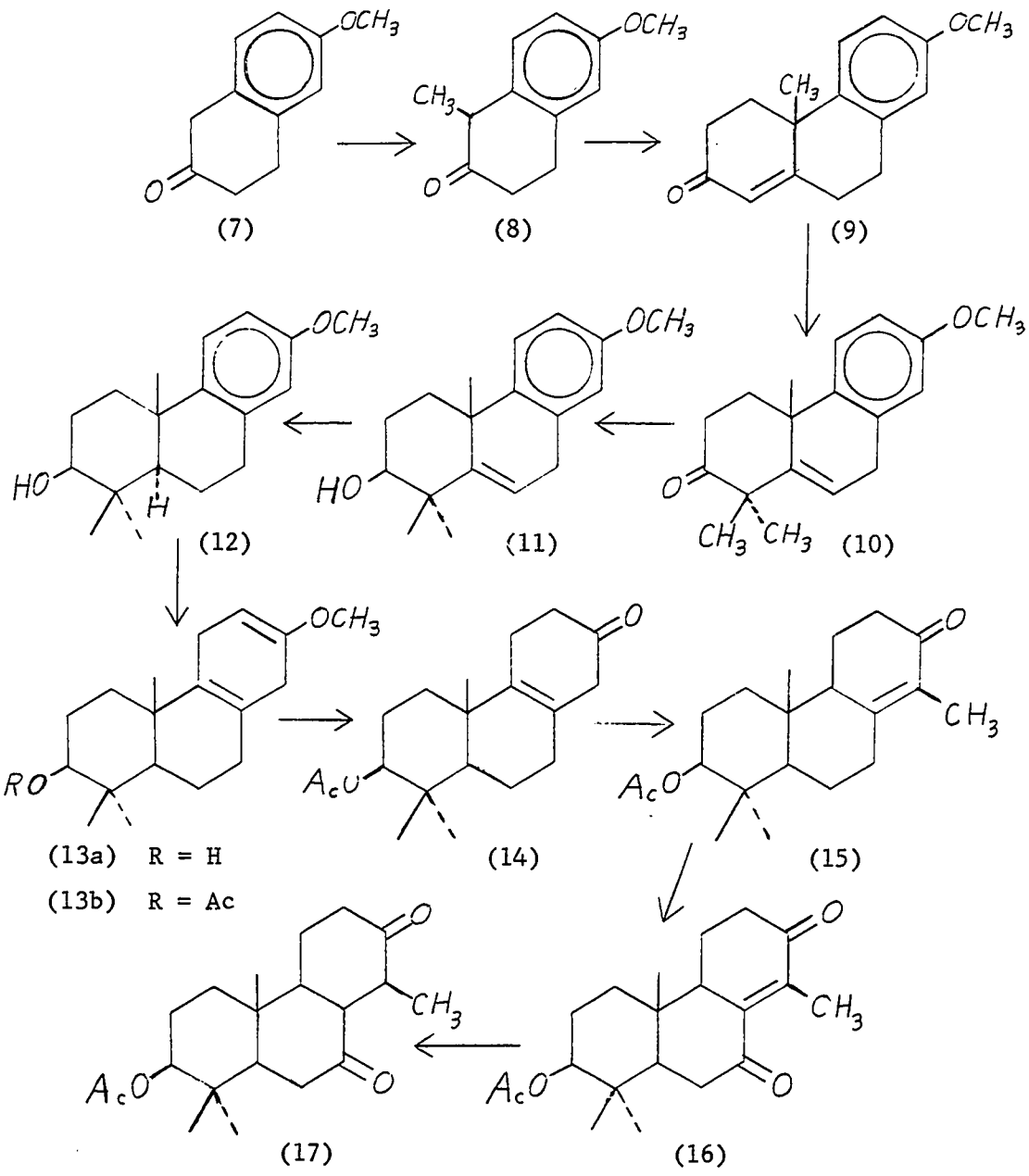
The starting material for this synthesis (see Chart I) was 6-methoxy-2-tetralone (7).[18,19] Methylation of (7) by the Stork enamine procedure[20] afforded 6-methoxy-1-methyl-2-tetralone (8).[21] Sodium hydride catalyzed condensation of (8) with dimethylaminobutanone methiodide provided the tricyclic $\alpha,\beta$-unsaturated ketone (9).[21] Treatment of (9) with methyl iodide and potassium t-butoxide[22] effected dimethylation to give the $\beta,\gamma$ -unsaturated ketone (10). Lithium aluminum hydride reduction of (10) to the alcohol (11) and subsequent hydrogenation over platinum generated the hydroxyanisole (12).[23]

The reduction of compound (12) with lithium and liquid ammonia[24] afforded the dihydroanisole (13a) which was converted into the corresponding acetate (13b) by treatment with acetic anhydride and pyridine. Aqueous oxalic acid smoothly hydrolyzed (13a) to the $\beta,\gamma$ -unsaturated ketone (14). Hydrolysis of (13a) with mineral acid, however, gave a mixture of (14) and the corresponding $\alpha,\beta$-unsaturated ketone (18).

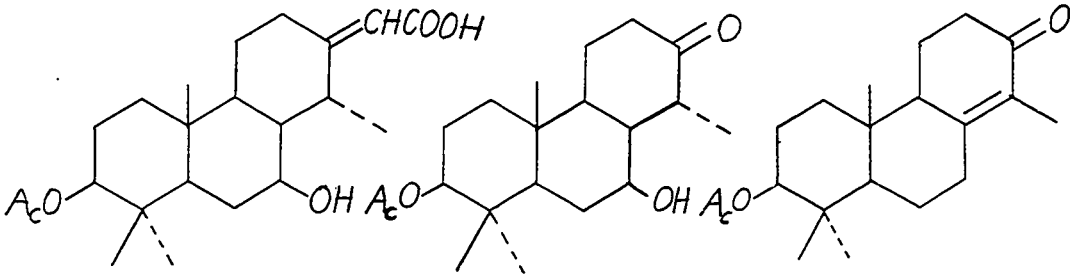



(18)

Chart I



When compound (14) was treated with approximately one equivalent of methyl iodide in the presence of potassium t-butoxide[25,26] and the crude product was reacetylated and chromatographed, the monomethylated $\alpha,\beta$-unsaturated ketone (15) was obtained. The infrared absorption spectrum of (15) taken in carbon disulfide solution was identical with that of an optically active (dextrorotatory) compound (21) which was obtained from cassaic acid in the following manner. Reduction of cassaic acid acetate methyl ester with sodium borohydride formed a single hydroxyester (19) which could be ozonized to give the hydroxyketone (20). Compound (20) was dehydrated by treatment with p-toluenesulfonic acid in refluxing toluene to yield (21). This correlation of the synthetic and natural series established that the structure of ring A proposed by Humber and Taylor[9] was correct.

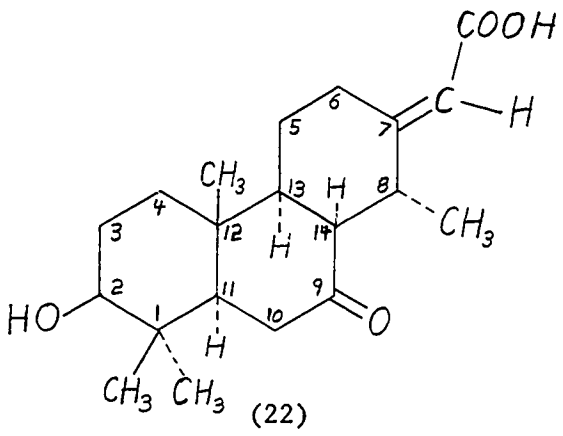



(19) (20) (21)

The C.9-keto group was introduced by oxidation of the $\alpha,\beta$-unsaturated ketone (15) with chromium trioxide in glacial acetic acid. The product, compound (16), exhibited ultraviolet and infrared absorption spectra identical with the spectra of the natural enedione (6) prepared

from cassaic acid. The reduction of (16) with zinc and acetic acid gave the diketone (17) whose infrared spectrum in carbon disulfide solution was identical with the spectrum of the natural diketone (5) obtained from cassaic acid.

The stereochemistry that was assigned to the seven asymmetric centers of cassaic acid is shown in structure (22). The evidence for these assignments was as follows. The C.2-hydroxyl group was considered to be equatorial on the basis of studies of the retropinacol rearrangement of the ring A system of cassaic acid.[10] In addition, the lithium aluminum hydride reduction of compound (10) was expected to give the equatorial alcohol.[16] Whether the equatorial C.2-hydroxyl orientation was $\alpha$ or $\beta$ depended on the nature of the A/B ring fusion and would be $\beta$ if this fusion were trans. The close analogy between the catalytic reduction of (11) to (12) and the similar reduction in the total synthesis of dehydroabietic acid,[27] which led unambiguously to a trans-fused product, suggested that the A/B system in cassaic acid had a trans configuration. A stronger argument was provided by the correlation of cassaic acid with vinhaticoic acid (23),[28] in which the A/B trans arrangement had been established by correlation with abietic acid.[29,30]

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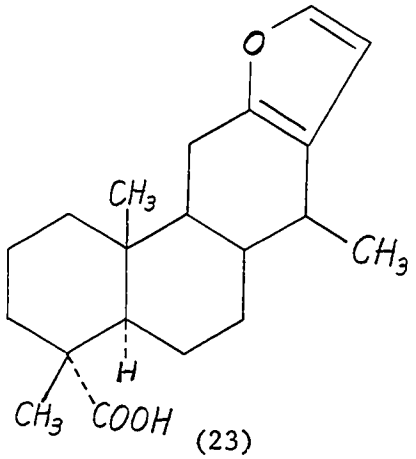
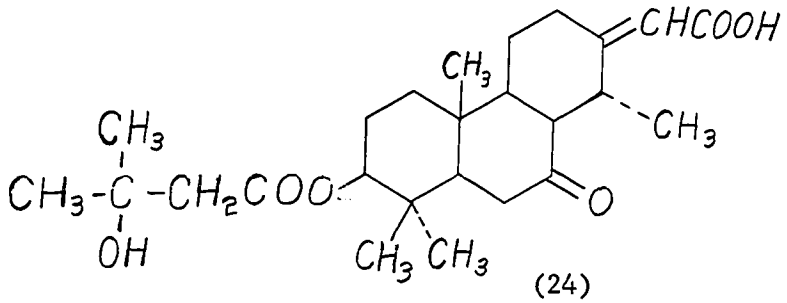



(23)

The nature of the B/C fusion was less well established. This fusion was firmly established to represent a thermodynamically stable configuration by the many instances in which derivatives of cassaic acid had been subjected to the action of base without inversion at the epimerizable center C.14. As an example, coumingic acid (24) was hydrolyzed to cassaic acid by treatment for 1.5 hours in refluxing 0.4 N aqueous alcoholic potassium hydroxide.[31] Dihydrocassaic acid had also been demonstrated to be stable to base.[5,6] The important point that no change in stereochemistry had been effected in the hydrolytic cleavage of cassaine to give cassaic acid was established by the regeneration of the alkaloid from this acid.[4]

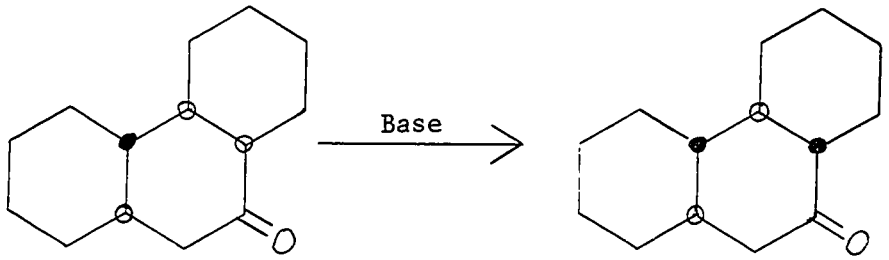



(24)

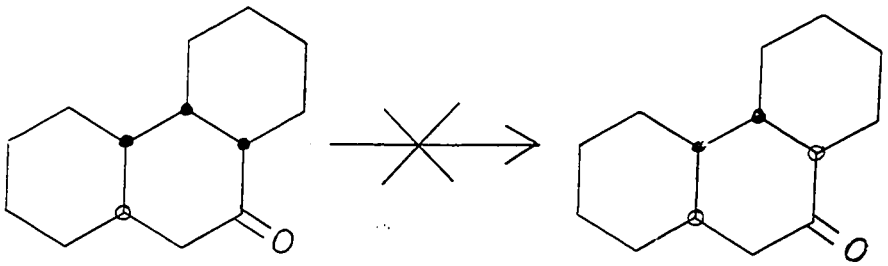
With the demonstration of the trans nature of the A/B ring fusion and the thermodynamic stability of the overall A/B/C system there were only two possible sets of configurations for C.13 and C.14, indicated for the corresponding 9-ketoperhydrophenanthrenes by structures (26) and (27) (Chart II). The trans-anti-trans structure (26) was well known[32] to be of greater thermodynamic stability than the trans-anti-cis arrangement (25). Linstead and Whetstone[33] noted that the trans-syn-cis system (27) did not undergo isomerization to the corresponding trans-syn-trans system (28). This result was explained by Johnson's observation[34] that (28) required ring B to assume a "boat" configuration, while in (27) all three rings could have the more favorable "chair" conformation.

The two stable configurations for the cassaic acid ring system, (26) and (27), differ only in the orientation of the hydrogen atom at C.13. From studies of optical rotatory properties, Klyne[35] had drawn the conclusion that this atom was $\alpha$-oriented in the great majority of diterpenoids. The best direct evidence for the C.13 configuration was obtained from the synthetic sequence previously discussed. The acetoxyketone (15) was formed in the presence of strong base (potassium t-butoxide), thereby insuring equilibration of configuration at C.13. This center would be expected to have the proton $\alpha$-oriented, since only this arrangement permits the preferred equatorial relationship of the C.5-C.13 bond with respect to ring B. Presumably, this orientation was maintained in the preparation of the enedione (16) and its reduction to the diketone (17). The formation of compound (5), the optically active form of (17), from cassaic acid by reactions that do

Chart II




(25) (26)



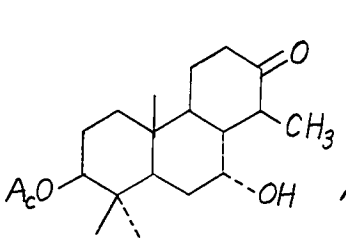

(27) (28)

not involve the asymmetric center at C.13 indicated that, to a very high degree of probability, the trans-anti-trans formulation (26) was correct for cassaic acid.

Consideration was then given to the configuration of the C.8 methyl group (assigned the $\alpha$ orientation in structure (22)). The ozonization of cassaic acid acetate methyl ester to give the diketone (4) which was easily isomerized into (5) has been mentioned previously. As the B/C ring fusion had been shown to be in a thermodynamically stable configuration, this conversion of (4) into (5) could be explained only as representing a change of configuration of the C.8 methyl group from axial ($\alpha$) to equatorial ($\beta$), or, in unusual circumstances, from equatorial to axial.

That the epimerization at C.8 involved, in fact, the conversion of an axial methyl into an equatorial methyl was deduced from consideration of the behavior of the two monoketals (31) and (34), which were prepared and correlated as follows.[10] Ozonization of the hydroxyester (19) gave the compound (20) which, unlike the corresponding acetoxy-diketone (4), was not epimerized by prolonged treatment with base. The stability of the hydroxyketone (20) could be readily explained on the basis of the assigned structure, since a change of the C.8 methyl group from the $\alpha$-configuration to the $\beta$-configuration would introduce an unfavorable 1,3-interaction between the methyl group and the C.9 hydroxyl group. Of course, this argument is equally true for the alternative 8$\beta$, 9$\alpha$ arrangement (29). In this connection, it should be noted that the unstable diketone (4) was formed when (20) was oxidized with chromium trioxide-acetic acid, indicating that the C.8

configuration in (20) is the same as that in cassaic acid. The use of a suitably oriented hydroxyl group at C.9 to maintain an otherwise unfavorable C.8 methyl configuration proved to be vital in the completion of the synthesis of cassaic acid to be discussed later.

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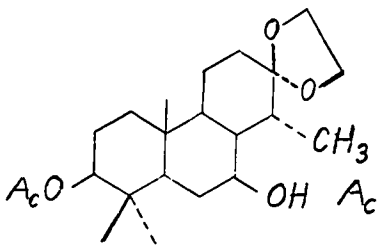


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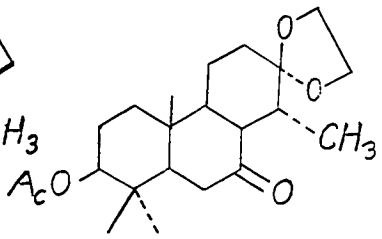
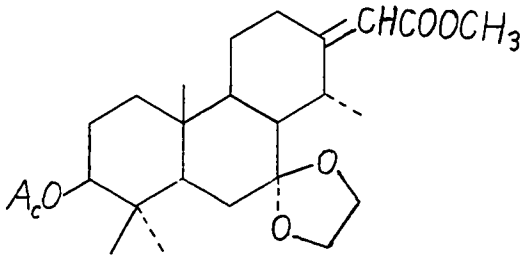


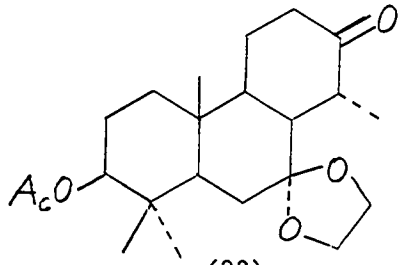

(31)

When (20) was refluxed with 2-butanone ethylene ketal and p-toluenesulfonic acid,[36] the corresponding ketal (30) was formed. Oxidation of (30) gave the monoketal (31), which was reconverted into (30), and thence into (20), by reduction with sodium borohydride and ketal exchange with acetone.

Ozonization of the ketal (32) prepared from cassaic acid acetate methyl ester afforded a second monoketal (33). The remaining two monoketals were obtained in the following manner. Treatment of the stable acetoxydiketone (5) for a short time with 2-butanone ethylene ketal and p-toluenesulfonic acid[36] yielded the monoketal (34) through attack on the less hindered carbonyl (C.7). Further dioxolanation of (34) gave a bisketal assigned structure (35). Partial exchange of (35) with




(32)

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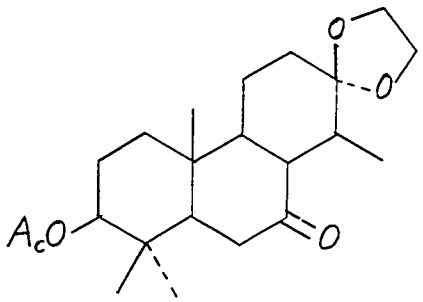


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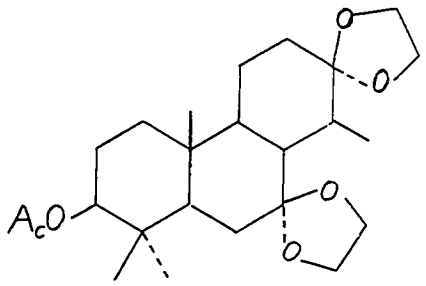
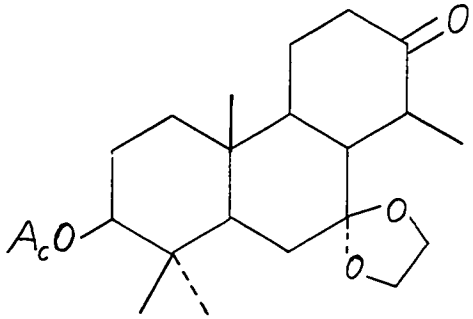



(35)

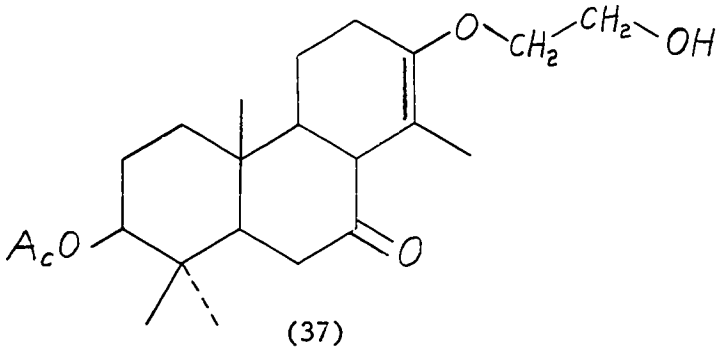
acetone and p-toluenesulfonic acid at room temperature provided the final monoketal (36).




(36)

When either (31) or (34) was refluxed in benzene with p-toluene-sulfonic acid for a prolonged period, the same mixture of products was

obtained, consisting of approximately equal amounts of (31) and (34). This equilibration probably proceeded through the acid-catalyzed opening of the ketal ring to give the common enol-ether intermediate (37).[37]



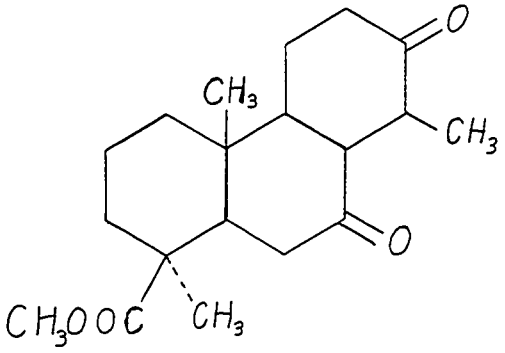

(37)

Therefore, the C.8 methyl configuration that is strongly favored in the acetoxydiketone (5) was somewhat destabilized in the corresponding monoketal (34). Consideration of classical steric effects predicted this destabilization since, if the configurational assignment in (34) were correct, the equatorial methyl group, but not the axial one, would be expected to encounter hinderance from the ketal ring. This would decrease the stability difference between the monoketals (31) and (34) as compared to the diketones (4) and (5). On this basis the methyl group at C.8 in cassaic acid was assigned the configuration shown in (22).

A detailed study of the nuclear magnetic resonance spectra of cassaic acid methyl ester by Hauth, Stauffacher, Niklaus, and Melera[38] confirmed the stereochemical assignments for cassaic acid made on the

basis of the evidence presented above and, in addition, indicated that the double bond had the trans configuration depicted in (22).

