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DATED...October.20.....1972 USA.

NL-91 (10-68)

TO MY HUSBAND JIM

AND TO MY PARENTS

THE UNIVERSITY OF ALBERTA

THE TOTAL SYNTHESIS OF AJMALINE

by

© YUMIKO YASUNARI HOYANO

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

of

DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

FALL, 1972

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled

THE TOTAL SYNTHESIS OF AJMALINE

submitted by YUMIKO YASUNARI HOYANO, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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Supervisor

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External Examiner

Date. October 27, 1972

ABSTRACT

The synthesis of the complex indole alkaloid ajmaline from a simple indole derivative has been accomplished. The successful synthesis required the preparation of the key intermediate aldehyde (55) by a route in which the C5-C16 bond formation preceded the construction of the β-carboline ring system. Compound (55) was converted to ajmaline by a straight forward series of reactions.

The first step in our successful synthesis was the condensation of N-methylindole-3-acetyl chloride with the magnesium complex of ethyl hydrogen-2-(Δ^3-cyclopentenyl)malonate to afford the β-keto-ester (59). Reaction of (59) with methoxylamine hydrochloride yielded the methoxime (64) which was reduced with aluminum hydride to the amino-alcohol (65). The amine and hydroxyl groups of (65) were then protected by conversion to the dibenzoate (68). The double bond in the cyclopentene ring of (68) was selectively oxidized with osmium tetroxide to afford the diol (69). Periodate cleavage of the diol yielded a dialdehyde which was predominantly in the hemiaminal form (70). The acid catalyzed cyclization of (70) afforded exclusively the α-cyclized aldehyde (71) presumably because of the presence of the C5-C16 bond.

The introduction of the ethyl group on the α-carbon of the aldehyde (71) was effected by first converting to the cyano compound (84) followed by treatment with sodiotriphenylmethane and ethyl iodide to afford the ethylated cyano compound (85). Hydrolysis of the O-benzoate group yielded the cyano-alcohol (86) which was then oxidized with dicyclohexylcarbodiimide to afford the aldehyde (55) (same as $(92)_n$).

The acid catalyzed cyclization of the aldehyde group of $(92)_n$ to the indole nucleus was effected in acetic acid-acetic anhydride saturated with hydrogen chloride gas to afford $(95)_n$ which was catalytically hydrogenated in strong acid to the alcohol $(97)_n$. Reduction of $(97)_n$ with lithium aluminum triethoxyhydride gave the benzylamide $(99)_n$ which on hydrogenolysis yielded the secondary amine $(102)_n$. This amine was converted by lithium aluminum hydride to ajmaline.

Related to the condensation of the carbinolamide (70) to the exclusively α-condensed product (71) in our ajmaline synthesis was a report by van Tamelen *et al.* in which the condensation of the dialdehyde (103) was proposed to yield the double cyclized product (104). Careful reexamination of the latter work showed that only a single cyclization had occurred.

A C K N O W L E D G E M E N T S

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CHAPTER I

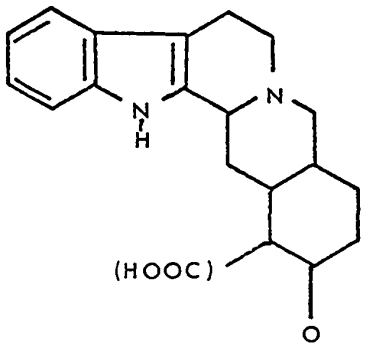
THE TOTAL SYNTHESIS OF AJMALINE

Introduction

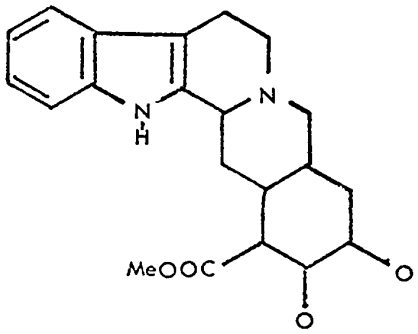
Indole alkaloids have received a great deal of attention in the last few decades presumably because of the discovery of their remarkable physiological properties. The extensive investigation of indole alkaloids afforded some 700 compounds of which the structures of approximately 400 have been elucidated.[1]

About seventy indole alkaloids have been isolated from more than sixty different Rauwolfia species. Rauwolfia alkaloids are a thoroughly investigated group of compounds because of the isolation of reserpine in the early 1950's. Reserpine was found to be of clinical importance as an antihypertensive and tranquilizer. These valuable properties of reserpine inspired the study of other Rauwolfia alkaloids, including ajmaline. Rauwolfia alkaloids may be classified into four groups: yohimbine-type (1), reserpine-type (2), ajmalicine-type (3), and ajmaline-type (4) as shown in Chart I.[2] Although ajmaline (5), first isolated in pure form in 1931 by Siddiqui and Siddiqui,[3] had been recognized to possess some medical usefulness [4] for a long time in India, its chemical exploration lay dormant until the commercial usefulness of reserpine became evident.

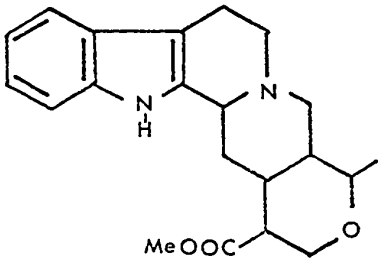
The Oxford group of Robinson [5] initiated extensive



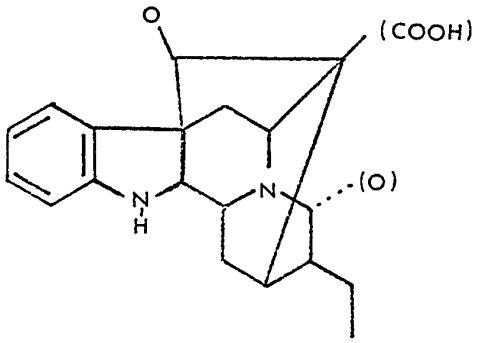
yohimbine-type (1)



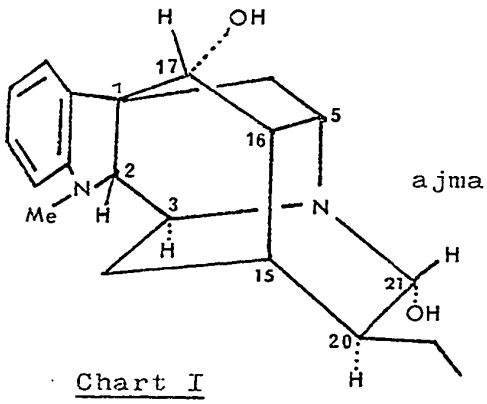
reserpine-type (2)



ajmalicine-type (3)



ajmaline-type (4)



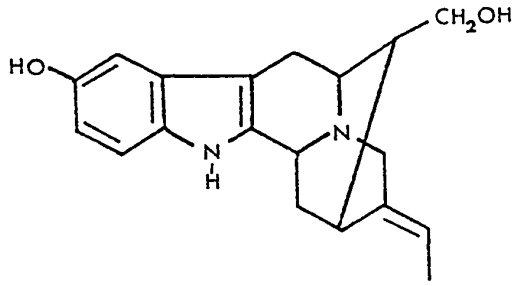
ajmaline (5)

Chart I

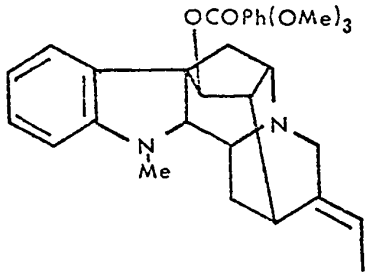
studies on the structural elucidation of ajmaline and established the fundamental chemical and physical properties and outlined the unique structural features of this alkaloid. In 1956 Woodward and Schenker [6] finally determined the correct pentacyclic system and the position of the C17 hydroxyl group. The CIBA group [7] reported in 1962 that they had performed a series of degradative experiments including the conversion of ajmaline to a corynantheidane derivative of known stereochemistry. The work of Robinson, Woodward, and the CIBA group is briefly described in a later section of this chapter. Thus, except for its synthesis, the chemistry of ajmaline had for the most part been completed by the early 1960's.

Following the structure determination of ajmaline, several other alkaloids isolated from Rauwolfia species were assigned to the ajmaline group of alkaloids by interrelation with known ajmaline derivatives. Some examples are sarpagine (6),[8] rauvomitine (7),[9] sandwicine (8),[10] tetraphyllicine (9),[11] and ajmalidine (10)[9] which are shown below.

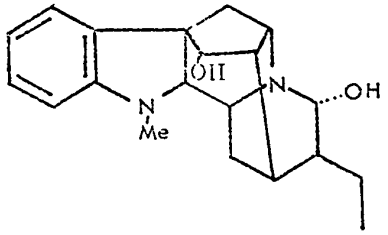
Until 1950, the structural elucidation of natural products required a great deal of laborious work; however, present-day investigation of natural products, particularly structure determination, has become much simpler. The isolated pure base can now be subjected to ultraviolet, infrared, nuclear magnetic resonance and



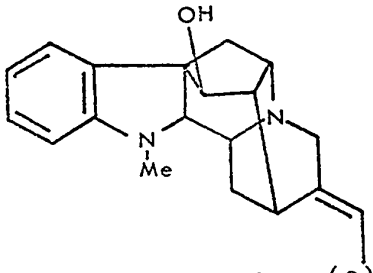
sarpagine (6)



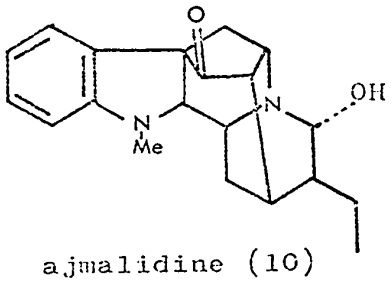
rauvomitine (7)



sandwicine (8)



tetraphyllicine (9)



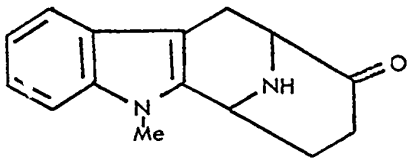
ajmalidine (10)

Chart II

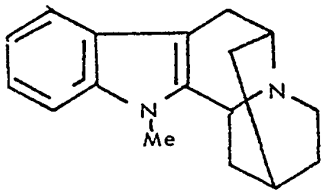
mass spectral measurements. X-ray diffraction for structure determination is also now being widely used to provide absolute proof of structure. When the above methods are available in the organic chemistry laboratory, even very complex structures can be determined almost routinely. However, the synthesis of these natural products presents a challenge to organic chemists. A number of elegantly designed syntheses of complex natural products were reported in the 1950's and 1960's. Some of the indole alkaloids synthesized before the present work were strychnine (1954, R. B. Woodward),[12] reserpine (1956, R. B. Woodward), [13] yohimbine (1958, E. E. van Tamelen),[14] ajmalicine (1961, E. E. van Tamelen),[15] aspidospermine (1963, G. Stork),[16] and ibogamine (1965, G. Buchi).[17]

Since the establishment of the unique skeletal framework of ajmaline and its stereochemistry, there have been numerous attempts aimed at a synthesis of this highly complex indole alkaloid. In 1963, Hobson and co-workers [18] reported the synthesis of tetracyclic ketone (11), a potentially useful intermediate. In 1965 Yoneda [19] synthesized 12-methyl-2,3,4,6,7,12,12b-octahydro-2,6-methano-indole-(2,3a)-quinolizine (12). This compound contains the fundamental skeleton of the sarpagine-type alkaloids and introduction of suitable functional groups would lead to the completion of a synthesis

of ajmaline.



(11)



(12)

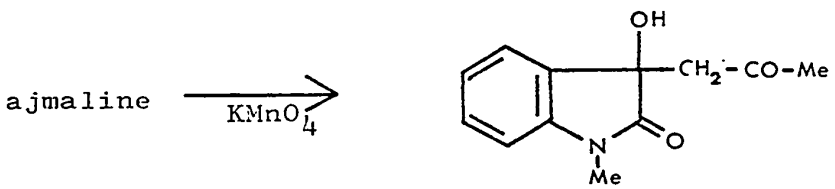
The first total synthesis of ajmaline, described in detail in this section, was published in a preliminary form in 1967.[20] Subsequently, in 1969, Mashino and Sato [21] reported the synthesis of isoajmaline, a C21 epimer and in 1970 van Tamelen and Oliver [22] published another total synthesis of ajmaline. After the synthesis of ajmaline had been completed in this Laboratory, a related synthetic study on Strychnine-Curare alkaloids was carried out. This work is outlined in Chapter II.

The process of the structural elucidation of ajmaline is interesting in that the development of modern physical methods in the 1950's is uniquely illustrated. In the early 1950's, when the Oxford group started investigations on the structure of ajmaline, infrared and ultraviolet spectroscopy and optical rotation were the only physical methods available. The classical chemical reactions of making various derivatives, melting points and elemental analysis were fully utilized for the characterization of compounds. Because the degradative studies suggested an

appropriate synthetic route, these are now briefly outlined below.

The molecular formula of ajmaline [mp 158-160°, $[\alpha]_D^{25°}$ -98($CHCl_3$)] reported by the Oxford group [5] was $C_{20}H_{26}N_2O_2$. When heated above its melting point, ajmaline was transformed into isoajmaline (mp 265°). The indoline nucleus in the molecule of ajmaline was detected by its characteristic ultraviolet absorption, color reactions, and substitution products. For example, bromo-ajmaline (mp 192°) was obtained from the reaction with bromine in dry chloroform. Catalytic hydrogenation provided hexahydro-ajmaline (mp 149-150°) which showed no unsaturation.

The location of the methyl group on the indoline nitrogen (N-a) was established when the oxidation of ajmaline with potassium permanganate in acetone gave 3-acetonyl-2,3-dihydro-3-hydroxy-2-oxoindole (N-methyl-isotinacetone)(13).[5]



(13)

The infrared spectrum of ajmaline did not show a carbonyl absorption in the solid state. However, in chloroform solution a carbonyl function was observed. These observations were interpreted as a ring opening-closing tautomerism between the second nitrogen (N-b) and the adjacent alcohol group (C21-OH). The open-ring form of ajmaline was called chano-ajmaline. Attempts to prepare an immonium salt of ajmaline failed. Therefore the second nitrogen must be located on a bridge head.

In order to disclose the environment of the second nitrogen (N-b), a series of degradative reactions were applied to ajmaline. With hydroxylamine hydrochloride in water, ajmaline afforded an oxime (14) which was transformed into anhydroajmaline oxime (15) (mp 254-255°) when heated with dry hydrogen chloride gas in a mixture of acetic acid and acetic anhydride followed by methanolic potassium hydroxide.[5] Wolff-Kishner reduction on chano-ajmaline provided deoxydihydro chano-ajmaline (16) which on chromic acid oxidation in aqueous sulfuric acid afforded ethyl methyl ketone. When chano-ajmaline was reduced with potassium borohydride, the corresponding alcohol dihydro chano-ajmaline (17) was obtained.[5] Upon treatment with Raney-nickel at 130°, chano-ajmaline afforded decarbono-chano-ajmaline (18), which on chromic acid oxidation gave butyric acid. Reaction with a primary amine converted chano-ajmaline into an imine

which with base gave alkylamino-isoajmaline (19).[23] The foregoing reactions were determined mainly by Robinson's group and are summarized in Chart III.

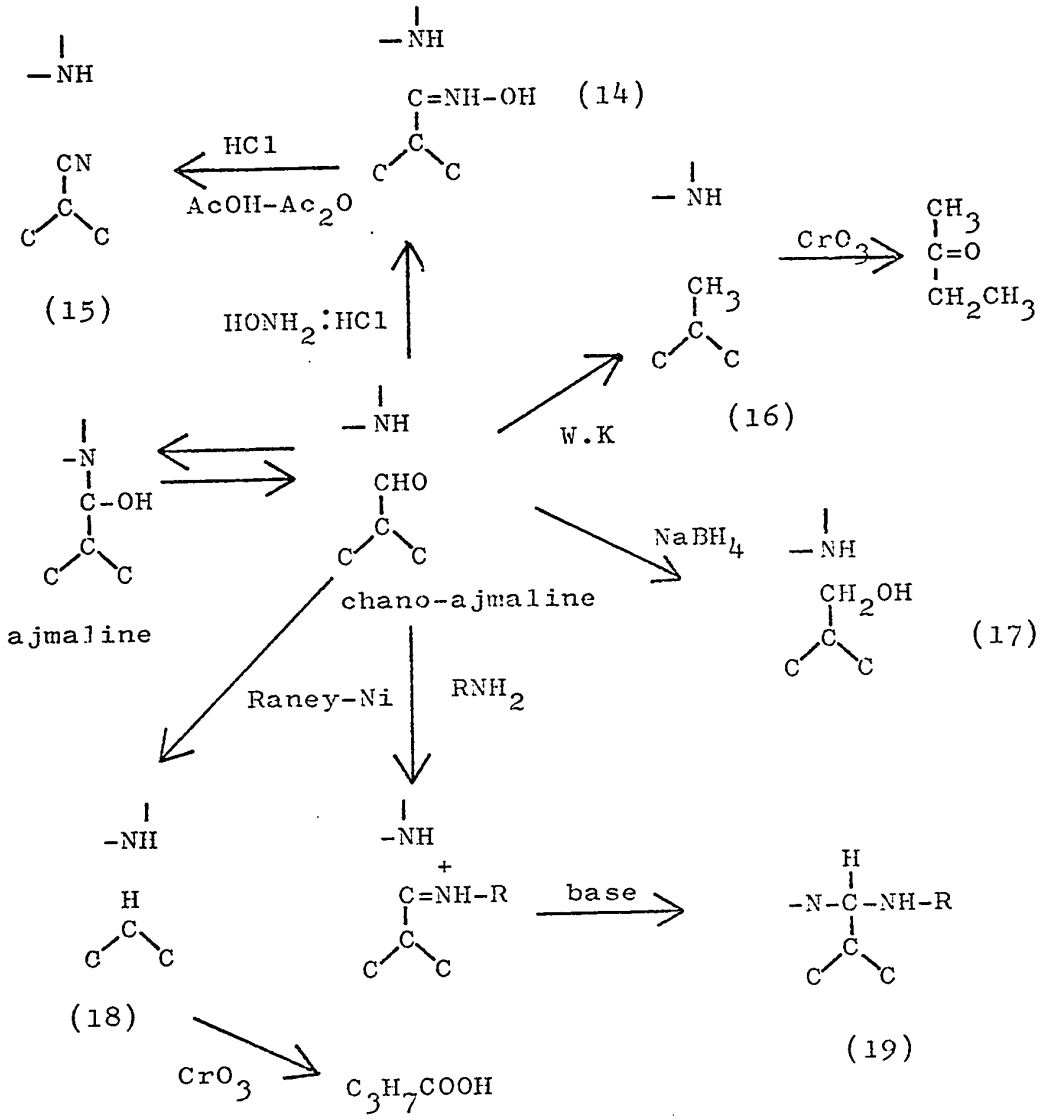
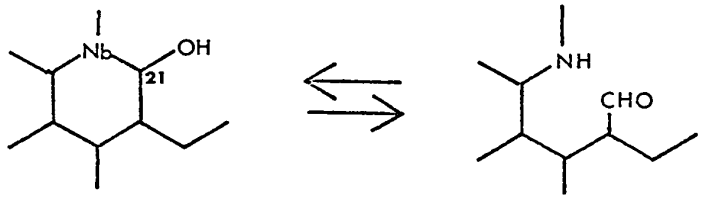


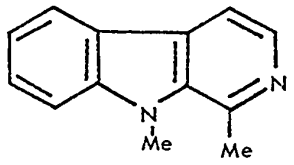
Chart III

These results strongly indicated the presence of a partial structure in the vicinity of the (Nb) atom as shown below.

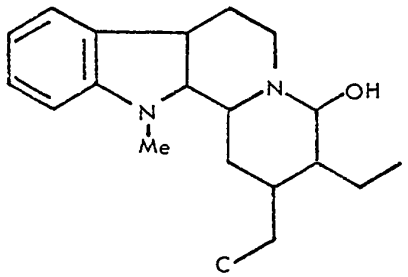


ajmaline ⇌ chano-ajmaline

Degradation of ajmaline by heating with soda-lime at 280-300° gave N-methylharman (20) as the main product and the partial structure (21) was proposed.



(20)

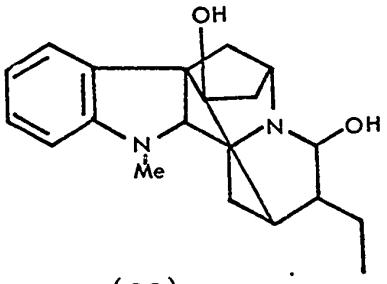


(21)

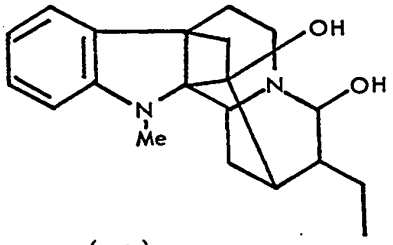
Although the second hydroxyl group (C17-OH) could be acetylated normally, its resistance towards chromic acid, thionyl chloride and several other reagents led Robinson's group to propose a tertiary hydroxyl group.

From the above results, Robinson proposed that aj-

maline very likely possesses structure (22) or (23) with expressed preference for the former structure.[24]

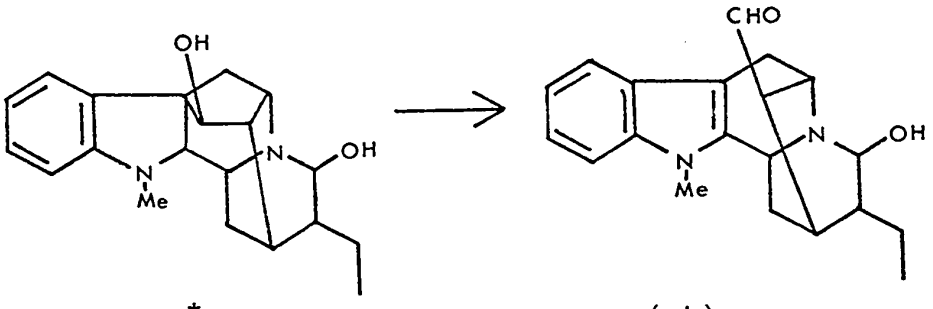


(22)



(23)

Woodward and Schenker [6] performed a series of degradations on ajmaline. Lead tetraacetate oxidation of ajmaline produced an indole-aldehyde (24) which indicated that the C17 hydroxyl group, formerly thought to be tertiary was in fact secondary since the product of the oxidation was an aldehyde and not a ketone. The Oppenauer oxidation of ajmaline with benzophenone and potassium



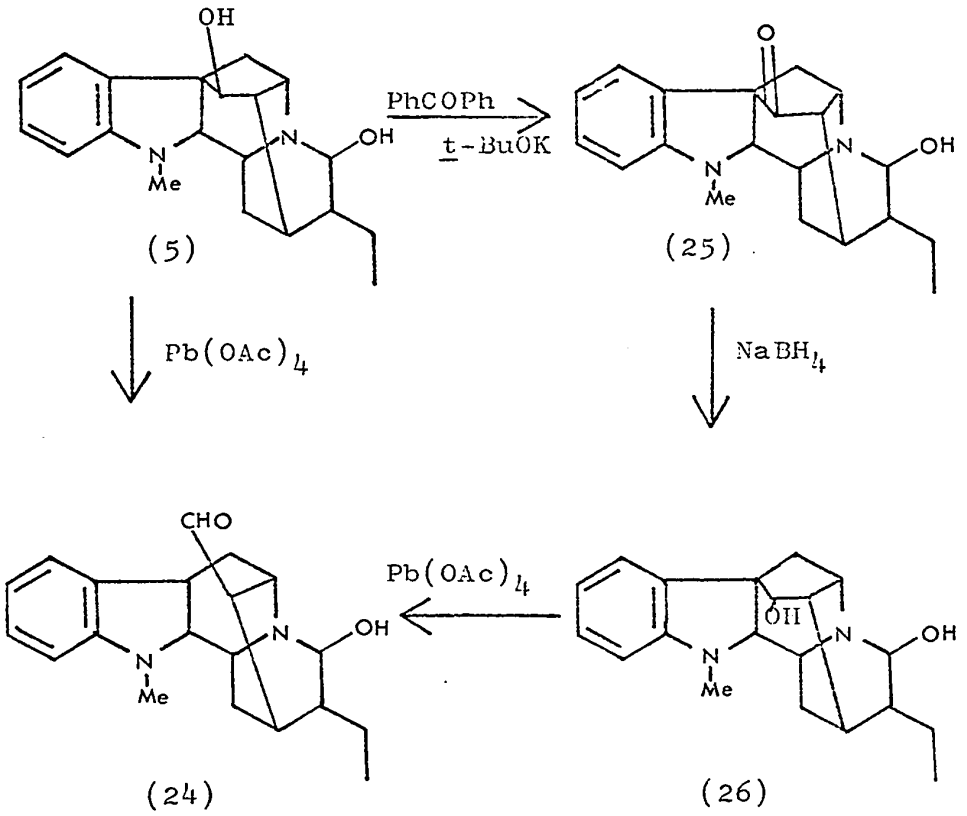
(5)* (24)

tertiary butoxide yielded a dihydro indole ketone (25)

* This representation of the ajmaline structure is equivalent to that shown on page 2.

whose infrared spectrum absorption at 1745 cm^{-1} suggested a carbonyl group on a five-membered ring. Sodium borohydride reduction of this ketone gave epi-ajmaline (26) which in turn led to the same aldehyde (24) upon lead tetraacetate oxidation.

Combination of all the experimental results of Woodward and Robinson established the structure of ajmaline as (5).



After the determination of the structure of ajmaline, its stereochemistry became the subject of interest. The CIBA group [7] achieved the stereospecific conversion of the ajmaline skeleton to a compound of known stereochemistry. From 21-deoxyajmaline (27), a series of degradation steps ultimately led to N-methyltetradehydrocorynantheidane(28), the stereochemistry and absolute configuration of which had been determined earlier. Thus the absolute stereochemistry of all but four asymmetric centres (C2, C17, C20, and C21) was established. Also 21-deoxyisoajmaline was converted to compound (28). The stepwise degradation process of 21-deoxyajmaline is outlined in Chart IV.

The stereochemistry of the C17 hydroxyl group was determined by nmr spectroscopy.[7] The coupling constant (J) between the protons at C16 and C17 (see p.2) in various derivatives of ajmaline was less than 2 Hz whereas for the C17 epimers (J) was ca. 9 Hz. These (J) differences indicated that the C17 proton in the five-membered ring was trans to the C16 proton in ajmaline and cis in its C17 epimer.