Chapman, et al.,[39] in work on the structure of cassamic acid, a substance closely related to cassaic acid, have tentatively assigned a $\beta$-configuration to the C.8 methyl group in the parent acid and in the derived diketone (38). Compound (38) was reported to be unstable




(38)

with respect to its C.8 epimer. This instability was credited by Chapman[39] to a greater steric interaction of the 8$\beta$ methyl group with the ketonic oxygens at C.7 and C.9 relative to that of the 8$\alpha$ methyl. However, an examination of models indicated that an 8$\beta$ methyl group lies almost in the nodal plane of the C.7 keto group* and that the C.9 keto group has essentially the same steric relationship with either an 8$\alpha$ or an 8$\beta$ methyl group. Extrapolation of the

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* This appears to be the preferred configuration, since the methyl group in the stable form of 1-methyl-trans-2-decalone has been rigorously established to be cis to the adjacent ring proton, i.e., equatorial.[40,41]

suggestion of the British workers to the problem of cassaic acid would indicate that the C.8 configurations assigned to compounds (4) and (5) should be reversed and that cassaic acid should have an 8$\beta$ methyl group. This point awaits further clarification, since the experimental evidence presented in the Chapman paper does not exclude the possibility of epimerization in certain key steps.* The bulk of the information, therefore, seems to indicate the correctness of the assignment of structure (22) to cassaic acid.

The conversion of the stable diketone (5) into the hydroxyketone (20) by the transformations (5)$\longrightarrow$(34)$\longrightarrow$(31)$\longrightarrow$(20) provided a means to obtain material in which the C.8 stereochemistry required in cassaic acid was enforced.

A partial synthesis of cassaic acid from the optically active acetoxyhydroxyketone (20) has been accomplished.[12] Compound (20) was treated with zinc and methyl bromoacetate followed by oxidation of the crude product with chromium trioxide and dehydration with thionyl chloride. Chromatography of the final product over alumina afforded material identical in all respects with an authentic sample of cassaic acid acetate methyl ester (39) and convertible by hydrolysis into a sample of cassaic acid indistinguishable from material obtained from cassaine.

As cassaic acid had been converted into cassaine (40),[4] and cassaine had been converted into cassaidine (41),[42] this partial

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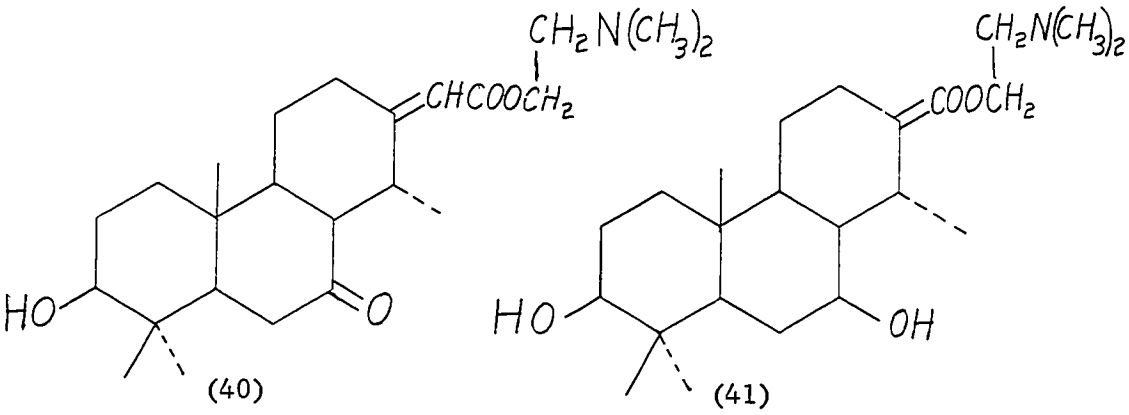
* The transformations (I; X=O)$\longrightarrow$(I; X=$H_2$)$\longrightarrow$(IV; X=$H_2$) of reference 39 are critical.

synthesis of cassaic acid represented, also, a partial synthesis of these two alkaloids.




(40) (41)

Completion of the total synthesis of cassaic acid imposed the formal condition of resolution at some point in the synthetic sequence shown in Chart I.[10,11] As the racemic compounds (15) and (17) were available in optically active form, (21) and (5), respectively, from the degradation of cassaic acid, they were the obvious compounds to select for resolution attempts. In these compounds, only the keto groups at C.7 and C.9 and the hydroxyl group at C.2 (present as acetate) could be used for the preparation of diastereoisomeric derivatives.*

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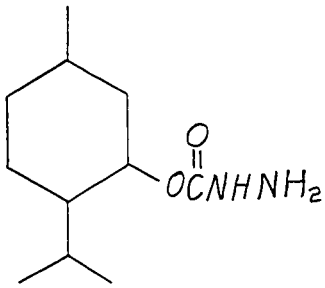
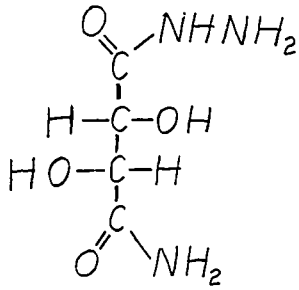
* Attempted resolution at earlier stages in the synthesis was discouraged by a personal communication from Dr. Gilbert Stork that in the course of work leading to the total synthesis of $\alpha$-onocerin[23] approximately one year was spent in unsuccessful experiments to effect the resolution of compounds identical with (9), (10), (12), and (18).

The initial attempt[44] involved the use of l-menthydrazide (42), which had been utilized successfully by Woodward[43] for the resolution of dl-camphor. When the optically active (dextrotatory) $\alpha,\beta$-unsaturated ketone (21) was treated with l-menthydrazide, a nicely crystalline derivative was obtained with a melting point of 157-158°. When the same reaction was performed using the racemic material (15), the product after several recrystallizations melted at 219-220°. This was thought to be a case in which the undesired diastereoisomer was the more easily isolated. The fact that menthydrazide can be obtained in both d and l forms would permit isolation of the desired diastereoisomer by merely using the antipodal form of the menthydrazide. However, when the menthydrazone melting at 219-220° was hydrolyzed, it gave an $\alpha,\beta$-unsaturated ketone melting at 134-135° that was identical to the racemic compound (15) (lit[10] 136-137°). The optically active material (21) melted at 152.5-153.5°,[11] so it was evident that no resolution had been accomplished. Instead, an extremely stable 1:1 complex of the two diastereoisomeric menthydrazones had been formed and could not be separated by crystallization or chromatography. It should be noted that, as far as the author is aware, the use of the optically active menthydrazones for the resolution of ketones has been successful only in the case of dl-camphor.



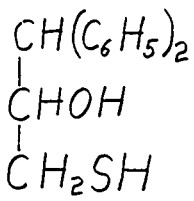
(42)



(43)

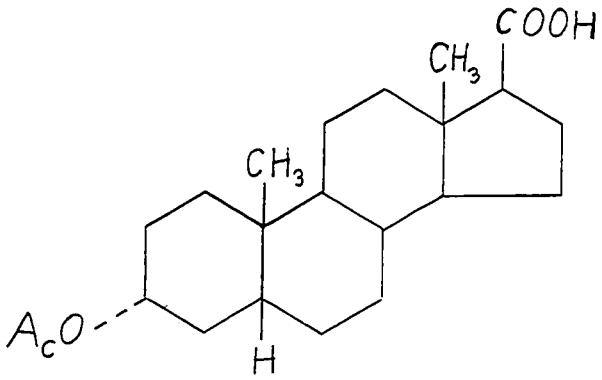
Nerdel and Henkel[45] reported the use of d-tartaramide hydrazide (43) for the resolution of 3,7-dimethyloctaldehyde. When this procedure was tried with the ketones (15) and (17), the only solid material obtained was a small amount of a yellow substance that melted at 252-253°. The same material was produced when d-tartaramide hydrazide was subjected to the same reaction conditions, but without any ketone present.[44] The nature of this substance was not investigated further.

Both optical isomers of 1,1-diphenyl-2-hydrozy-3-mercaptopropane (44) had been prepared[46,47] using the diastereoisomeric hemithioketals formed from (dl-44) and cholestan-3-one. This suggested the use of one of the antipodal forms of (44) as an agent for the resolution of either (15) or (17). However, all attempts to achieve such a resolution were unsuccessful.[48]



(44)

If the C.2 acetate in compounds (15) and (17) were hydrolyzed, it was thought that the resulting hydroxyl group could be caused to react with an optically active acid to provide a means of resolution. When this was tried using 3-acetoxy-11-ketoetiocholanic acid (45), no crystalline products were obtained, and no separation of the diastereoisomers was observed.



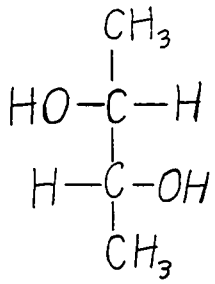

(45)

# II. DISCUSSION

## DISCUSSION

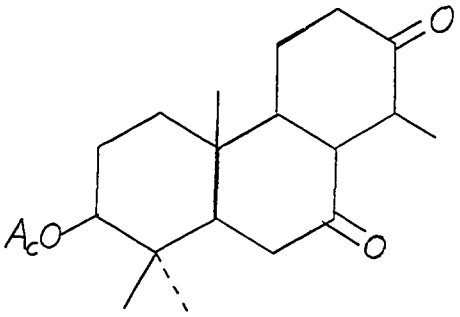
At the time this work was begun the structure of cassaic acid (22) was well established,[10,11] and a synthetic procedure was available for the preparation of compounds (15), (16), and (17) (see Chart I). These three compounds could also be obtained in optically active form from cassaic acid by published methods.[10,11] A partial synthesis of cassaic acid acetate methyl ester (39) had been accomplished[12] which used as its starting material the acetoxyhydroxyketone (20), obtainable from (5) by a series of reactions discussed previously and summarized in Chart III. Completion of the total synthesis of (39) by effecting a resolution at some stage in the synthetic scheme shown in Chart I, in particular involving (15) or (17), proved to be quite difficult.[44,48]

In 1961 Casanova and Corey[49] reported the successful resolution of dl-camphor through the use of D(-)-2,3-butanediol (46)[50] to give a mixture of diastereoisomeric ketals which were then cleanly separated by vapor phase chromatography. Hydrolysis of the two ketals so obtained afforded (+)-camphor and (-)-camphor having 76.5-77.5% optical purity.

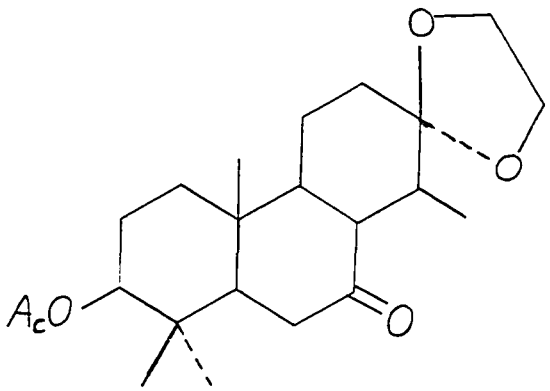


(46)

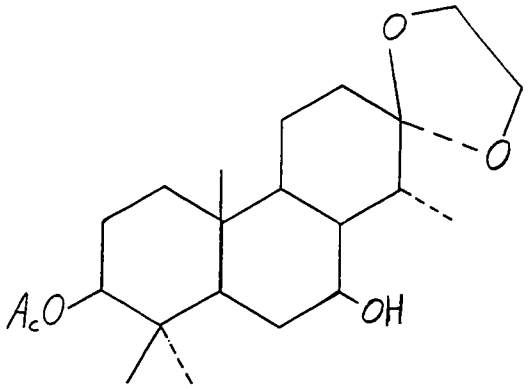
Chart III



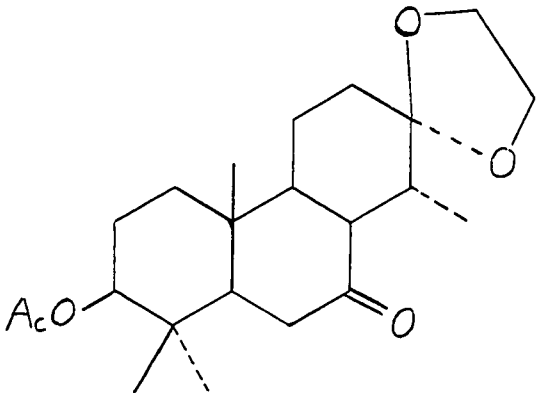

(5)



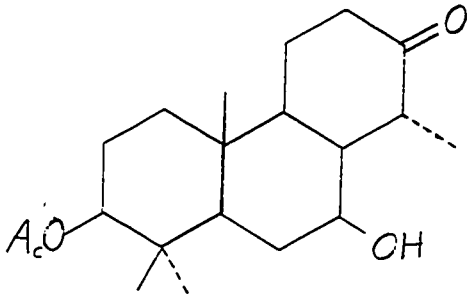

(35)




(31)

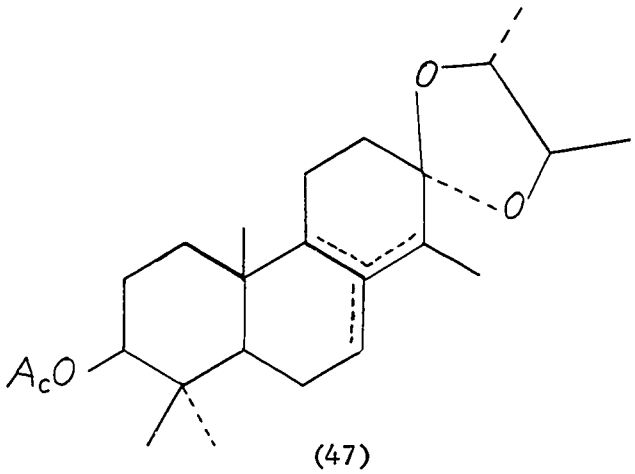



(32)




(20)

Resolution via the ketal was first tried with the $\alpha,\beta$-unsaturated ketone (15) (dl-21). The optically active ketone (21) was allowed to react with the diol to prepare a sample of the desired ketal. When (21) was refluxed for 10 hours in benzene with p-toluenesulfonic acid and an excess of D(-)-2,3-butanediol,* the crude product showed considerable conjugated ketone absorption in the infrared (5.99$\mu$). Comparison of the relative intensities of the acetate carbonyl band at 5.80$\mu$ and of the conjugated ketone absorption at 5.99$\mu$ indicated only 50-60% completion of the reaction. This mixture was chromatographed on alumina, and the ketal fraction was crystallized several times to give material melting at 96.5-98° and assigned the structure (47). As the dotted lines in (47) indicate, the location of the double




(47)

bond was not established, migration from the C.8-C.14 position in the ketone (21) being possible during the course of the reaction.

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* Dr. D.R. Whitaker, National Research Council, Ottawa, Canada, graciously provided a generous sample of D(-)-2,3-butanediol.

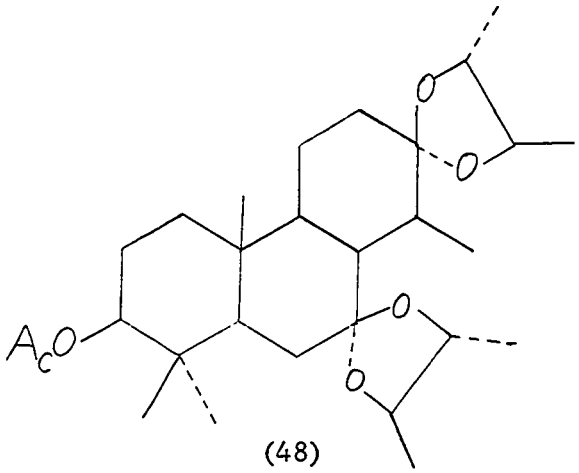
When the racemic ketone (15) was subjected to the same ketalization conditions as for (21), but for 14 hours instead of for 10 hours, complete conversion to ketal material was obtained. No separation of the diastereoisomers was observed when this mixture was chromatographed on a column of neutral alumina.

The problem of finding a suitable combination of adsorbant and eluent for the separation of this mixture was studied using thin-layer techniques. The only pair that proved to be successful was silver nitrate impregnated silicic acid developed with chloroform. With this combination, the ketal mixture from (15) gave two spots having $R_f$ values of 0.52 and 0.43, respectively. A direct comparison on the same thin-layer plate showed that the spot having $R_f$ = 0.52 corresponded exactly with the spot produced by the ketal (47) obtained from the natural ketone (21). Several attempts were made to adapt this procedure to preparative scale through the use of columns of silver nitrate impregnated silicic acid, but these gave only very poor separation.

Attention was then turned to the diketone (17). The two corresponding diastereoisomeric bisketals would incorporate two molecules of the optically active glycol for each molecule of diketone, thereby increasing their probable steric differences as compared to the monoketals from (15), and making chromatographic separation somewhat easier.

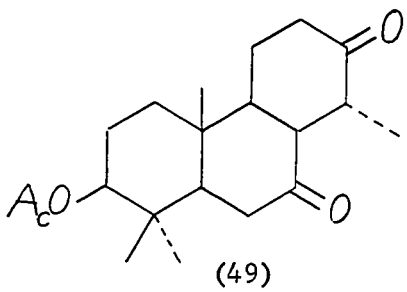
This dioxolanation was first run using the optically active ketone (5) in order to have a sample of the desired bisketal for later comparison. The same conditions as for ketones (15) and (21)

were used, complete conversion of (5) into the bisketal, mp 196.5-197°, assigned structure (48), being achieved after 8 hours.



(48)

In order to obtain a sample of the racemic diketone (17), the Morin synthesis[10] was repeated. The results which were obtained agreed with the published information with the exception of the zinc-acetic acid reduction of the enedione (15). This reduction was reported by Morin[10] to give the thermodynamically stable diketone (17) as determined by the identity of its infrared spectrum with that of the diketone obtained from cassaic acid. In the present investigation, this reaction gave as the sole product the diketone (49), whose infrared absorption spectrum was identical with that of the natural thermodynamically unstable diketone (4). Treatment of (49) with sodium



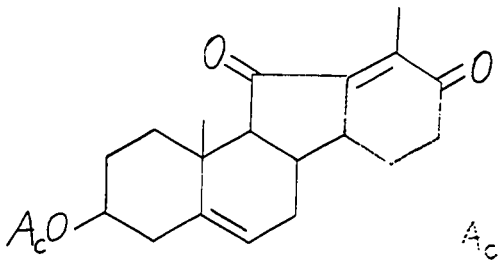
(49)

methoxide in methanol and reacetylation gave material different from (49) and assigned the 8$\beta$ methyl structure (17) on the basis of a comparison of its infrared spectrum with that of the natural stable diketone (5).

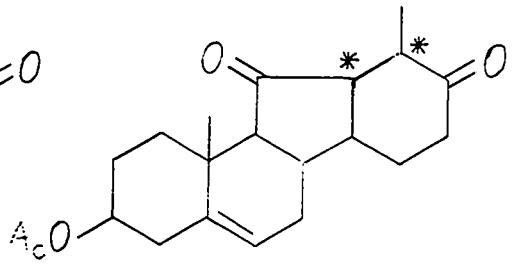
There was no reason to doubt the correctness of the results reported earlier by Morin.[10] It has been well established that the ketone (4) is easily epimerized to give (5), this transformation being accomplished by treatment of (4) with base or even by chromatography on some types of alumina.[10,11] Evidently, some slight difference between the reaction conditions or work-up procedure used by Morin and those used in this work resulted in inversion of the C.8 methyl configuration of the initially formed unstable diketone (49) in the earlier experiments.*

---

* It has been reported by Fried and Klingsberg[51] that the enedione (i) obtained in the degradation of jervine was reduced readily by zinc and acetic acid to give diketonic material. Chromatography of this material on alumina gave a crystalline substance, mp 171-172°, assigned the structure (ii) and a second fraction, mp 142-155°. When the lower melting substance was rechromatographed, additional compound melting at 170-171° was obtained followed by material melting at 147-153°. This lower melting substance was thought to be an epimer of (ii) at one, or both, of the starred centers.

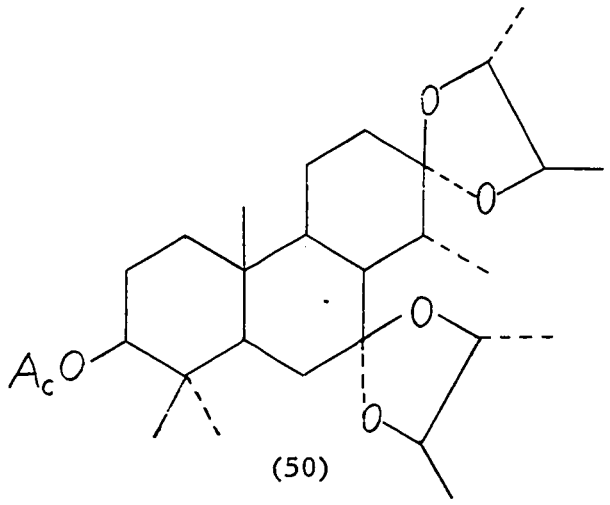



(i)




(ii)

When the racemic unstable diketone (49) was refluxed for 8 hours in benzene with p-toluenesulfonic acid and a large excess of the optically active diol, a mixture of monoketal and bisketal material was obtained. Chromatography of this mixture on alumina provided the pure bisketal. This material had a melting point of 173-175° and when mixed the bisketal (48) gave a depression to 143-155°. The infrared absorption spectra of these two bisketals were also different in the 8-15$\mu$ region. Accordingly, this bisketal was assigned the structure (50), the C.8 epimer of (48).




(50)

The bisketal prepared from (4) in the same manner proved to be identical in all respects with (50), including infrared spectra and mixture melting point determinations.

As has been mentioned previously, the stable diketone (5) was completely converted into bisketal (48) after 8 hours. However, in the same length of time, the unstable diketone (4) gave a considerable amount of monoketal material, indicating incomplete reaction. To effect complete conversion of (4) into (50), it was necessary to

lengthen the reaction time to over 20 hours. A study of molecular models indicated that the 8$\alpha$ methyl group in (4) provided somewhat more steric hinderance to reactions involving attack on the C.9 carbonyl group than does the 8$\beta$ methyl group in (5), thereby giving rise to a steric inhibition of the rate of bisketal formation. Further qualitative evidence of the steric retardation of bisketal formation with 2,3-butanediol was found in a comparison of the conditions necessary to effect complete conversion of diketone (5) into the two bisketals (35) and (48). Preparation of the bis-ethylene ketal (35) was complete after 5.5 hours.[10,11] However, 8 hours was needed to obtain full conversion of (5) into the bisketal (48).

It should be noted that none of the bisketal (48) was obtained from the preparation of (50), indicating that no isomerization had taken place at C.8, although the conditions for this reaction were quite similar to those reported[10,12] to effect equilibration of the monoethylene ketals (31) and (34). The $\alpha$-methyl group of the C.9 ketal in (50) would be expected to provide even greater steric hinderance to the transformation of the C.8 methyl from the $\alpha$-configuration into a $\beta$-configuration than does the hydroxyl group in the hydroxyketone (20). This latter compound has been reported to be stable to conditions which result in epimerization of the corresponding diketone (4). Therefore, it was not surprising that the steric hinderance present in (50) should prevent inversion of the C.8 methyl orientation.