The indolenium salt (29) derived from deoxyajmaline-17-O-acetate was utilized to investigate the stereochemistry at C2.[7] When this salt was catalytically hydrogenated, only the C2 epi-compound was obtained. This result was further supported by the comparison of the optical rotatory dispersion curves of deoxyajmaline-17-O-acetate

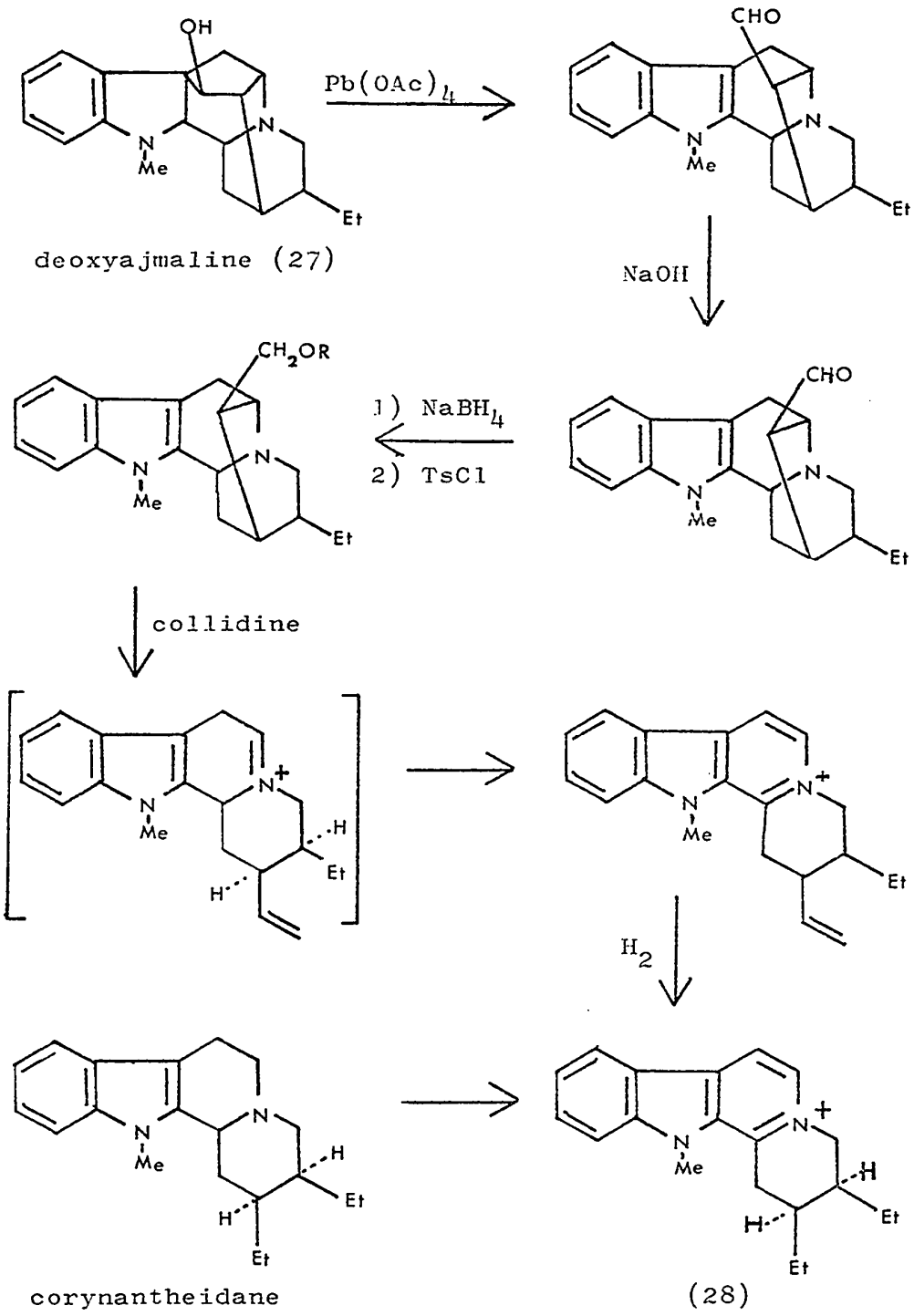
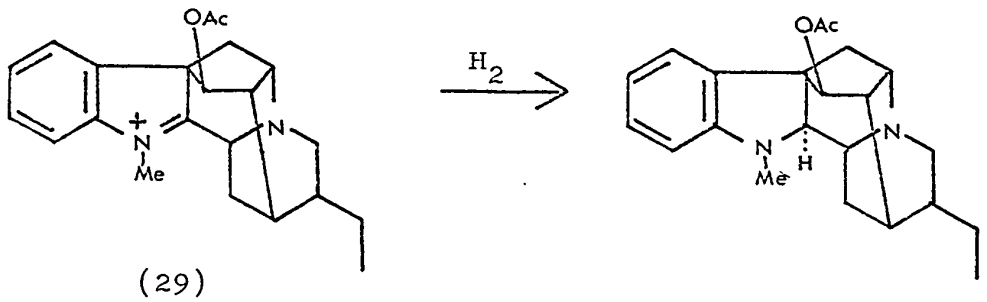

OH
Pb(OAc)4
CHO
deoxyajmaline (27)
NaOH
CH2OR
1) NaBH4
2) TsCl
CHO
collidine
H2
corynantheidane
(28)

Chart IV

and its C2 epimer. The mirror image relationship of the two curves suggested a stereochemical change adjacent to the chromophore. The exclusive formation of the epi compound was interpreted by the CIBA group [7] as due to severe steric hindrance on the β-side of the molecule.

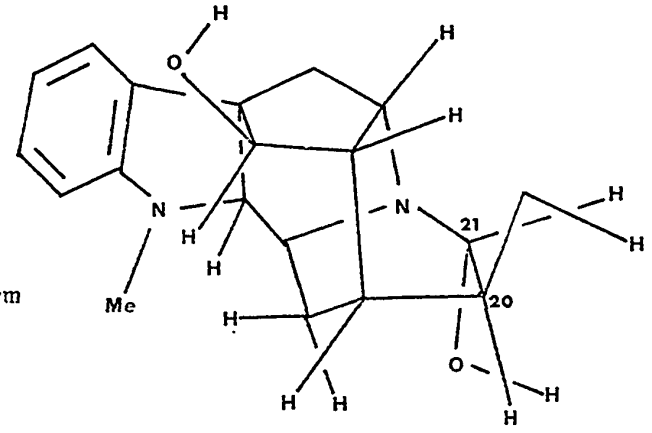


(29)

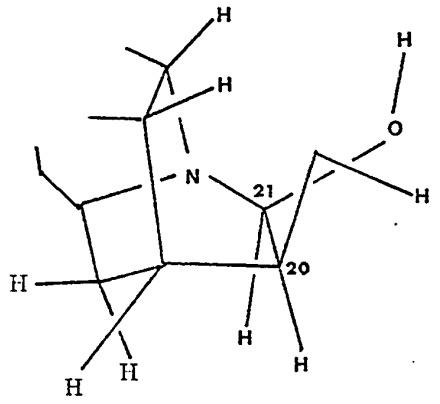
When the chano-ajmaline ring closes to ajmaline, the most stable C21 epimer would be expected where the C21 hydroxyl group takes up a configuration trans to the neighboring C20 ethyl group. If the C20 ethyl and C21 hydroxyl groups were in the cis relationship, there would be increased steric interactions as shown below. Because the trans relationship of these two groups in ajmaline is the most probable form, other steric interactions within the ajmaline molecule must account for the ready isomerization to isoajmaline upon heating at ca 200°(see p.7).

The above proposal on the stereochemistry of ajmaline at C20 and C21 is supported by alkylation rate studies.[25]

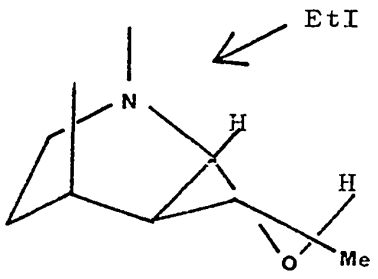
trans-form



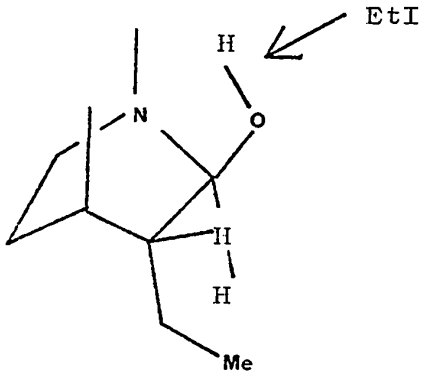
cis-form



The rate of ethiodide formation on (Nb) showed distinct differences between the ajmaline series and its isomers. In all cases there were greater hindrances to the ethiodide formation for the isoajmaline derivatives. The quinuclidine system is slightly skewed and the C21 substituent in the isoajmalines offered greater hindrance to the incoming ethyl group than the ajmaline derivatives. When the C21 hydroxyl function was removed (21-deoxy-ajmaline series), the rate of ethiodide formation increased and became almost identical in both series.

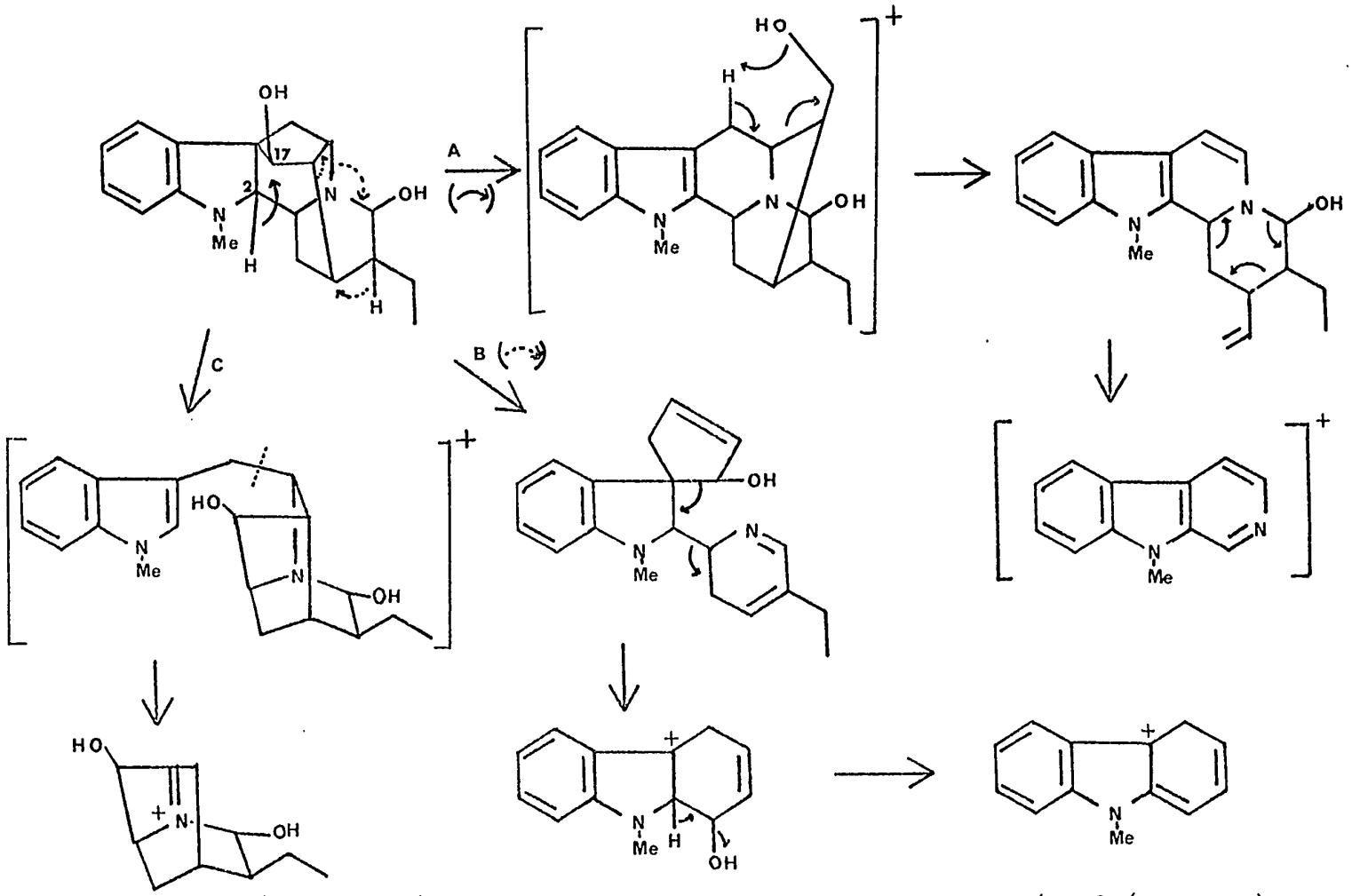


ajmaline



isoajmaline

Accumulation of mass spectral data [26] on ajmaline derivatives made some generalizations for fragmentation possible. The fragmentation patterns were found to be dependent on stereochemistry and provided useful information on configurations in the molecule. Characteristic patterns were observed for three groups: compounds similar to ajmaline, the C2 epimers, and those possessing C17 carbonyl functions. As seen in Chart V, when the C2 hydrogen is cis to the C17 bridge (normal series), the hydrogen migrates to the C17 under electron impact-induced cleavage, generating the sarpagine skeleton which could give rise to the characteristic peak at m/e 182 (m/e 183 if protonated). These peaks were absent in the C2 epi compounds. The m/e 182 peak can be derived as the β-carboline ion $C_{12}H_{10}N_2$ by path A, as well as paths B



m/e 182 ($C_{10}H_{16}NO_2$)

Chart V

m/e 182($C_{13}H_{12}N$)

and C ($C_{13}H_{12}N$ and $C_{10}H_{16}NO_2$) to a lesser extent. For the C17 carbonyl compounds the peaks at m/e 182 and 183, which are suggested to be characteristic for the ajmaline skeleton, are of low intensity but intense peaks are observed at m/e 198 of composition $C_{13}H_{12}NO$. The elimination of CO from the cyclopentenone ring is observed only for the carbonyl series and gives rise to the peak at m/e 296 which leads to the most intense peak at m/e 144, $C_{10}H_{10}N$ (see Chart VI).

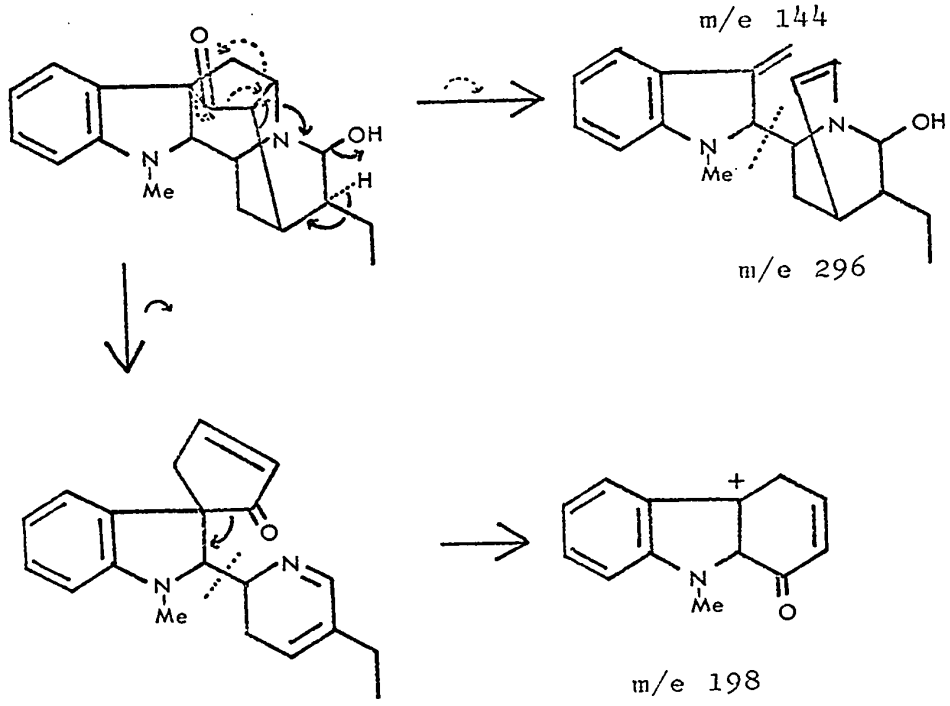


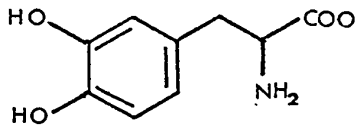
Chart VI

The X-ray crystallographic analysis of two sarpagine derivatives [27] established the skeleton of ajmaline-sarpagine type alkaloids and confirmed the proposed structure outlined above.

Various hypotheses on the biogenetic pathway to indole alkaloids have provoked stimulating debates ever since the question was first raised in the early 1930's. That tryptophan is the precursor for the indole nucleus was shown by E. Leete [28] when the administration of radioactive tryptophan into plants resulted in the isolation of radioactive indole alkaloids. The exact origin of the remaining non-indolic 9 to 10 carbon units of indole alkaloids still remains uncertain inspite of intensive studies.

After the structure determination of ajmaline, Woodward [6] and Robinson [29] both suggested that the portion consisting of C3 and C14 to C20 is derived from 3,4-dihydroxyphenylalanine (30). Wenkert [30,31] proposed that these carbons are derived from prephenic acid (31). In both hypotheses C21 is derived from a one carbon fragment. However, poor incorporation of radioactive sodium formate into alkaloids in feeding experiments [32,33] did not support either hypothesis.

In another hypothesis independently conceived by Thomas [34] and Wenkert,[31] all non-indolic carbons were considered to arise from a monoterpene having the carbon



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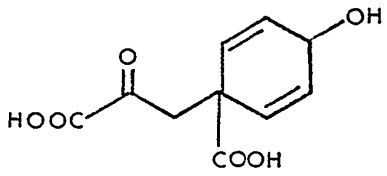


(31)

skeleton (32). This hypothesis was formulated apparently because several non-alkaloidal glycosides were discovered in plants [35] and they contain the basic skeleton (32). The transformations of the monoterpene (32) into four major alkaloids are outlined in Chart VII. The cyclopentane ring is cleaved at the dotted line to give the corynanthe skeleton (33).

In order to rationalize the rearrangement paths A and B, Wenkert [36] proposed that at the full alkaloid level the rearrangement takes place after the combination of tryptamine with the monoterpene unit. This theory was further extended to predict that the corynanthe alkaloids would be the progenitors of the more complex system.

The monoterpene (32) was found to originate from the head-to-tail combination of two C_5-units. Radioactive mevalonic acid (34) was incorporated into the alkaloids [37] and from the labelling pattern in the alkaloids, it became evident that mevalonic acid was converted to the monoterpene(32), the proposed precurser of the non-

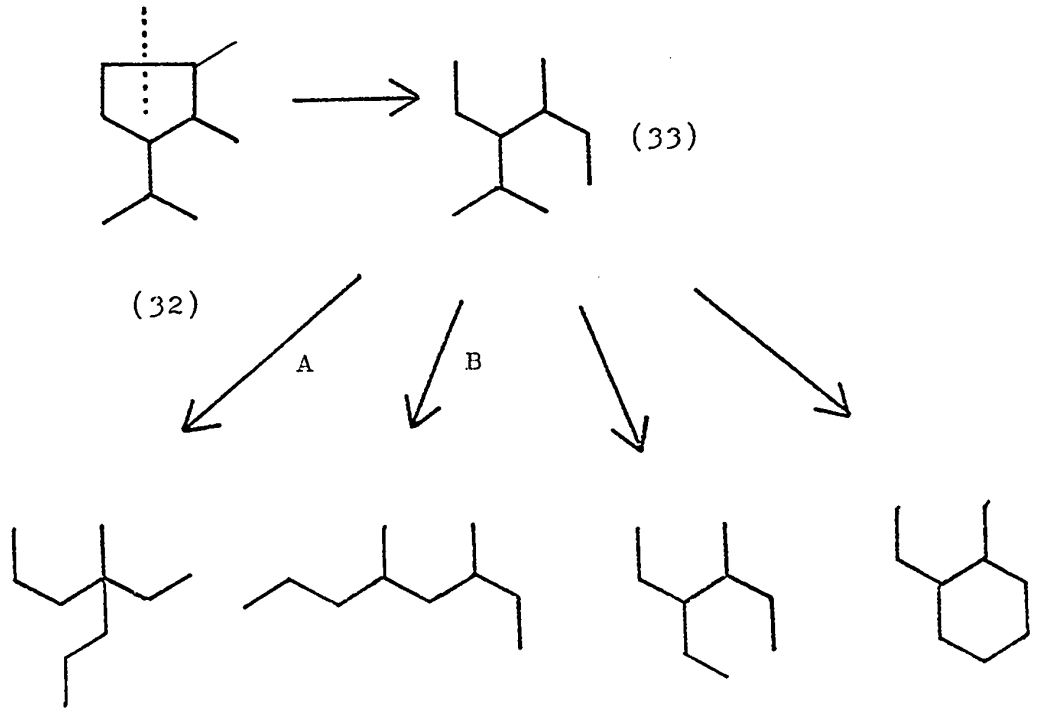
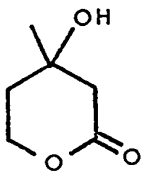


Chart VII

indolic portion of the indole alkaloids. According to the 'isoprenoid biosynthesis', a combination of two C_5-units should lead to geraniol (35) which could be the precursor for the monoterpene (32). Feeding experiments using labelled geraniol [38] resulted in high incorporation into three major alkaloids.



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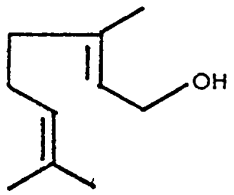
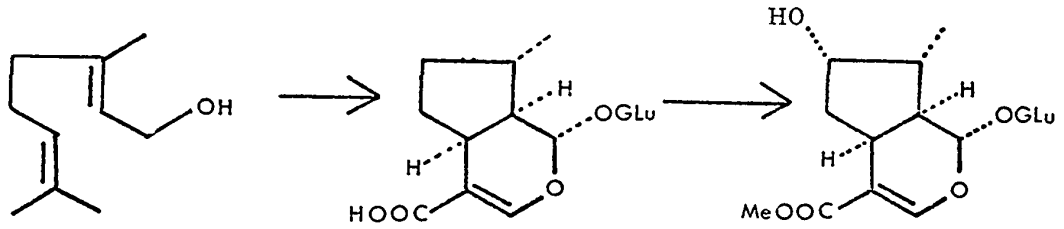


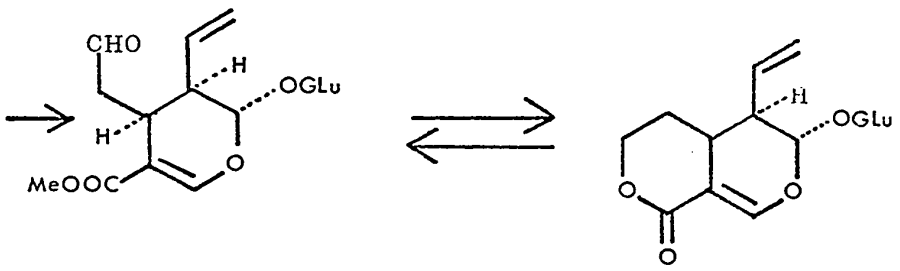
(35)

In the mid 1960's studies related to the monoterpene work revealed that loganin (36) was a more likely bio-intermediate.[39] As seen in Chart VIII, loganin is derived from geraniol via deoxyloganin [40] which corresponds to monoterpene (32) in the Thomas-Wenkert theory. Seco-loganin (37) can be equilibrated with the secolactone sweroside (38) which has been biogenetically converted to the three main classes of indole alkaloids.[41]

The combination of tryptamine with secologanin to form vincoside (39) was carried out in Battersby's laboratory [42] and vincoside was found to serve as a precursor for the three major alkaloids. The conversions of vincoside to the indole alkaloids are outlined in Chart IX.



(35) deoxyloganin loganin (36)



secologanin (37) sweroside (38)

Chart VIII

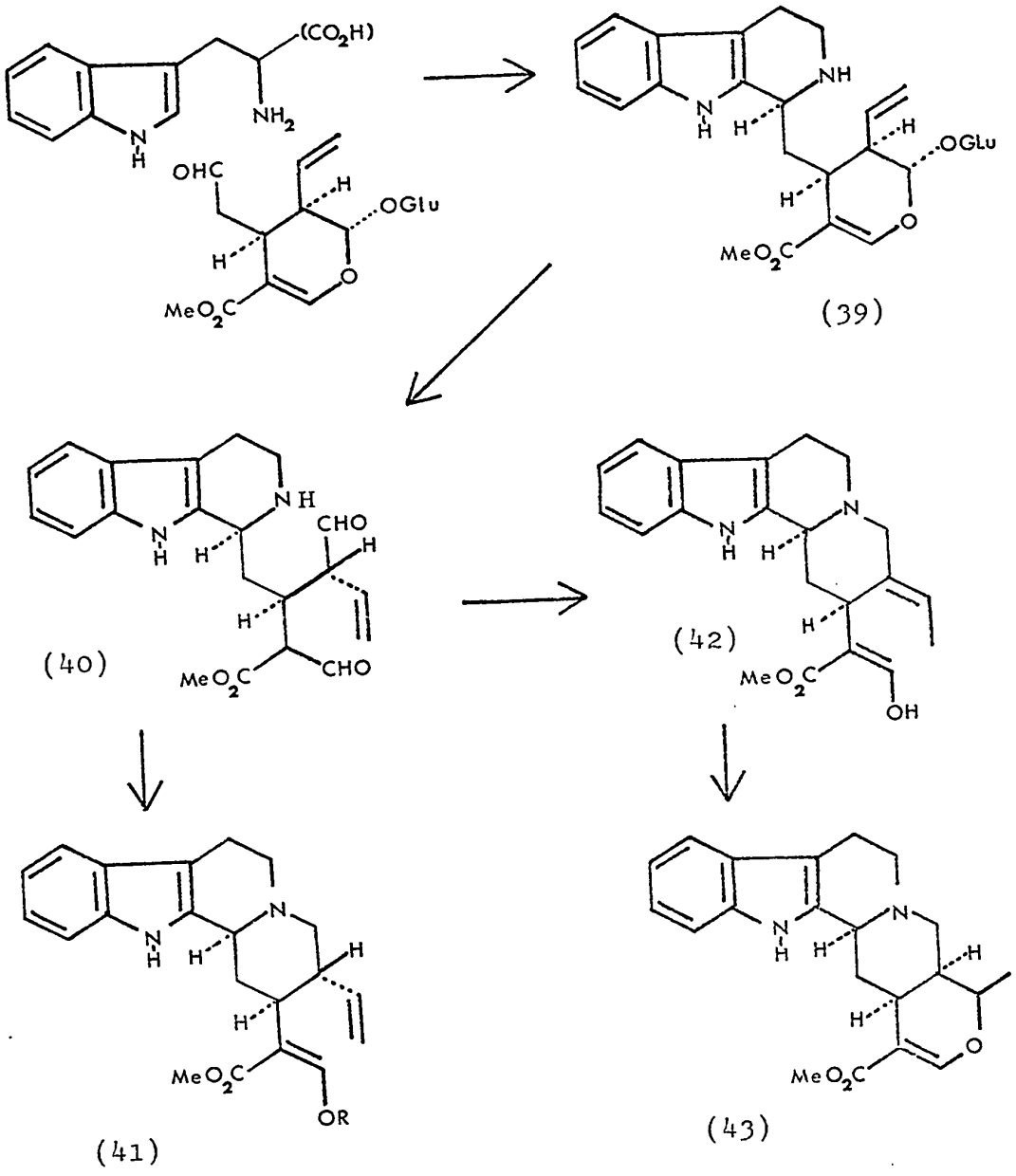
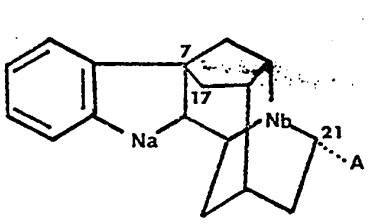


Chart IX

After enzymatic hydrolysis of the glucosidic residue, the aldehyde group in (40) undergoes condensation to give either corynantheine aldehyde (41) or geissoschizine (42) the immediate precursor of ajmalicine (43). The β-aldehyde-ester function in corynantheine aldehyde (41) and geissoschizine (42) contain a most favorable orientation whereby subsequent skeletal rearrangement might evolve.