The bisketal (50) was hydrolyzed by prolonged treatment (27 hours) in reluxing acetone containing p-toluenesulfonic acid to give a mixture

of diketone and monoketal material. Chromatographic separation afforded a single diketone fraction which had a melting point of 168.5-170° after recrystallization from ether-petroleum ether and proved to be identical in all respects with an authentic sample of the optically active unstable acetoxydiketone (4). When the monoketal fraction was refluxed for an additional 36 hours under the same conditions, complete cleavage to a mixture of the diketones (4) and (5) resulted. The apparent stability of the 8α methyl diketone (4) under these cleavage conditions was somewhat unexpected. As all earlier work[10,11,12] on the isomerization at C.8 involved basic conditions, these results merely reflect the greater ease of enolization in base than in acid.

As procedures had been established for the conversion of (4) into cassaic acid (22),[12] and thence into cassaine (40)[4] and cassaidine (41),[41] this resolution completed the total synthesis of these compounds.

# III. EXPERIMENTAL

## EXPERIMENTAL

Preparation of (-)-2$\beta$-Acetoxy-8$\alpha$-methylpodocarpane-7,9-dione (4). A solution of 81 mg of cassaic acid acetate methyl ester (38)[11] in 4 ml of ethyl acetate and 4 ml of glacial acetic acid was cooled in an ice-salt bath and was treated with 4.5 molar equivalents of ozone over a period of 30 seconds. The solution was allowed to stand in the ice-salt bath for 1.5 hours. Then 250 mg of zinc dust and 0.2 ml of water were added, and the cold mixture was stirred for 15 minutes. After standing at room temperature for 30 minutes, the mixture was filtered, and the zinc dust was washed well with ether. The filtrate and ether washings were combined and were washed well with water, dilute sodium hydroxide solution, water, dilute hydrochloric acid solution, water, and saturated sodium chloride solution. The ether solution was filtered through magnesium sulfate and was evaporated to give 69 mg of the unstable diketone (4). The infrared absorption spectrum of this material, when taken in carbon disulfide solution, was identical with that of an authentic specimen. $\lambda_{max}^{CS_2}$ 5.71, 5.80, 8.02$\mu$.

Preparation of (-)-2$\beta$-Acetoxy-8$\beta$-methylpodocarpane-7,9-dione (5). To a solution of 104 mg of sodium in 3 ml of methanol was added a solution of 247 mg of the acetoxydiketone (4) in 20 ml of methanol. The resulting solution was refluxed under nitrogen for 3 hours. The bulk of the methanol was blown off under a stream of nitrogen gas, and the residue was taken up in ether and water. Dilute hydrochloric acid solution was added, and the ether layer was washed with water and saturated sodium chloride solution and was filtered through magnesium

sulfate. Evaporation of the ether afforded a white solid which was acetylated with acetic anhydride and pyridine. The crude product was chromatographed on alumina to provide 87 mg of the stable acetoxydiketone (5) whose infrared spectrum in carbon disulfide solution was identical with that of an authentic sample. $\lambda_{max}^{CS_2}$ 5.73, 5.81, 8.05$\mu$.

Preparation of 1,2,3,4,9,12-Hexahydro-7-methoxy-1,1,12-trimethyl-2-oxophenanthrene (10). A suspension of 8.103 gm of (9) in 100 ml of dry t-butyl alcohol was purged well with nitrogen. Then a solution of 4.01 gm of potassium metal in 100 ml of t-butanol was added, followed by a solution of 28 gm of methyl iodide in 20 ml of t-butanol. The resulting mixture was stirred at 30° for 1.5 hours and then was refluxed for 30 minutes. After the mixture had cooled, 210 ml of 1 M hydrochloric acid was added, and the solution was extracted several times with ether. The ether extracts were combined and were concentrated under reduced pressure. The organic solution was washed with water, dilute sodium hydroxide solution, water, and saturated sodium chloride solution and was filtered through magnesium sulfate. The combined aqueous washes were extracted with ether, and this ether extract was washed and dried as above. The combined ether layers were evaporated under reduced pressure to remove the solvent, and the dark red residue was placed directly on a short column of Florisil. Elution with petroleum ether-benzene (80:20) gave 8.578 gm of crude (10) as a red oil whose infrared spectrum was identical with that of an authentic sample. This material was quite sensitive to exposure to the atmosphere,[10] so it was immediately reduced to (11). $\lambda_{max}^{CS_2}$ 5.85$\mu$.

Preparation of 1,2,3,4,9,12-Hexahydro-7-methoxy-1,1,12-trimethyl-2-hydroxyphenanthrene (11) and trans-1,2,3,4,9,10,11,12-Octahydro-7-methoxy-1,1,12-trimethyl-2-hydroxyphenanthrene (12). A solution of 8.578 gm of crude (10) in 100 ml of ether was added dropwise over a period of 1.5 hours to 3.166 gm of lithium aluminum hydride in 250 ml of refluxing ether. A nitrogen atmosphere was maintained throughout the reaction. The reaction mixture was stirred for 30 minutes after addition of the ketone solution was complete, the excess reagent was destroyed with methanol, and dilute hydrochloric acid was added. The ether layer was washed with water, dilute sodium hydroxide solution, water, and saturated sodium chloride solution and was filtered through magnesium sulfate. Removal of the solvent under reduced pressure gave (11) as a light yellow solid. $\lambda_{max}^{CS_2}$ 2.80$\mu$.

The crude (11) was dissolved in 100 ml of glacial acetic acid and was hydrogenated over 1.07 gm of 10% palladium on charcoal at room temperature. Hydrogen uptake ceased after 17 hours with 760 ml of hydrogen being absorbed. The mixture was filtered, and the catalyst was washed well with ether. The combined filtrate and ether washings were diluted with more ether and were washed with dilute sodium hydroxide solution, water, and saturated sodium chloride solution. The ether solution was dried by filtration through magnesium sulfate. Removal of the ether afforded 7.587 gm of compound (12) as white crystals whose infrared spectrum in carbon disulfide solution was identical with that of a sample of authentic (12) prepared by Morin.[10] Crystallization of the crude material from ether-petroleum ether gave white crystals, mp 138.5-140° (lit.[10] 140-141°). $\lambda_{max}^{CS_2}$ 2.80$\mu$.

Preparation of trans-1,2,3,4,5,8,9,10,11,12-Decahydro-7-methoxy-1,1,12-trimethyl-2-hydroxyphenanthrene (13a). To a stirred solution of 1.016 gm of (12) in 150 ml of ether, 15 ml of ethanol, and 300 ml of liquid ammonia was added 1.45 gm of lithium wire in small pieces over a period of 45 minutes. After an additional 30 minutes the residual blue color was discharged by the addition of ammonium chloride. The ammonia was evaporated under a stream of nitrogen gas, and the residue was taken up in ether and water. The ether layer was washed with ice water and then with saturated sodium chloride solution. After drying over magnesium sulfate the ether was removed to give 1.254 gm of crude (13a). $\lambda_{max}^{CS_2}$ 2.80$\mu$.

The corresponding acetate (13b) was prepared by the acetic anhydride-pyridine method. $\lambda_{max}^{CS_2}$ 5.78, 8.05$\mu$.

The infrared spectra of compounds (13a) and (13b) were identical with those of authentic specimens.

Preparation of 2$\beta$-Acetoxypodocarp-13(14)-en-7-one (14). A solution of 1.08 gm of the crude enol-ether acetate (13b) and 2.323 gm of oxalic acid in 35 ml of ethanol and 2 ml of water was stirred at room temperature for 2 hours under a nitrogen atmosphere. The reaction was poured over ice and was extracted with ether. The ether extract was washed with dilute sodium hydroxide solution, water, and saturated sodium chloride solution and was filtered through magnesium sulfate. Evaporation of the ether gave 1.020 gm of the $\beta,\gamma$-unsaturated ketone (14), identified by comparison of its infrared spectrum with that of an authentic sample of (14) prepared by Morin.[10] $\lambda_{max}^{CS_2}$ 5.78, 8.05$\mu$.

Preparation of 2$\beta$-acetoxy-8-methylpodocarp-8(14)-en-7-one (15). To a solution of 524 mg of (14) in 50 ml of t-butanol was added 3.72 ml of a solution of 362 mg of potassium metal in 10.0 ml of t-butanol. The resulting light yellow solution was heated to reflux temperature under nitrogen, and 0.13 ml of methyl iodide in 50 ml of t-butanol was added dropwise over a period of 1 hour. The reaction mixture was refluxed for an additional 30 minutes and then was cooled in ice water. Dilute hydrochloric acid was added until the solution was slightly acidic. The mixture was poured over ice and was extracted with ether. The ether extract was washed with dilute sodium hydroxide solution, water, and saturated sodium chloride solution and was filtered through magnesium sulfate. Evaporation of the ether gave 507 mg of an orange oil that was acetylated with acetic anhydride and pyridine to give 531 mg of crude (15). Crystallization of this material from petroleum ether gave 151 mg of pure (15), mp 135-136.5° (lit[10] 136-137°). $\lambda_{max}^{CS_2}$ 5.78, 5.99, 8.05$\mu$.

The infrared absorption spectrum of this material was identical with that of an authentic sample.

Preparation of 2$\beta$-Acetoxy-8-methylpodocarp-8(14)-en-7,9-dione (16). A solution of 150 mg of chromium trioxide in 6 ml of 90% acetic acid was added to a solution of 326 mg of (15) in 10 ml of glacial acetic acid. The solution was stirred at 65° for 1.75 hours and then was poured into a mixture of ice and water. This mixture was extracted twice with ether. The ether extracts were washed with water, dilute sodium hydroxide solution, water, and saturated sodium chloride solution and were filtered through magnesium sulfate. Removal of the ether

afforded 261 mg of a partly solid material. Three recrystallizations from ether-petroleum ether gave 67 mg of the enedione (16), mp 133-135° (lit[10] 136-137°). $\lambda_{max}^{EtOH}$ 264 mμ, $\epsilon$ 11,100; $\lambda_{max}^{CS_2}$ 5.78, 5.95, 8.07μ.

Reduction of (16) to give dl-2β-Acetoxy-8α-methylpodocarpane-7,9-dione (49). A mixture of 335 mg of zinc dust and 45 mg of (16) in 6 ml of glacial acetic acid was heated to reflux temperature for 2 hours. The mixture was diluted with ether and was filtered, and the filtrate was washed with dilute sodium hydroxide solution, water, and saturated sodium chloride solution. The ether solution was dried over magnesium sulfate and was evaporated to give 16 mg of the diketone (49) whose infrared spectrum in carbon disulfide solution was identical with that of the diketone (4) prepared from cassaic acid acetate methyl ester. $\lambda_{max}^{CS_2}$ 5.71, 5.80, 8.02μ.

The analytical sample, obtained in a second experiment, melted at 163-164.5°.

Anal. Calcd. for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04

Found: C, 71.60; H, 8.73.

Epimerization of (49) into dl-2β-Acetoxy-8β-methylpodocarpane-7,9-dione (17). Ten milligrams of sodium was dissolved in 2 ml of methanol, 13.6 mg of (49) was added, and the solution was refluxed for 3 hours. The bulk of the solvent was blown off under a stream of nitrogen gas, and the residue was taken up in ether and water. Dilute hydrochloric acid was added, and the ether layer was removed and was washed with water and saturated sodium chloride solution. After filtration through magnesium sulfate, the ether was evaporated to give 9.7 mg of

an oil which was acetylated by the acetic anhydride-pyridine method to provide 11.2 mg of crude material. This was chromatographed on alumina, and the diketone fraction was crystallized several times from ether-petroleum ether to give the acetoxydiketone (17), mp 161-162.5° (lit[10] 158-160°). The infrared spectrum of this compound taken in carbon disulfide solution was identical with that of an authentic sample of the stable optically active acetoxydiketone (5) and differed in the fingerprint region from the spectrum of (49). $\lambda_{max}^{CS_2}$ 5.78, 5.82, 8.06 .

Preparation of Ketal (47) from Optically Active Ketone (21). A solution of 24.6 mg of the natural $\alpha,\beta$-unsaturated ketone (21) in benzene containing 10.2 mg of p-toluenesulfonic acid and 521 mg of D(-)-2,3-butanediol was refluxed for 10 hours and then was allowed to stand at room temperature overnight. The reaction mixture was taken up in ether, and the ether solution was washed with water, dilute sodium hydroxide solution, water, and saturated sodium chloride solution. The organic layer was dried by filtration through magnesium sulfate, and the solvent was removed under a stream of nitrogen gas. The product was 29.9 mg of a faintly orange oil that showed a band at 6.00 $\mu$ having a decreased intensity relative to the acetate band at 5.80 $\mu$, thereby indicating a mixture of ketal (47) and unreacted starting material.

This crude product was chromatographed on alumina (Woelm activity II-III) to give 7.4 mg of ketal material which was crystallized from ether-petroleum ether and then from methanol-water to afford 1.3 mg of white crystals, mp 96.5-98°. There was insufficient material for

analysis, but the infrared absorption spectrum was consistent with the ketal structure (47). $\lambda_{max}^{CS_2}$ 5.78, 8.03$\mu$.

Attempted Resolution of the Racemic $\alpha,\beta$-Unsaturated Ketone (15). A solution of the racemic ketone (15) obtained from R.B. Turner was dissolved in benzene (15 ml) with D(-)-2,3-butanediol (700 mg) and p-toluenesulfonic acid (20.5 mg). The mixture was refluxed for 14 hours and was allowed to stand for 1.5 hours at room temperature. Ether was added, and the ether solution was washed and dried as usual. The crude product, 113 mg, was combined with 53 mg from another run and was chromatographed on alumina (Woelm activity II-III) to give 103 mg of a very poorly separated mixture of ketals.

Partion chromatography using ethanol on silicic acid as the stationary phase and methylene chloride containing 4% ethanol as the mobile phase also gave very poor separation of this mixture. Two major spots were observed, having $R_f$ values of 0.43 and 0.52, respectively, when the ketal mixture was subjected to thin-layer chromatography on a plate of silver nitrate impregnated silicic acid developed with chloroform. The spot having $R_f$ = 0.52 corresponded exactly with the spot produced by the ketal (47) prepared from the optically active ketone (21). This comparison was done using duplicate spots on the same plate. Several attempts were made to use a column of silver nitrate impregnated silicic acid to separate this mixture on a preparative scale, but the results were not satisfactory.

Preparation of Bisketal (48) from the Natural Stable Diketone (5). Fifteen milligrams of the optically active stable diketone (5) was dissolved in 3 ml of benzene with 509 mg of D(-)-2,3-butanediol and 6 mg of p-toluenesulfonic acid, and the solution was refluxed for 8 hours. The usual workup afforded 36.9 mg of a cream-colored oil that gave 21.8 mg of the bisketal (48) when chromatographed on alumina (Woelm activity II-III). Crystallization from ether-petroleum ether yielded white crystals, mp 196.5-197°. $\lambda_{max}^{CS_2}$ 5.78, 8.02$\mu$.

The sample for analysis was prepared by further recrystallization from ether-petroleum ether and melted at 199-200°.

Anal. Calcd. for $C_{28}H_{46}O_6$: C, 70.26; H, 9.69

Found: C, 70.38; H, 9.71.

Preparation of Bisketal (50) from the Natural Unstable Diketone (4). A solution of 40 mg of the optically active unstable diketone (4), 480 mg of D(-)-2,3-butanediol, and 7.4 mg of p-toluenesulfonic acid in 7 ml of benzene was refluxed for 29 hours. The solution was cooled, and ether was added. The ether solution was washed and dried in the usual manner to give 61 mg of a colorless oil. The bisketal fraction (40.5 mg) from chromatography on alumina (Woelm activity I-II) crystallized from ether-petroleum ether as colorless needles, mp 173.5-174°. The analytical sample melted at 175.5-176.5°. $\lambda_{max}^{CS_2}$ 5.78, 8.05$\mu$.

Anal. Calcd. for $C_{28}H_{46}O_6$: C, 70.26; H, 9.69

Found: C, 70.30; H, 9.58.

Resolution of the Racemic Unstable Diketone (49). A solution of 15.8 mg of (49), 508 mg of D(-)-2,3-butanediol, and 4 mg of p-toluenesulfonic acid in 5 ml of benzene was refluxed for 8 hours. After standing at room temperature overnight, the solution was refluxed an additional 2 hours. The usual workup procedure was followed, giving 40.8 mg of a cloudy oil that was chromatographed on alumina (Woelm activity II-III) to provide 8.2 mg of bisketal material as well as some monoketal and diketone fractions. The bisketal fraction was crystallized several times from ether-petroleum ether to afford 3.0 mg of colorless needles, mp 173-175°. The infrared spectrum of this material taken in carbon disulfide solution was identical with that of bisketal (50) obtained from (4). A mixture melting point with (50) was undepressed, but a mixture melting point with (48) was lowered to 143-154°.

Two milligrams of p-toluenesulfonic acid and 24.8 mg of (50) were refluxed in acetone for 27 hours. The reaction mixture was diluted with water and was extracted with ether. The ether extract was washed with water, dilute sodium hydroxide solution, water, and saturated sodium chloride solution and was filtered through magnesium sulfate. Evaporation of the ether and chromatography of the residue on alumina (Woelm activity II-III) gave various bisketal and monoketal fractions followed by a single diketone fraction (6.2 mg) whose infrared absorption spectrum in carbon disulfide solution was identical with that of an authentic sample of the natural unstable diketone (4). The diketone fraction was crystallized several times from ether-petroleum ether to give 1.9 mg of material melting at 168.5-170° (lit[10,11] 169-170°). A mixture melting point with authentic (4) was undepressed.

Treatment of the monoketal and bisketal fractions under these same conditions for 36 hours gave complete formation of diketone material. Chromatography of this product showed it to be a mixture of the diketones (4) and (5) in approximately equal amounts. These diketones were identified by comparison of their infrared spectra with the spectra of authentic samples prepared from cassaic acid.

# IV. REFERENCES

REFERENCES

1. G. Dalma, Ann. Chim. applicata, 25, 569 (1935).

2. For reviews of earlier work see T.A. Henry, "The Plant Alkaloids," 4th ed., J. and A. Churchill, London (1949), p 725; and E.L. McCrawley, Chap. 39, in "The Alkaloids," R.H.F. Manske and H.L. Holmes, Vol. V, Academic Press, New York, N.Y. (1955).

3. G. Dalma, Helv. Chim. Acta, 22, 1497 (1939).

4. F. Faltis and L. Holzinger, Ber., 72, 1443 (1939).

5. L. Ruzicka and G. Dalma, Helv. Chim. Acta, 22, 1516 (1939).

6. L. Ruzicka, G. Dalma, and W.E. Scott, ibid., 24, 179E (1941).

7. A. Ronco, "Zur Kenntnis der Erythrophleum-Alkaloide, Ueber die Konstitution der Cassainsaure," Kommerzdruck und Verlags, A.G., Zürich (1945).

8. L. Ruzicka, B.G. Engel, A. Ronco, and K. Berse, Helv. Chim. Acta, 28, 1038 (1945).

9. L.G. Humber and W.I. Taylor, J. Chem. Soc., 1044 (1955).

10. R.B. Morin, Dissertation, Rice Institute, Houston, Texas (1959).

11. R.B. Turner, E. Herzog, and A. Riebel, Tetrahedron Letters, No. 2, 7 (1959).

12. R.B. Turner, O. Buchardt, E. Herzog, R.B. Morin, A. Riebel, and J.M. Sanders, J. Am. Chem. Soc., 88, 1766 (1966).

13. B.G. Engel, Helv. Chim. Acta, 42, 131 (1959).

14. W.P. Campbell and G.C. Harris, J. Am. Chem. Soc., 63, 2721 (1941).

15. L. Ruzicka, Ed. Rey, and A.C. Muhr, Helv. Chim. Acta, 27, 472 (1944).

16. E.R.H. Jones and T.G. Halsall, Chap. 2, in "Progress in the Chemistry of Organic Natural Products," L. Zechmeister, Ed., Vol. 12, Springer Verlag, Vienna (1955).

17. J. Simonsen and W.C.J. Ross, "The Terpenes," Vol. 4, University Press, Cambridge (1957), p 64.

18. R. Robinson and P. Weygand, J. Chem. Soc., 386 (1941).

19. J.W. Cornforth, R.H. Cornforth, and R. Robinson, ibid., 689 (1942).

20. G. Stork, R. Terrell, and J. Szmuszkovicz, J. Am. Chem. Soc., 76, 2029 (1954).

21. Cf. F.H. Howell and D.A.H. Taylor, J. Chem. Soc., 1248 (1958).

22. R.B. Woodward, A.A. Patchett, D.H.R. Barton, D.A.J. Ives, and R.B. Kelly, J. Chem. Soc., 1131 (1957).

23. Cf. G. Stork, J.E. Davies, and A. Meisels, J. Am. Chem. Soc., 81, 5516 (1959).

24. A.L. Wilds and N.A. Nelson, ibid., 75, 5360, 5366 (1953).

25. N.W. Atwater, ibid., 79, 5315 (1957).

26. F. Sondheimer and Y. Mazur, ibid., 79, 2906 (1957).

27. G. Stork and J.W. Schulenberg, ibid., 78, 250 (1956).

28. F.E. King, T.J. King, and J.M. Uprichard, J. Chem. Soc., 3428 (1958).

29. D.H.R. Barton and G.A. Schmeidler, ibid., 1197 (1948).

30. D.H.R. Barton, ibid., S232, Suppl. No. 1 (1949).

31. L. Ruzicka, G. Dalma, and W.E. Scott, Helv. Chim. Acta, 24, 63 (1941).

32. R.P. Linstead, W. von E. Doering, S.B. Davis, P. Levine, and R.R. Whetstone, J. Am. Chem. Soc., 64, 1985 (1942), et seq.

33. R.P. Linstead and R.R. Whetstone, J. Chem. Soc., 1428 (1950).

34. W.S. Johnson, Experientia, 7, 315 (1951).

35. W. Klyne, J. Chem. Soc., 3072 (1953).

36. H.J. Dauben, B. Löken, and H.J. Ringold, J. Am. Chem. Soc., 76, 1359 (1954).

37. Cf. M.E. Wall and H.A. Walens, ibid., 77, 5661 (1955).

38. H. Hauth, D. Stauffacher, P. Niklaus, and A. Melera, Helv. Chim. Acta, 48, 1087 (1965).

39. G.T. Chapman, B. Jaques, D.W. Mathieson, and V.P. Arya, J. Chem. Soc., 4010 (1963).

40. R.B. Turner and J. Lin, unpublished results.

41. Cf. N.L. Allinger and H.M. Blatter, J. Am. Chem. Soc., 83, 994 (1961); and S.S. Butcher and E.B. Wilson, J. Chem. Phys., 40, 1671 (1964).

42. B.G. Engel, Helv. Chim. Acta, 42, 1127 (1959).

43. R.B. Woodward, T.P. Kohman, and G.C. Harris, J. Am. Chem. Soc., 63, 120 (1941).

44. R.B. Turner, unpublished results.

45. F. Nerdel and E. Henkel, Ber., 85, 1138 (1952).

46. C. Djerassi, M. Gorman, and J.A. Henry, J. Am. Chem. Soc., 77, 4647 (1955).

47. C. Djerassi and J. Grossman, J. Am. Chem. Soc., 79, 2553 (1957).

48. R.B. Turner and O. Buchardt, unpublished results.

49. J. Casanova and E.J. Corey, Chem. and Ind. (London), 1664 (1961).

50. S.A. Morell and A.H. Auernheimer, J. Am. Chem. Soc., 66, 792 (1944).

51. J. Fried and A. Klingsberg, ibid., 75, 4929 (1953).

# PART II

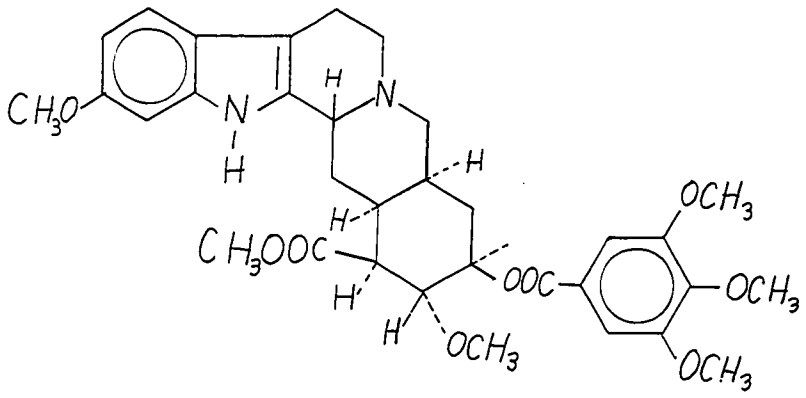
## I. INTRODUCTION

# INTRODUCTION

Rauwolfia serpentina, Benth, has been an exceedingly abundant source of alkaloids of various structural types. More than 15 different bases have been isolated from this plant.[1] The interest in R. serpentina, as well as in other Rauwolfia species, is due to the physiological activity of extracts prepared from them.

Extracts from R. serpentina, Benth, have long had a reputation as having sedative properties[2] and have been used as an hypnotic for children in Bihar.[3] The most important physiological property of these preparations, their hypertensive action, was discovered by Indian pharmacologists.[4]

Although reserpine (1) has been claimed to be the alkaloid mainly responsible for the sedative and hypertensive properties of

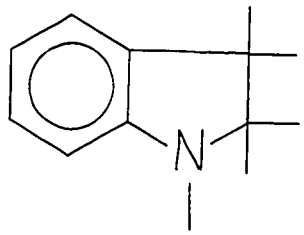


(1)

R. serpentina,[5] the major alkaloid in this plant has been named ajmaline.[6] It is identical with the alkaloid isolated from the same plant by van Itallie and Steenhauer, which these workers called rauwolfine.[7]

Ajmaline, $C_{20}H_{26}N_2O_2$,[6] was found to be a diacidic base, forming both a monohydrochloride and a dihydrochloride.[8] Its infrared spectra showed no carbonyl absorption,[3] and it was possible to prepare an O-acetate and an O,O-diacetate,[3] the latter substance forming less readily. No N-acetyl derivatives were found,[3] indicating the tertiary nature of both nitrogens. Hydrolysis with acid or base, or reduction with lithium aluminum hydride, converted both the monoacetate and the diacetate into ajmaline.[3]

The ultraviolet spectrum and color reactions of the alkaloid indicated that it had the dihydroindole part structure (2).[3] Ajmaline

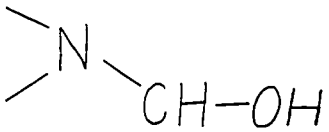


(2)

monomethiodide showed the same ultraviolet spectrum and color reactions as did ajmaline,[3] indicating that the dihydroindole nitrogen, $N_a$, was not quarternized.

The nature of the other nitrogen atom, $N_b$, was deduced from the following transformations. Although showing no carbonyl absorption in the infrared and being stable to lithium aluminum hydride in ether, ajmaline gave a positive Tollen's test and formed ajmaline oxime,

$C_{20}H_{27}N_2O_2$, with aqueous hydroxylamine hydrochloride.[3] Dehydration of the oxime with acetic anhydride followed by base treatment gave anhydroajmaline oxime, $C_{20}H_{25}N_3O$, which proved to be a nitrile in which one of the nitrogen atoms of ajmaline had become secondary.[3] Reduction of anhydroajmaline oxime with lithium aluminum hydride gave ajmaline.[3] This indicated the part structure (3) for the portion of the ajmaline molecule involved in these transformations.



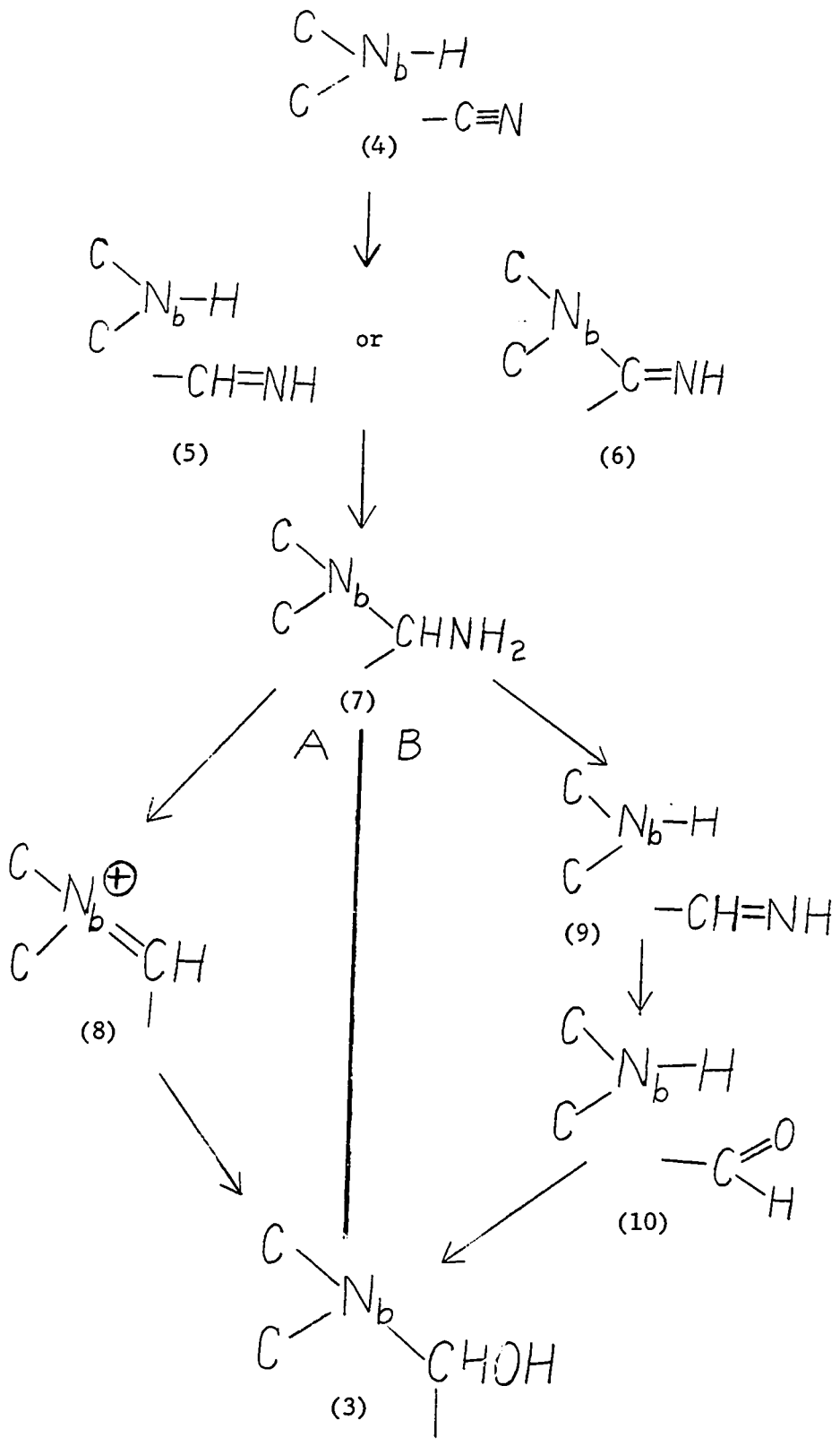

(3)

The two possible mechanisms for the formation of ajmaline by the reduction of anhydroajmaline oxime, represented as part structure (4), are presented in Chart I. Both mechanisms involve the formation of compound (7) via one of the intermediates (5) or (6). Compound (7) is probably the initial product of the reduction of (4), with ajmaline being formed during the aqueous workup.

As (7) may be considered to be the nitrogen analog of the carbinolamine (3), it might be in equilibrium with the immonium form (8) in the same way that carbinolamines can be in equilibrium with the corresponding imines (path A). The immonium form (8) could be hydroxylated to give the carbinolamine (3).

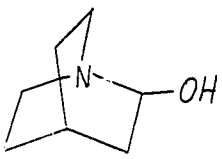
Alternatively, the formation of (3) could occur by way of the opened form (9) (path B). This is analogous to the known equilibrium between carbinolamines and the corresponding aminoaldehydes. Hydrolysis of the imine moiety of (9) would give the aminoaldehyde (10) which would cyclize to give ajmaline(3).

Chart I

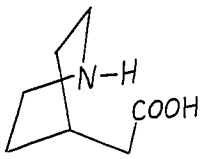


A choice can be made in favor of path B on the basis of the following information. Hydrolysis of anhydroajmaline oxime (4) provides an amino acid which does not form a lactam even under quite vigorous conditions.[3] Evidently, some factor is present in the ajmaline system that greatly destabilizes the lactam relative to the amino acid.

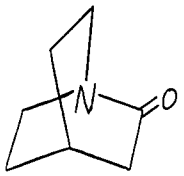
From evidence to be presented later, the carbinolamine moiety of ajmaline has been established to be part of a quinuclidine ring system, as shown in the part structure (11). The amino acid obtained by hydrolysis of anhydroajmaline oxime and the corresponding lactam may be represented as (12) and (13), respectively.




(11)

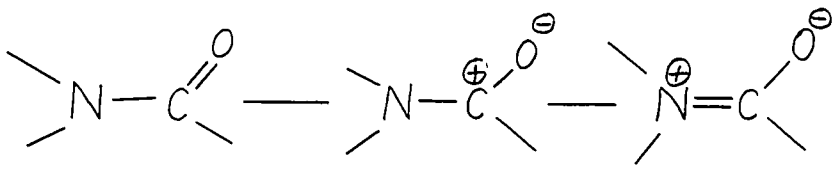



(12)



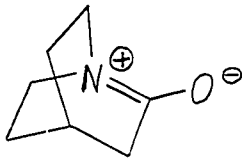

(13)

(14), (15), and (16) are the major amide resonance forms. The contributing structure (16), which involves participation by the unshared pair of electrons of the nitrogen atom, decreases the




(14) (15) (16)

susceptability of the amide to cleavage through nucleophilic attack on the carbonyl carbon. However, in the case of the bicyclic structure (13), the unshared pair of electrons on the nitrogen atom cannot be involved in any resonance interaction such as (16), because such participation would give a double bond at the bridgehead of a bridged-bicyclic system. A structure of this type, i.e., (17), is forbidden on steric grounds (Bredt's rule). This is the cause of the observed decrease in stability of (13) relative to (12).

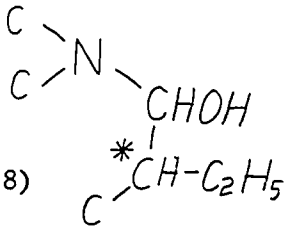


(17)

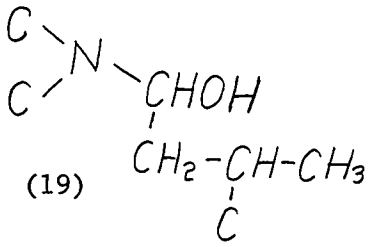
The formation of the immonium structure (8) in path A of Chart I involves participation by $N_b$ in a manner analogous to (17). As a system of this nature violates Bredt's rule, path A must be discarded as a possible mechanism for the formation of (3). No such unfavorable structures are formulated in path B. Accordingly, this is considered to be the course of the reductive formation of ajmaline from anhydro-ajmaline oxime.

Wolf-Kishner reduction of ajmaline gave deoxydihydroajmaline, $C_{20}H_{25}N_2O$, in high yield.[3] Kuhn-Roth determinations showed that ajmaline contains one C-methyl group and that deoxydihydroajmaline contains two such substituent groups.[3] The reduction product was a secondary amine which gave an N-acetyl derivative showing the same color reactions as had been observed for ajmaline.[3] Therefore, the

carbinolamine involves $N_b$. Oxidation of deoxydihydroajmaline with chromic acid gave methyl ethyl ketone.[3] This could be explained if ajmaline had either of the part structures (18) or (19).



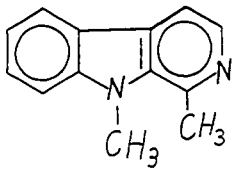
(18)



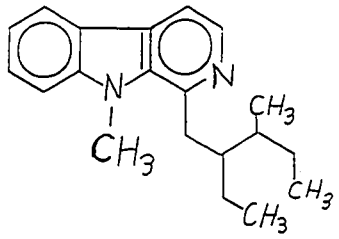
(19)

A choice was made in favor of (18) from the evidence that ajmaline isomerizes to isoajmaline in the presence of strong base.[3] This isomeric compound gave reactions analogous to those of ajmaline. In particular, isoajmaline gave deoxydihydroisoajmaline, which also gave methyl ethyl ketone on oxidation with chromic acid.[3] Only structure (18) provides a reasonable explanation for these results. The transformation of ajmaline into isoajmaline involves inversion of the configuration at the starred center through the base catalyzed epimerization of the corresponding aminoaldehyde and reclosure to the isomeric carbinolamine.[3]

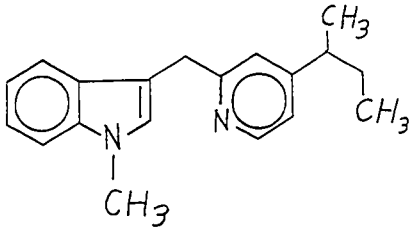
The oxygen of the carbinolamine system could be removed by reduction of ajmaline with sodium borohydride in methanol followed by pyrolysis of the hydrobromide at 300°.[8] The product, deoxyajmaline, $C_{20}H_{26}N_2O$, formed an O-acetate but no N-acetate, indicating that both nitrogen atoms were still tertiary. Dehydrogenation of deoxyajmaline with palladium and charcoal gave N-methylharman (20), ajarmine (21), and ajmyrine (22).



(20)

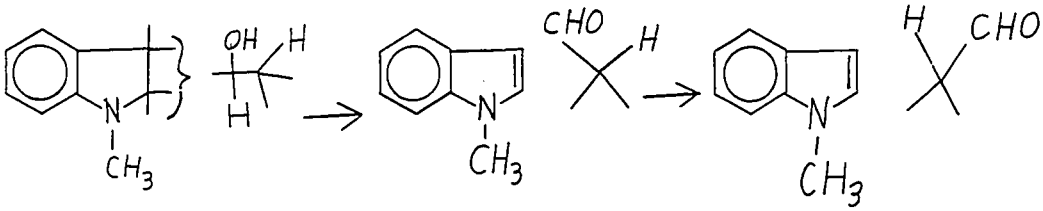


(21)



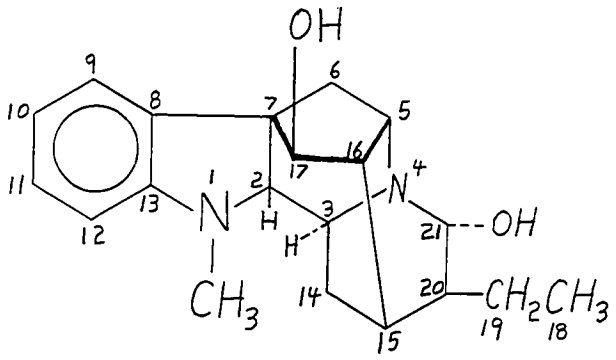
(22)

The second oxygen in ajmaline is resistant to chromium trioxide oxidation and was first thought to be tertiary.[3] However, prolonged Oppenauer oxidation of deoxyajmaline gave a product identified as a five-membered ring ketone by its infrared spectrum.[9] Reduction of this ketone with sodium borohydride[10] or lithium aluminum hydride[9,10] afforded a single alcohol isomeric with deoxyajmaline.[10] Treatment of deoxyajmaline with lead tetraacetate provided an indole aldehyde, deoxyajmalal-A, which isomerized into deoxyajmalal-B in the presence of base.[10] These transformations were formulated as shown below (23 → 24 → 25).[10]



(23) (24) (25)

From the evidence presented above, ajmaline was formulated in terms of structure (26).[8,9,10] The numbering system used considers ajmaline to be a derivative of an $\alpha$-type (yohimbine) alkaloid[3] and assigns to the atoms the numbers of their supposed yohimbine equivalents.



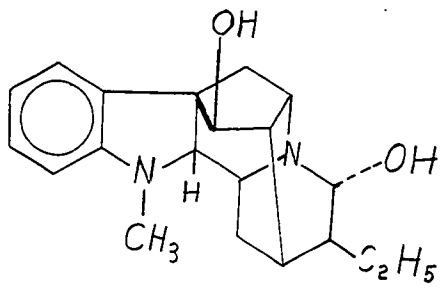

(26)

The reactions that have been used for the establishment of the structure of the ajmaline molecule are outlined in Chart II.

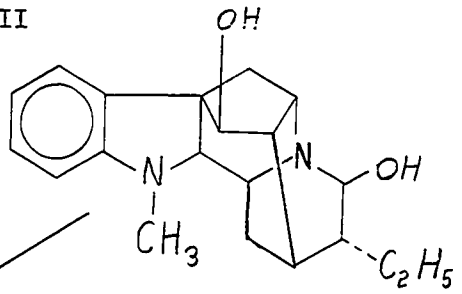
The relative configurations of the asymmetric centers C.3, C.5, C.7, C.15, and C.16 are defined by the steric requirements for the formation of the hexacyclic ring system.

The C.2 proton was assigned the $\beta$-orientation shown in (26) on the basis of the following transformations (Chart III). Oxidation of 21-dioxyajmaline-17-acetate (41) with excess lead tetraacetate formed the indolenine (42).[11] When (42) was reduced catalytically, the product was 2-epi-1-demethyl-21-deoxyajmaline-17-acetate (43) as the result of approach of the catalyst from the least hindered side of the indolenine double bond.[11] Methylation of (43) gave 2-epi-21-deoxy-ajmaline-17-acetate (44).[11]

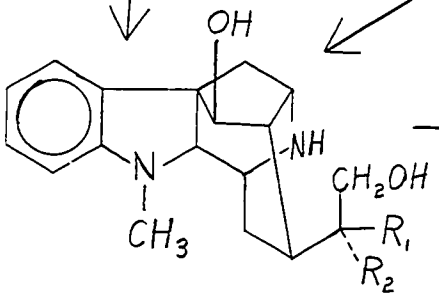
Chart II



(26)

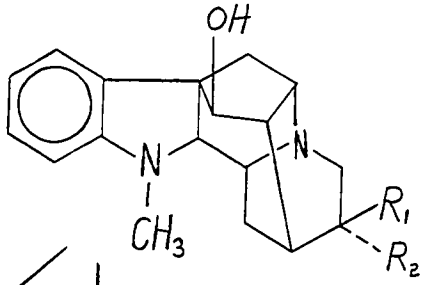


(31)



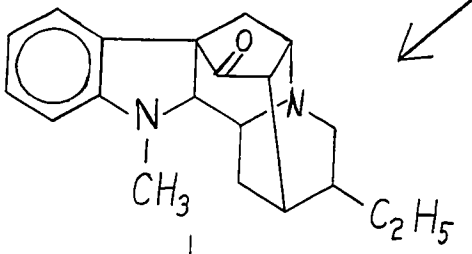
(29) $R_1 = C_2H_5$, $R_2 = H$

(30) $R_1 = H$, $R_2 = C_2H_5$

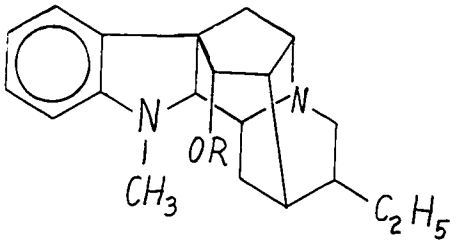


(32) $R_1 = C_2H_5$, $R_2 = H$

(33) $R_1 = H$, $R_2 = C_2H_5$

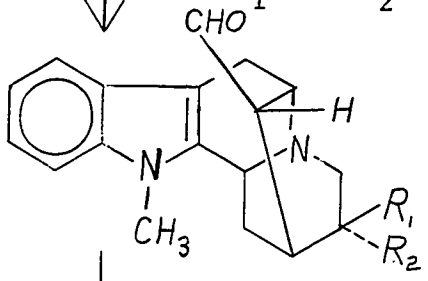


(34)



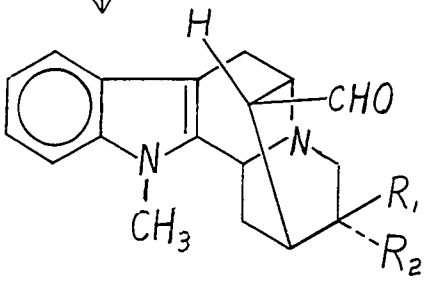
(35) R = H

(36) R = Ac



(37) $R_1 = C_2H_5$, $R_2 = H$

(38) $R_1 = H$, $R_2 = C_2H_5$



(39) $R_1 = C_2H_5$, $R_2 = H$

(40) $R_1 = H$, $R_2 = C_2H_5$

Chart II (cont.)