Results and Discussion

The synthesis of ajmaline was initiated principally because of its unique structural framework of rigid polycyclic rings. The C5-C16 bond is unique to the ajmaline-sarpagine alkaloids and gives rise to the unusual quinuclidine moiety. Initially the synthesis of the basic ajmaline skeleton (44) as seen below can be reduced to the synthesis of (45) because the C7-C17 and C21-Nb linkages can be constructed by utilizing previous experimental results. The structure (45) if further simplified by breaking two bonds to give (46) makes it possible for one to visualize the construction of the complex ajmaline molecule from a simple indole derivative.



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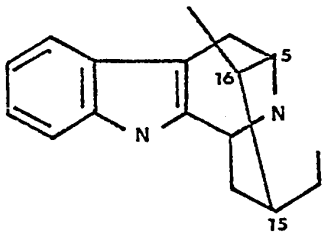
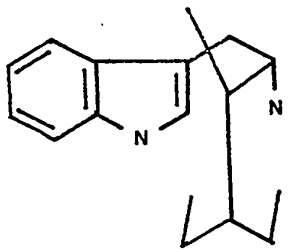


(45)



(46)

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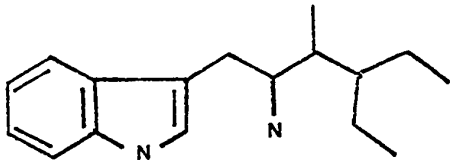
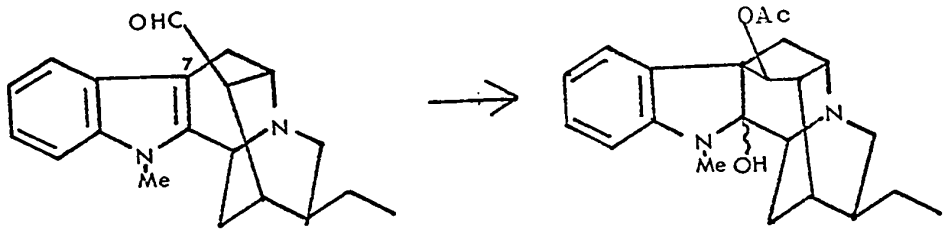
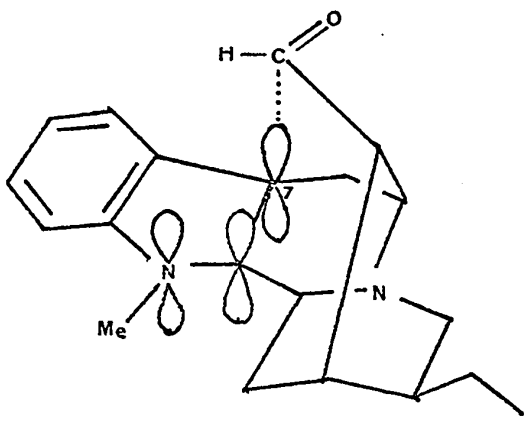


(46)

The reported experimental results on the C7-C17 and C21-Nb bond formations provide some insight into possible schemes for the ajmaline synthesis. These will now be briefly outlined. The bond formation between C7 and C17 has been reported by the CIBA group.[43] When deoxyajmalal (47) was treated with the strong acid mixture of acetic acid - acetic anhydride and hydrochloric acid followed by base (ammonium hydroxide), deoxyajmaline-2-hydroxy-17-O-acetate (48) which possessed the same configuration at C17 as ajmaline was obtained. The selective bond formation can be rationalized because the nucleophilic β-position (C7) of the indole nucleus and the electrophilic C17-aldehyde group are favorably located for bond formation as shown below (49). Formation of a C17-C2 bond would require much higher energy. The stereochemistry of the hydroxyl group at C2 of (48) is unknown but introduction of the correct configuration at C2 is discussed below.

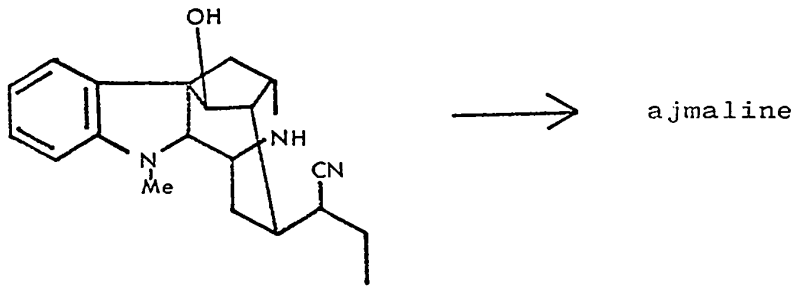


(47) (48)



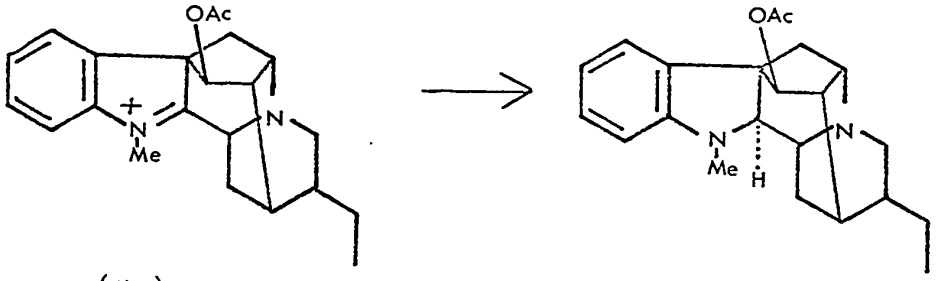
(49)

The ring closure of C21 to Nb has been accomplished by Robinson's group [5] by reducing anhydroajmaline oxime (50) with lithium aluminum hydride to yield ajmaline. The cyano group was reduced to an aldehyde which cyclized to Nb. Since the reaction product was ajmaline, this reaction provides the correct configurations at C20 and C21. The above two ring closing reactions are applied at a late stage of the synthesis reported here.



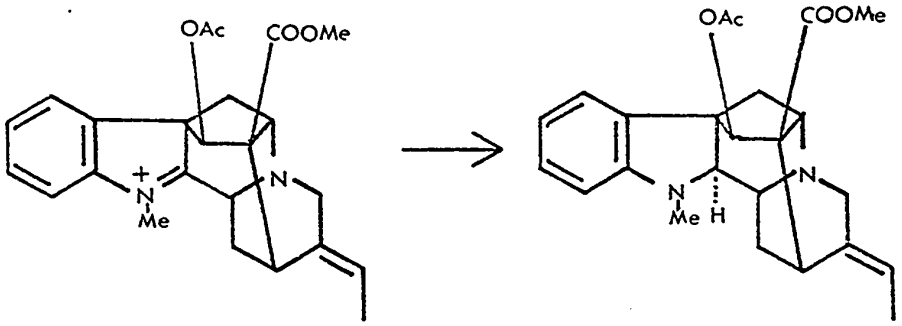
(50)

Like most indole alkaloids ajmaline possesses numerous asymmetric centers. The vital part of the synthesis is the construction of the skeleton with the correct asymmetric centers. Ajmaline has nine such centers with five of these fixed by the ring system of the molecule. The remaining four centers at C2, C17, C20 and C21 are to be introduced into the molecule during the synthesis. As described above the correct C17 configuration can be introduced by using the CIBA method [43] and Robinson's experimental conditions [5] to bring about the C21-Nb ring closure would result in the correct stereochemistry at C20 and C21. Concerning the C2 configuration, there have been a number of previous results which present some problems to be solved. As reported by the CIBA group,[7] the oxidation of 21-deoxy-ajmaline-17-acetate with lead tetraacetate yielded an indolenium salt (51), which on catalytic hydrogenation gave 2-epi-21-deoxyajmaline-17-acetate (52).



(51) (52)

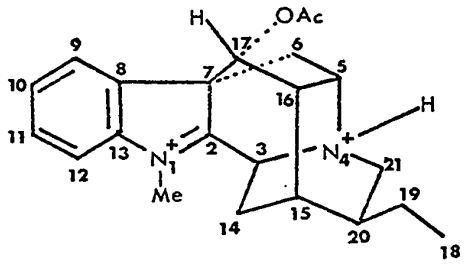
Also according to the report by Janot and co-workers,[44] the compound (53) derived from 2-hydroxy vincamedine, when catalytically hydrogenated in acidic media, yielded only dihydro vincamedine (54) with the epi configuration.

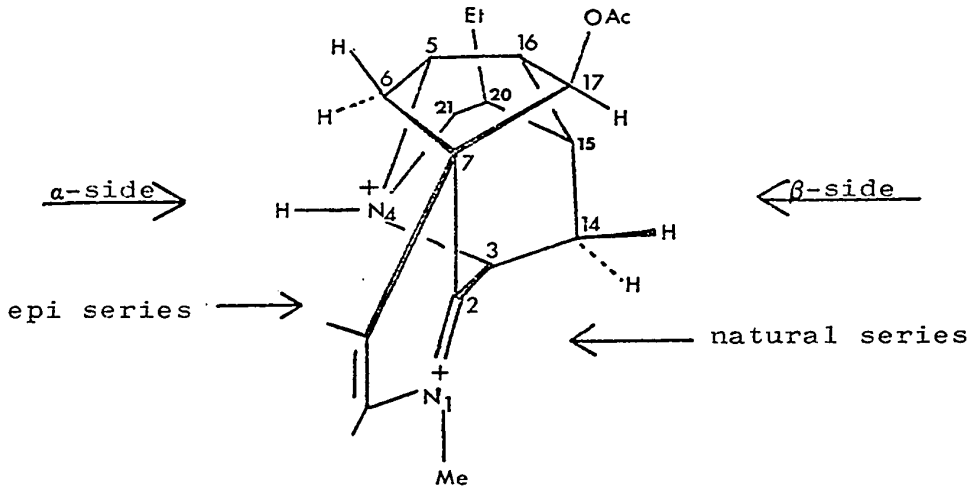


(53) (54)

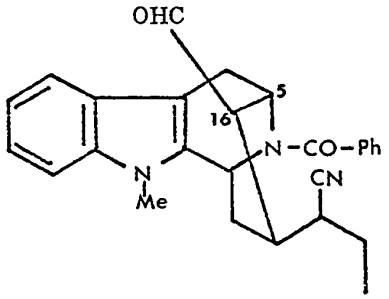
Both deoxyajmaline with natural configuration at C2 and the epimer were recovered unchanged when subjected to the conditions used for hydrogenation. It thus appeared that the acid is not the cause of epimerization at C2. Moreover, from the study of the Dreiding model of compound (51)(see p.32), only slight differences exist in steric hindrance between the α- and β-sides of the molecule, which indicates that this could not be the main factor resulting in the exclusive formation of the epi series. It is reasoned that in acidic media, Nb would be expected to be protonated on the α-side of the molecule and the positive charge on the nitrogen may have some effect in causing the sole epimer formation. Therefore, the epimer formation may

perhaps be prevented by benzoylation of Nb. The benzoyl group neutralizes the charge on the nitrogen as well as increasing the steric bulkiness on the α-side.





Returning to the basic structure (45), which was illustrated in the beginning of this section, it is now possible to specify the substituents required in order to achieve the synthesis of ajmaline. As outlined above, C17 should be an aldehyde group, C21 a cyano group and the Nb substituent a benzoyl group so that known sequences can be utilized to bring about the final two ring closures. Thus, it appeared that the preparation of the compound (55) would lead to the successful total synthesis of ajmaline.

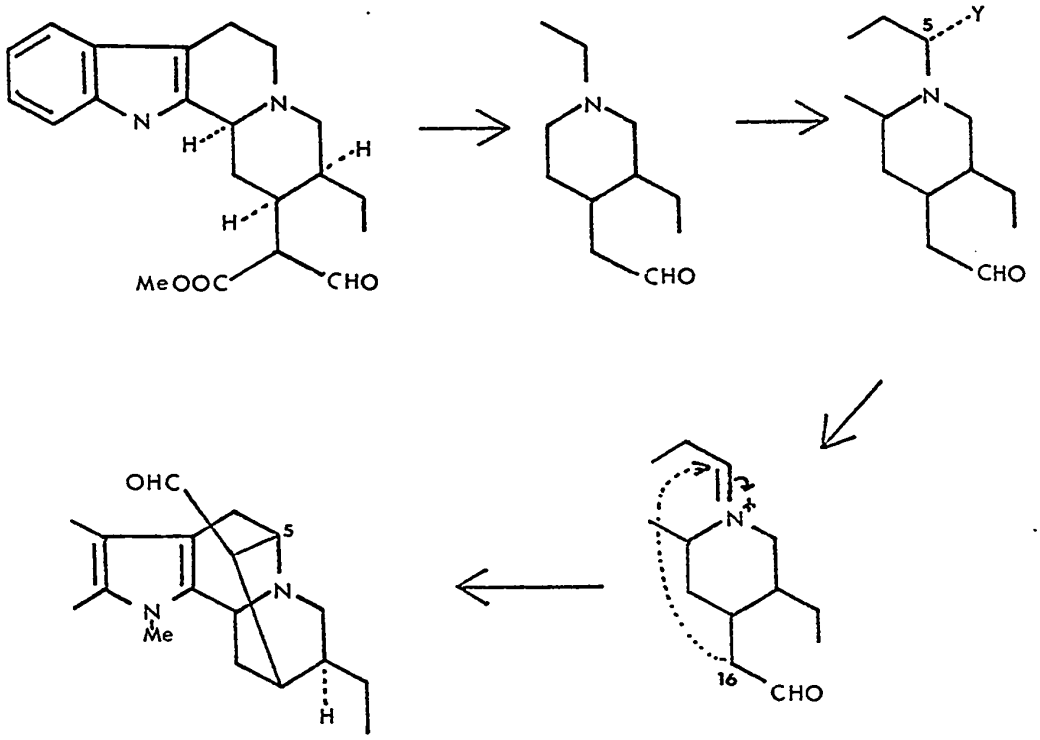


(55)

In our synthetic scheme toward compound (55), two alternative routes having the C5-C16 bond formation as the key step were considered. Our original attempt to bring about the C5-C16 bond formation <u>after</u> the tetrahydrocarboline ring formation was unsuccessful and is briefly described below. The successful route employing the C5-C16 bond formation <u>preceding</u> the tetrahydrocarboline system formation will be discussed in detail with

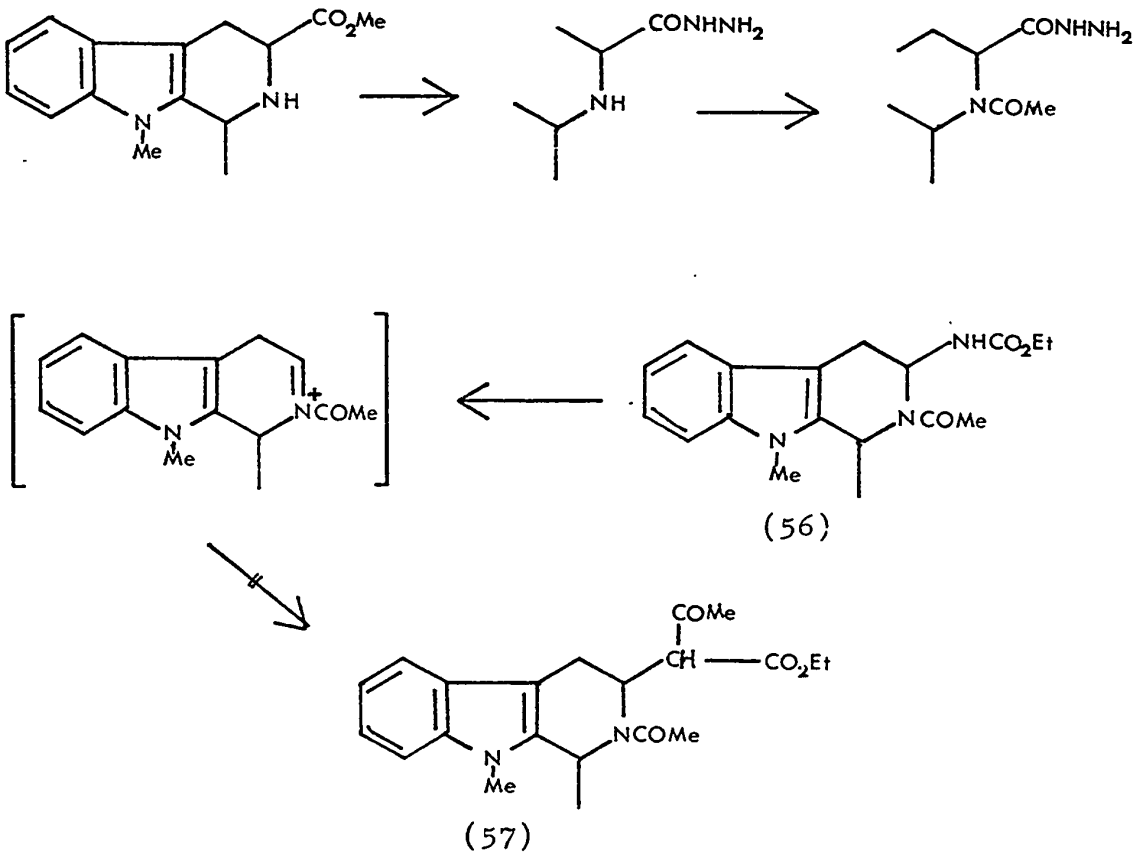
emphasis on the critical steps.

Of many possible synthetic routes to the compound (55), the one which follows the likely biological pattern is first considered and is shown below. The crucial step in



this synthetic scheme appears to be a Mannich-type reaction to effect the C5-C16 bond formation. Our efforts [45] were focused on this reaction and several model reactions were examined.

The tetrahydro-β-carboline derivative (56) was chosen as the model for examining the Mannich reaction and was prepared by the sequence of reactions outlined below; the product was found to be unstable to heat and oxygen. All attempts to effect the Mannich reaction on (56) with acetoacetic ester or other reagents (with or without an acid catalyst), with the expectation of obtaining compound (57) via the iminium salt shown, resulted in the recovery of starting compound or an intractable tar. During these attempts the solution immediately darkened



(56)

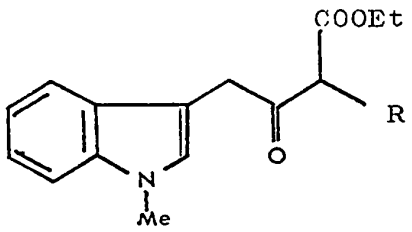
(57)

probably due to either disproportionation or autooxidation and possibly preceded by migration of the double bond.

At this juncture this approach toward the synthesis of (55) was abandoned. However, after our initial report of a successful ajmaline synthesis by a route which will be described below, van Tamelen and Oliver [22] reported the synthesis of ajmaline using the above route. These authors employed the novel reagent dicyclohexyl carbodiimide-p-toluenesulfonic acid (DCC) [46] to effect the Mannich-type reaction. They accomplished the synthesis by the sequence shown on page 34 choosing the carboxyl function (COOH) as the leaving group Y. The reagent DCC appears to facilitate the formation of the iminium salt which then spontaneously undergoes the C5-C16 bond formation.

The failure of the first route to the compound (55) led to the other synthetic approach which involved the C5-C16 bond formation preceding the construction of the β-carboline ring system. Since indole-3-acetic acid was commercially available, the synthesis was initiated from this compound. If the β-keto-ester (58) is prepared, where R possesses five carbon atoms for the skeleton construction, introduction of the nitrogen atom at the keto group should be achieved readily. Thus, the preparation of the β-keto-ester (59) was the starting point

in this route to ajmaline. The substituent R= (cyclopentene) will be used to construct the quinuclidine ring and the ester group will be reduced to form the C7-C17 bond.



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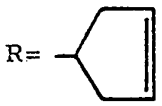
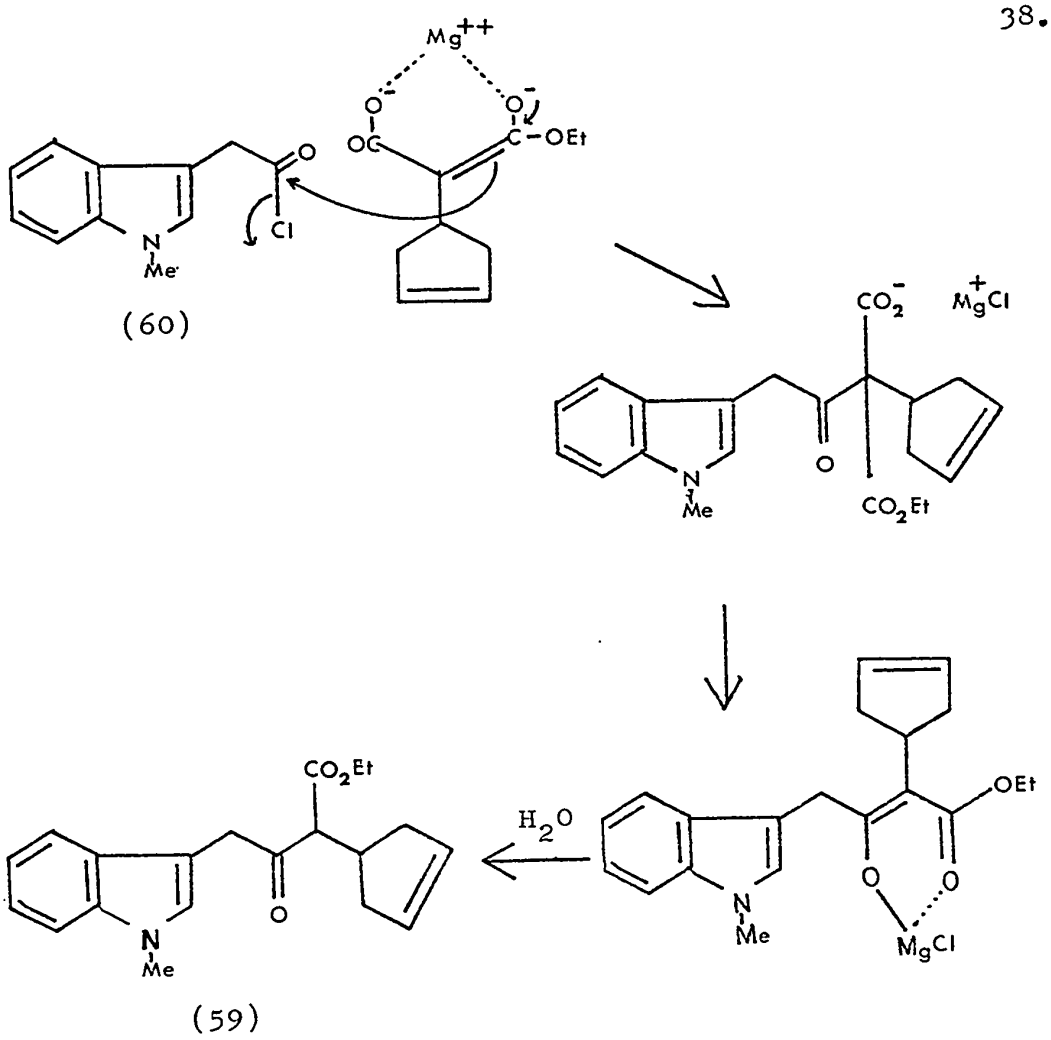


(59)

Of many methods available for preparing the β-keto-ester (59), the one chosen in our synthesis was that of Ireland and Marshall.[47] The condensation of N-methylindole-3-acetyl chloride (60) with ethyl hydrogen 2-(Δ^3-cyclopentenyl)malonate [48] was effected as follows. The ester was converted to the magnesium complex by reaction with two moles of isopropyl magnesium bromide in dry tetrahydrofuran at 0°; the gas evolution (propane) indicated the progress of this reaction. This complex was then treated with N-methylindole-3-acetyl chloride in dry tetrahydrofuran. After evolution of carbon dioxide had ceased, the β-keto-ester (59) was isolated and purified by silicic acid chromatography. The reaction mechanism is shown below.

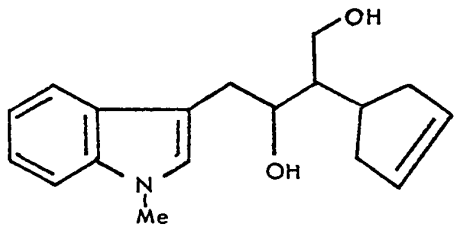


(60)

(59)

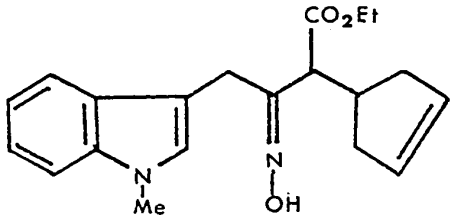
The structure of the β-keto-ester (59) was established from its spectral data. The infrared spectrum showed absorptions at 1740 and 1720 cm^{-1} which indicated the β-keto-ester; the nmr spectrum showed peaks at τ 8.8 and 5.9 (ethyl group), τ 6.3 (N-methyl), τ 6.0 (methylene), τ 4.4 (olefinic), τ 3.0 (α-hydrogen of indole ring), and τ 2.7 (aromatic protons). The structure was further

confirmed by lithium aluminum hydride reduction to the diol (61). Though a mixture of stereoisomers was expected, the crystalline diol melted sharply at 141.4-142.5° with a new hydroxyl absorption at 3480 cm^{-1} in the infrared spectrum and a peak at m/e 285 in the mass spectrum which corresponds to the molecular weight of the diol(61).