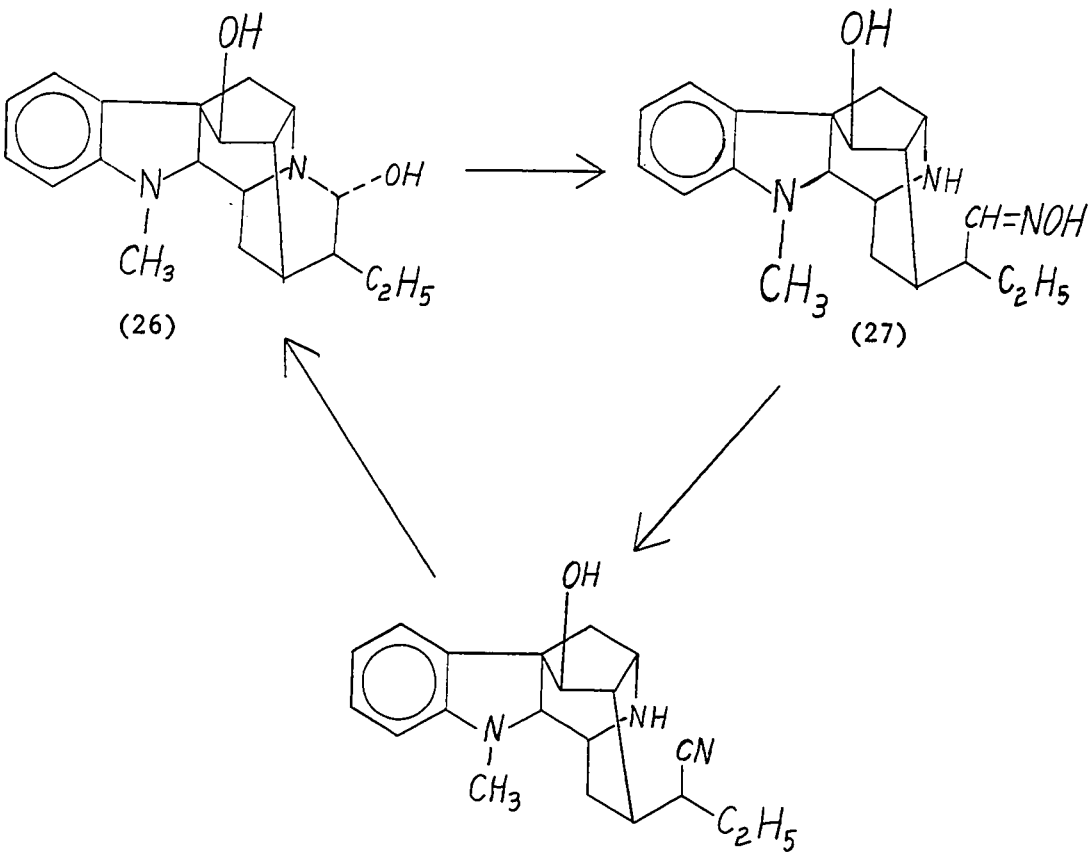
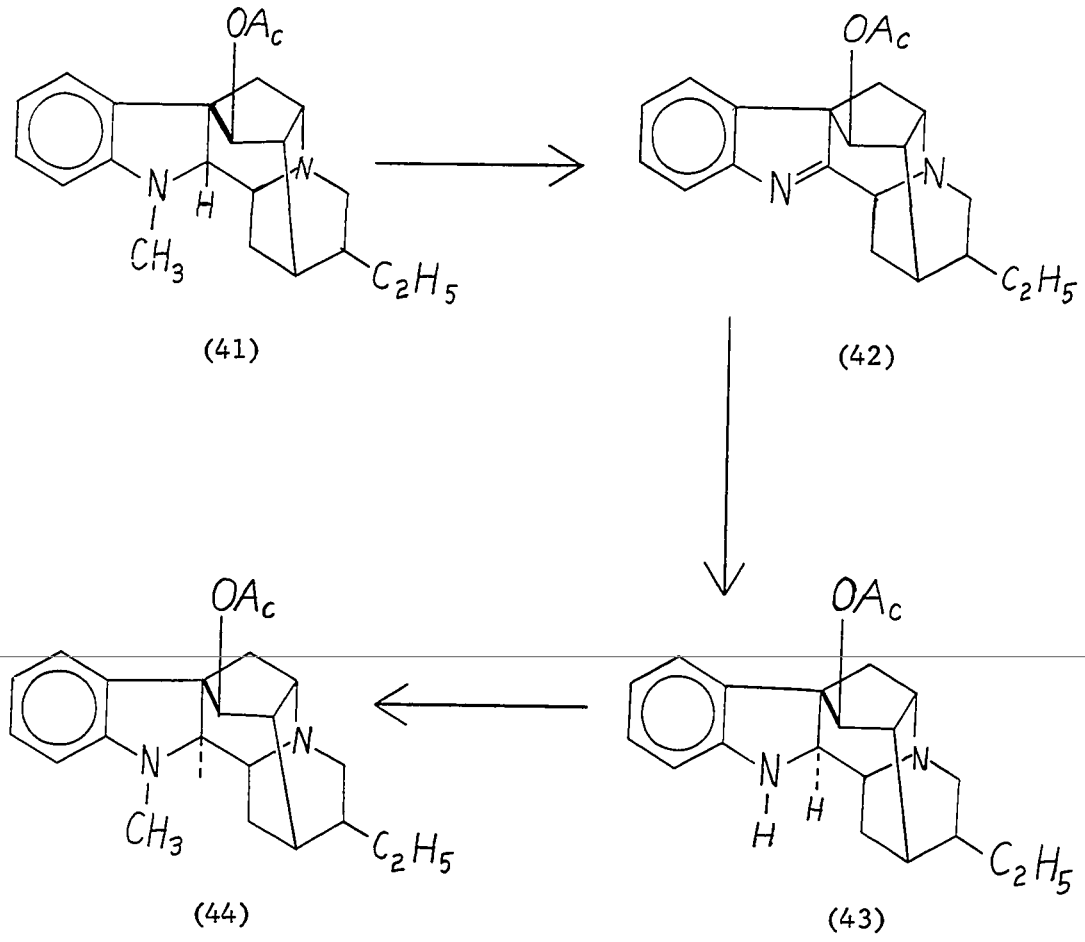


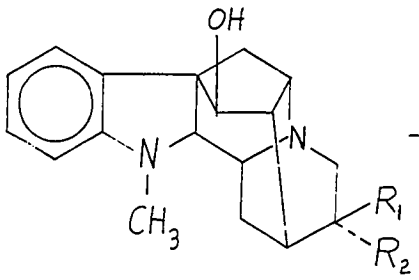
Chart III


OAc
N
H
CH3
C2H5
(41)
OAc
N
N
C2H5
(42)
OAc
N
H
H
C2H5
(43)
OAc
N
N
CH3
C2H5
(44)

The configuration of the C.20 ethyl group was established to be that shown in (26) by an elegant correlation of 21-deoxyajmaline (32) and 21-deoxyisoajmaline (33) with corynantheidine (55) and corynantheine (56), as shown in Chart IV.[11] Deoxyajmalal-B (39) was reduced to deoxyajmalol-B (45) by treatment with sodium borohydride. Compound (45) was converted into the corresponding tosylate (46) which was refluxed in collidine to give 1-cis-3-ethyl-1,2,3,4-tetrahydro-12-methyl-2-vinylindolo[2,3-a]quinolizinium tosylate (51) as the result of either air oxidation or disproportionation of the intermediate (49). When (51) was converted into its perchlorate and was reduced catalytically, $N_a$-methyltetradehydrodihydrocorynantheidane perchlorate (53) was formed which was identical with material prepared from corynantheidine (55), whose structure was well established.[12] In a completely analogous series of reactions, 21-deoxyisoajmaline (33) was converted via (40), (47), (48), (50), and (52) into 1-trans-2,3-diethyl-1,2,3,4-tetrahydro-12-methylindolo[2,3-a]quinolizinium perchlorate (54) identical with material from corynantheine (56).[12]

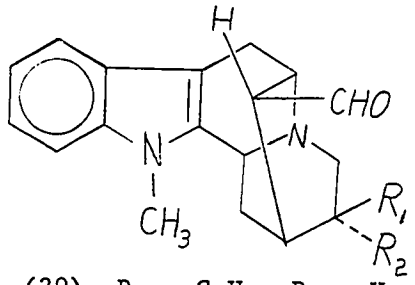
The assignment of the C.17 hydroxyl configuration was based on the oxidation of 21-deoxyajmaline (32) to the ketone (34) followed by reduction of this compound with lithium aluminum hydride to the epimeric alcohol (35)[11] (see Chart II). This reduction would be expected to give the more hindered alcohol through hydride attack from the least hindered side of the C.17 carbonyl group. Support for this assignment was found in a comparison of the nuclear magnetic resonance spectra of compounds (57) and (59) and their C.17 epimers (58) and (60).[11] In all four compounds the C.17 proton was observed to be a

Chart IV



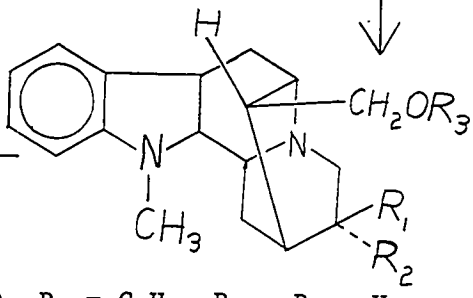
(32) $R_1 = C_2H_5$, $R_2 = H$

(33) $R_1 = H$, $R_2 = C_2H_5$



(39) $R_1 = C_2H_5$, $R_2 = H$

(40) $R_1 = H$, $R_2 = C_2H_5$

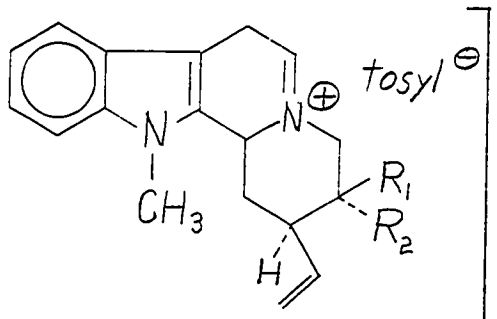


(45) $R_1 = C_2H_5$, $R_2 = R_3 = H$

(46) $R_1 = C_2H_5$, $R_2 = H$, $R_3$ = tosyl

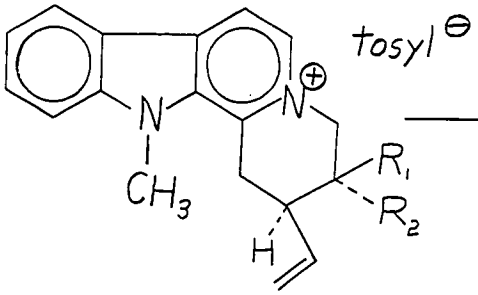
(47) $R_2 = C_2H_5$, $R_1 = R_3 = H$

(48) $R_2 = C_2H_5$, $R_1 = H$, $R_3$ = tosyl



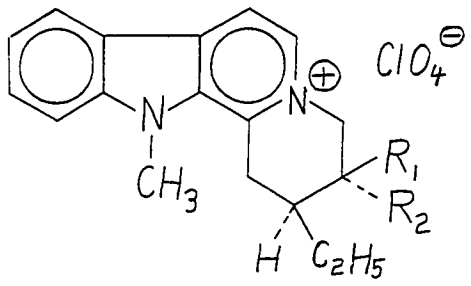
(49) $R_1 = C_2H_5$, $R_2 = H$

(50) $R_1 = H$, $R_2 = C_2H_5$



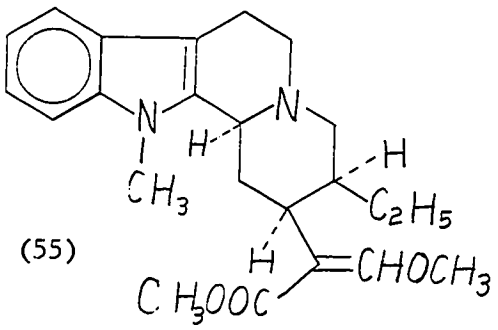
(51) $R_1 = C_2H_5$, $R_2 = H$

(52) $R_1 = H$, $R_2 = C_2H_5$

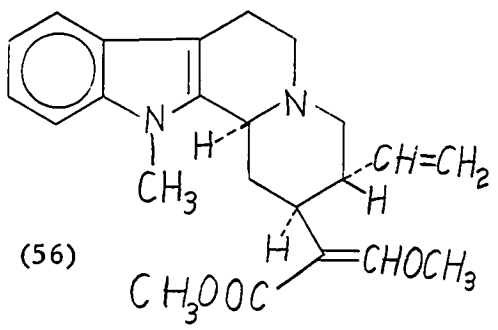


(53) $R_1 = C_2H_5$, $R_2 = H$

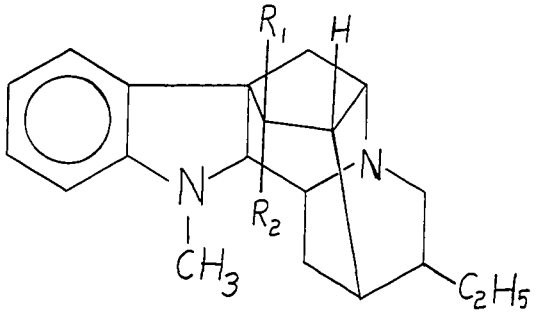
(54) $R_1 = H$, $R_2 = C_2H_5$



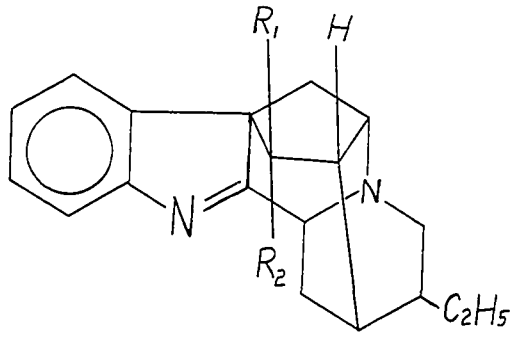
(55)



(56)




(57) $R_1$ = OAc, $R_2$ = H
(58) $R_1$ = H, $R_2$ = OAc

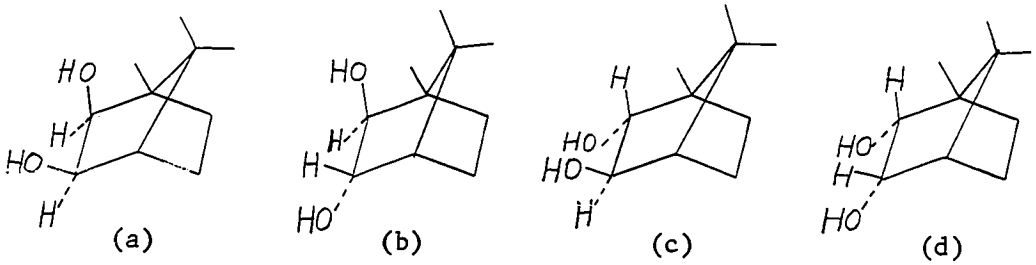



(59) $R_1$ = OAc, $R_2$ = H
(60) $R_1$ = H, $R_2$ = OAc

doublet as the result of coupling with the proton at C.16. However, the coupling constants, $J_{16\text{-}17}$, for the ajmaline series, (57) and (59), were much smaller than were the coupling constants for their C.17 epimers, (58) and (60). The peaks of the doublet for the C.17 proton in both compounds (57) and (59) were separated by 1.8 cps, but this separation was 8.7 cps and 8.9 cps in compounds (58) and (60), respectively. These coupling constants indicate that the protons on C.16 and C.17 are trans in the ajmaline series, (57) and (59), and are cis in the epimeric series, (58) and (60).

Analogous values were observed by F.A.L. Anet[13] in comparisons of the four camphane-2,3-diols, (a)-(d). In these rigid cyclopentane rings the dihedral angles between the C.2 and C.3 carbon-hydrogen bonds are 0° for (a) and (d) and ca. 120° for (b) and (c). From the Karplus relationship of J with the dihedral angle,[14] the calculated values for

$J_{2,3}$ were found to be 8.2 cps for (a) and (d) and 2.1 cps for (b) and (c). These calculated values agreed closely with the observed values of (a) = 8.9 cps, (b) = 2.2 cps, (c) = 2.3 cps, (d) = 7.7 cps.




There have been only two reported attempts to synthesize the ring system present in ajmaline, a partial synthesis of 21-deoxyajmaline (32) by Bartlet, Lambert, Werblood, and Taylor[15] and a total synthesis by Hobson, Raines, and Whiteoak[16] of compound (81), from which ajmaline might conceivably be prepared by further reactions.

The partial synthesis of (32) achieved by Taylor's group[15] is outlined in Chart V. In preliminary studies, deoxyajmalal-A (37) was reduced to deoxyajmalol-A (61) which was converted into the corresponding tosylate (62). When (62) was heated at 80° under reduced pressure or treated at room temperature with pyridine, an intramolecular substitution occurred to give (63), which was hydroxylated during the workup procedure to give 2-hydroxy-17,21-dideoxyajmaline (64). Lithium aluminum hydride afforded reduction of (64), but the product was 2-epi-17,21-dideoxyajmaline (65). If the reduction of (64) was effected using

Chart V

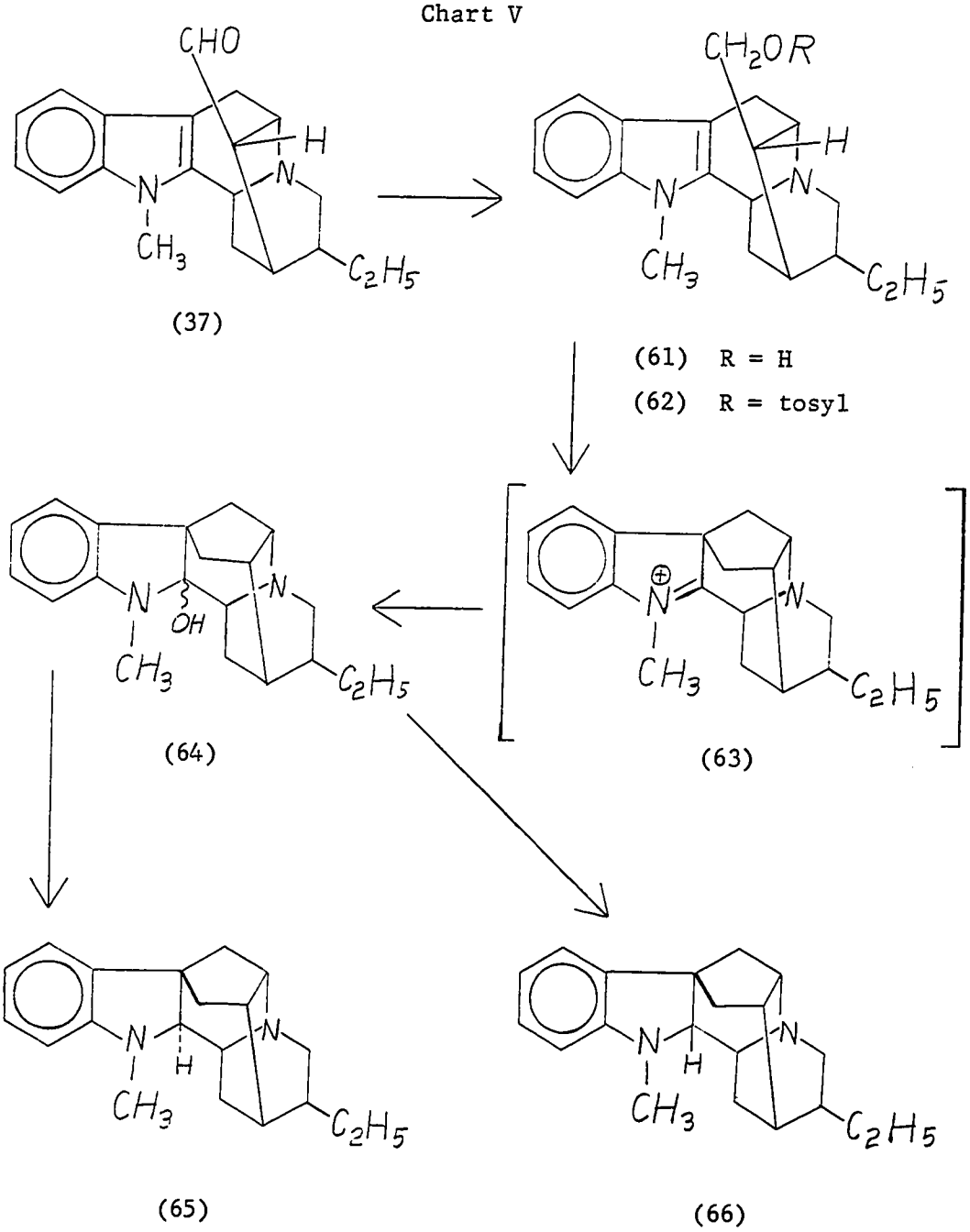
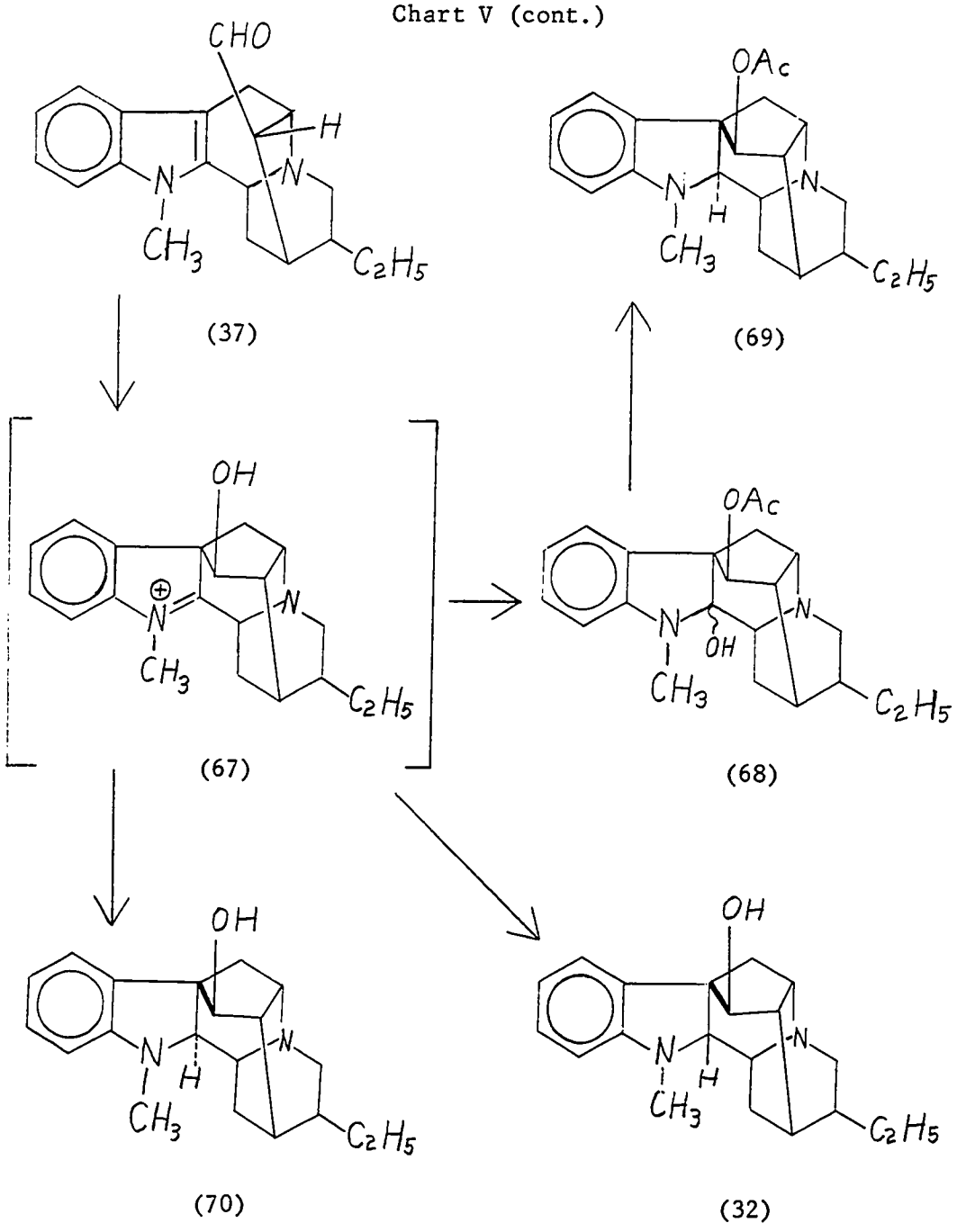


Chart V (cont.)

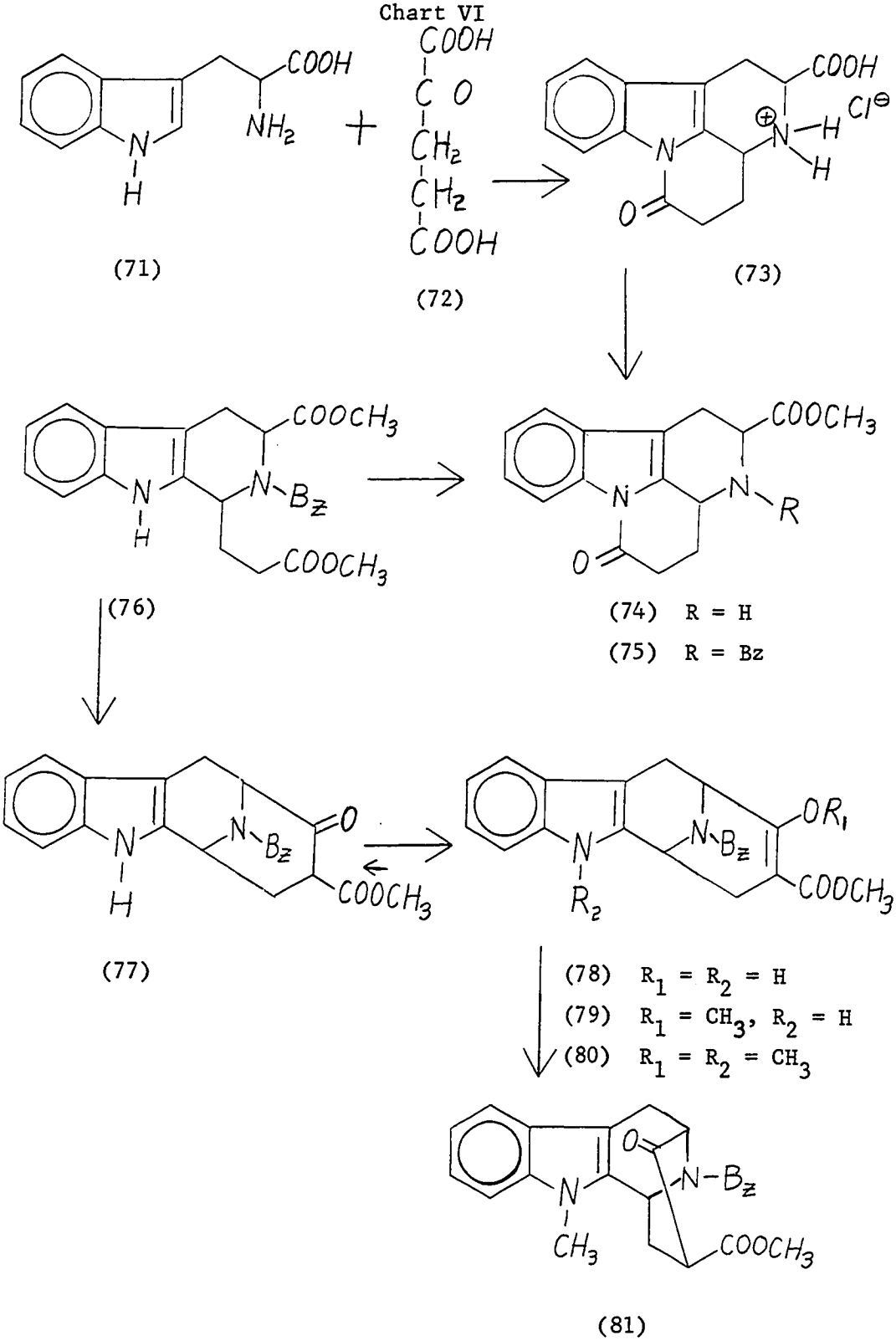

CHO
H
N
N
CH3
C2H5
(37)
OAc
N
H
N
CH3
C2H5
(69)
OH
N
N
CH3
C2H5
(67)
OAc
N
OH
N
CH3
C2H5
(68)
OH
N
H
N
CH3
C2H5
(70)
OH
N
H
N
CH3
C2H5
(32)

zinc and hydrochloric acid, a mixture of (65) and its C.2 epimer, the desired 17,21-deoxyajmaline, (66), was produced.

Deoxyajmalal-A (37) was subjected to a variety of acidic conditions in attempts to effect an analogous ring closure to form 21-deoxyajmaline (32). Such a reaction would be expected to pass through the indolenium intermediate (67). In fact, when (37) was treated at 0° with acetic anhydride and acetic acid saturated with hydrogen chloride, this intermediate was trapped as the hydroxyacetate (68). Reduction of (68) with sodium borohydride gave 2-epi-21-deoxyajmaline-17-acetate (69). Zinc dust and 5 N hydrochloric acid or hydrogen and platinum in constant boiling hydrochloric acid gave reduction of deoxyajmalal-A (37) to 2-epi-21-deoxyajmaline (70) in yields of 36-40%. The desired product, 21-deoxyajmaline (32), was finally obtained, although only in approximately a 3% yield, when the reductive ring closure was carried out with zinc dust and 6 N perchloric acid at 80° or with concentrated hydrochloric acid and zinc dust at room temperature.[15]

Chart VI presents the synthetic sequence devised by Hobson, Raines, and Whiteoak[16] for the preparation of compound (81). When dl-tryptophan (71) was condensed with 2-oxoglutaric acid (72) in 4 N hydrochloric acid at 90°, the expected product (73) was formed and could be esterified to give compound (74). Treatment of (74) with benzoyl chloride in pyridine afforded compound (75) which was hydrolized with alkali and was treated with diazomethane to give the diester (76). Dieckmann condensation of (76) using sodium hydride in tetrahydrofuran produced the $\beta$-ketoester (77), which appeared to exist entirely as the enol (78). The enol-ether (79) was formed from (78) by treatment with diazomethane and was

Chart VI

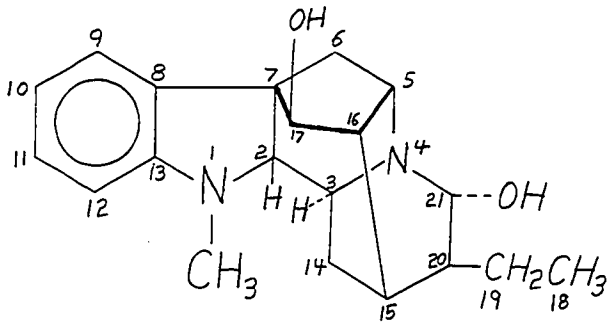

COOH
NH2
N
H
(71)
COOH
C O
CH2
CH2
COOH
(72)
COOH
Cl⊖
⊕N–H
H
N
O
(73)
COOCH3
N–Bz
COOCH3
(76)
COOCH3
N
N
R
O
(74) R = H
(75) R = Bz
O
N–Bz
COOCH3
(77)
OR1
N–Bz
R2
CODCH3
(78) R1 = R2 = H
(79) R1 = CH3, R2 = H
(80) R1 = R2 = CH3
O
N–Bz
CH3
COOCH3
(81)

converted into the $N_a$-methyl compound (80) with sodium hydride and methyl iodide. Hydrolysis of (80) gave (81).

# II. DISCUSSION

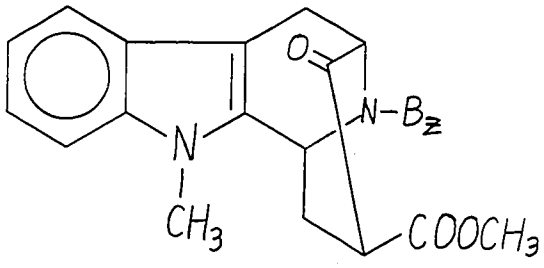
## DISCUSSION

The Rauwolfia alkaloid ajmaline has been firmly established to be represented by the structure (26).[8,9,10] Hobson, Raines, and Whiteoak[16]




(26)

have reported the preparation of compound (81) via reactions shown in Chart VI and have suggested that this material would be a possible intermediate for the synthesis of ajmaline. This transformation would




(81)

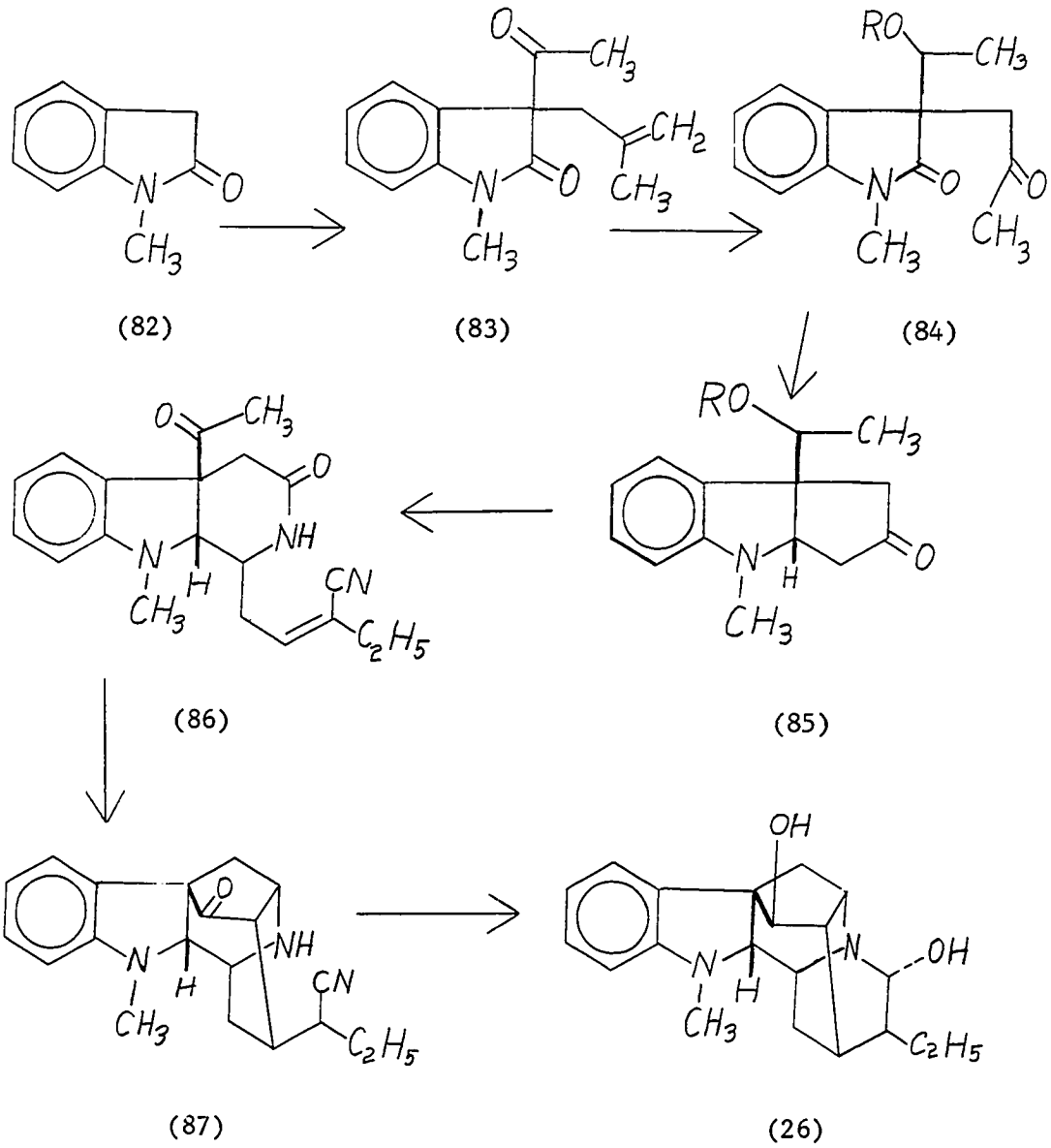
involve completion of the carbinolamine system, introduction of the C.20 ethyl group, and generation of a suitably substituted C.17 function

to permit closure of the five-membered ring. This approach does not offer much promise in view of the results reported by Bartlett, Lambert, Werblood, and Taylor[15] for a series of attempts to produce 21-deoxyajmaline (32) by the closure and simultaneous reduction of deoxyajmalal-A (37) (see Chart V). This conversion could be effected, but only in very poor yields (ca. 3%) and only under carefully controlled conditions. In the majority of cases studied by Taylor's group the undesired product 2-epi-21-deoxyajmaline (65) was obtained in fairly good yields (ca. 36-40%). It is evident that any proposed synthetic sequence which involves formation of the C.7-C.17 bond in a manner analogous to the conversion of deoxyajmalal-A into 21-deoxyajmaline will suffer from this apparent preference for the generation of the epimeric C.2 configuration.

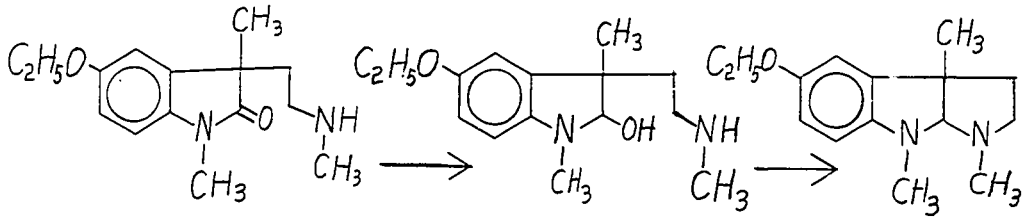
Chart VII presents the general outline of a synthetic sequence which does not suffer from the defect mentioned above. The formation of the C.6-C.7 and C.7-C.17 bonds prior to the introduction of the C.2-C.3 bond increases the probability of achieving the desired stereochemistry at C.2. Incorporation of the C.2-C.3 bond as part of a system of two fused five-membered rings would be expected to generate the desired cis orientation of the C.2 proton with respect to the adjacent side chain. Further reactions would not be likely to change this stereochemistry.

The work presented here was concerned with an exploration of various methods which might be used for the synthesis of compounds having the general structural features of (83) and (84) in Chart VII. 1-Methyloxindole (82) was selected as the starting material in this

Chart VII



study for several reasons. The C.3 position of the oxindole system, which is destined to become C.7 in ajmaline, condenses readily with carbonyl compounds and alkyl halides in the presence of base. Also, Julian[17,18] has reported reduction of suitably substituted 3,3-dialkyl-oxindoles such as (88) with sodium and alcohol to give, initially, the carbinolamine (89) which then cyclized to the tricyclic system (90).

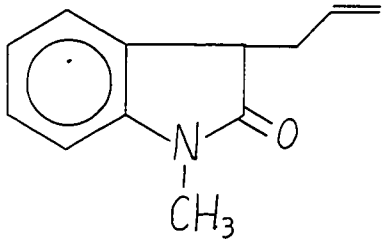


(88) (89) (90)

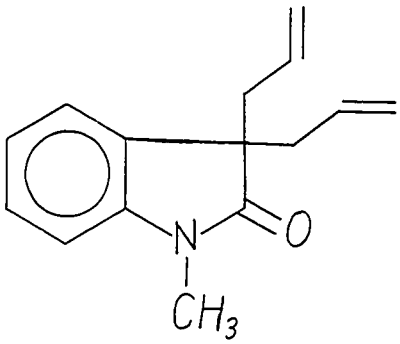
Another factor in the selection of the starting material was the much lessened sensitivity of oxindole compounds to oxidative decomposition as compared to indole derivatives. The use of oxindoles instead of indoles in the synthetic procedure would require much less stringent precautions to prevent decomposition of the materials from exposure to the atmosphere.

When an ethanolic solution of 1-methyloxindole (82) was treated with one equivalent of allylbromide and sodium ethoxide, the product was not the desired 3-allyl-1-methyloxindole (91) but was a mixture of two compounds which could be separated by chromatography on alumina. The second fraction to be eluted was identified as the starting

1-methyloxindole from its infrared and nuclear magnetic resonance spectra. The earlier fraction was an oil that appeared to be an oxindole derivative on the basis of the presence of absorption at 5.81 $\mu$ in its infrared spectrum. The integrated nuclear magnetic resonance spectrum of this substance showed clearly that it was 3,3-dially-1-methyloxindole (92). The four aromatic protons appeared as a multiplet at 6.67-7.38 $\delta$, and the N-methyl group gave a three proton singlet at 3.12 $\delta$. The presence of two equivalent allyl groups was indicated by the presence of multiplets at 4.67-5.72 $\delta$ and 2.45-2.56 $\delta$ which integrated for six protons and four protons, respectively. Evidently, the monoallyl compound (91) alkylates much more rapidly than does the unalkylated oxindole.



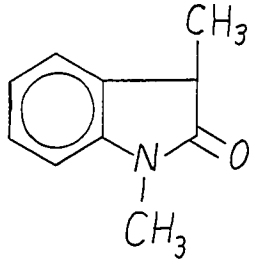
(91)



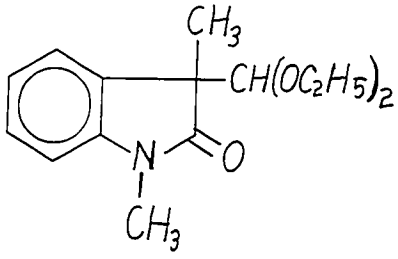
(92)

Similar results had been reported by Julian[21] for the alkylation of 1-methyl- and 1,2-dimethyloxindole. As an example, the unalkylated compound (82) does not condense with bromoacetal, but the 3-methyl derivative (93) reacts smoothly to give the acetal (94).[19] Compound (93) could not be obtained by direct alkylation of 1-methyloxindole,

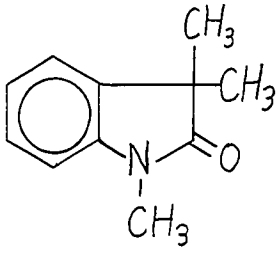
the reaction giving instead the 1,3,3-trimethyloxindole (95).[21]



(93)



(94)

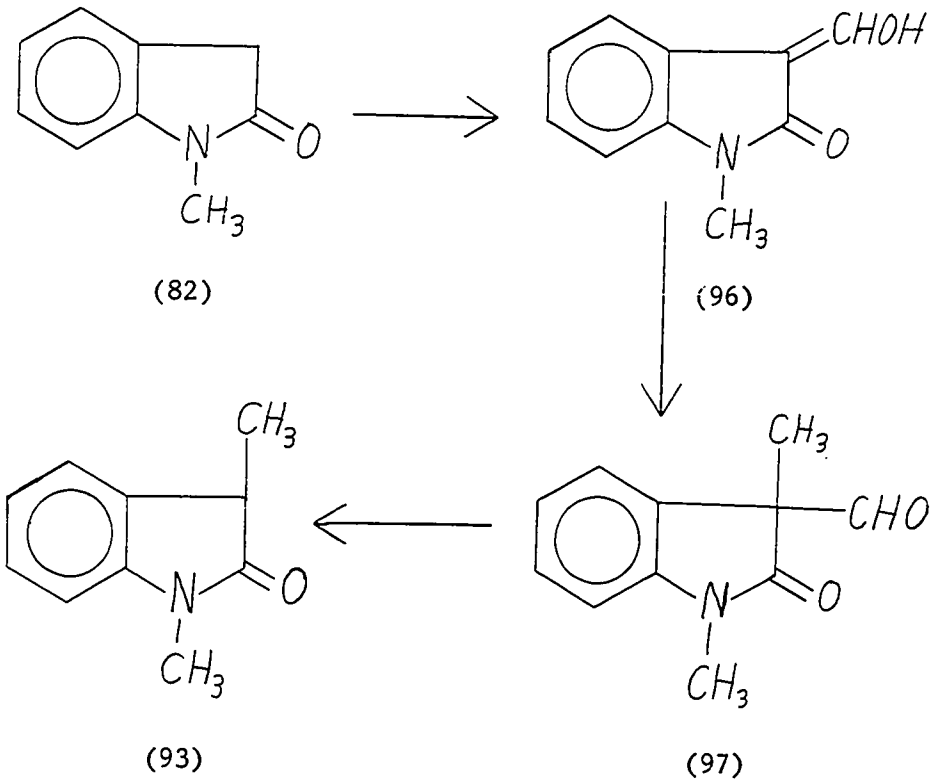


(95)

1,3-Dimethyloxindole was prepared in good yield by the indirect method shown in Chart VIII.[20] Condensation of 1-methyloxindole with ethyl formate in ethanolic sodium ethoxide gave 3-hydroxymethylene-1-methyloxindole (96). This compound was warmed with one equivalent of methyl iodide and sodium ethoxide in ethanol to give the desired 1,3-dimethyloxindole (93). The formation of (93) probably results from the slow cleavage of the initially formed alkylation product (97).