(61)

The next step of the synthesis was the introduction of the nitrogen atom which will become Nb. In this scheme the keto group in the β-keto-ester (59) was converted to an oxime which on subsequent reduction afforded an amino group. When the β-keto-ester (59) was treated with hydroxylamine hydrochloride and sodium ethoxide in ethanol, a very small amount of product was isolated. The infrared spectrum of the product indicated the absence of the β-keto carbonyl group and did not show a hydroxyl absorption. This implied that the obtained product was not the expected oxime (62) but (63).



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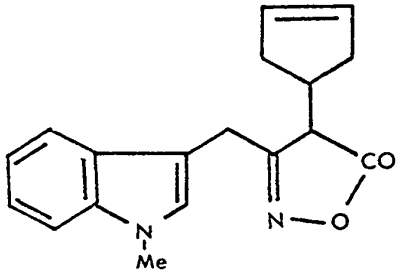
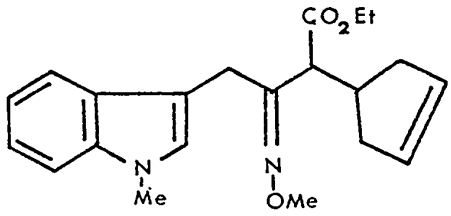


(63)

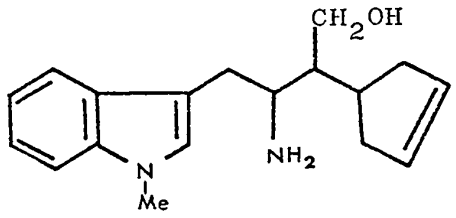
When methoxylamine hydrochloride was used instead of hydroxylamine hydrochloride, the desired methoxime (64) was obtained quantitatively. An infrared spectrum of (64) showed the absence of the 1720 cm^{-1} peak and its nmr spectrum showed that the product was a mixture of two geometrical isomers. The crude product was used for the next reaction without purification.



(64)

Aluminum hydride reduction of oximes to amines as introduced by H. C. Brown [49] was applied to the methoxime

(64) to afford an amino alcohol (65). Aluminum hydride was prepared according to Brown's method by treating lithium aluminum hydride in dry tetrahydrofuran with 100% sulfuric acid which was prepared from 30% fuming sulfuric acid and 95% sulfuric acid. The methoxime (64) in dry tetrahydrofuran was added to the aluminum hydride solution dropwise; the resulting exothermic reaction caused the tetrahydrofuran to reflux. The reaction mixture was kept at reflux for a further thirty minutes and then the excess aluminum hydride was decomposed with water and sodium hydroxide and the reaction porduct was extracted with ether. An infrared spectrum of the crude product showed amine and hydroxyl absorptions and no carbonyl absorption. Thin layer chromatographic study of the amino alcohol (65) revealed that the reduction product consisted of two major compounds.

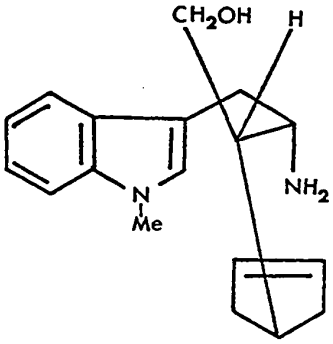


(65)

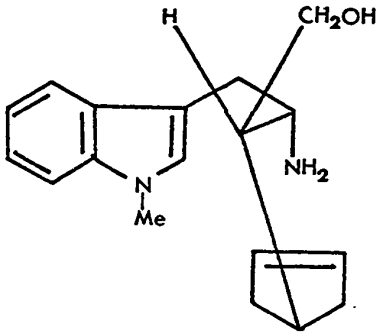
Readily separated by alumina chromatography, the two products were obtained in an approximately 2:1 ratio and

tentatively were assigned the structures (65a) and (65b) respectively (see below). The fact that these two compounds were epimeric was revealed by identical mass spectra. Although (65a) could not be induced to crystallize, (65b) was a crystalline compound and was recrystallized from ethanol (mp 113.5-114.5°). When both (65a) and (65b) were acetylated, crystalline acetates were obtained. The diacetyl derivative (66a) had mp 140-141° and the compound (66b), mp 129-130°.

When the structures of the amino alcohols (65) are rewritten, it is clear that (65a) is the useful isomer for the synthesis of ajmaline and (65b) for the synthesis of sarpagine. Furthermore these two series of compounds are interconvertible at a later stage of the synthesis (see below). The stereochemistry was not determined absolutely at this stage but was confirmed later by eventual conversion of one isomer to a degradation product of the natural ajmaline. From this point on, the synthesis was carried out separately on the two isomers (a- and b-series) until one was converted to a degradation product of ajmaline and confirmed our stereochemical assignment. In the experimental section, experimental details are given only for the a-series.

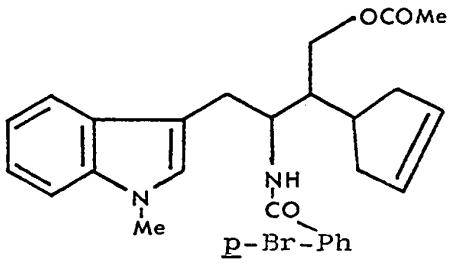


(65a)



(65b)

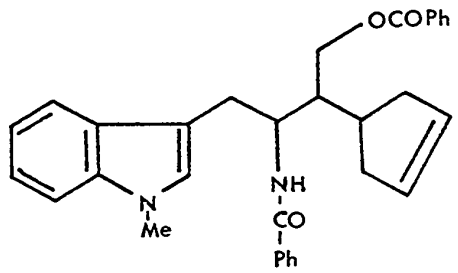
For the purpose of X-ray structure determination,[50] the isomer (65b) was converted to the crystalline O-acetyl-p-bromobenzamide (67). This compound (67) was prepared by treating (65b) with 0.95 equivalent of p-bromobenzoyl



(67)

chloride and pyridine in benzene followed by acetylation. The crude crystalline product which was obtained was chromatographed on silicic acid and recrystallized from methanol, mp 151-153°.

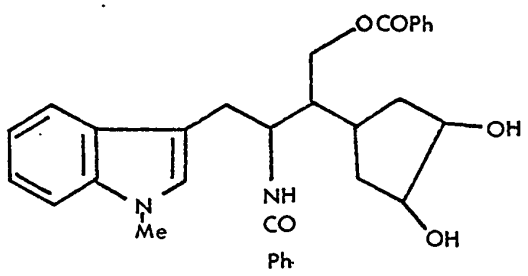
Before the selective hydroxylation of the cyclopentenyl double bond in the next step, the hydroxyl and amino groups in (65) were first protected by conversion to the dibenzoyl derivative (68). The N-benzamide portion will become the N-b-benzamide at a late stage of the synthesis. The ir spectrum of the dibenzoyl derivative showed two new carbonyl absorptions at 1730 and 1667 cm^{-1}.



(68)

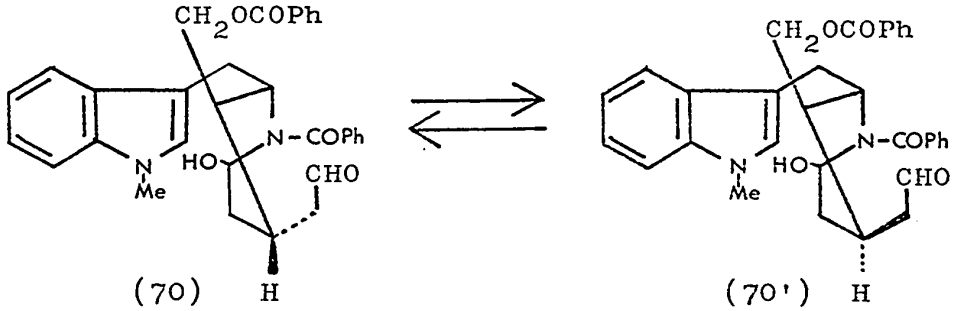
The cleavage of the double bond in the cyclopentene ring must be achieved by mild reaction conditions to keep the indole ring intact.[51] Probably the mildest reaction condition available is osmylation followed by sodium periodate cleavage. When a stoichiometric amount of osmium tetroxide in dry tetrahydrofuran was added to the dibenzoyl derivative (68) in tetrahydrofuran at 0°, the diol (69)

was obtained quantitatively. The diol was purified by silicic acid chromatography and spectroscopic data (ir spectrum: 3450, 1730 and 1667 cm^{-1}; nmr spectrum: no cyclopentenyl olefinic protons) indicated that the osmylation had proceeded selectively at the double bond in the cyclopentene ring and the indole group was indeed left intact.



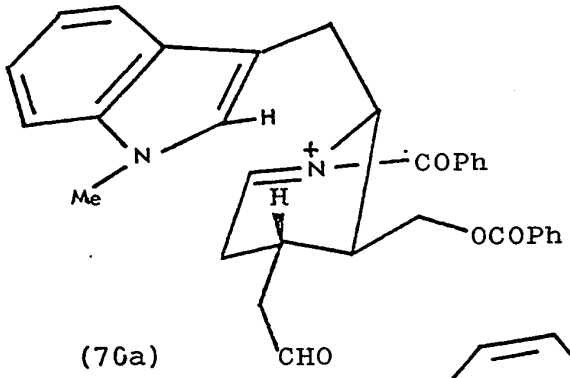
(69)

Periodate cleavage of the diol (69) in aqueous dioxane yielded the compound (70). The hydroxyl absorption (3420 cm^{-1}) in the ir spectrum suggested a carbinolamide formation between one of the aldehyde groups and the amide group as shown below. Both (70) and (70') are logical

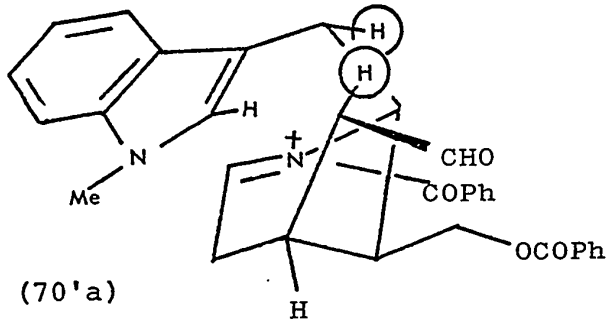


(70) H (70') H

structures for the hemiaminal and are likely to be equilibrated. However, (70') appears to be unfavorable for the α-cyclization because of non-bonded interactions expected for this C15 epimer as shown below.

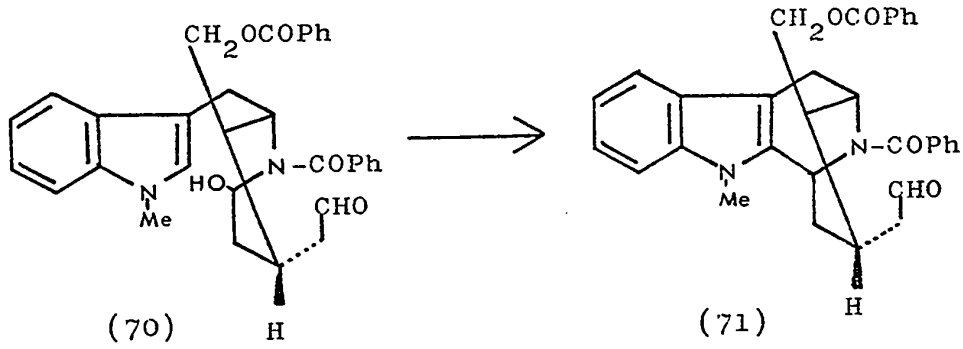


(70a)

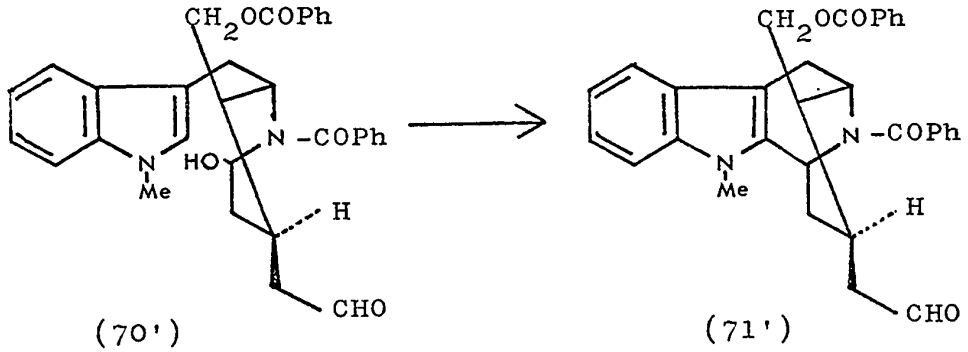


(70'a)

Cyclization of (70) would lead to (71) with the correct configuration at C15 for the final ring closure of the aldehyde group to the amide (N-b) while (70') would yield the undesired form. Because of the non-bonded interactions in (70') the cyclization should proceed entirely through (70), while (70') is being equilibrated into (70), to provide the desired stereochemistry at C15.



(70) (71)

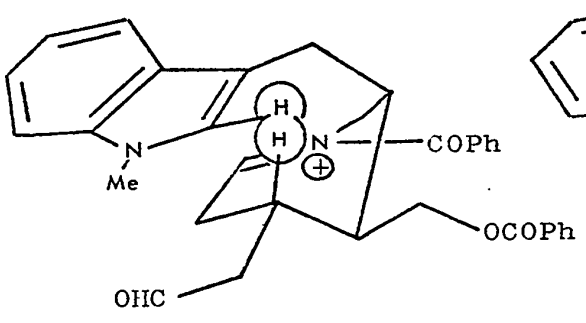


(70') (71')

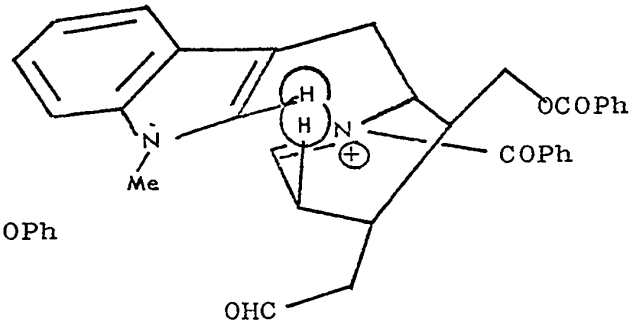
The cyclization of (70) and/or (70') to (71) was effected in warm (50°) acetic acid. The reaction product (71) was purified by silicic acid chromatography; the ir spectrum showed no hydroxyl absorption and the nmr spectrum showed the disappearance of the characteristic indole-α-hydrogen resonance at τ3.00. The ultraviolet spectrum of (71) indicated the presence of the indole nucleus by its characteristic absorption at 280 mμ. The fact that a (70) and (70') mixture provides an excellent yield (near-quantitative) of (71), but not a mixture of

(71) and (71'), strongly supports the hypothesis discussed above.

For the above acid-catalyzed condensation, there are two possible positions of condensation with the indole nucleus, C2 and C7. The direct condensation at C2 to form (71) has already been discussed. Another pathway leading to the product (71) involves the nucleophilic attack of carbon C7 at the electrophilic immonium salt to give the β,β-disubstituted indolenium salt [52] and then the new bond migrates to the α-position. However this initial β-condensation is unlikely to proceed because of severe non-bonded interaction between the two circled hydrogens whether the piperidine ring is in the chair or boat form as shown below. The presence of the C5-C16 linkage creates this unique situation which contrasts sharply with that to be discussed in Chapter II.



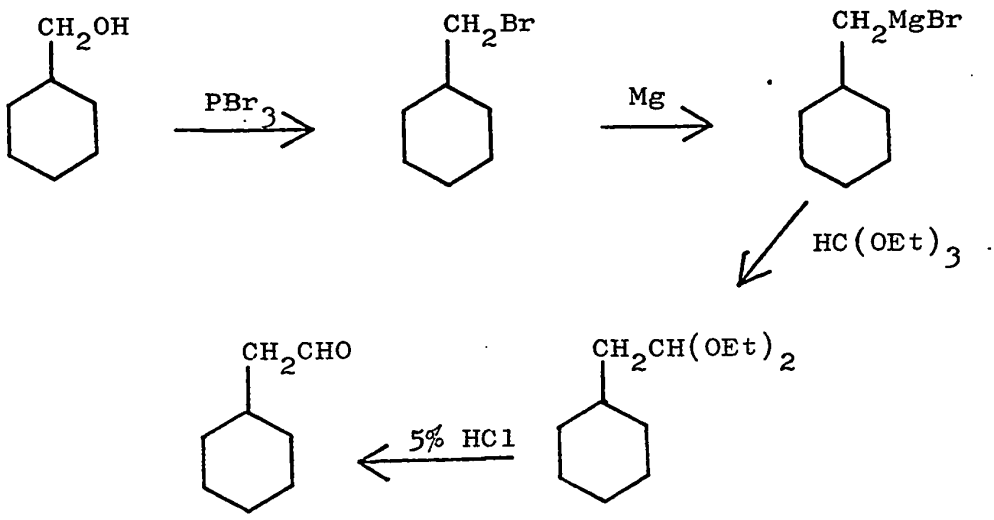
(70-chair form)



(70-boat form)

Following the successful preparation of the aldehyde (71), the next step in our synthetic route was the ethylation at the α-carbon of the acetaldehyde side chain which proved to be one of the critical steps in our ajmaline synthesis. The α-alkylation of carbonyls is often accompanied by undesired side reactions such as aldol condensation and uncontrolled polyalkylation. To overcome these difficulties a number of methods have been developed [53,54] and appear to be useful for ketones. However, for acetaldehydes only a limited number of methods for α-alkylation are available. The most promising reaction developed by Stork [55] involves the formation of an imine and subsequent treatment with Grignard reagent. Although this Stork method could not be applied to our synthesis directly because of possible side effects on the other functional groups in the molecule, it may be applicable to compound (71) if the imine anion can be prepared without use of a Grignard reagent. Therefore, efforts were made to seek a base that would provide the imine anion under mild conditions.

Cyclohexylacetaldehyde (72), prepared by the sequence of reactions shown below, was chosen as a model. By treating the aldehyde (72) with isopropylamine and dry potassium carbonate in dry tetrahydrofuran at room temperature overnight, the N-isopropylimine (73) was obtained. The imine formation was confirmed by the nmr

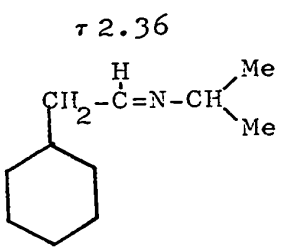


(72)

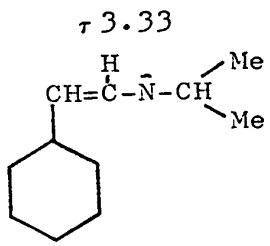
spectrum which showed a new isopropyl methyl absorption at τ 8.9 and the ir spectrum indicated the absence of the aldehyde absorption.

N-lithiohexamethyldisilazane failed to convert the imine (73) to its corresponding anion. A related base, N-lithiodiisopropylamine (prepared from n-butyl lithium and diisopropylamine) and the imine (73) were reacted at -30° and the resultant tetrahydrofuran mixture was studied by nmr. The reaction mixture showed an α-hydrogen absorption at τ 3.33 (doublet, J=13 Hz) in contrast with the α-hydrogen of the starting imine (73) which absorbs at τ 2.36 (triplet, J=5.2 Hz). The nmr spectrum of the enamine (74), which would be expected to be similar to the

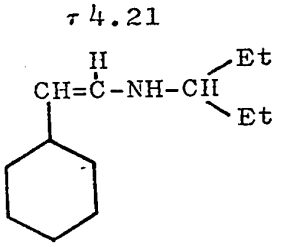
expected imine anion (75), shows an absorption at τ 4.21 (doublet, J=14 Hz) for the same hydrogen. Thus the formation of the imine anion (75) was clear. Ethyl iodide was added to the tetrahydrofuran solution of (75) at -50° and the mixture was stirred at room temperature overnight. Hydrolysis was effected with boiling 10% hydrochloric acid and the isolated product was first examined by gas chromatography (UCW98) which revealed that the ethylated compound (77) was the major component (more than 80%). The mass spectrum (MS-12) showed the molecular ion peak at m/e 154 while the nmr spectrum was consistent with α-ethyl cyclohexylacetaldehyde (77).



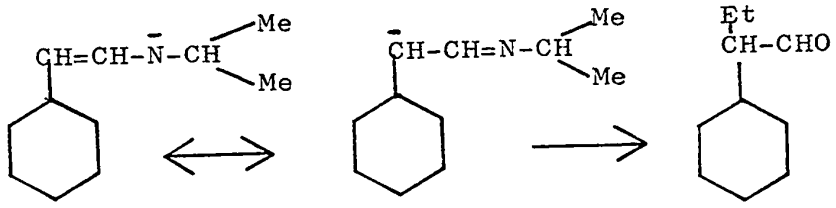
(73)



(75)



(74)

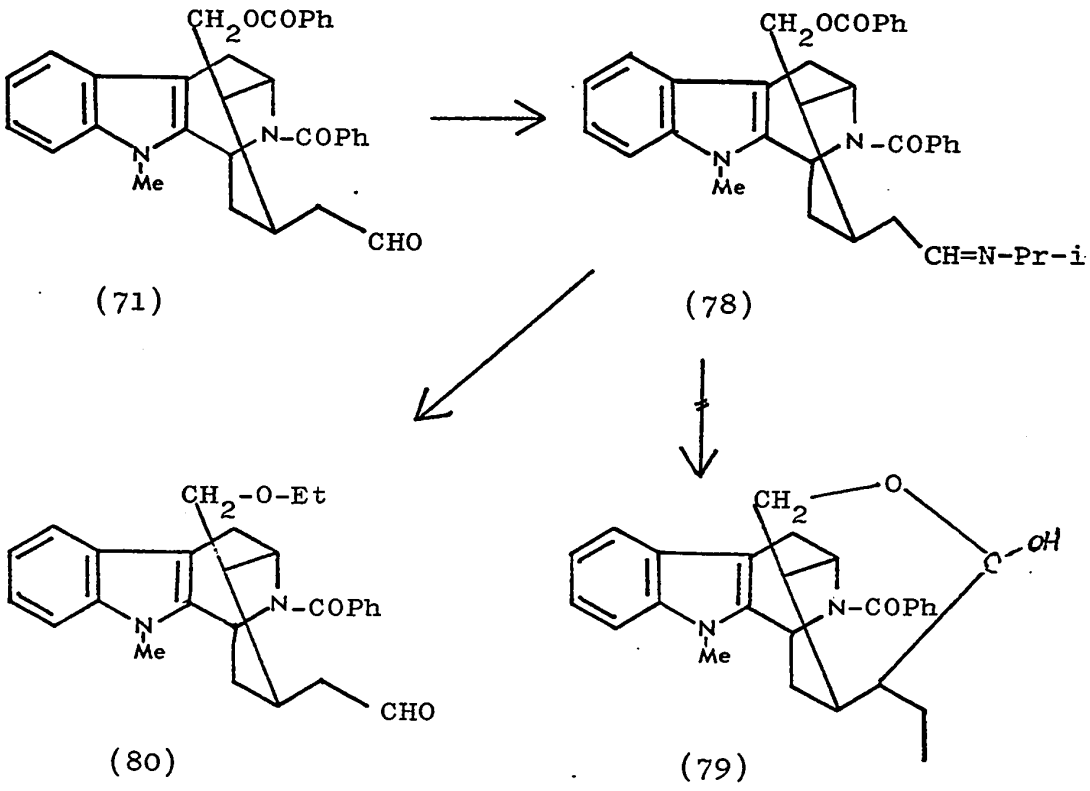


(75) (76) (77)

When applying the above alkylation to the ajmaline system (compound (71)), the hydrolysis condition of boiling 10% hydrochloric acid seems too severe for the complex ajmaline derivative. Attempts to effectively hydrolyze the model compound ethyl N-isopropylimine (76) under milder conditions with p-toluenesulfonic acid, perchloric acid and concentrated hydrochloric acid at room temperature were unsuccessful. However, pyruvic acid in aqueous acetic acid proved to be an effective exchange reagent and mild enough for the ajmaline system.

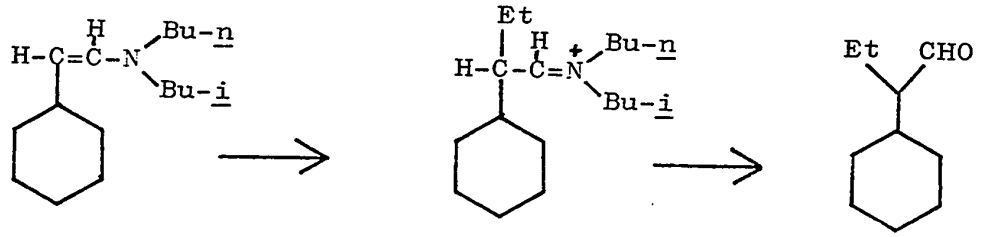
Thus the aldehyde (71) was treated with isopropylamine and potassium carbonate in dry tetrahydrofuran at room temperature to afford the desired imine (78); its formation was confirmed by the nmr spectrum which exhibited a new isopropyl group at τ 8.9 and by the mass spectrum which showed a parent peak at m/e 547. This imine (78) was then subjected to the same ethylation condition as for the model compound followed by the pyruvic acid mixture for hydrolysis. The isolated product exhibited two main spots on thin layer chromatography. The mass spectrum of the reaction products showed peaks at m/e 506 and 402. The former peak corresponds to the molecular weight of the unreacted aldehyde (71) and the latter appeared, at first, to be the hemiketal (79) which can be derived from the ethylated aldehyde by hydrolysis of the benzoyl group. However, chromato-

graphic study of this latter component revealed that it was rather non-polar to be the hemiketal and it subsequently turned out to be the O-ethylated aldehyde (80). At this point this approach was discontinued.

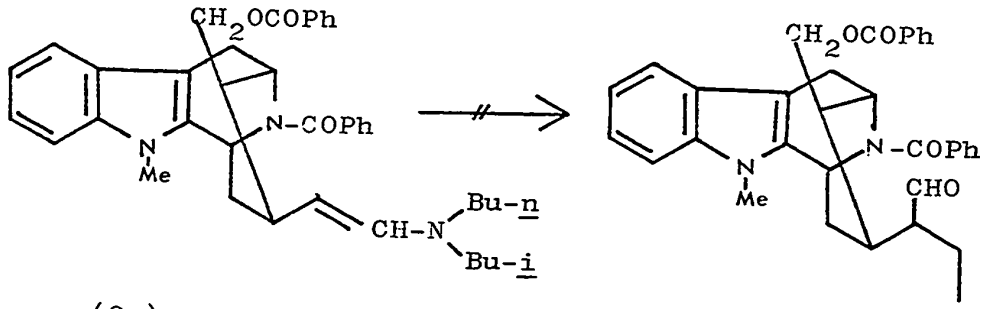


After the failure of the Stork type alkylation, attention was turned tc 'C-alkylation of aldehyde enamines' as reported by T. J. Curphy.[56] Generally enamine alkylation of aldehydes gives N-alkylation and aldol condensation rather than C-alkylation. Curphy and co-workers found that by increasing the steric bulk

of the alkyl group attached to the enamine nitrogen, C-alkylation could be induced in good yield (50-80%). This method was applied to the model cyclohexylacetaldehyde (72) using n-butylisobutylamine and potassium carbonate for the enamine formation and ethyl iodide as the ethylating agent. After hydrolysis with sodium acetate buffer solution, ethyl cyclohexylacetaldehyde (77) was obtained in more than 80% yield. However, when compound (71) was subjected to this same ethylation condition, in spite of the enamine formation (82), mass spectroscopic study revealed that the ethylation reaction had failed.