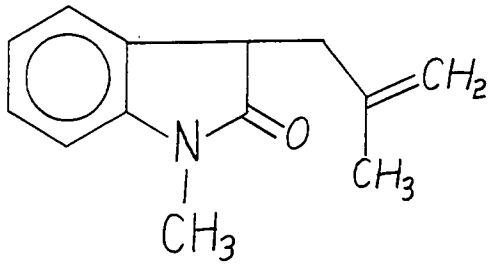
When compound (96) was treated under these same conditions using allyl bromide instead of methyl iodide, the oily product exhibited an infrared spectrum almost identical to that of the diallyl compound (92). However, the nuclear magnetic resonance spectrum of this material indicated the presence of three vinyl protons (broad multiplet at 4.78-5.87$\delta$) and two allylic protons (multiplet at 2.21-2.96$\delta$). In addition, there was a broad one proton multiplet located at 2.96-3.58$\delta$. This agrees well with the singlet at 3.12$\delta$ from the C.3 methylene group of 1-methyloxindole (82). Accordingly, this material was assigned the

Chart VIII



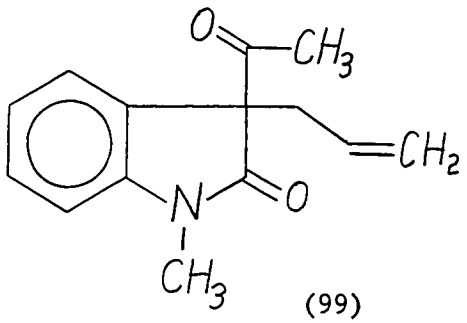

(82) (96) (97) (93)

monoallyl structure (91). A somewhat lower yield of the corresponding monomethallyl compound (98) was obtained through a similar procedure using methallyl chloride and the sodium salt of (96). This structural assignment was confirmed by nuclear magnetic resonance analysis (see Experimental).



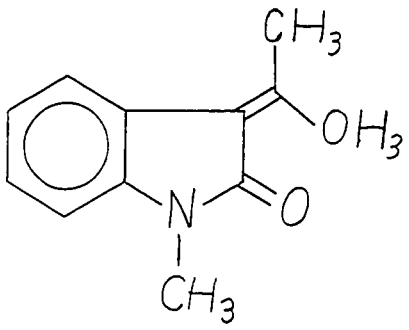
(98)

The monoallyloxindole (91) gave a slow evolution of hydrogen when treated with a suspension of sodium hydride in dry benzene. The sodium salt formed in this manner was allowed to react with acetyl chloride in the expectation of forming 3-acetyl-3-allyl-1-methyloxindole (99) in an irreversible process. The reaction product appeared to be a mixture which contained some of the desired material (99). This reaction was not investigated further because compound (99) became available in high yield from an alternate procedure.

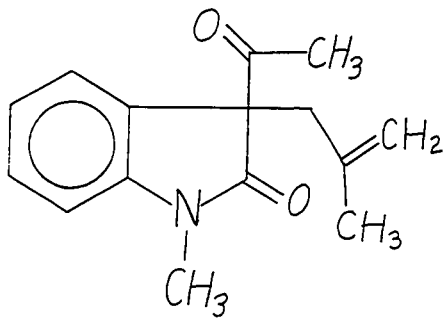


(99)

Condensation of 1-methyloxindole with ethyl acetate and ethanolic sodium ethoxide formed 3-(1-hydroxyethylidene)-1-methyloxindole (100).[19,20] When a solution of (100) in dry benzene was added to a suspension of sodium hydride in benzene, a very rapid evolution of hydrogen was observed. The resulting suspension of the sodium salt of (100) was refluxed with an excess of allyl bromide. Small samples of the reaction mixture were removed at intervals and were tested with a 1% aqueous solution of ferric chloride. After the reaction had run for twenty hours, this test gave no color production. The crude product was distilled under reduced pressure to give an 87% yield of the desired compound (99) as an oil (bp 100-108°/0.005 mm) which crystallized on standing in the cold. This material was recrystallized from ether-petroleum ether to give white plates, mp 55.5-56°. The infrared spectrum of this substance, taken in carbon disulfide solution, showed two peaks of almost equal intensity at 5.78$\mu$ and 5.81$\mu$. The nuclear magnetic resonance spectrum was consistent with the structure (99). (See Experimental section for details of the spectrum.) When methallyl chloride was substituted for allyl bromide in this procedure, a positive ferric chloride test was still obtained after over eighty hours of reaction, and a somewhat lower yield (ca. 50-60%) of the desired compound (101) was achieved.

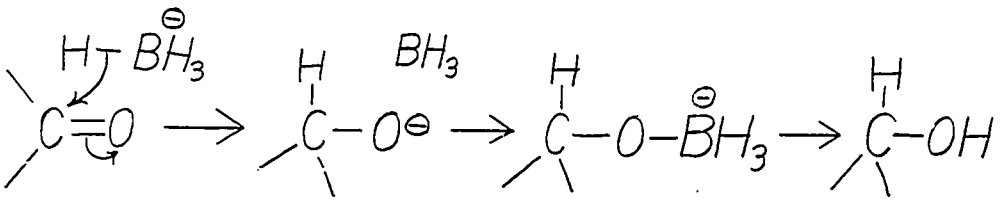


(100)



(101)

When compound (99) was treated with sodium borohydride in diglyme, the only product isolated was 3-allyl-1-methyloxindole (91). The reduction of ketones by borohydride ion in aprotic solvents, such as diglyme, proceeds through attack by hydride ion on the carbonyl carbon followed by formation of an alkoxyborohydride anion, as shown below.[22] Hydrolysis of the oxygen-boron bond during the workup procedure gives the alcohol. Loss of the acetyl group from (99) under these conditions can be explained as involving a reverse-aldol type cleavage of one of the three structure (102), (103), or (104).



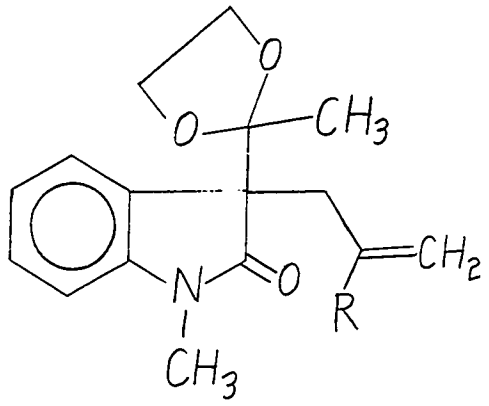
(102) (103) (104)

Two procedures were tried in the hope of trapping the reduced material before cleavage could take place. The first method involved quenching of the reduction mixture with acetic anhydride and pyridine. When this modification was applied to the reduction of (99) and (101), the only products isolated were (91) and (98), respectively, resulting from loss of the acetyl group. The second trapping experiment involved the use of acetic anhydride as the solvent for the reduction of (99). In this case, the sodium borohydride reacted preferentially with the solvent, resulting in an almost quantitative recovery of the starting ketone.

If the loss of the acetyl group in these reductions was due to cleavage of one of the anions (102) or (103) and not to cleavage of the alcohol (104), reduction of (99) with hydrogen and platinum might give the alcohol directly. Accordingly, compound (99) was treated with hydrogen and platinum in diglyme at room temperature. Reduction ceased after approximately three hours with the uptake of one molar equivalent of hydrogen. The infrared spectrum of the product showed absorption in the carbonyl region identical with that of (99), indicating that only the methylene double bond had been reduced. The resistance of the acetyl group to hydrogenation is attributed to steric hinderance of the approach of the keto group to the face of the catalyst. The bulkiness of the groups attached to C.3 in (99) does not permit the carbonyl double bond to lie flat on the surface of the platinum.

The apparent very facile cleavage of the acetyl group in compounds (99) and (101) during reduction required seeking another means of protecting this ketone function in subsequent reactions. Conversion of

(99) and (101) into the corresponding ketals (105) and (106) would provide such protection, as all the reactions for which masking of the ketone is desired can be run under basic conditions, which would not affect the ketal group.



(105) R = H

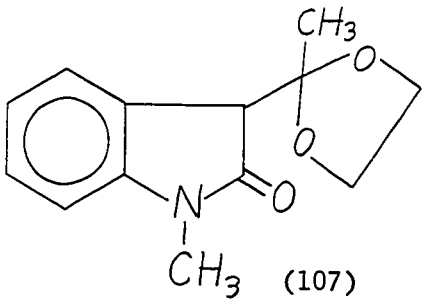
(106) R = $CH_3$

Compound (99) was used for the study of the feasibility of the preparation of these ketals. When (99) was refluxed for three hours with 2-butanone ethylene ketal and p-toluenesulfonic acid,[23] only the starting ketone was recovered. An attempt to prepare ketal (105) by direct reaction of (99) with ethylene glycol in the presence of acid gave material identical to the monoallyloxindole (91). Apparently, cleavage of the acetyl group is favored over ketal formation under these conditions.

The use of milder reaction conditions was thought to be less likely to give such extensive loss of the acetyl function. Compound (99) was stirred at room temperature for seventy hours in a mixture of dioxane, ethylene glycol, and anhydrous copper sulfate, a modification of the conditions that have been used to effect conversion of glycols

into the corresponding acetonides.[24] In this case, the starting material was recovered quantitatively.

The possibility of converting the acetyloxindole (99) into the ketal (107) prior to alkylation was also investigated. Heating a solution of (99) and p-toluenesulfonic acid in a mixture of benzene and ethylene glycol gave no ketal material. Instead, a 95% yield of 1-methyloxindole (83) was obtained.



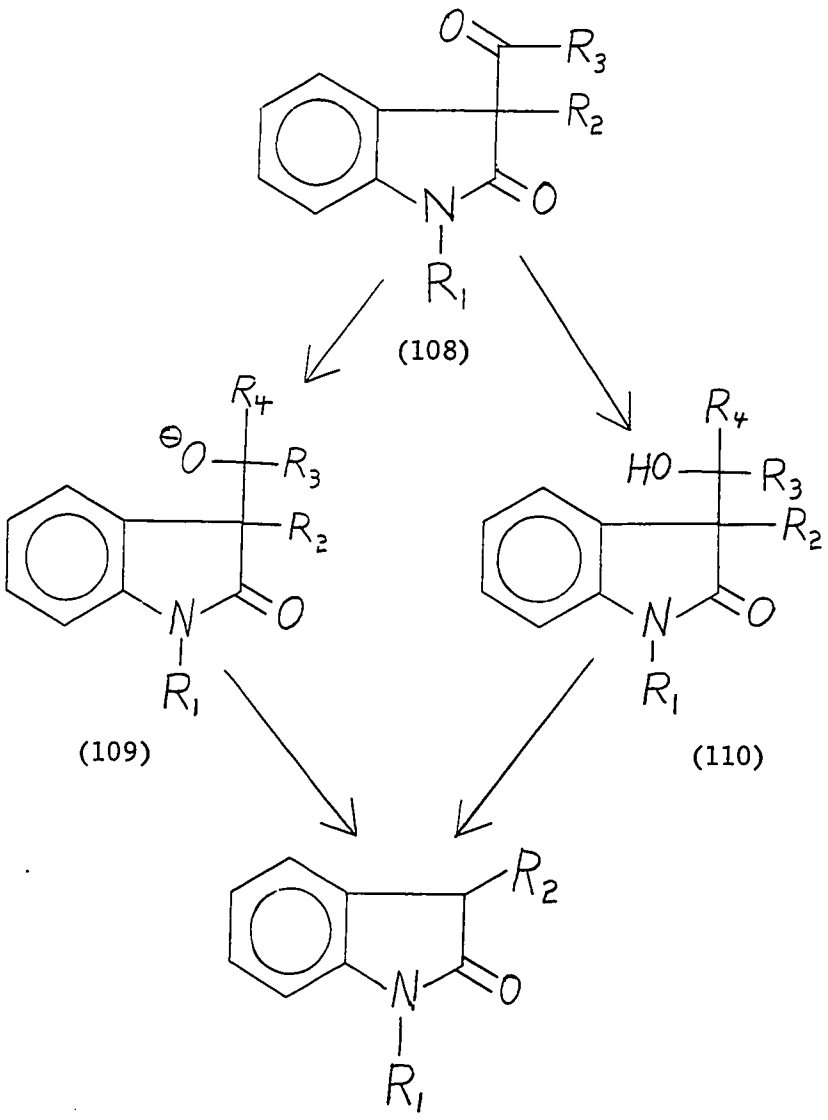
(107)

Evidently, any reaction of a 3-acyl-3-alkyloxindole such as (108) which involves either of the intermediates (109) or (110) will rapidly give loss of the acyl group to form the 3-alkyloxindole (111) (see Chart IX).

The oxidation of the carbon-carbon double bond in (99) and (101) was also investigated in this work. This question is of interest in connection with the possible preparation of compounds related to (84) in Chart VII.

The first method to be studied was hydroxylation of the double bond with osmium tetroxide followed by cleavage of the glycol with sodium periodate. Treatment of (99) with osmium tetroxide in ether gave material whose infrared spectrum indicated the presence of hydrogen bonded hydroxyl (3.00$\mu$) and acetate functions (5.78, 8.08$\mu$).

Chart IX

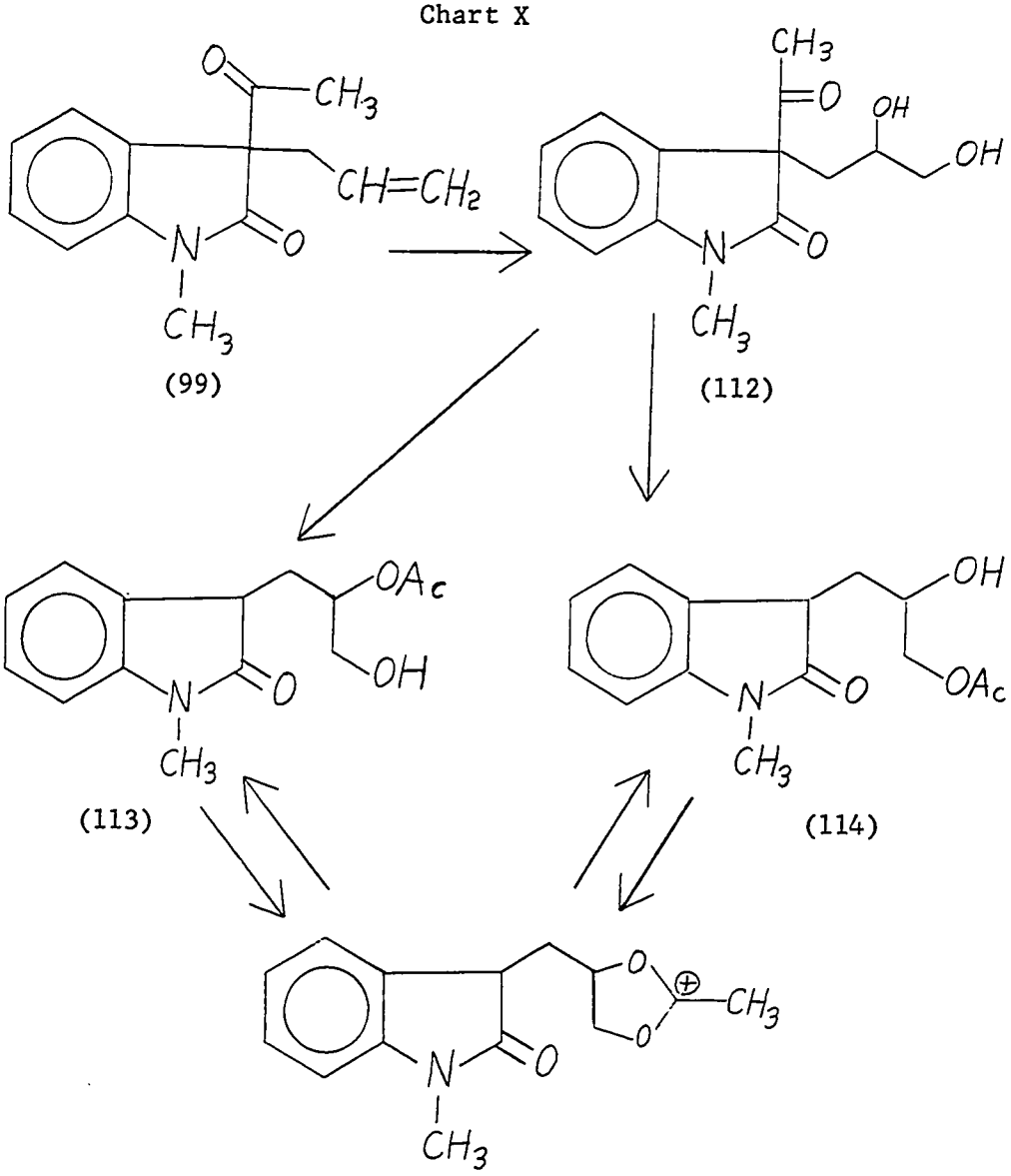

O
R3
R2
N
O
R1
(108)
R4
⊖O
R3
R2
N
O
R1
(109)
R4
HO
R3
R2
N
O
R1
(110)
R2
N
O
R1
(111)

This spectrum was consistent with the reaction sequence shown in Chart X. The glycol (112) which would be expected from the hydroxylation of (99) could give either of the hydroxyacetates (113) or (114) by an internal cleavage of the $\beta$-ketolactam system. In all probability, a mixture of (113) and (114) was formed. When the crude material from the osmium tetroxide reaction was allowed to stand for seventeen hours in benzene with p-toluenesulfonic acid, the infrared spectrum of the product was quite similar to the spectrum of the starting material. The major difference was a decrease in the intensity of the 8.08$\mu$ band and an increase in the intensity of a band at 7.99$\mu$ that was present as only a small shoulder in the hydroxylation product. The absorption maxima due to C=O and O-H were unchanged. These spectral changes are interpreted as indicating that the mixture of hydroxyacetates (113) and (114) from the hydroxylation reaction did not contain the equilibrium concentrations of the two substances and that equilibration occurred during the acid treatment. Such an equilibrium could have been attained through the formation of the intermediate (115).

Treatment of the methallyloxindole (101) with osmium tetroxide gave a very dark oil that also showed the appearance of infrared bands attributable to hydroxyl and acetate functions. In addition, a very intense maximum was present at 5.9$\mu$. The nature of this product was not investigated further.

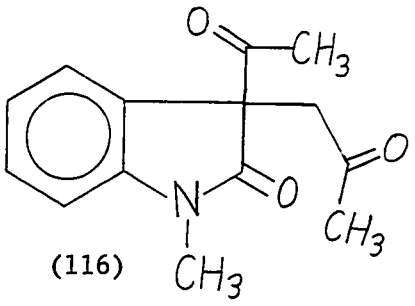
Pappo, Allen, Lemieux, and Johnson[25] have reported the oxidation of carbon-carbon double bonds directly to the coresponding aldehydes or ketones through the use of sodium periodate with a catalytic amount

Chart X


O
CH3
CH=CH2
N
O
CH3
(99)
CH3
O
OH
OH
N
O
CH3
(112)
OAc
OH
N
O
CH3
(113)
OH
OAc
N
O
CH3
(114)
O
⊕
CH3
O
N
O
CH3
(115)

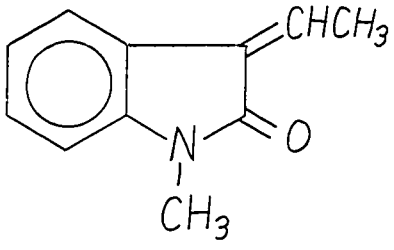
of osmium tetroxide. When this procedure was tried in the case of the allyl compound (99), the product was a dark oil which could not be separated into any characterizable material.

Ozonization of (99) with reductive workup gave a product which appeared to oxidize and decompose during chromatography on alumina. Ozonization of compound (101) appeared to proceed more cleanly to give a mixture whose spectra (infrared and nmr) indicated the presence of unreacted starting material and possibly the desired diketone (116).

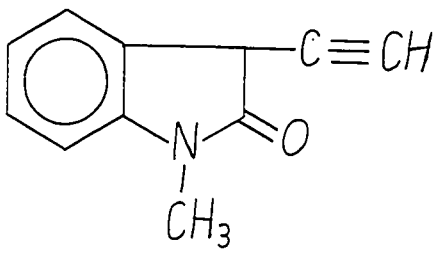


(116)

The apparent very easy cleavage of the acetyl group in compounds (99) and (101) would indicate that the proposed synthetic scheme (Chart VII) should be modified to replace this function by a group that would be convertible into the desired methyl ketone moiety at a later point. Such a modification might be the use of a compound such as (117) or (118). The introduction of a suitable substituent at C.3

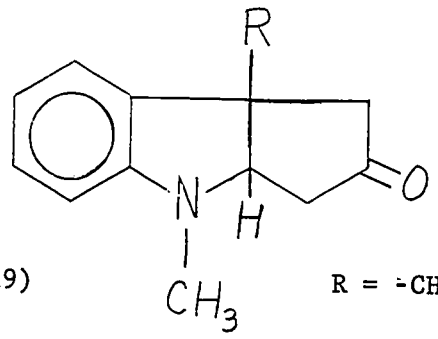


(117)



(118)

in (117) or (118) would give material which might conceivably lead to the formation of (119).




(119) R = -CH=CH$_2$ or -C≡CH

The remainder of the synthesis might be carried out as outlined in Chart VII, with the methyl ketone being generated from (119) when needed. It should be noted that the formation of the five-membered ring in (119) would be expected to give the indicated cis-fused system. In the subsequent reactions this stereochemistry should remain unchanged. Thus the desired cis relationship of the C.3 proton with the C.7-C.17 bond that is present in ajmaline (26) would be generated at an early stage in the synthesis and would be locked into the molecule.

This proposed scheme appears to offer considerable promise, but much work remains to be done to determine actual methods to effect the reactions that have been outlined.

# III. EXPERIMENTAL

## EXPERIMENTAL

Preparation of 1-Methyloxindole (82). In a 500 ml, 3-neck flask equipped with a mechanical stirrer, thermometer, and nitrogen inlet and outlet was placed 77 gm of N-methylchloroacetanilide. Anhydrous aluminum chloride (200 gm) was added in small portions to the stirred contents of the flask over a period of 30 minutes. In the first five minutes the mixture became liquid, and the temperature rose rapidly to 130°. External heating of the flask was begun at this point and was adjusted to maintain the contents at a temperature of 180-190°. After 1.5 hours the hot mixture was poured directly into 2500 ml of crushed ice and was stirred mechanically until the ice had melted (ca. 3 hours). Then 50 ml of concentrated hydrochloric acid was added, and stirring was continued for 30 minutes. The aqueous suspension of brown solid was extracted with two portions of 1500 ml of ether. The ether extracts were combined and were washed with water and with saturated sodium chloride solution. This solution was filtered through magnesium sulfate and was evaporated to dryness under reduced pressure to give 53 gm of 1-methyloxindole (82) which crystallized from petroleum ether as light yellow needles, mp 85-87° (lit[26] 88-89°).

$\lambda_{max}^{CS_2}$ 5.81$\mu$ $\lambda_{max}^{EtOH}$ 251 m$\mu$ ($\epsilon$ 15,800).