(77)

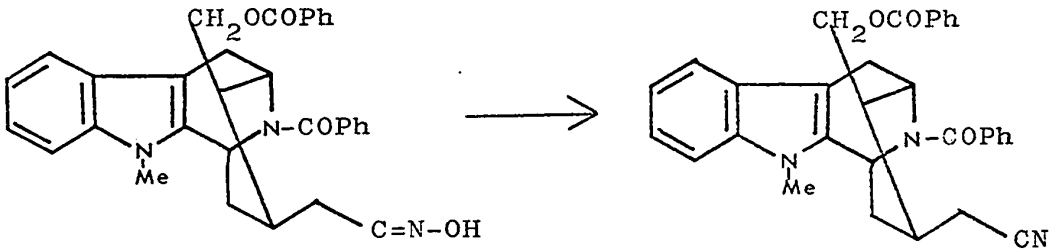


(82)

A direct ethylation reaction, via the enolate anion, on cyclohexylacetaldehyde using ethyl iodide and potassium tertiary butoxide in t-butanol - benzene, also proved unsuccessful.

Since in our synthetic scheme the aldehyde group in (71) is eventually converted to the cyano group in order to effect the final ring closure, the preparation of the cyano compound (84) was next considered. Introduction of the ethyl moiety to the cyano compound may be a more tractable approach.

The aldehyde group in (71) was first converted to its corresponding oxime by treatment with hydroxylamine hydrochloride and pyridine in absolute ethanol. The ir spectrum of the crude product showed a new hydroxyl absorption at 3300 cm^{-1} which confirmed the formation of the oxime (83). The crude oxime was then dissolved in dry pyridine and treated with benzoyl chloride to effect dehydration. Workup afforded the cyano compound (84) whose formation was confirmed by its characteristic ir absorption at 2260 cm^{-1}.



(83) (84)

The scrupulously dried compound (84) was then subjected to ethylation with sodio-triphenylmethane and ethyl iodide in dry ether. The product was isolated and purified by chloroform extraction and silicic acid chromatography. The introduction of the ethyl group on the α-carbon was confirmed by spectroscopic data: the nmr spectrum showed a new ethyl group absorption as a broad peak at τ 9.00; the ir spectrum indicated the presence of the cyano group as well as O- and N-benzoate groups; the mass spectrum showed a peak at m/e 531 which corresponds to the molecular weight of the ethylated compound (85). At this point, careful comparison of all spectral data (ir, nmr, mass) and thin layer chromatography of the synthetic compound (85) and the natural compound $(85)_n$* derived from the degradation of ajmaline was made to confirm that they were indeed identical in all respects.** It is rather surprising that the ethylated product (85) consisted of a single isomer contaminated with less than 10% of its epimer. The selectivity of this ethylation reaction is difficult to explain.

In order to further confirm the structure of (85), the O-benzoate group was removed by brief treatment of

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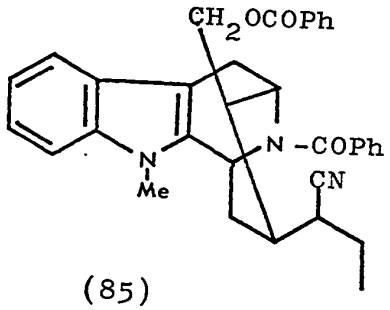
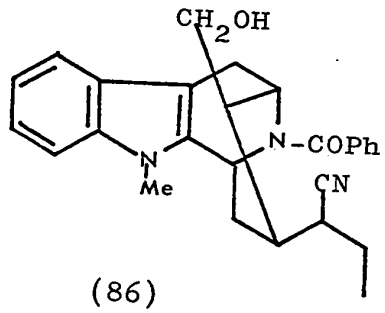
* Throughout this Chapter the subscript n refers to compounds obtained from the natural source.
** Except for ORD.

(85) with sodium methoxide. The crystalline cyano-alcohol (86), mp 200.5-202.5°, showed the presence of the ethyl group in the nmr spectrum and the absence of the O-benzoate carbonyl in the ir spectrum. The cyano-alcohol (86) also proved to be spectroscopically identical to the natural cyano-alcohol $(86)_n$ derived from ajmaline.



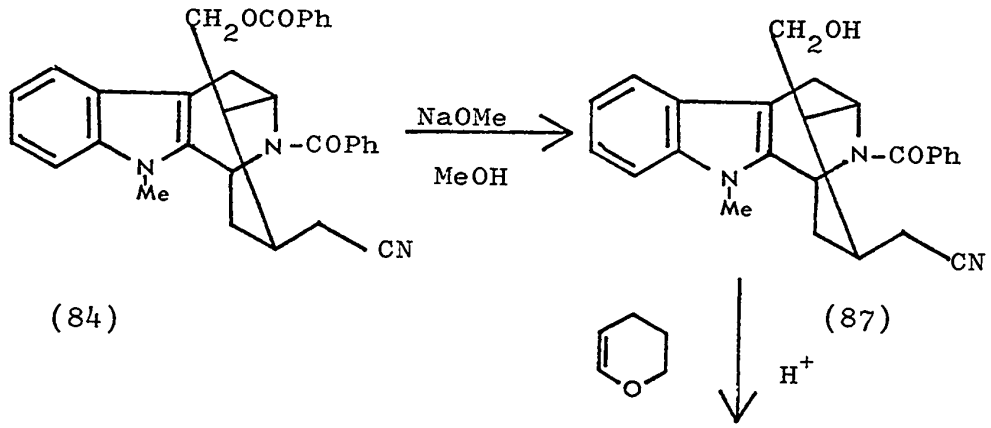
(85)



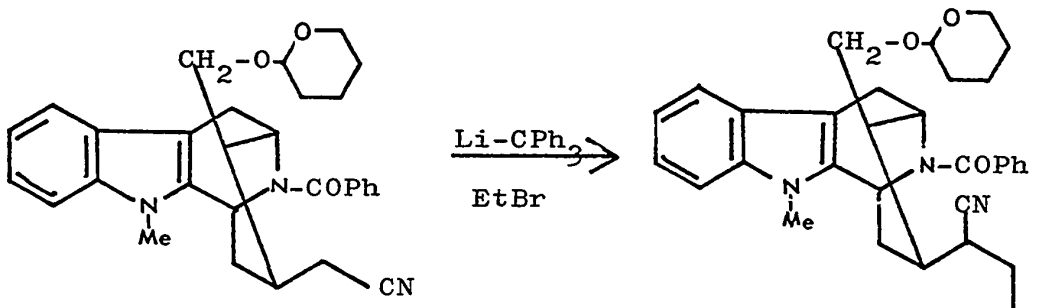
(86)

Although the yield of (85) was about 60%, the reaction procedure involved a great deal of technical difficulty in drying thoroughly samples of amorphous (84). Since the O-benzoate group was fairly easily hydrolyzed even with a weak base, it appeared that a small alteration on the compound (84) was necessary before ethylation. Efforts were then made to convert the benzoate group to its corresponding pyranyl ether which is a base-resistant protecting group. The benzoate group in (84) was hydrolyzed by brief treatment with sodium methoxide in methanol to an alcohol (87). The alcohol (87) was subjected to acid-catalyzed reaction with dihydropyran

to afford the pyranyl ether (88) in moderate yield. The pyranyl ether (88) was purified by silicic acid chromatography and its ir spectrum indicated the absence of the hydroxyl group and the nmr spectrum showed the pyranyl group absorption. The mass spectrum showed the molecular ion peak at m/e 483. Ethylation of (88) was performed using lithio triphenylmethane and ethyl bromide in dry dimethoxyethane. The product isolated consisted of two major compounds, the ethylated pyranyl ether (89) and the non-ethylated alcohol (87) obtained from unexpected hydrolysis of the pyranyl ether group. However this alcohol can be recycled in the ethylation reaction to bring up the yield.



(84) (87)



(88) (89)

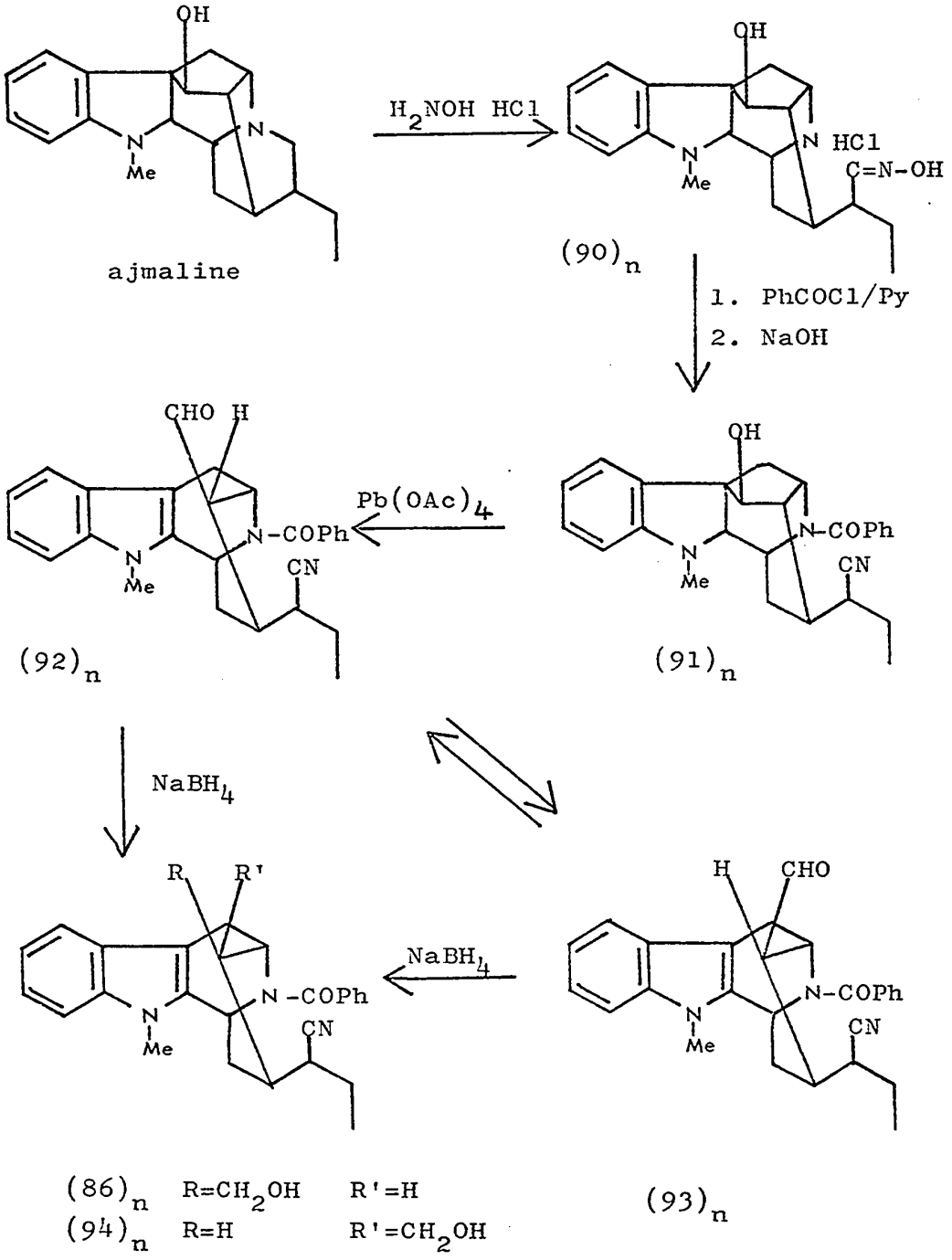
The ethyl pyranyl ether (89) was then subjected to acid hydrolysis to remove the protecting group. The alcohol produced (86) was again identical, by comparison of the ir, nmr, and mass spectra and thin layer chromatography, to the alcohol prepared by sodiotriphenylmethane ethylation as well as to the natural sample $(86)_n$. Because of the extra reaction steps, the second ethylation method seems to have no notable advantage over the first with regard to reaction yields.

The degradation of natural ajmaline [57] to the alcohol $(86)_n$ suggested an appropriate synthetic scheme for the conversion of the synthetic alcohol (86) to ajmaline. The reported degradation of ajmaline will now be described briefly. Treatment of ajmaline with hydroxylamine hydrochloride in boiling water afforded ajmaline oxime $(90)_n$ [5] which was then treated with benzoyl chloride in warm pyridine followed by sodium hydroxide to provide cyano-benzamide $(91)_n$, mp 265-266°. Reaction of $(91)_n$

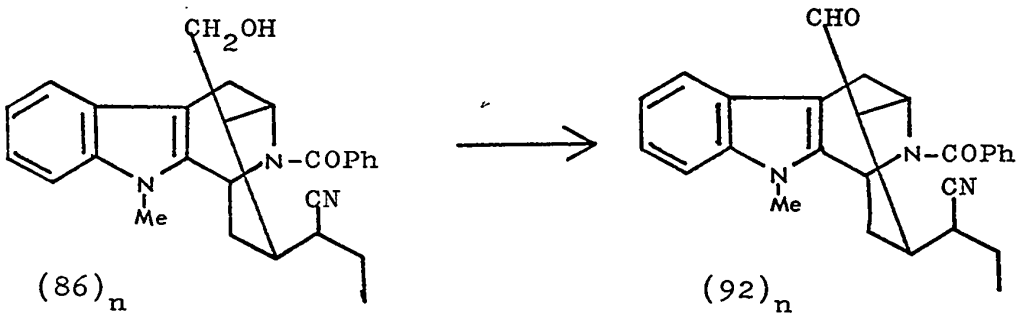
with lead tetraacetate [58] followed by neutral workup afforded an aldehyde $(92)_n$, mp 219-220°: the nmr spectrum showed peaks at τ0.45 (CHO), τ6.46 (N-methyl): $(92)_n$ was subsequently reduced with sodium borohydride to the natural alcohol $(86)_n$, mp 228-230° and 261-262° (polymorphic). The natural compound $(85)_n$ was prepared from $(86)_n$. The latter two natural compounds have previously been shown (page 56) to be identical to the synthetic alcohol (86) and the benzoyl derivative (85).

In the presence of alumina the aldehyde $(92)_n$ was equilibrated with its isomer $(93)_n$ at C16 in a 3:7 ratio in favor of $(93)_n$. As mentioned previously (page 42-43), because of this equilibrium, the amino alcohol (65a) and (65b) can be brought to this stage separately and subjected to the eventual conversion of one isomer to the one with the desired stereochemistry at C16. The nmr spectrum of $(93)_n$ exhibited peaks at τ 0.32 (CHO) and τ6.54 (N-methyl). The sodium borohydride reduction of $(93)_n$ provided a hydroxyl compound $(94)_n$.

Because the synthetic ethyl cyano-alcohol (86) was available in limited amounts, trial oxidations of the hydroxyl group at C17 to the corresponding aldehyde were performed on the synthetic cyano-alcohol (87), the


OH
N
Me
N
ajmaline
H_2NOH HCl
OH
N
Me
N HCl
C=N-OH
$(90)_n$
1. PhCOCl/Py
2. NaOH
OH
N-COPh
CN
$(91)_n$
$Pb(OAc)_4$
CHO H
N-COPh
CN
$(92)_n$
$NaBH_4$
R R'
N-COPh
CN
$(86)_n$ R=CH_2OH R'=H
$(94)_n$ R=H R'=CH_2OH
$NaBH_4$
H CHO
N-COPh
CN
$(93)_n$

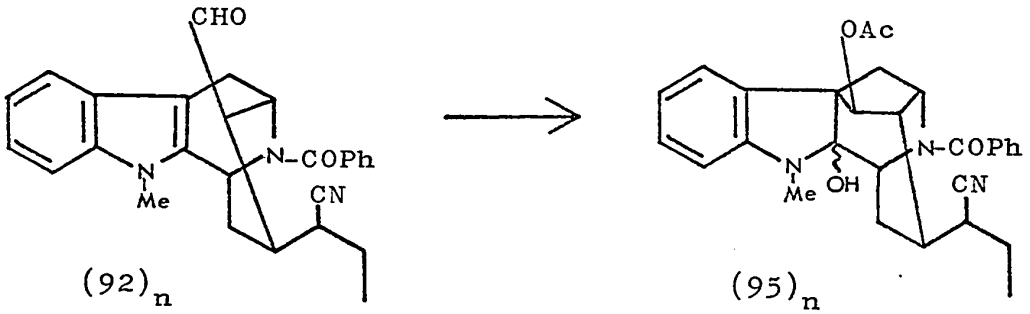
natural ethyl cyano-alcohol $(86)_n$ and its isomer $(94)_n$. These cyano-alcohols were each treated with dicyclohexylcarbodiimide in a mixed solvent (dimethylsulfoxide, benzene, pyridine and trifluoroacetic acid) and the crude product obtained was purified by silicic acid chromatography. The ir spectrum of each product indicated the presence of the aldehyde group with an absorption at ca. 1730 cm^{-1} along with cyano and benzamide absorptions.



$(86)_n$ $(92)_n$

The ring closure of the C17 aldehyde group to C7 in the indole nucleus [43] was examined on the natural aldehyde $(92)_n$ or the one derived from the natural cyano-alcohol $(86)_n$ via oxidation. Hydrogen chloride gas was bubbled through a solution of $(92)_n$ in acetic acid - acetic anhydride.[59] The success of the cyclization was confirmed by the ir spectrum of the product $(95)_n$ obtained after basic workup, which showed absorptions at 3550 (OH), 2220 (CN), 1740 (O-Ac), and 1630

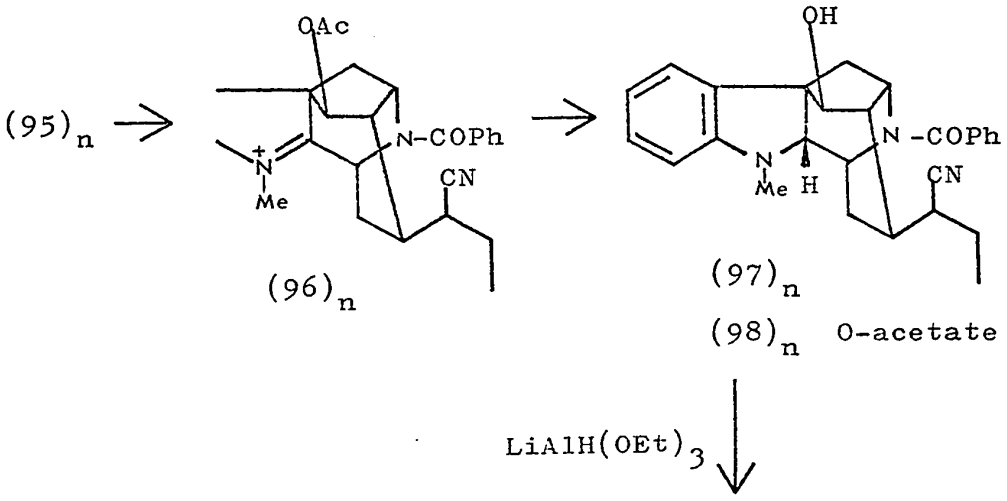
(N-CO) cm^{-1} and the absence of the aldehyde absorption. Furthermore, it was found that $(93)_n$, the C16 epimer of $(92)_n$ was also able to undergo cyclization, apparently preceded by the conversion of this epimer to $(92)_n$ under the conditions of cyclization.

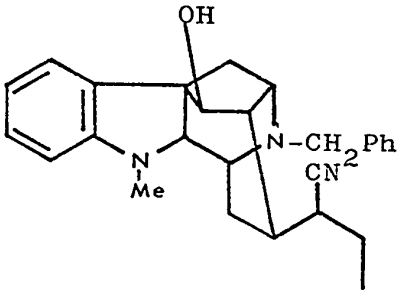


$(92)_n$ $(95)_n$

The above cyclized product $(95)_n$ was then subjected to catalytic hydrogenation in strong acid (6N hydrochloric acid) where the compound $(95)_n$ would exist as an indolenium salt $(96)_n$. As discussed previously, $(95)_n$ has been prepared with the expectation that catalytic hydrogenation would provide the correct stereochemistry at C2. The alcohol $(97)_n$ could not be induced to crystallize but its acetate was a crystalline compound $(98)_n$, mp 200-202°. The alcohol $(97)_n$ was identical in all spectral properties to the compound $(91)_n$ which was obtained from ajmaline by degradation as previously described (page 59).

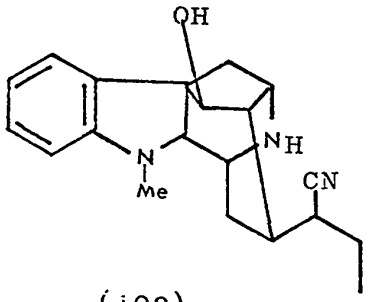
Lithium aluminum triethoxyhydride reduction of $(97)_n$ which was originally expected to reduce the nitrile to the imine leaving the benzamide group intact, turned out to reduce the benzamide group to the benzyl group giving $(99)_n$, mp 170.5-171.5°, along with very small amounts of the amino-alcohol $(100)_n$ and the aldehyde $(101)_n$. Hydrogenolysis of the benzyl compound $(99)_n$ in acetic acid removed the benzyl group and afforded the corresponding secondary amine $(102)_n$, mp 259-262°, which was found to be identical with the natural amine obtained by Robinson.[5] This secondary amine has already been converted to ajmaline with lithium aluminum hydride [5] and completes the synthesis.





$(99)_n$

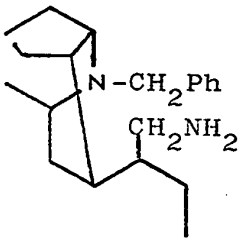
H_2



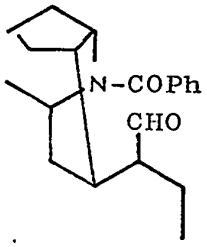
$(102)_n$

$LiAlH_4$

ajmaline



$(100)_n$



$(101)_n$

EXPERIMENTAL

General Considerations

All reactions were carried out under a dry nitrogen atmosphere using standard taper glassware unless otherwise stated. Solvents and reagents were commercially available reagent grades which were purified or dried by conventional methods when necessary. Special equipment, techniques or chemicals used are described in the appropriate procedures for specific compounds.

Most of the column chromatographic separations were carried out using silicic acid (Mallinckrodt 100 Mesh) prepared as a chloroform slurry. In some cases alumina (Woelm) was used.

Melting points were obtained on a Fischer-Johns melting point apparatus and are uncorrected. Elemental analyses were performed by the microanalytical laboratory of this department.

Infrared spectra were obtained on Perkin-Elmer models 21 and 457 spectrometers using 0.1 mm sodium chloride cells with chloroform as solvent unless otherwise noted.

Ultraviolet spectra were obtained on a Perkin-Elmer 202 UV-VIS recording spectrophotometer with 95% ethanol as solvent.

Nuclear magnetic resonance spectra were recorded using Varian A-60 and HA-100 instruments. Values are given in tau units with internal tetramethylsilane as reference at tau 10. The solvent for all nmr spectra was deuteriochloroform. The following abbreviations are used throughout: (s)-singlet, (d)- doublet, (t)-triplet, (q)-quartet, (m)-multiplet, (br)-broad.

Mass spectra were recorded with an Associated Electrical Industries MS-9 spectrometer by direct probe introduction of the sample. The MS-12 instrument was also used.

All of the above also applies to the experimental procedures in Chapter II.

Procedures

Δ^3-Cyclopentenol [60] --- Diborane (250 mmol) in 250 ml of tetrahydrofuran was added dropwise to 150 ml (1.84 mol) of cyclopentadiene in 300 ml of tetrahydrofuran at 0° over a period of 50 minutes. Stirring was continued for 20 minutes at 0° and then 30 minutes at room temperature. The excess cyclopentadiene and the solvent were removed at reduced pressure keeping the flask at 30-40°. The oily residue was dissolved in 600 ml of ether and 300 ml of 3N sodium hydroxide followed by the slow addition of 150 ml of 30% hydrogen peroxide, with stirring and cooling. The organic layer was separated from the aqueous layer after gas evolution had ceased and the aqueous layer was continuously extracted with ether. The combined extracts were dried and then concentrated at reduced pressure. Fractional distillation of the remaining crude oil gave 23.3 g (9.3%) of Δ^3-cyclopentenol: bp 64-66° (35 mm).

Δ^3-Cyclopentenyl Tosylate --- A solution of 23.3 g (0.28 mol) of Δ^3-cyclopentenol in 230 ml of dry pyridine was cooled to 0° and 58 g (0.3 mol) of p-toluenesulfonyl chloride was added. The flask was allowed to stand at 0° overnight and then the reaction mixture was poured onto 300 g of ice and vigorously stirred to induce crystallization of the tosylate. The crystals were separated

by filtration, washed with cold water, and dried over phosphorous pentoxide to yield 57.5 g (86.5%) of the tosylate: mp 47-51°; nmr τ 2.38 (q-AB pattern J=8.0 Hz, 4, phenyl), 4.33 (s, 2, olefinic), 4.8 (m, 1, CH_2-C<u>H</u>-O-), 7.45 (d, 4, $-CH_2-$), 7.7 (s, 3, CH_3-).

<u>Diethyl 2-(Δ^3-Cyclopentenyl)malonate</u> --- This compound was prepared according to the method of C. C. Lee.[48] Into a 2-litre three-necked flask fitted with a mechanical stirrer, a pressure equalizing dropping funnel, and a condenser, was placed 14.8 g (0.30 mol) of sodium hydride which had been washed with dry <u>n</u>-pentane five times to remove mineral oil and then dried in a stream of nitrogen. To the dry sodium hydride, 500 ml of tetrahydrofuran was added and 57.5 g (0.30 mol) of diethyl malonate was added dropwise with stirring at a rate slow enough to prevent reflux. The resulting mixture was stirred for 15 minutes at room temperature. A solution of 57.5 g (0.24 mol) of cyclopentenyl tosylate in a minimum amount of dry tetrahydrofuran was added within five minutes and then the mixture was refluxed overnight. After cooling, 50 ml of water was added to the reaction mixture and then neutralized by passing carbon dioxide into the solution. The solvent was concentrated under reduced pressure and then ice water (<u>ca</u>. 200 ml) was added to the residue. The solution was extracted with three 100-ml portions of ether, and the combined organic layers were dried over magnesium

sulfate. Fractional distillation gave 32.3 g (62.8%) of diethyl 2-(Δ^3-cyclopentenyl)malonate: bp 70-74°; nmr τ 4.29 (s, 2, olefinic), 5.77 (q, 2, $-C\underline{H}_2-CH_3$), 6.5-8.0 (t, 3, CH_3-).

Ethyl Hydrogen 2-(Δ^3-cyclopentenyl)malonate --- A 32.24 g (0.143 mol) sample of diethyl 2-(Δ^3-cyclopentenyl)-malonate and 146 ml of 0.965N potassium hydroxide (0.143 mol) in aqueous ethanol (50%) were stirred for two hours at room temperature and then refluxed for one hour. After cooling, the solution was concentrated to half volume and extracted with benzene to remove the neutral portion. The aqueous layer was cooled in an ice bath and acidified with 6N hydrochloric acid to pH 3. While maintaining at ice-bath temperature the solution was extracted with two 100-ml portions of methylene chloride and dried. Evaporation of the solvent and distillation of the residue afforded 24.0 g (85%) of ethyl hydrogen-2-(Δ^3-cyclo-pentenyl)malonate: nmr τ -1.2 (s, 1, COOH), 4.33 (s, 2, olefinic), 5.76 (q, 2), 6.55 (d, 1), 7.0-7.9 (m, 5), 8.70 (t, 3, CH_3-).

N-Methylindole-3-acetic Acid --- Liquid ammonia (1.3 liters) was condensed (at -78°) into a 3-liter three-necked flask equipped with a pressure equalizing dropping funnel, a mechanical stirrer, a dry ice con-denser, and a nitrogen inlet. When a 0.5 g piece of sodium was added, the whole solution turned deep blue.

Then 700 mg of ferric nitrate was added and the remainder of the sodium (13 g total) was added in small pieces over a period of 30 minutes. After stirring for one hour the blue color disappeared and became greyish brown. A suspension of 35.5 g (0.202 mol) of indoleacetic acid in 300 ml of dry ether was added to the sodium amide solution over a period of 30 minutes at -78°. The mixture was stirred for 30 minutes before 30 ml of methyl iodide was added dropwise and then stirring was continued for an additional 30 minutes. The dry ice condenser was replaced with a standard water-cooled condenser and the ether and ammonia were allowed to evaporate while the cooling bath was allowed to gradually reach room temperature. The white mass was treated with 250 ml of water and the insoluble particles were removed by filtration through Celite. The yellow-brown filtrate was acidified with concentrated hydrochloric acid with cooling and the resulting precipitate was collected. The solid was dissolved in 200 ml of dichloromethane and dried over sodium sulfate. After evaporation of the solvent, the residue was crystallized from benzene to yield 32.6 g (90%) of the product: mp 121-123°.

N-Methylindole-3-acetyl Chloride (60) --- A suspension of 15 g (79.3 mmol) of N-methylindole-3-acetic acid in 250 ml of dry ether was cooled to -40° in a dry ice - acetone bath. To it was added 17.5 g (84.0 mmol)

of phosphorous pentachloride and then the mixture was stirred for one hour while the flask was allowed to reach 0°. The solvent was evaporated at 0° and the resulting residue was treated with two 100-ml portions of cold toluene which were in turn combined and evaporated at reduced pressure (oil pump) and 0°. The reddish residue was extracted with three 300-ml portions of dry n-pentane; concentration of the nearly colorless combined extracts afforded 17.1 g (100%) of the acid chloride as an oil: ir 1770 cm^{-1} (acid chloride carbonyl). This chloride was used for the next reaction without further purification.

Ethyl 2-(Δ^3-Cyclopentenyl)-3-keto-4-(N-methylindole-3)-butyrate (59) --- This compound was prepared according to the procedure of Ireland and Marshall for β-keto-esters.[47] Ethyl hydrogen-2-(Δ^3-cyclopentenyl)malonate (12.6 g, 63.5 mmol) was placed in a 1-liter three-necked flask equipped with a mechanical stirrer, a pressure-equalizing dropping funnel and a volumetric gas measuring device. Isopropyl magnesium bromide (167 ml of a 0.76M tetrahydrofuran solution) was added dropwise with vigorous stirring; the mixture was stirred until 2 equivalents of propane had evolved. Then a solution of 17.1 g (82.5 mmol) of N-methylindole-3-acetyl chloride (60) in 100 ml of dry tetrahydrofuran was added dropwise over 30 minutes; stirring was continued until evolution of the theoretical

amount of CO_2 was observed. The solvent was evaporated at reduced pressure and the residue was dissolved in 250 ml of dichloromethane, washed with ammonium chloride and sodium chloride, and then dried. Removal of the solvent afforded the crude product which was purified by silicic acid chromatography (650 g, chloroform elution) to give 21.8 g (100%) of the β-keto-ester (59): nmr τ 2.49 (m, 1, phenyl), 2.76 (m, 3, phenyl), 3.00 (s, 1, indole-α-proton), 4.4 (s, 2, olefinic), 5.93 (q, 2, $-C\underline{H}_2-CH_3$), 6.06 (s, 2, $-C\underline{H}_2-O-$), 6.32 (s, 3, $N-C\underline{H}_3$), 6.7-8.5 (m, 8), 8.80 (t, 3, $-CH_3$); ir 1740, 1720, 1615, 1435, 1373 and 1330 cm^{-1}.

Reduction of (59) with Lithium Aluminum Hydride to (61) --- A solution of 330 mg (1.02 mmol) of the β-keto-ester (59) in 5 ml of dry ether was added dropwise to 5 ml of 1M ethereal lithium aluminum hydride at room temperature. The solution was stirred for one hour and then the excess lithium aluminum hydride was decomposed by dropwise addition of 30 ml of water saturated ether. The precipitate was removed by filtration through Celite and the filter cake was washed with several portions of boiling ether. The combined filtrate and washings were evaporated to give a crystalline residue which when recrystallized from ethanol afforded 186 mg (68%) of the product (61): mp 141.5-142.5°; ir 3480, 1618, 1028 cm^{-1}; nmr τ 2.75 (m, 4, phenyl), 3.01 (s, 1, indole-α-hydrogen),

4.23 (s, 2, olefinic), and 6.32 (s, 3, N-CH_3); mass spectrum, calculated molecular weight for $C_{18}H_{23}NO_2$ 285 and found m/e 285.

Anal. Calcd. for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12. Found: C, 75.46; H, 7.68.

Preparation of the Methoxime (64) --- To a solution of 21.8 g (67.3 mmol) of the β-keto-ester (59) in 200 ml of absolute ethanol was added 18.98 g (224 mmol) of dry methoxylamine hydrochloride and 24 ml of dry pyridine. The mixture was refluxed for two hours and then concentrated to half volume. The residue was diluted with 100 ml of water and 100 ml of dichloromethane; the organic layer was separated. The aqueous layer was extracted with two 300-ml portions of dichloromethane and the combined organic layers were washed successively with water, sodium bicarbonate, and sodium chloride, then dried and evaporated to yield 23 g (100%) of (64): ir 1738, 1626, 1555, 1475, 1378, 1334, 1050 cm^{-1}; nmr τ 2.80 (m, 4, phenyl), 4.42 (s, 2, olefinic), 6.02 (s, 3, O-CH_3), 6.33 (s, 3, N-CH_3), 8.88 (q, 2, -CH_2-CH_3), and 9.05 (t, 3, CH_3).

Reduction of the Methoxime (64) to the Amino Alcohol (65) with Aluminum Hydride --- A lithium aluminum hydride solution (160 ml, 1M in tetrahydrofuran) and 150 ml of dry tetrahydrofuran were placed in a 2-liter three-necked flask fitted with a condenser, a rubber serum stopper, and a magnetic stirring bar. Dropwise addition

of 10.2 g (5.58 ml) of 100% sulfuric acid (prepared by mixing the appropriate amounts of 30% fuming sulfuric acid and 95% concentrated sulfuric acid) resulted in the evolution of 0.232 mole of hydrogen gas which was collected in a gas buret. The white turbid solution was stirred for an additional hour at room temperature and then 18.38 g (52 mmol) of the methoxime (64) in 500 ml of dry tetrahydrofuran was added with stirring. After addition was complete, the solution was refluxed for 30 minutes and then cooled to room temperature. A mixture of 25 ml of water and 25 ml of tetrahydrofuran was added to the reaction mixture, followed by 100 ml of water containing 10 g of sodium hydroxide. The tetrahydrofuran layer was separated and the remaining aqueous layer and solids were extracted with several portions of ether. The ether portions and the tetrahydrofuran layer were combined and dried over anhydrous sodium carbonate and then evaporated at reduced pressure to yield a residue which was dissolved in 100 ml of dichloromethane and dried over sodium sulfate. Removal of the solvent gave the crude amino alcohol (16.56 g) which was chromatographed on neutral alumina (500 g). Chloroform elution provided 5.04 g of isomer (65a) as an amorphous mass and elution with 5% methanol - chloroform afforded 5.48 g of the other isomer (65b) as a crystalline compound, total yield 68%. Isomer (65b)

was recrystallized from 95% ethanol: mp 113.5-114.5°; ir 3500, 3350, 1610, 1480, 1375, and 1325 cm^{-1}; nmr τ 2.45 (m,1), 2.80 (s, 3), 3.13 (s,1), 4.28 (s, 2), 6.25 (s, 3), 6.95 (s, 3), and 6.6-8.0 (m, 11). Intermediate fractions containing mixtures of the two isomers were repeatedly chromatographed to give a final separated 2 :1 ratio (65a : 65b).

Acetylation of the Amino Alcohol (65a) --- A solution of 50 mg of the amino alcohol (65a) in one ml of acetic anhydride and 0.5 ml of pyridine was heated at 50° for one hour and then the solvents were removed at reduced pressure. The residue was crystallized from ether and later from methyl acetate - pentane to afford white crystals (100%) of product (66a): mp 140-141°; ir 3450, 1743, 1673, and 1515 cm^{-1}; nmr τ 2.35 (m, 1), 2.75 (s,3), 3.11 (s, 1), 4.36 (s, 2), 5.65 (d, 2), 6.25 (s, 3), 7.90 (s, 3), and 8.06 (s, 3); mass spectrum showed a molecular ion peak at m/e 368, the calculated molecular weight.

Anal. Calcd for $C_{22}H_{28}N_2O_3$: C, 71.71; H, 7.66. Found: C, 71.97; H, 7.39.

Acetylation of the Amino Alcohol (65b) --- The same reaction conditions were applied to (65b) as above. The crystals obtained (100%) were recrystallized from ethanol: mp 129-130° (mixed mp with 66a was 117.5-118.5°); ir 3470, 1743, and 1680 cm^{-1}; nmr τ 2.75 (m,4), 3.11 (s, 1),

4.37 (s, 2), 5.66 (overlapped with broad peak), 6.25 (s, 3), and 8.05 (s, 3).

Anal. Calcd for $C_{22}H_{28}N_2O_3$: C, 71.71; H, 7.66. Found: C, 71.51; H, 7.54.

Preparation of the O-acetyl-p-bromobenzamide (67) --- Dry pyridine (3 ml) was added to a solution of 1 g (3.52 mmol) of the amino alcohol (65b) and 0.74 g (3.38 mmol) of p-bromobenzoyl chloride in 15 ml of benzene and the mixture was stirred for two hours. The reaction mixture was then poured onto ice-water (100 g) and diluted with 50 ml of chloroform. The cloudy solution was filtered through Celite and the organic layer was separated. This chloroform layer was washed with sodium chloride solution and dried over sodium sulfate. Removal of the solvent and chromatography of the residue on silicic acid (30 g, chloroform elution) afforded 501 mg of the p-bromobenzamide which was then subjected to O-acetylation with 5 ml of acetic anhydride and 5 ml of pyridine. After removing excess reagents at reduced pressure, the gum obtained was purified by silicic acid chromatography (15 g). Chloroform elution gave a compound which was crystallized first from ethyl acetate and then from methanol to afford colorless prisms of (67): mp 151-153°; ir 3400, 1730, 1660, 1590, and 1515 cm^{-1}.

Anal. Calcd for $C_{27}H_{29}N_2O_3Br$: C, 63.65; H, 5.73; N, 5.49; Br, 15.68. Found: C, 63.73; H, 5.54; N, 5.63;

Br, 15.73.

Preparation of the Dibenzoyl derivative (68)--Benzoyl chloride (12.4 g, 88 mmol) was added dropwise to a 0° solution of 11.3 g (39.8 mmol) of the amino alcohol (65a) in 30 ml of dry pyridine. The mixture was stirred for 30 minutes at room temperature and then poured onto ice-water. Then the aqueous solution was extracted with three 100-ml portions of chloroform; the combined extracts were washed successively with 10% hydrochloric acid, 5% sodium bicarbonate, and water before being dried and evaporated. Silicic acid chromatography of the crude benzoate gave, upon chloroform elution, 16.05 g (94%) of the compound (68): ir 3450 (N-H), 1713, and 1653 cm^{-1}; nmr τ 3.15 (s, 1, indole-α-hydrogen), 4.45 (s, 2, olefinic), 6.36 (s, 3, $-N-CH_3$).

Preparation of the Diol (69) --- To a stirred solution of 8.04 g (18.6 mmol) of the compound (68) in 200 ml of dry tetrahydrofuran, 5 g (19.7 mmol) of osmium tetroxide in 50 ml of tetrahydrofuran was added dropwise while keeping the reaction solution at 0°. The solution was allowed to stand at 0° overnight; hydrogen sulfide was then passed for 30 minutes into the solution still maintained at 0° and then the resulting mixture was filtered through Celite. The filter cake was washed with five 100-ml portions of tetrahydrofuran and the combined filtrate was evaporated at reduced pressure to

afford a residue which was chromatographed on silicic acid. Elution with 5% methanol - chloroform yielded 8.04 g (82%) of the diol (69): ir 3450 (OH, NH), 1730, 1667, 1612, 1588, 1520, and 1493 cm^{-1}; nmr τ 3.13 (s, 1, indole-α-proton), 5.37 (s, 1, OH), and 6.88 (s, 3, $N-CH_3$).

Preparation of the Dialdehyde (70) --- A 41.5 ml portion of 0.418M sodium metaperiodate in water - dioxane (7 : 5) was added to a solution of 8.04 g (15.3 mmol) of the diol (69) in a mixture of 60 ml of dioxane and 40 ml of water. The mixture was allowed to stand at room temperature overnight. The white precipitate was separated by filtration and the filtrate was concentrated at reduced pressure to half volume, diluted with water and extracted with two 100-ml portions of chloroform. The combined chloroform layers were washed with sodium chloride solution, dried, and evaporated at reduced pressure. The crude product (7.52 g, 93.5%) was used for the next reaction without further purification: ir 3400, 2720, 1720, and 1650 cm^{-1}.

Preparation of the Tetracyclic Aldehyde (71) --- A solution of 7.5 g (14.3 mmol) of the dialdehyde (70) in 100 ml of acetic acid and 25 ml of water was heated at 50° for four hours. The solution was concentrated at reduced pressure and the resulting residue was diluted with 100 ml of water and extracted with two 100-ml portions of chloroform. The extract was washed with 5%

sodium bicarbonate and water and then dried and evaporated to yield 7.7 g of a crude residue which, upon silicic acid chromatography (chloroform elution), afforded the pure aldehyde (71) (100%): nmr τ 0.1 (s, 1, CHO), 2.0-3.0 (m, 14, phenyl), 6.35 (s, 3, N-CH_3); ir 2720, 1720, and 1650 cm^{-1}.

Preparation of α-Bromomethylcyclohexane --- Cyclohexyl methanol (32.58 g, 0.286 mol) was placed in a 200 ml flask and cooled to -10°. Freshly distilled phosphorous tribromide (28.4 g, 0.105 mol) was added dropwise while maintaining the bath temperature below 0°. After addition was complete, the cooling bath was removed and the flask was allowed to warm to room temperature and then stirred overnight. Distillation of the reaction mixture yielded 28.56 g of the crude product: bp 75-80° (22-23 mm). The crude bromide was dissolved in 200 ml of dichloromethane and washed with three 50-ml portions of concentrated sulfuric acid, sodium bicarbonate solution (200 ml), and then water (200 ml). Finally, the solution was dried and evaporated, yielding a residue which was distilled to afford 26.5 g (52.5%) of the bromide: bp 68-70° (22mm).

Preparation of Cyclohexyl Acetaldehyde Acetal --- The Grignard reagent of α-bromomethylcyclohexane was prepared from 31.6 g (0.178 mol) of the bromide and 5.18 g of magnesium in 70 ml of dry ether. Triethyl

orthoformate (31.6 g, 0.178 mol) was added to the Grignard solution with vigorous stirring. After refluxing for three hours, the ether was removed by distillation and the hot residue was poured into 70 ml of 30% acetic acid. The reaction solution was extracted with ether; the extract was washed with 5% sodium bicarbonate and water, dried and evaporated to give 32.6 g (80%) of the diacetal: nmr τ 5.46 (t, 1, -C<u>H</u>-OEt), 6.48 (m, 11, ring protons), and 8.82 (t, 3, -C<u>H</u>$_2$-CH$_3$).

Preparation of Cyclohexylacetaldehyde (72) --- A mixture of 32.6 g of the diacetal prepared above and 300 ml of 5% hydrochloric acid was refluxed for two hours. After cooling, the product was extracted with dichloromethane (150 ml), washed with 5% sodium bicarbonate, water and then dried and evaporated. The residue was distilled to afford 17.1 g (83%) of the aldehyde: bp 69-73° (15 mm); nmr τ 0.35 (t, 1, CHO), 7.76 (m, 2, -C<u>H</u>$_2$-CHO); mass spectrum exhibited the hightest peak at m/e 126 corresponding to the molecular ion.

Preparation of the N-Isopropylimine (73) --- A mixture of 5.0 g (39.8 mmol) of cyclohexylacetaldehyde, 2.36 g (39.8 mmol) of isopropylamine , and 5.5 g (39.8 mmol) of anhydrous potassium carbonate in 10 ml of dry tetrahydrofuran was stirred overnight. The solids were separated by filtration and the filtrate was evaporated. The residue was distilled to give 6.0 g (90%) of the

imine (73): bp 90-93° (7 mm); nmr τ 2.35 (t, 1, -CH-N), 6.74 (septet, 1, C<u>H</u>-CH_3), 7.90 (t, 2, -C<u>H</u>-CH), 8.37 (m, 11, cyclohexyl), and 8.86 (d, 6, C-CH_3).

<u>Preparation of 2-Cyclohexyl Butyraldehyde (77), (Ethylation of Cyclohexylacetaldehyde)</u> --- One ml of a 1<u>M</u> diisopropylamine solution in tetrahydrofuran was placed in a 25 ml three-necked flask equipped with an argon inlet and cooled to 0°. An <u>n</u>-hexane solution of <u>n</u>-butyllithium (0.625 ml of a 1.6<u>M</u> solution, 1 mmol) was added and stirred for 15 minutes at 0°. Then the solution was cooled to -30° as 126 mg (1 mmol) of the N-isopropyl-imine (73) in 1 ml of dry tetrahydrofuran was added. The mixture was stirred for 15 minutes at -30° and then cooled to -50° as 2 mmol of ethyl iodide in 2 ml of tetrahydrofuran was added at once. The resulting solution was allowed to warm to room temperature and stirred overnight. A mixture of 1.5 ml of glacial acetic acid, 0.8 ml of water and 0.5 ml of pyruvic acid was added to the reaction mixture and stirred for 6 hours at room temperature. Dilution of the mixture with 10 ml of water and 20 ml of dichloromethane was followed by separation of the organic layer. The aqueous layer was extracted with dichloromethane (30 ml) and the combined organic layers were washed with water until the pH of the water became 7. The extract was dried and evaporated. Glpc analysis of the residue showed that over 80%

product had been formed. The residue was distilled at reduced pressure using a molecular distillation apparatus. Glpc indicated that the product was pure: nmr τ 0.45 (d, 1, CHO), 9.13 (t, 3, CH_3); ir 1723 (CHO), 2710 (CHO); mass spectrum showed the highest peak at m/e 154 which corresponds to the molecular ion.

Preparation of the N-Isopropylimine (78) --- A 506 mg (1 mmol) sample of the aldehyde (71) was stirred overnight in a 25 ml flask with 138 mg (1 mmol) of dry potassium carbonate and 2 ml of 1M isopropylamine in 2 ml of tetrahydrofuran. After filtration, the filtrate was evaporated and the residue (600 mg) was dried over phosphorous pentoxide. The mass spectrum of the product exhibited a molecular ion peak at m/e 547 and the nmr showed a new isopropyl methyl resonance at τ 8.90 (d).

Attempted Ethylation of the Imine (78) --- An n-butyllithium solution (0.94 ml of a 1.6M n-hexane solution) was added over 15 minutes to a 0° tetrahydrofuran solution of 1M diisopropylamine (1.5 ml). The bath was cooled to -30° and the imine (78) (1 mmol) in 1 ml of tetrahydrofuran was added dropwise. Following 2 hours stirring at -30°, the bath was cooled to -50°, 2 ml of 1M ethyl iodide in 2 ml of tetrahydrofuran was added, and the mixture was stirred overnight at room temperature. A mixture of 1.5 ml of acetic acid, 0.8 ml of water, and 0.5 ml of pyruvic acid was added and the

reaction mixture was stirred for 6 hours. To the mixture was added 10 ml of water and 20 ml of dichloromethane and the separated organic layer was washed with water, sodium bicarbonate and then dried and evaporated to give 527 mg of crude material. Silicic acid chromatography (15 g) served to separate the mixture into two components, the O-ethyl aldehyde (80) (174 mg, 41.5%) and the recovered aldehyde (71) (259 mg, 51%) as identified by mass spectroscopy.

Preparation of the N-n-Butylisobutyl Enamine (81) of Cyclohexylacetaldehyde --- A solution of 2 g (15.9 mmol) of cyclohexyl acetaldehyde in 10 ml of dry tetrahydrofuran was added dropwise to a 0° suspension of 2.1 g (16.0 mmol) of n-butylisobutylamine and 2.18 g (15.9 mmol) of potassium carbonate. After addition of the aldehyde, the mixture was stirred at room temperature overnight. The mixture was filtered and the filtrate was evaporated to give 3.61 g of the crude product which was distilled to yield 2.5 g (66%) of the pure enamine: bp 85-90° (0.7 mm); ir 1645 (C=C); nmr τ 4.13 (d, 1, -CH-N-), 6.00 (d,d, 1, -CH-CH-N-), and 9.15 (d, 9, $-CH_3$).

Preparation of 2-Cyclohexyl Butyraldehyde (77), (Ethylation of the Enamine (81))--- A mixture of 2.5 g (10.5 mmol) of the enamine (81), 1.68 ml (21 mmol) of ethyl bromide, and 10 ml of dry acetonitrile was sealed under vacuum at liquid nitrogen temperature in a 50 ml

thick-walled Pyrex tube. The tube was heated at 100° overnight and then, after cooling, the reaction mixture was transferred into a flask containing a buffered solution (1 g sodium acetate, 2 ml acetic acid and 10 ml water) and the mixture was refluxed for four hours. Upon cooling, the solution was diluted with 15 ml of water and extracted with 50 ml of benzene. The benzene extract was washed successively with dilute hydrochloric acid (50 ml), sodium bicarbonate (50 ml), and water (50 ml). Drying and evaporation gave 2.17 g of the crude product which was purified by molecular distillation (bath temp. 100-110°, 15 mm) to afford 1.3 g (80%) of pure product (77). The spectroscopic properties were identical to (77) prepared by ethylation of the imine.

Preparation of the N-n-Butylisobutyl Enamine (82) --- A 200 mg (0.396 mmol) sample of the aldehyde (71) in 3 ml of tetrahydrofuran was added to a suspension of 55 mg (0.40 mmol) of potassium carbonate and 78 mg (0.595 mmol) of n-butylisobutylamine in 7 ml of tetrahydrofuran. The mixture was stirred overnight at room temperature. After removal of the potassium carbonate by filtration, the solvent was evaporated at reduced pressure to afford 220 mg of the crude enamine (82): nmr τ 9.15 (d, 9, $-CH_3$). The crude enamine was used in the ethylation reaction without further purification. As noted in the discussion section, attempted ethylation of (82) gave no reaction.

Preparation of the Tetracyclic Aldehyde Oxime (83) --- To a solution of 344 mg (0.68 mmol) of the aldehyde (71) in 7 ml of absolute ethanol, 344 mg of hydroxylamine hydrochloride was added followed by 3.5 ml of dry pyridine. The mixture was refluxed for two hours and then the resulting solution was concentrated to half volume. Dilution of the residual solution with 20 ml of dichloromethane followed by washing with dilute hydrochloric acid, 5% sodium bicarbonate and water yielded, upon drying and concentration, 391 mg of the oxime: ir 3310, 1715, and 1630 cm^{-1}.

Preparation of the Tetracyclic Cyano Compound (84) --- Benzoyl chloride (0.25 ml, 1.4 mmol) was added to a solution of 391 mg (0.76 mmol) of the oxime (83) in 3 ml of pyridine. The mixture was stirred at room temperature for one hour and then refluxed for 30 minutes. After cooling, the reaction mixture was diluted with 30 ml of dichloromethane and the resulting solution was washed consecutively with 1.5 N hydrochloric acid, 5% sodium bicarbonate and water, then dried and evaporated to afford 563 mg of compound (84) which was chromatographed on silicic acid (chloroform elution) to give 357 mg (95%) of pure (84): ir 2260, 1630, 1523, 1520, and 1430 cm^{-1}.

Ethylation of the Cyano Compound (84) --- Sodiotriphenylmethane (4 ml of 0.13 M ether solution, 0.52 mmol)

was added to a solution of 153 mg (0.314 mmol) of the cyano compound (84) in 5 ml of dry tetrahydrofuran. Ethyl bromide (0.3 ml, 5 mmol) was added at once and stirring was continued overnight. The reaction mixture was diluted with 10 ml of chloroform and the organic layer was separated and washed with 10 ml of water. Drying and concentration under reduced pressure gave a crude residue which was chromatographed on silicic acid (20 g) to afford 120 mg (60%) of the ethylated compound (85): ir 2240, 1725, and 1630 cm^{-1}; nmr τ 6.32 (s, 3, $N-CH_3$) and 8.75 (br t, 3, $-CH_3$); the mass spectrum exhibited a peak at m/e 534 corresponding to the molecular ion.

Ester Exchange of O-Benzoate with Sodium Methoxide --- A sodium methoxide solution (0.2 ml of 0.85 M methanol solution) was added to a stirred solution of 53.8 mg (0.10 mmol) of compound (85) in 4 ml of absolute methanol. The solution was heated at 50° for 40 minutes. The cooled solution was neutralized with carbon dioxide and then concentrated. The residue was extracted with dichloromethane and the extract was washed with sodium chloride solution, dried and evaporated yielding a crude residue (51 mg) which was purified by silicic acid chromatography (5 g). The fraction from elution with 5% methanol - chloroform gave a crystalline compound (33 mg, 77%) which was recrystallized from ethyl acetate

to afford pure (86): mp 200.5-202.5°; ir 3440, 2230, and 1620 cm^{-1}.