$\delta$ (ppm from TMS)

6.58-7.25 (4H) multiplet

3.33 (2H) singlet

3.12 (3H) singlet

Preparation of 3-Hydroxymethylene-1-methyloxindole (96). To a stirred solution of 2.864 gm of sodium in 60 ml of ethanol at 65° was added rapidly a solution of 11.08 gm of ethyl formate and 8.310 gm of 1-methyloxindole in 20 ml of ethanol. The reaction mixture quickly set to a solid mass of pale crystals. This mixture was taken up in water and was acidified with dilute hydrochloric acid to give a cream-colored precipitate which was removed by suction filtration. The filter cake was washed with ethanol and then with ether to give 8.378 gm of crude 3-hydroxymethylene-1-methyloxindole (96). This product was crystallized from ethanol and ether to give material melting at 191-192° (lit[21] 192°).

$\lambda_{max}^{EtOH}$ 263 mμ (ε 22,150), 307 mμ (ε 10,730).

Preparation of 3,3-Diallyl-1-methyloxindole (92). A solution of 595 mg of (82) and 0.5 ml of allyl bromide in 20 ml of benzene was heated to reflux temperature, and a solution of 123 mg of sodium metal in 2 ml of ethanol and 15 ml of benzene was added dropwise over a period of 1.5 hours. The mixture was heated for 20 hours under a nitrogen atmosphere. The reaction mixture was cooled and was taken up in water and ether. The ether layer was washed with saturated sodium chloride solution and was filtered through magnesium sulfate. Removal of the ether afforded 707 mg of a yellow oil which was chromatographed over alumina. The first material to be eluted (450 mg) was identified as 3,3-diallyl-1-methyloxindole on the basis of its infrared absorption and nuclear magnetic resonance spectra.

$\lambda_{max}^{CS_2}$ 5.81$\mu$.

$\delta$ (ppm from TMS)

| | |
|---|---|
| 6.66-7.37 (4H) multiplet | 3.12 (3H) singlet |
| 4.67-5.72 (6H) multiplet | 2.45-2.55 (4H) doublet |

The second material obtained from the column was identical with the starting material.

Preparation of 3-Allyl-1-methyloxindole (91). To a solution of 2.387 gm of 3-hydroxymethylene-1-methyloxindole (96) and 1.815 gm of allyl bromide in 150 ml of ethanol was added 8.30 ml of a solution of 2.088 gm of sodium metal in 50 ml of ethanol. An additional 50 ml of ethanol was added, and the mixture was refluxed for 20 hours. The solution changed from its initial yellow color to a deep red color in the first 15 minutes and gradually became lighter as the reaction proceeded. The mixture was cooled, and the bulk of the ethanol was removed under reduced pressure. The residue was taken up in water and was extracted with ether. The ether layer was washed with saturated sodium bicarbonate solution, dilute sodium hydroxide solution, water, and saturated sodium chloride solution, and was filtered through magnesium sulfate. The ether was evaporated under reduced pressure. The residue, 2.233 gm of a dark orange-red oil, was chromatographed on alumina to give 1.182 gm of 3-allyl-1-methyloxindole (91) as a faintly yellow oil which could not be induced to crystallize. $\lambda_{max}^{CS_2}$ 5.81$\mu$.

The structural assignment was based on an analysis of the nuclear magnetic resonance spectrum of this substance.

$\delta$ (ppm from TMS)

| | |
|---|---|
| 6.57-7.33 (4H) multiplet | 3.11 (3H) singlet |
| 5.37-5.86 (1H) multiplet | 2.96-3.58 (1H) multiplet |
| 4.77-5.23 (2H) multiplet | 2.21-2.95 (2H) multiplet |

Preparation of 3-Methallyl-1-methyloxindole (98). A solution of 4.518 gm of 3-hydroxymethylene-1-methyloxindole (96) in 75 ml of hot ethanol was added rapidly to a solution of 592 mg of sodium metal in 25 ml of ethanol at 60°. A white precipitate of the sodium salt of (96) formed quickly. The mixture was cooled slowly to room temperature and then was chilled in an ice bath. The solid was filtered with suction, was washed with cold ethanol and with ether, and was dried under vacuum at room temperature to give 4.50 gm of the salt as a white powder.

A suspension of 2.030 gm of the salt prepared above in 75 ml of ethanol was heated to reflux temperature. The salt dissolved to give a deep red solution. To this hot solution was added dropwise 1.1 ml of methallyl chloride in 50 ml of ethanol. This addition required a period of 45 minutes, and then the solution was heated for 24 hours. The bulk of the ethanol was removed under reduced pressure, and the residue was taken up in water and ether. The aqueous layer was washed twice with ether, and the ether layers were combined and were washed with cold water and with saturated sodium chloride solution. The ether solution was dried over magnesium sulfate and the solvent was removed to give 2.708 gm of a dark red oil. This material was distilled under reduced pressure to afford 690 mg of a yellow oil, bp 104-109°/0.05 mm,

which appeared to be a mixture of 1-methyloxindole (82) and the desired 3-methallyl-1-methyloxindole (98).

This mixture was refluxed for a short time in an ethanolic solution of sodium ethoxide and ethyl formate. The ethanol was evaporated under a stream of nitrogen gas, and the residue was taken up in water. The aqueous solution was acidified with dilute hydrochloric acid and was extracted with ether. The ether extract was washed very thoroughly with saturated sodium bicarbonate solution and with saturated sodium chloride solution. The organic phase was dried over magnesium sulfate, and the solvent was evaporated to give 541 mg of a yellowish oil which did not crystallize. This material was assigned the 3-methallyl-1-methyloxindole structure on the basis of its infrared absorption and nuclear magnetic resonance spectra. $\lambda_{max}^{CS_2}$ 5.80$\mu$.

$\delta$ (ppm from TMS)

| | |
|---|---|
| 6.57-733 (4H) multiplet | 2.75-3.58 (1H) multiplet |
| 4.60-4.87 (2H) broad doublet | 2.10-2.71 (2H) multiplet |
| 3.08 (3H) singlet | 1.74 (3H) broad singlet |

Preparation of 3-(1-Hydroxyethylidene)-1-methyloxindole (100). To a stirred solution of 7.515 gm of sodium in 110 ml of ethanol under a nitrogen atmosphere was added 23.494 gm of ethyl acetate followed by the dropwise addition of 5.178 gm of 1-methyloxindole (82) dissolved in 30 ml of ethanol. The mixture was heated and the ethanol was slowly distilled (35 ml being collected in 1.5 hours). During the course of the reaction the solution turned deep purple, and a copious tan precipitate was formed. This mixture was poured into ice water and was

extracted with three 75 ml portions of ether. The deep purple aqueous layer was acidified with dilute hydrochloric acid, discharging the purple color and giving a tan precipitate. The solid was removed by suction filtration and was washed with ice water. This material was crystallized from ethanol-water to give 4.903 gm of (100) as light tan needles, mp 109-111°.

$\lambda_{max}^{CS_2}$ 3.20-4.20, 6.00 $\mu$ $\lambda_{max}^{EtOH}$ 262 m$\mu$ ($\epsilon$ 21,400), 267 m$\mu$ ($\epsilon$ 24,350), 305 m$\mu$ ($\epsilon$ 10,810).

The analytical sample melted at 110-111° (lit 109°[19], 113-114°[20]).

Anal. Calcd. for $C_{11}H_{11}O_2N$: C, 69.85; H, 5.85.

Found: C, 69.79; H, 5.93.

Preparation of 3-Acetyl-3-allyl-1-methyloxindole (99). To a suspension of 477 mg of sodium hydride (51.2% dispersion in mineral oil) was added a solution of 2.023 gm of (100) in 50 ml of benzene. When the evolution of hydrogen had ceased, 1 ml of allyl bromide in 10 ml of benzene was added rapidly with stirring, and the resulting mixture was stirred at room temperature under nitrogen for 2 hours. At the end of this time, a test portion gave a very deep purple color with a 1% aqueous ferric chloride solution.

The reaction was heated to reflux temperature for 1.5 hours, and 0.5 ml of allyl bromide was added. Two more 1 ml portions of allyl bromide were added after periods of 1.5 and 5 hours. The mixture was then refluxed for 14 hours. At the end of this time, no color was produced when a test portion was added to aqueous ferric chloride solution.

The reaction mixture was cooled to room temperature and was taken up in ether and water. The ether layer was washed well with cold saturated sodium bicarbonate solution and with saturated sodium chloride solution and was filtered through magnesium sulfate. Evaporation of the ether afforded a partly solid, dark red material whose infrared absorption spectrum showed two strong peaks of equal intensity at 5.78$\mu$ and 5.81$\mu$ and no other maxima in the 5-6$\mu$ region. Distillation of this substance under reduced pressure gave 2.030 gm of a light yellow oil (bp 100-108°/0.005 mm) which solidified on standing in the refrigerator. Crystallization from ether-petroleum ether afforded (99) as white plates, mp 55-56°. $\lambda_{max}^{CS_2}$ 5.78, 5.81$\mu$.

The analytical sample melted at 55.5-56°.

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.69; N, 6.11.

Found: C, 73.50; H, 6.65; N, 6.12.

$\delta$ (ppm from TMS)

6.71-7.44 (4H) multiplet

4.67-5.32 (3H) multiplet

3.23 (3H) singlet

3.69-3.91 (2H) multiplet

1.91 (3H) singlet

Preparation of 3-Acetyl-3-methallyl-1-methyloxindole (101). A solution of 2.623 mg of compound (100) in 60 ml of benzene was added dropwise to a suspension of 436 mg of sodium hydride (51.2% dispersion in mineral oil) in 100 ml of benzene. After the evolution of hydrogen had ceased, 5 ml of methallyl chloride was added, and the mixture was refluxed under nitrogen for 24 hours. At this time a test portion of the mixture gave a positive test with 1% ferric chloride solution.

Six milliliters of methallyl chloride was added, and the reaction was heated for an additional 67 hours. The solution still gave a positive ferric chloride test.

The mixture was poured into ice water, and dilute hydrochloric acid was added until the aqueous layer was slightly acidic. Ether was added, and the organic layer was washed well with water, saturated sodium bicarbonate solution, water, and saturated sodium chloride solution. The ether solution was filtered through magnesium sulfate, and the solvent was removed by warming under reduced pressure. The residue, 3.225 gm of a dark red-brown oil, was vacuum distilled to give 2.300 gm of a yellow oil, bp 114-115°/0.05 mm, that solidified on standing. Repeated recrystallization of this material from petroleum ether gave 3-acetyl-3-methallyl-1-methyloxindole (101) as beautiful white needles, mp 53-55°. $\lambda_{max}^{CS_2}$ 5.77, 5.81$\mu$.

The structure assigned to this substance was confirmed by its nuclear magnetic resonance spectrum.

$\delta$ (ppm from TMS)

| | |
|---|---|
| 6.67-7.33 (4H) multiplet | 2.85 (2H) broadened singlet |
| 4.42-4.58 (2H) multiplet | 1.88 (3H) sharp singlet |
| 3.20 (3H) sharp singlet | 1.19-1.35 (3H) multiplet |

Reduction of (99) with Sodium Borohydride.

(a) Ninety-four milligrams of (99) was dissolved in 2.5 ml of freshly purified diglyme. Sodium borohydride (3.3 mg) was added, and the reaction mixture was stirred at room temperature for 3.5 hours. An additional 7.5 mg of sodium borohydride was added, and the reaction was

continued for 1 hour. The mixture was diluted with ether and was shaken well with dilute hydrochloric acid. The organic layer was washed with water and with saturated sodium chloride solution and was filtered through magnesium sulfate. Removal of the ether gave 74 mg of material whose infrared absorption spectrum was identical with the spectrum of 3-allyl-1-methyloxindole (91).

(b) Compound (91) was also the only product isolated when 95 mg of (99) was treated for 1.75 hours with a solution of 5.3 mg of sodium borohydride in 4 ml of diglyme and the reaction was quenched with 1.5 ml of acetic anhydride and pyridine (4:1).

(c) Attempted reduction of 106 mg of (99) with 19.4 mg of sodium borohydride in 2 ml of diglyme and 2 ml of acetic anhydride gave a 98% recovery of the starting material.

Reduction of (101) with Sodium Borohydride. Sixty-eight milligrams of (101) was dissolved in 4 ml of diglyme, and 10 mg of sodium borohydride was added. The mixture was stirred under nitrogen at room temperature for 2.5 hours. One milliliter of a 2:1 mixture of acetic anhydride and pyridine was added, and the resulting solution was stirred for 1.5 hours. The reaction mixture was poured into ice water and was extracted with ether. The ether solution was washed well with ice water and with saturated sodium chloride solution and was filtered through magnesium sulfate. Removal of the solvent gave 65 mg of an oil whose infrared absorption spectrum was identical with the spectrum of 3-methallyl-1-methyloxindole (98).

Catalytic Reduction of (101). A solution of 88 mg of (101) in 4 ml of diglyme was added to a suspension of platinum catalyst prepared by the reduction of 21 mg of platinum dioxide suspended in 4 ml of diglyme. The mixture was hydrogenated at room temperature and atmospheric pressure. After 3.5 hours, the uptake of hydrogen ceased, with one molar equivalent being used. The catalyst was removed by filtration. The filtrate was poured into water and was extracted with ether. The ether extract was washed with water and with saturated sodium chloride solution and was filtered through magnesium sulfate. Removal of the solvent left 77 mg of a colorless oil whose infrared spectrum was identical with the spectrum of the starting material in the 5-6 $\mu$ region. No hydroxyl absorption was present.

Treatment of (99) with Osmium Tetroxide. A solution of 167 mg of osmium tetroxide and 162 mg of (99) in 10 ml of ether was allowed to stand at room temperature in the dark for 69 hours. The ether was decanted carefully, and the dark brown residue was dissolved in 30 ml of methylene chloride. This dark solution was stirred vigorously with an aqueous solution of 1.05 gm of mannitol to which 2 ml of 2 N sodium hydroxide had been added. After 1.75 hours, the organic phase had become pale yellow. The aqueous layer was extracted several times with chloroform, and these extracts were combined with the methylene chloride layer. The resulting organic solution was washed with saturated sodium chloride solution and was dried over magnesium sulfate. The solvents were removed under reduced pressure to give 120 mg of a dark brown oil that showed infrared absorption bands indicating the presence of

hydrogen bonded hydroxyl, acetate, and oxindole functions (3.00, 5.78, 5.81, 8.08$\mu$).

When this crude material was stirred at room temperature in 5 ml of benzene containing 11 mg of p-toluenesulfonic acid, the product was 70 mg of a yellow oil whose infrared spectrum was identical with that of the above product in the 2-6$\mu$ region. This oil still showed absorption at 8.08$\mu$, but a more intense maximum had appeared at 7.90$\mu$. This peak was present as only a small shoulder in the product from the osmium tetroxide treatment of (99).

Treatment of (99) with Osmium Tetroxide and Sodium Periodate. Twelve milligrams of osmium tetroxide was added to a solution of 96 mg of (99) in 10 ml of freshly purified dioxane and 3.5 ml of water. The mixture, which rapidly became very dark, was stirred for 5 minutes at room temperature. Sodium periodate (386 mg) was added in small portions over a period of 20 minutes. The reaction mixture was stirred at room temperature for 7 hours. Water was added, and the solution was extracted several times with ether. The organic extracts were combined and were washed with saturated sodium chloride solution. The ether solution was dried over magnesium sulfate. Evaporation of the solvent gave 81 mg of a very dark oil which could not be purified by chromatography.

Treatment of (101) with Osmium Tetroxide. A solution of 166 mg of osmium tetroxide and 106 mg of (101) in 6 ml of ether was allowed to stand at room temperature in the dark for 46 hours. The dark brown solid that was formed was dissolved in 10 ml of methylene chloride.

This solution was stirred vigorously with a solution of 1.114 gm of mannitol in 10 ml of water and 1.5 ml of 2 N sodium hydroxide solution. The methylene chloride layer became pale yellow after 10 minutes. The aqueous phase was saturated with sodium chloride and was extracted with methylene chloride. The combined organic layers were washed with water and with saturated sodium chloride solution and were filtered through magnesium sulfate. Removal of the solvent gave 78 mg of a very dark oil whose infrared absorption spectrum showed bands at 2.90, 5.76, 5.81, 5.85, 5.92, and 8.15$\mu$. The nature of this material was not further investigated.

Ozonization of (99). A solution of 102 mg of (99) in 4 ml of ethyl acetate and 4 ml of acetic acid was cooled in an ice-salt mixture and was treated with 2.2 mmoles of ozone. The solution was allowed to stand in the cold bath for 1 hour. Powdered zinc (366 mg) was added, and the mixture was stirred for 20 minutes in the cold and then for 15 minutes at room temperature. The zinc was removed by filtration and was washed well with ether. The filtrate and ether washings were combined and were washed with saturated sodium bicarbonate solution and with saturated sodium chloride solution. The organic phase was dried over magnesium sulfate. Evaporation of the ether gave 57 mg of a yellow substance that could not be characterized.

Ozonization of (101). A solution of 119 mg of (101) in 2 ml of glacial acetic acid and 2 ml of ethyl acetate was cooled in an ice-salt mixture. The cold solution was treated with 4.5 mmoles of ozone and was allowed to stand in the cooling mixture for 15 minutes.

Powdered zinc (560 mg) was added, and the mixture was stirred for 10 minutes in the cold and then for 65 minutes at room temperature. The zinc was removed by filtration and was washed with ether. The filtrate and ether washings were combined and were worked up in the usual manner to give 79 mg of material that appeared to be a mixture of (101) and (116).

Attempted Preparation of the Ketal (105).

(a) A solution of 57 mg of (99), 4.6 mg of p-toluenesulfonic acid, and 1.5 ml of ethylene glycol in 4 ml of benzene was refluxed overnight. The reaction mixture was poured into cold aqueous sodium bicarbonate solution and was extracted with ether. The ether layer was washed with water and with saturated sodium chloride solution and was filtered through magnesium sulfate. Evaporation of the solvent gave 42 mg of material identical with 3-allyl-1-methyloxindole (91).

(b) A solution of 52 mg of (99) and 1 ml of ethylene glycol in 6 ml of dioxane was stirred for 70 hours with 567 mg of powdered anhydrous copper sulfate. The mixture was filtered, and the copper sulfate was washed well with ether. The combined filtrate and ether washings were washed with saturated sodium chloride solution and were filtered through magnesium sulfate. Evaporation of the solvent afforded 64 mg of an oil that was identified as the starting material containing a small amount of ethylene glycol.

(c) A solution of 53 mg of (99) and 5 mg of p-toluenesulfonic acid in 6 ml of 3-butanone ethylene ketal[23] was refluxed for 3 hours and then was slowly distilled (3 ml being removed in 1.5 hours). The

reaction mixture was worked up as in (a) to give 56 mg of crude material whose infrared spectrum in carbon disulfide solution was identical with that of the starting material.

Attempted Ketal Preparation from Compound (100). A solution of 505 mg of (100), 54 mg of p-toluenesulfonic acid, and 10 ml of ethylene glycol in 50 ml of benzene was refluxed for 49 hours. The reaction mixture was poured into cold aqueous sodium bicarbonate solution and was extracted with ether. The ether extract was washed with water and with saturated sodium chloride solution and was filtered through magnesium sulfate. Evaporation of the solvent gave 366 mg of solid material that was identical in all respects with 1-methyloxindole (82).

# IV. REFERENCES

REFERENCES

1. J.E. Saxton, Quart. Revs., 10, 108 (1956).

2. "Herbarium Amboinense" (1741).

3. F.A.L. Anet, D. Chakravarti, R. Robinson, and E. Schlittler, J. Chem. Soc., 1242 (1954).

4. R.N. Chopra, J.C. Gupta, and B. Mukherjee, Indian J. Med. Res., 21, 261 (1933); cf., ibid., 24, 1125 (1937), 29, 763 (1941), 30, 319 (1942), 31, 71 (1943).

5. L. Dorhman, A. Furlenmeier, C.F. Huebner, R.A. Lucas, H.B. MacPhillamy, J.M. Mueller, E. Schlittler, R. Schwyzer, and A.F. St. André, Helv. Chim. Acta, 37, 59 (1954).

6. S. Siddiqui and R.H. Siddiqui, J. Ind. Chem. Soc., 8, 666 (1931), 9, 539 (1932), 12, 37 (1935).

7. L. van Itallie and A.J. Steenhauer, Arch. Pharm., 270, 313 (1932).

8. R. Robinson, Chem. and Ind. (London), 285 (1955).

9. R.B. Woodward, Angew. Chem., 68, 13 (1956).

10. For a review of the reactions of ajmaline and related alkaloids see W.I. Taylor, Chap. 22, in "The Alkaloids," R.H.F. Manske, Vol. VIII, Academic Press, New York, N.Y. (1965).

11. M.F. Bartlett, R. Sklar, W.I. Taylor, E. Schlittler, R.L.S. Amai, P. Beak, N.V. Bringi, and E. Wenkert, J. Am. Chem. Soc., 84, 622 (1962).

12. E.E. van Tamelen, P.E. Aldrich, and T.J. Katz, J. Am. Chem. Soc., 79, 6426 (1957).

13. F.A.L. Anet, Can. J. Chem., 39, 789 (1961).

14. M. Karplus, J. Chem. Phys., 30, 11 (1959).

15. M.F. Bartlett, B.F. Lambert, H.M. Werblood, and W.I. Taylor, J. Am. Chem. Soc., 85, 475 (1963).

16. J.D. Hobson, J. Raines, and R.J. Whiteoak, J. Chem. Soc., 3495 (1963).

17. P.L. Julian and J. Pikl, J. Am. Chem. Soc., 57, 755 (1935).

18. Cf.R.B. Longmore and B. Robinson, Chem. and Ind. (London), 1297 (1965).

19. P.L. Julian and J. Pikl, J. Am. Chem. Soc., 57, 2026 (1935).

20. E. Wenkert, B.S. Bernstein, and J.H. Udelhofen, J. Am. Chem. Soc., 80, 4899 (1958).

21. P.L. Julian, J. Pikl, and D. Boggess, J. Am. Chem. Soc., 56, 1797 (1934).

22. H.O. House, "Modern Synthetic Reactions," W.A. Benjamin, Inc., New York, N.Y. (1965), p 38.

23. H.J. Dauben, B. Löken, and H.J. Ringold, J. Am. Chem. Soc., 76, 1359 (1954).

24. R.B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W.M. McLemore, J. Am. Chem. Soc., 74, 4223 (1952).

25. R. Pappo, D.S. Allen, Jr., R.V. Lemieux, and W.S. Johnson, J. Org. Chem., 21, 478 (1956).

26. R. Stollé, J. prakt. Chem. [2] 128, 1 (1930).