In an identical manner to the above, ester exchange of 2.0 g (3.94 mmol) of the cyano compound (84) afforded 1.45 g (80%) of the alcohol (87).

Preparation of the Tetrahydro-pyranyl Ether (88) --- To 80 ml of a solution of 1.45 g (3.63 mmol) of the alcohol (87) in tetrahydrofuran was added 10 ml of dihydropyran at room temperature. The solution was cooled to -20°and 50 mg of p-toluenesulfonic acid was added with stirring. The temperature of the solution was allowed to rise to 0° after one hour and then stirring was continued for another hour at room temperature. Potassium carbonate was then added until the solution became neutral to wet pH paper and then the solvent was evaporated. Extraction with 100 ml of ether and 100 ml of chloroform followed by evaporation of the combined extracts afforded 1.6 g of crude material which was chromatographed on alumina (50 g, grade III) with ether - methanol elution to yield 1.4 g (80%) of the pyranyl ether (88): ir 2260, 1643, and 1230-1290 cm^{-1} (small characteristic peaks for pyranyl ethers were observed in this region); nmr τ 7.6-8.5 (m, characteristic pyranyl proton resonances).

Ethylation of the Pyranyl Ether (88) --- A 620 mg (1.28 mmol) sample of the pyranyl ether (88) was dissolved

in 4.5 ml of dimethoxyethane and lithiotriphenylmethane (1.92 mmol) in 4.5 ml of the same solvent was added under nitrogen; the mixture was stirred for 30 minutes. To this solution was added 0.40 ml (5.0 mmol) of ethyl bromide at 0°. Upon addition of ethyl bromide the red color of the excess lithiotriphenylmethane disappeared to give a green solution which gradually faded to pale-green after stirring for one hour at room temperature. A mixture of 20 ml of ether and 10 ml of water was added to dilute the reaction mixture and then the whole solution was extracted with three 50-ml portions of dichloromethane. After drying and evaporating the solvent, the crude residue was chromatographed on alumina (20 g, grade III) to afford, upon ether - methanol elution, 430 mg of the non-ethylated alcohol (87) and 180 mg (28%) of the ethylated pyranyl ether (89): ir 2270, 1645, 1285, 1275, 1263, and 1240 cm^{-1}, the latter four peaks are characteristic of the pyranyl ether ring; nmr τ 9.16 (t, 3, $-CH_3$) and 8.60 (m, pyranyl ring protons); the mass spectrum showed the highest peak at m/e 513 which corresponds to the molecular ion.

Hydrolysis of the Ethylated Pyranyl Ether to the Alcohol (86) --- A 60 mg (0.117 mmol) sample of the pyranyl ether (89) was dissolved in 5 ml of methanol and to it was added 0.5 ml of 0.1 M hydrochloric acid. The mixture was stirred for 24 hours at room tempera-

ture and then extracted with three 30-ml portions of dichloromethane. The dichloromethane solution was dried and evaporated to give 61 mg of a crude material which was chromatographed on silicic acid (1.8 g) to yield, upon chloroform elution, 29 mg (58%) of the alcohol (86): ir and nmr were the same as given for the compound obtained by ester exchange of the O-benzoate; the mass spectrum exhibited the molecular ion peak at m/e 427.

Oxidation of the Alcohol $(86)_n$ to the Aldehyde $(92)_n$ --- To a solution of 0.5 ml of dimethylsulfoxide, 0.5 ml of benzene and 120 mg (0.28 mmol) of the alcohol $(86)_n$ was added 22 mg (0.29 mmol) of pyridine, 16 mg (0.14 mmol) of trifluoroacetic acid and 175 mg (0.84 mmol) of dicyclohexylcarbodiimide. The mixture was allowed to stand at room temperature overnight and the the reaction mixture was diluted with 10 ml of ether. The ethereal solution was treated with 115 mg of oxalic acid in 1 ml of methanol and the gas evolved (33 ml) was collected. When gas evolution ceased, the reaction mixture was diluted with water (30 ml) and the precipitated dicyclohexyl urea was removed by filtration. The filtrate was extracted with three 50 ml portions of ether-benzene (1:1) and the combined extracts were washed with water, sodium bicarbonate and sodium chloride, and then dried and evaporated. The residue (161 mg) was chromatographed on 8 g of silicic acid and elution with chloroform gave a crystalline

material (121 mg) which was rechromatographed on 25 g of silicic acid. The obtained material (110 mg) was suspended in benzene and the insoluble dicyclohexyl urea was separated by centrifuge. This treatment was repeated several times and then the benzene solution was evaporated to give 74.2 mg (62%) of the aldehyde $(92)_n$: ir 2700, 2230, 1730, 1630, 1470, and 1425 cm^{-1}.

Cyclization of the Aldehyde $(92)_n$ to the Acetate $(95)_n$ --- A 550 mg (1.2 mmol) sample of ethyl cyano-aldehyde $(92)_n$ was suspended in 10 ml of acetic acid and 10 ml of acetic anhydride. The solution was saturated with hydrogen chloride gas at 0° and maintained at that temperature for 4.5 hours. Then the mixture was made basic with ice cold ammonia (50 ml of 3% ammonium hyroxide and 50 ml of water) and extracted with three 30 ml portions of dichloromethane. The combined organic layers were washed with sodium chloride solution, dried, and then evaporated to give 407 mg (75.5%) of $(95)_n$: ir 3550, 2220, 1740, 1630, and 1480 cm^{-1}.

Hydrogenation of the Cyclized Acetate $(95)_n$--- A 180.1 mg (0.4 mmol) portion of the acetate $(95)_n$ was dissolved in 15 ml of 6 N hydrochloric acid and the solution was added to a hydrogenation flask containing 196 mg (0.86 mmol) of platinum dioxide in 2 ml of 6 N hydrochloric acid which had been equilibrated with a hydrogen atmosphere. After 8.3 ml uptake of hydrogen, the cata-

lyst was filtered and the filtrate was made basic with cold ammonia. The aqueous solution was extracted with four 30 ml portions of dichloromethane and the combined organic layers were washed with sodium chloride solution, dried and evaporated to give 138.6 mg (81%) of crude gum. Since the obtained alcohol $(97)_n$ could not be crystallized, it was converted to the compound $(98)_n$ as follows. The alcohol $(97)_n$ was dissolved in 0.6 ml of pyridine and 0.6 ml of acetic anhydride and heated at 50° for 1.5 hours. The solvents were evaporated with the aid of xylene to give 157.5 mg of the crude acetate which was chromatographed on silicic acid (8 g). Chloroform elution afforded a crystalline compound (100%) which was recrystallized from methanol: mp 200-202°; ir 2230, 1750, 1630, 1580,1495, 1385, 1150, 1140, 1133, and 1075 cm^{-1}.

Reduction of the Benzoyl Alcohol $(97)_n$ to the Benzyl Alcohol $(99)_n$ --- A solution of lithium triethoxyaluminum hydride was prepared by addition of 11.1 ml of an ethyl acetate - tetrahydrofuran solution (dilution of 6.5 g of ethyl acetate with 25 ml of tetrahydrofuran) to 25 ml of a 0.94 M solution of lithium aluminum hydride in ether. A 1.00 g (2.33 mmol) sample of the alcohol $(97)_n$ in 150 ml of tetrahydrofuran was added dropwise over a period of 30 minutes at 0°. Stirring was continued for 2 hours at 0° and then three drops of water were added. The whole mixture was filtered through Celite and the

filter cake was washed with three 20-ml portions of tetrahydrofuran. The combined filtrate was evaporated and the residue was taken into 25 ml of dichloromethane, dried, and evaporated to give 1.62 g of crude residue which was chromatographed on 50 g of silicic acid. Elution with 2% methanol - chloroform yielded 561 mg (58.5%) of the benzyl alcohol $(99)_n$ which was crystallized from methanol: mp 170.5-171.5°; ir 3500, 2230, 1610, and 1480 cm^{-1}; nmr τ 2.78 (s, 5, phenyl), 5.40 (s, 1), 6.05 (m, 2), 7.40 (s, 3), 8.75, and 8.85 (s,s, 3, $-CH_3$).

Anal. Calcd for $C_{27}H_{31}N_3O$: C, 77.66; H, 7.46. Found C, 77.92; H, 7.60.

Minor fractions were the alcohol (100) (46 mg), derived from the reduction of the cyano group to the primary amine and the aldehyde (101) (213 mg, mp 220-230°) derived from further reduction of the compound (99): ir spectrum of (100), 3350, 1610, and 1480 cm^{-1}; ir spectrum of (101) (nujol mull), 3330, 1720, 1710, and 1330 cm^{-1}.

Anal. Cacld for $C_{27}H_{30}N_2O_3$ (100): C, 75.32; H, 7.02. Found: C, 75.78; H, 7.15.

Hydrogenolysis of the N-Benzyl Alcohol $(99)_n$---
A solution of 207 mg (0.5 mmol) of the benzyl alcohol $(99)_n$ in 13 ml of glacial acetic acid was hydrogenated over 700 mg of 5% palladium-charcoal at atmosphere pressure. After take-up of the theoretical amount of hydrogen, the catalyst was removed by filtration and the solvent

was evaporated. The residue was dissolved in 20 ml of chloroform and then successively washed with 10 ml of 10% ammonia solution, 10 ml of sodium chloride, and finally dried and evaporated to give 199 mg of a residue, which was chromatographed on silicic acid (10 g). Elution with chloroform gave 97 mg of starting alcohol $(99)_n$ and 2% methanol - chloroform afforded 38 mg (23.4%) of the secondary amine $(102)_n$, which was crystallized from acetone: mp 260-262°. A mixture of this amine with anhydroajmaline oxime obtained directly from the degradation of ajmaline showed no melting point depression.

Conversion of (102) to ajmaline has been accomplished by Robinson's group [5] with a brief procedure given below.

Anhydroajmaline oxime (102) (50 mg) was dissolved in 2 ml of chloroform and added to lithium aluminum hydride (50 mg) in 20 ml of ether. The mixture was allowed to stand at room temperature for 2 hours and then decomposed with water. Dilute hydrochloric acid (5 ml) was added and the solution was warmed on a steam bath for 10 minutes. After addition of potassium hydroxide the solution was extracted with chloform and the extract was evaporated to dryness. The residue was treated with 2-3 ml of methanol causing it to crystallize: mp 154-158°, undepressed when mixed with ajmaline.

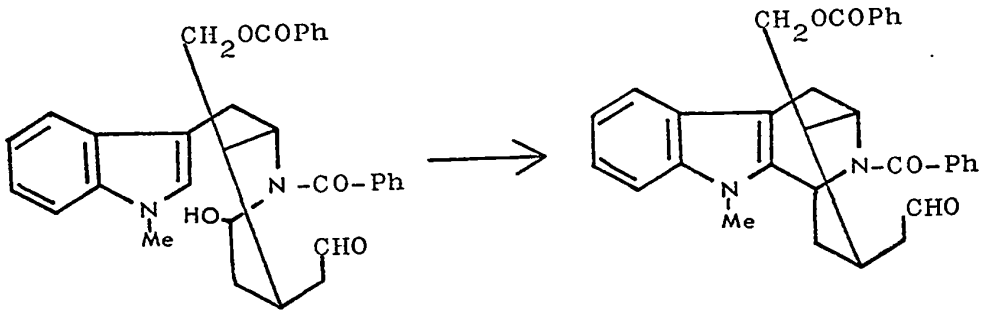
CHAPTER II

CONCERNING A BIOGENETICALLY-PATTERNED LABORATORY SYNTHESIS IN THE STRYCHNINE-CURARE ALKALOIDS

Introduction

In our ajmaline synthesis described in Chapter I one of the key steps was the condensation of carbinolamide (70) in acidic media to provide exclusively the α-condensation product (71). The condensation of a related dialdehyde (103) was reported in 1960 by van Tamelen *et al.*[61] to yield in one step the extraordinary double-cyclized product (104) possessing the strychnine-curare alkaloid skeleton. We were unable to rationalize this remarkable double cyclization when we attempted a crude conformational analysis of the reaction mechanism in a manner similar to that used in accounting for the formation of (71). This apparent anomaly led us to reinvestigate the reactions reported by van Tamelen and co-workers.

There have been a number of studies reported concerning the reaction mechanism and the selectivity of the indole nucleus toward electrophiles. A thorough study by Jackson *et al.*[52] suggests that although many factors may be involved in determining whether α- or β-cyclization occurs, it appears that a simple Schiff's base (105) is initially formed by condensation of



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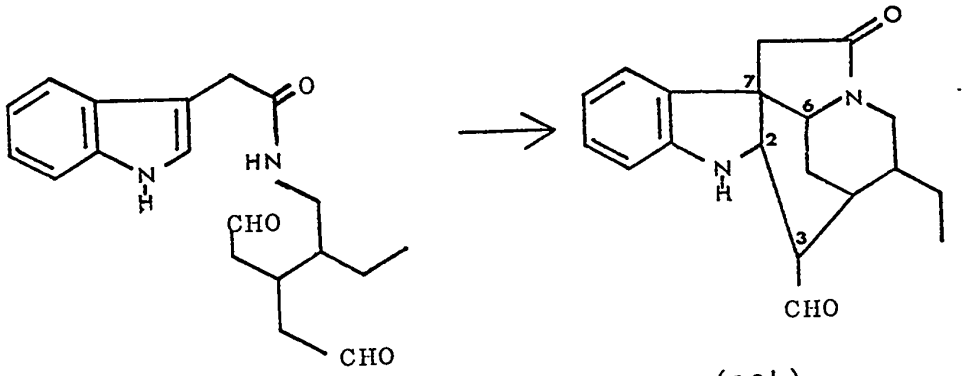
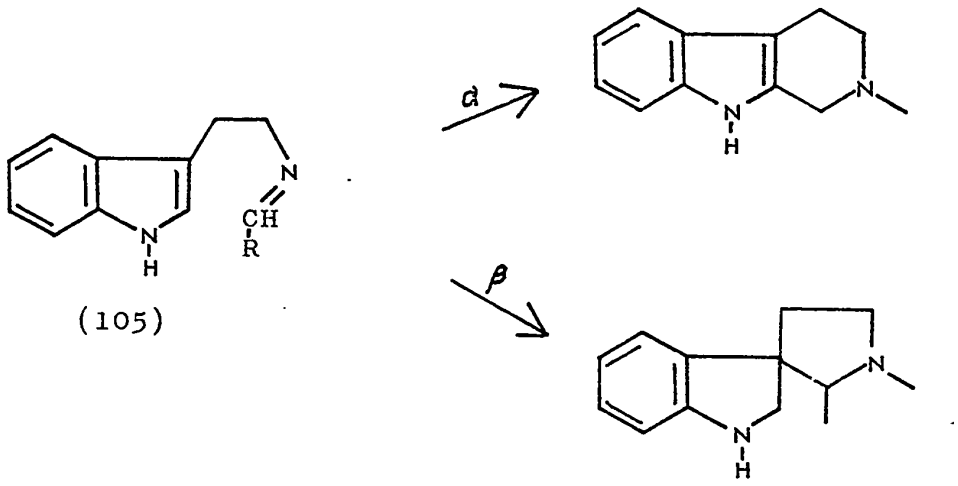


(103) (104)

tryptamine with an aldehyde and then attacks the highly nucleophilic β-position of the indole nucleus which may migrate to the α-position if the α-product is the one obtained. This alkyl migration (the selectivity of the condensation) may be mainly controlled by factors such as non-bonded interactions and ring strains. Examples of such α-products are yohimbine and ajmalicine while strychnine and aspidosperma type alkaloids are examples

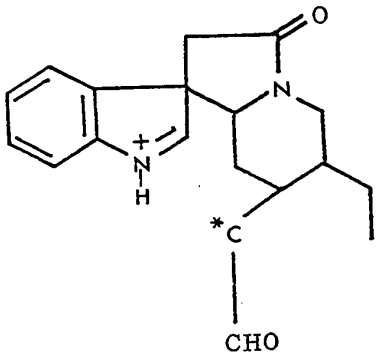
of β-condensed compounds. In the ajmaline synthesis, the



(105)

condensation of (70) provided exclusively the α-product (71). The presence of the C5-C16 bond apparently controlled the course of the condensation as well as the stereochemistry at C15. For the reported double cyclization of (103) the authors suggested that β-condensation preceded the final ring closure to the α-position. If this were the case, the OHC-CH_2- group (asterisked) must possess the proper stereochemistry for the final ring closure as shown in (106') and in order to achieve this desired configuration the β-cyclization must have overcome a severe interaction between the (psuedo) axial

side chain and the indole-α-hydrogen as depicted in (106'). Thus, this cursory analysis indicates that the preferred course of the initial β-cyclization should lead to the stereoisomer (106") which is no longer able to undergo the second ring closure.



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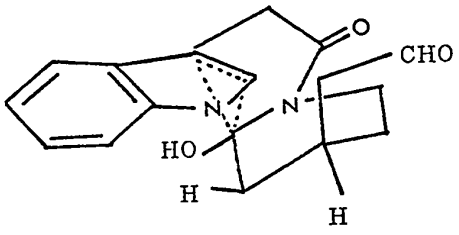

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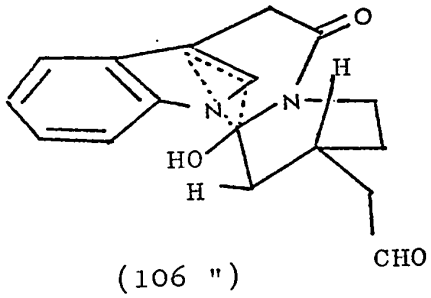

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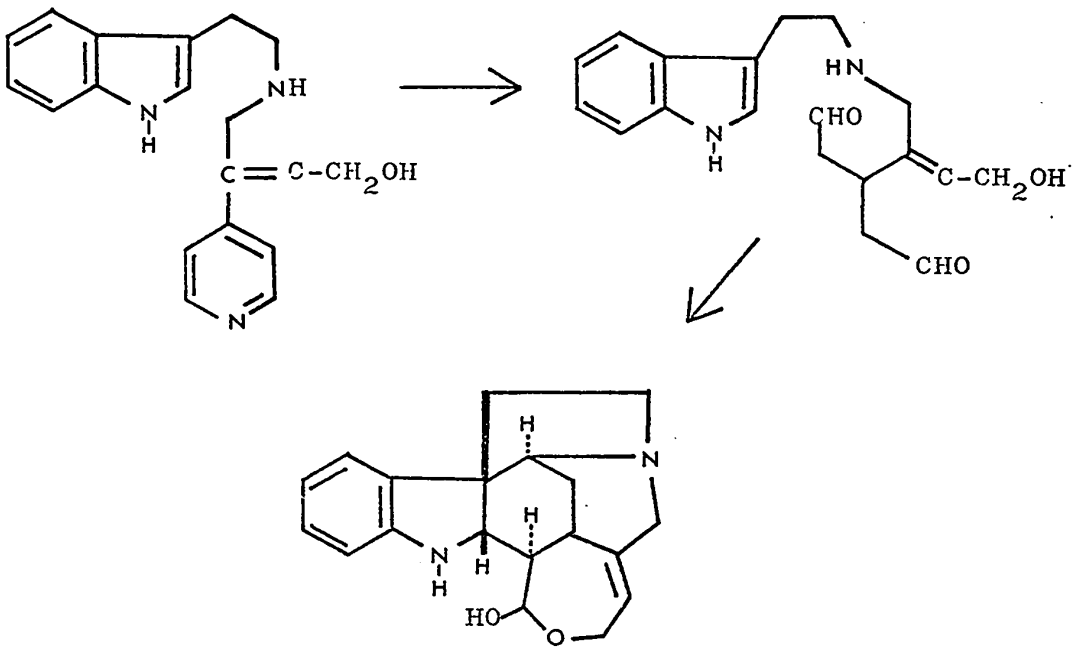
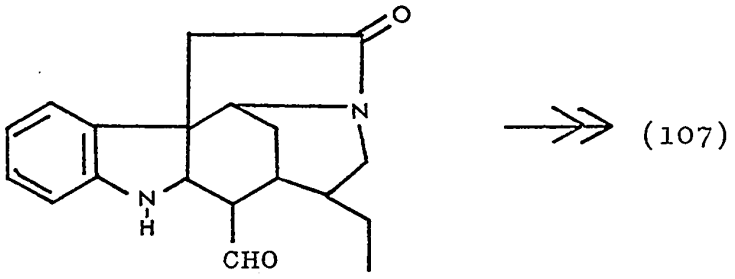


(107)

The proposed double cyclized product (104) can in principle lead to the Wieland-Gumlich aldehyde.



(104)

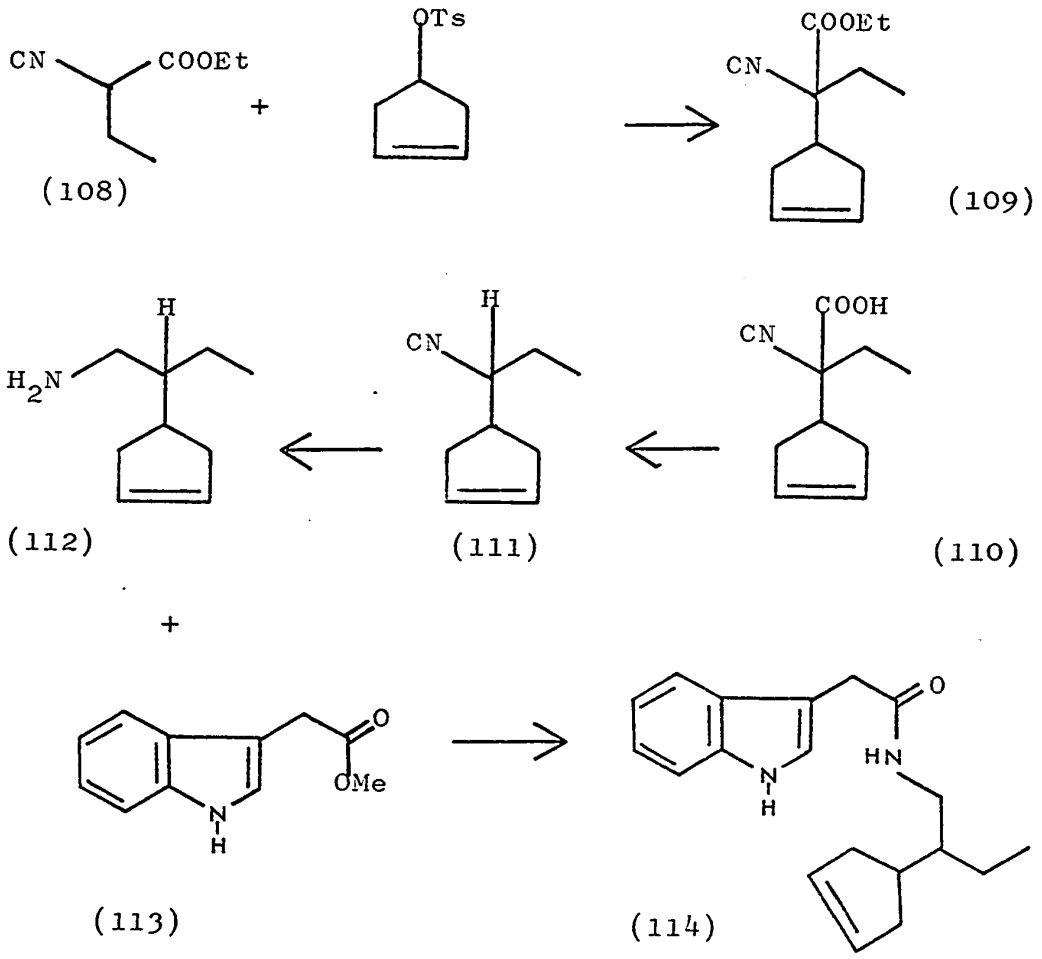
Our results from the reinvestigation of van Tamelen's proposed double cyclization will now be given.

Results and Discussion

Reinvestigation of van Tamelen's double cyclization product was initiated by preparation of dialdehyde (103). All the intermediates leading to (103) were prepared by following precisely the experimental procedures of van Tamelen and co-workers and the comparison of all spectral data and melting points showed that our products were identical with those obtained previously. Appropriate derivatives were also prepared to identify the compounds more fully.

The first series of reactions were performed in a straight forward manner according to the reported procedures. Ethyl 2-cyanobutyrate (108) which was prepared from ethyl cyanoacetate and acetaldehyde, was condensed with Δ^3-cyclopentenyl tosylate in ethanol in the presence of sodium ethoxide to afford ethyl 2-(Δ^3-cyclopentenyl)-2-cyanobutyrate (109). The latter was then subjected to ester hydrolysis with sodium hydroxide to yield the acid (110). Decarboxylation by heating in quinoline at 180° gave the nitrile (111) which was then reduced with lithium aluminum hydride to 2-(Δ^3-cyclopentenyl)butylamine (112).

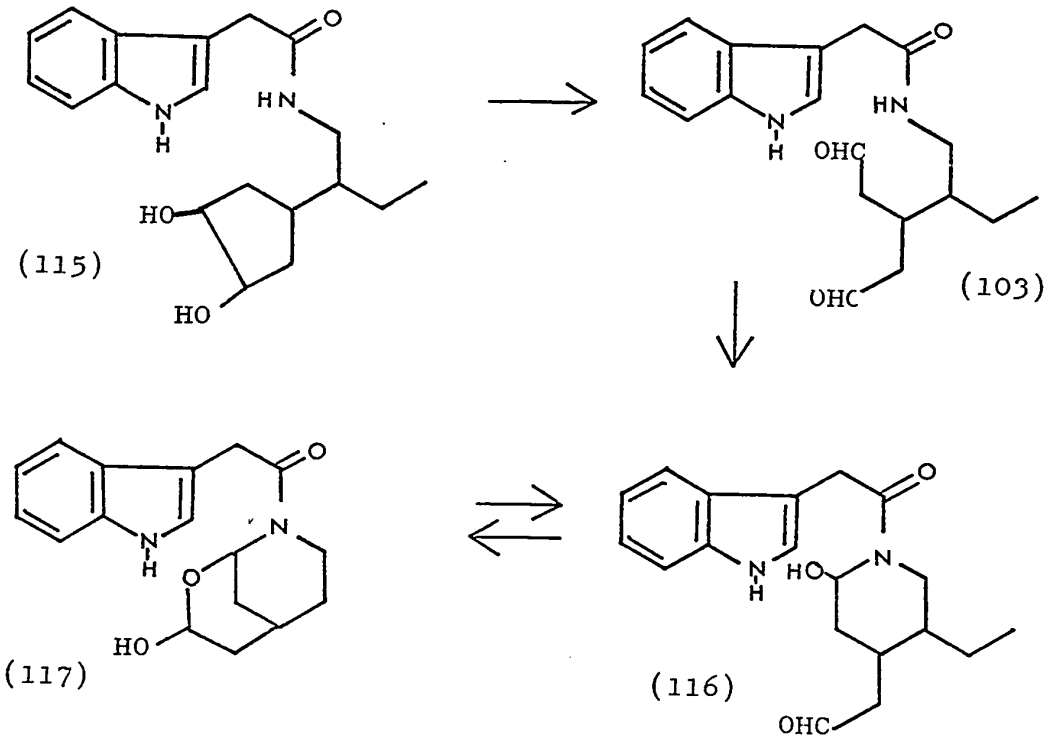
The condensation of methyl indoleacetate (113) with 2-(Δ^3-cyclopentenyl)butylamine (112) was effected by heating the mixture at 165-170° for 6 hours and the amide (114) was purified by silicic acid chromatography.



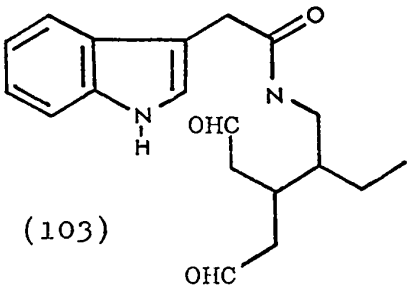
The selective hydroxylation of the double bond in the cyclopentenyl ring of (114) was performed by using a slightly modified procedure to van Tamelen's method in which mixed solvents were used and the osmium ester was isolated at -78°. In our ajmaline synthesis, the same type of reaction was performed at 0°. This latter method seemed easier to handle and its application to (114) gave a diol identical to that obtained by van

Tamelen. The amorphous diol (115) was purified by chromatography on silicic acid; the trinitrobenzene derivative of the diol (115) melted at 143-144° (reported, 145-146°).

The diol (115) was cleaved in aqueous dioxane to give the dialdehyde (103). The ir spectrum of the dialdehyde exhibited absorptions corresponding to the amide carbonyl, aldehyde and hydroxyl groups. The hydroxyl absorption suggested that one of the aldehyde groups forms a carbinolamide (116), and further the low intensity of the aldehyde carbonyl absorption implied an equilibrium between (116) and a hemiacetal (117).



The cyclization of the dialdehyde (103) was effected by heating in aqueous formic acid on a steam bath for one hour. The crude product (118) exhibited both aldehyde and amide carbonyl absorptions in the infrared spectrum but because of its instability, the product was quickly chromatographed on neutral alumina and reduced to the alcohol (119) with sodium borohydride in methanol.



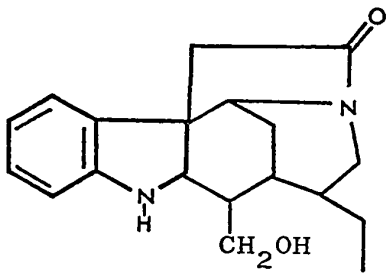
(103)

1. HCOOH
2. $NaBH_4$

Alcohol (119)

The alcohol (119) was purified by neutral alumina chromatography and sublimation at 150° (0.02 mm) afforded a crystalline product, mp 55-58° (reported 53-56°). The infrared spectrum showed a five membered lactam absorption at 1680 cm^{-1} (reported 1680 cm^{-1}). Thus, the obtained alcohol (119) was identical to van Tamelen's product. The first evidence to indicate that the proposed structure may be incorrect was obtained by mass spectroscopy. The spectrum exhibited the parent peak at m/e 314 which is two mass units higher than for the

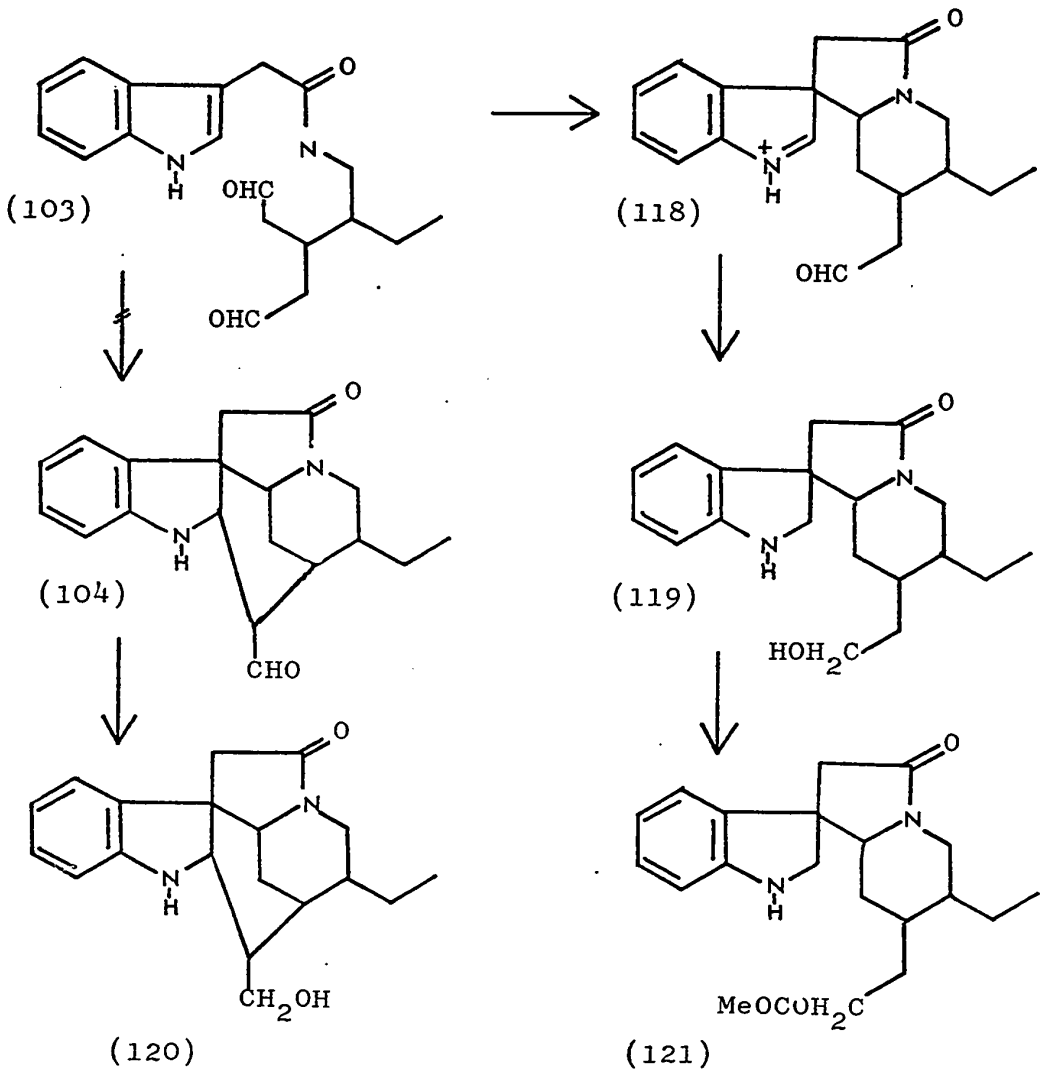
alcohol (120) proposed by van Tamelen.



(120)

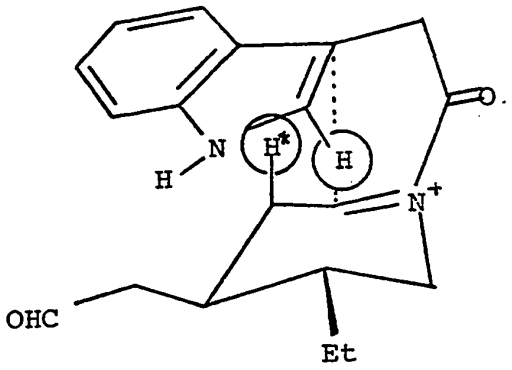
The alcohol (119) appeared to be rather unstable and was therefore acetylated in acetic anhydride and pyridine to give the diacetyl derivative (121). Thin layer chromatography of the diacetyl derivative exhibited two major spots and extensive silicic acid chromatography separated these compounds into a 3 : 1 ratio of (121a) and (121b) respectively. From studies of the uv, ir, and nmr spectra of (121a), the presence of the indoline moiety, as reported by the previous authors, was confirmed; however the mass spectrum of (121a) showed an intense peak at m/e 398 which again differed by two units and virtually no peak at m/e 396 expected for the pentacyclic acetate derived from (104). These observations strongly suggested that the structure (104) for the aldehyde proposed by van Tamelen was incorrect and indicated that the second cyclization did not take place beyond the indolenium salt. The indolenium salt was reduced

with sodium borohydride to the alcohol (119). The probable course of the reaction is shown below.

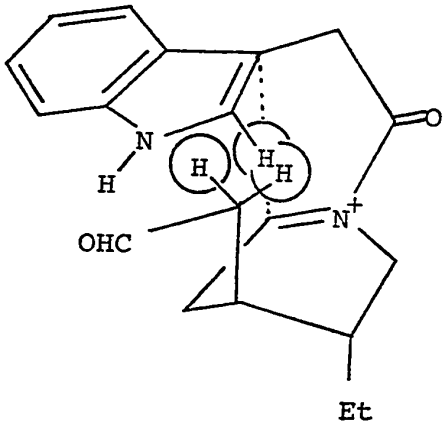


In order for the dialdehyde (103) to undergo the double cyclization, β- and then α-cyclization, the $OHC-CH_2-$ group should be <u>cis</u> to the bond initially formed between the termini indicated by the dotted line below. Suppose

that this β-cyclization proceeds in the chair form of the piperidine ring then a severe non-bonded interaction between the hydrogen (H*) and the indole-α-hydrogen would prevent

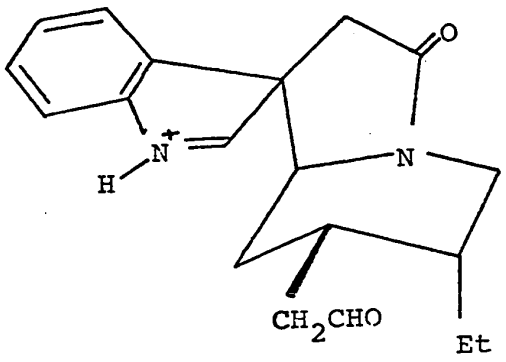


the β-cyclization. In the case of the boat form of the piperidine ring, the interaction between the indole-α-hydrogen and the OHC-CH_2- group makes the β-cyclization extremely difficult as depicted below.

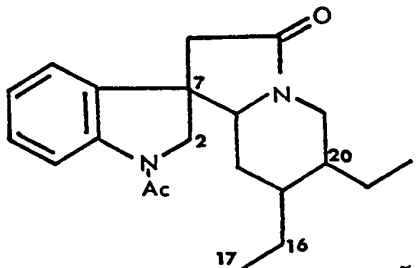


In contrast if the OHC-CH_2- group is oriented <u>trans</u> to the bond being formed by the initial cyclization, the non-

bonded interaction described above would not interfer with the β-cyclization. Thus, regardless of the piperidine conformation, the cyclized product most likely possesses the $OHC-CH_2-$ group in the unfavorable position for the second cyclization as seen below.



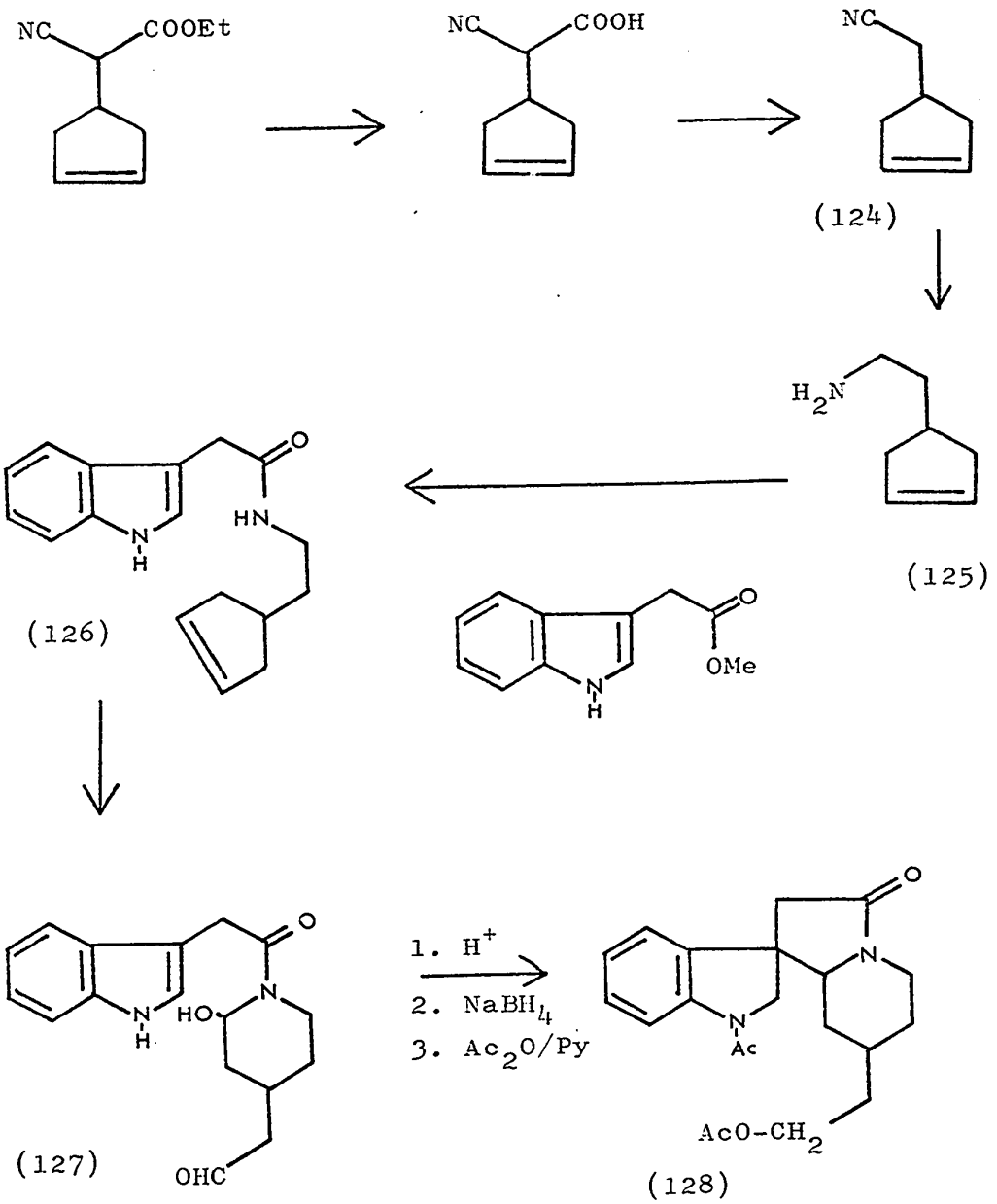
An nmr study of the diacetyl derivative (121a) and two other derivatives, the N-acetyl-alcohol (122) and the N-O-p-nitrobenzoyl derivative (123), add further support to our proposed structure of the alcohol (119). When the region of τ5.6 to τ7.2 was carefully inspected, a broad singlet (C2, 2H) invariably appeared at τ 6.93 to τ 6.99 partially overlapped with a multiplet (C7, 1H); a multiplet in the τ 5.7 to τ 6.45 region was assigned to the methylene protons at C17 as shown below.



τ 6.93-6.99 (s, 2H) RO-H_2C τ 5.7-6.45 (m, 2H)

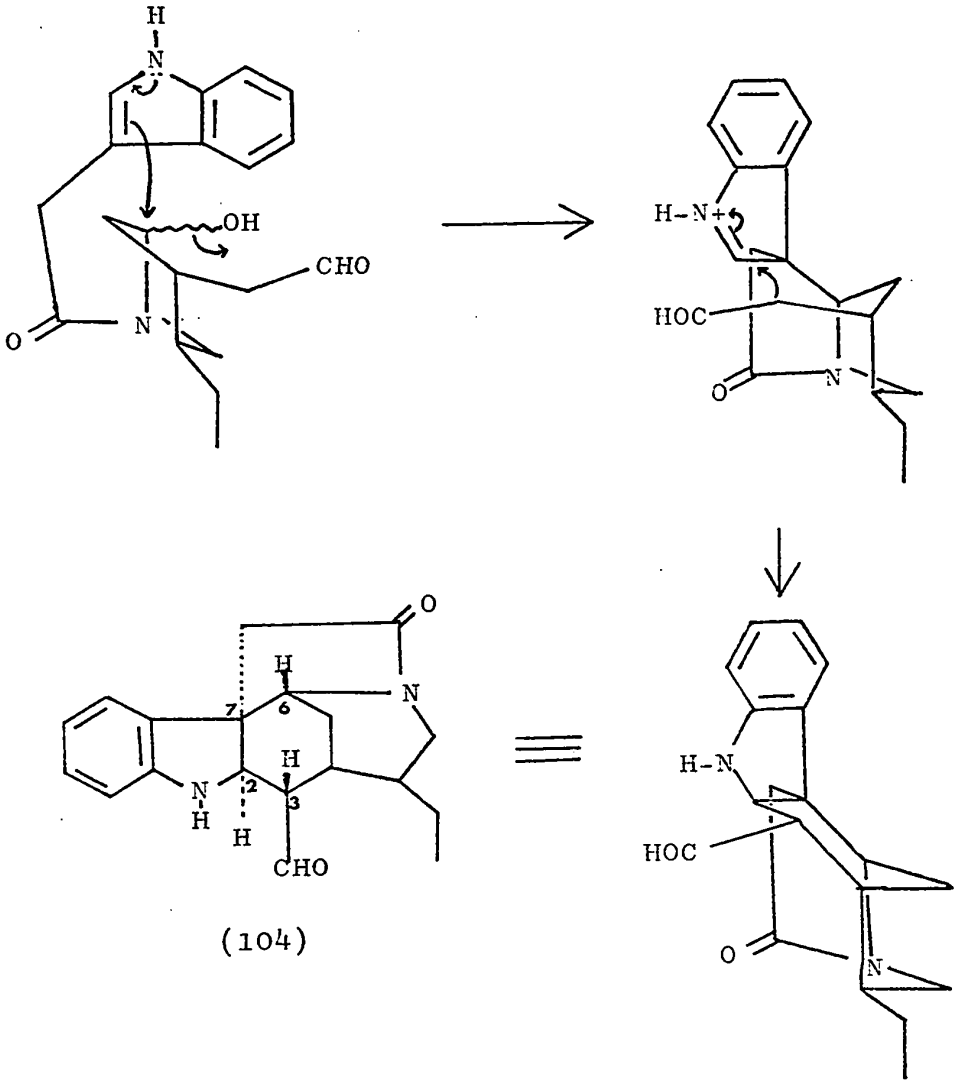
The mass spectrum of (121a) was superimposable on that of (121b) and indicated that (121b) is an isomer of (121a), very likely at C20, but not at C15, because the stereochemistry at C20 would be less decisive in controlling the stereochemistry of cyclization. In order to further substantiate this point a series of des-ethyl compounds were prepared and subjected to the cyclization. Methyl indoleacetate was condensed with Δ^3-cyclopentenyl ethylamine (125) followed by osmylation, sodium periodate cleavage, and acid catalyzed cyclization. Sodium borohydride reduction of the cyclized product gave an alcohol which was acetylated to afford the diacetyl derivative (128). Careful examination by thin layer chromatography revealed that (128) consisted of a single component. This observation strongly suggested that the isomer (121b) (see page 104) is the C20 isomer because when the ethyl group is removed, the cyclization product is a single compound. The mass spectrum of the diacetate

(128) showed a peak at m/e 370 again consistent with our proposed structure of a singly cyclized compound.



The criteria which van Tamelen *et al.* used for assigning the structure (104) for the cyclization product were the characteristic dihydroindole absorption in the ultraviolet spectrum and the five-membered lactam carbonyl absorption in the infrared spectrum. However, these spectral data would not show the difference between the doubly cyclized aldehyde (104) and the singly cyclized aldehyde (118). Both contain the dihydroindole moiety and the five-membered lactam carbonyl group. The elemental analysis of the alcohol (120) obtained by subsequent sodium borohydride reduction of the aldehyde (104) is satisfactory for the proposed (120) and also for (119); for (120), $C_{19}H_{24}N_2O_2$, the calculated figures are C, 73.02; H, 7.74; N, 8.97 and for (119), $C_{19}H_{26}N_2O_2$, the calculated values are C, 72.61; H, 8.28; N, 8.91 while the values obtained are C, 72.86; H, 7.92; N, 8.77. Moreover, our mass spectral evidence strongly indicates that (119) is the structure of the compound obtained.

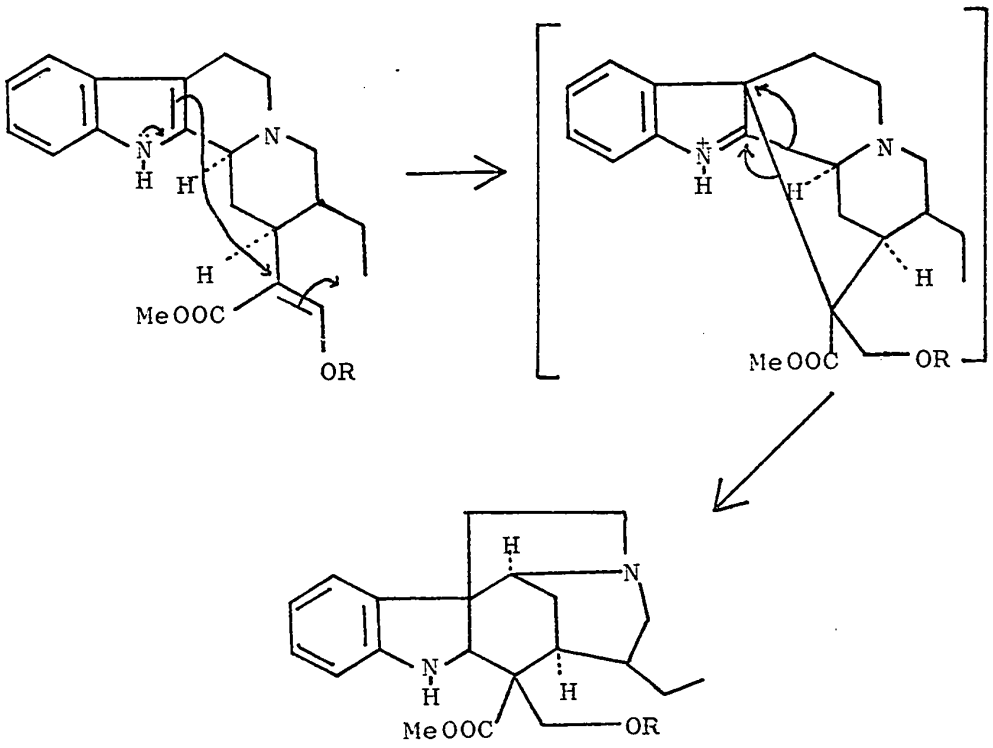
According to the authors' suggested double condensation mechanism of the dialdehyde (103) in acidic media,[61] as seen below, the condensation product (104) must possess the mirror image conformation where the configuration at C2, C3, C6, and C7 are opposite to those of the Wieland-Gumlich aldehyde (107)(see P. 99).



(104)

Obviously biosynthesis of strychnine alkaloids is controlled by the enzymic system and the scheme advanced by Robinson was discussed earlier in this Chapter. It might be appropriate to point out the following alternative pathway. The general biosynthetic scheme for indole alkaloids outlined in Chapter I suggests that when a corynantheine type alkaloid is appropriately functionalized

at C16, β-cyclization should occur followed by double rearrangement to exchange the substituent at the indole α- and β-positions to provide the desired pentacyclic compound. This scheme (outlined below) produces the same net results that were described by Robinson and completes the construction of the strychnine skeleton.



Experimental

General experimental techniques employed in this section were similar to those described in Chapter I. Experimental conditions for reinvestigated reactions were followed as precisely as possible. Some minor variations were employed provided they did not alter the properties of the products.

Preparation of Ethyl 2-Cyanobutyrate (108) --- A mixture of 56.6 g (0.50 mol) of ethyl cyanoacetate, 2 ml of piperidine and 26.5 g (0.60 mol) of acetaldehyde in 100 ml of glacial acetic acid was hydrogenated over 1 g of palladium-charcoal at room temperature and under two atmospheres of hydrogen for 12 hours. The reaction mixture was filtered and the filtrate was diluted with benzene, washed with sodium chloride solution and dried. The benzene solution was distilled to give 60.6 g (80%) of (108): bp 103-106° (20 mm); nmr τ 5.17 (q, 2, $-O-CH_2$), 6.3 (t, 1, -CH-O), 8.68 (t, 3, CH_3), and 8.95 (t, 3, CH_3).

Condensation of Ester (108) with Δ^3-Cyclopentenyl Tosylate --- To 36.2 ml (41.5 mmol) of 1.15 N sodium ethoxide in ethanol was added 5 g (34.7 mmol) of ethyl 2-cyanobutyrate and the solution was refluxed for three hours. After cooling, 8.9 g (38.0 mmol) of Δ^3-cyclopentenyl tosylate in 10 ml of absolute ethanol was added and refluxed overnight. The precipitate was removed by filtration and the filtrate was concentrated.

The residue was diluted with water and extracted with 150 ml of dichloromethane. The organic layer was separated, dried and evaporated to give 9.9 g of crude product which was distilled to afford 3.7 g (52%) of pure product: bp 136-140° (10 mm); nmr τ 4.3 (s, 2, olefinic), 7.55 (m, 2, $-C\underline{H}_2-CH_3$).

Hydrolysis of the Cyano Ester (109) --- A mixture of 30.5 g(0.147 mol) of the ester (109) and 150 ml of 0.98 M sodium hydroxide was refluxed overnight. After cooling, the reaction mixture was washed with ether to remove any neutral fraction and then the aqueous layer was cooled to 0° and carefully acidified with concentrated hydrochloric acid to pH 3 and extracted with three 100-ml portions of ether. The combined ether layers were dried and evaporated; the residue was diluted with 100 ml of dichloromethane and dried. Removal of the solvent gave 27.3 g (100%) of the acid (110): ir 1725 cm^{-1} (carboxyl carbonyl).

Decarboxylation of the Acid (110) --- A solution of 27.3 g (0.15 mol) of the acid (110) in 100 ml of quinoline was heated at 180° until gas evolution ceased (ca. 2.5 hours). After cooling, the reaction mixture was poured into cold dilute sulfuric acid (10%) and extracted with three 100-ml portions of ether. The combined extracts were evaporated and the residue was diluted with 100 ml of dichloromethane, washed with 100 ml of water, dried,

and evaporated to give 23.3 g of crude product which was distilled to yield 18.1 g (90%) of pure (111): bp 113-115° (30 mm); ir 2240, 1460, 1380, 1340, and 920 cm^{-1}.

Reduction of 2- Δ^3-Cyclopentenyl-2-cyanopropane (111) --- A solution of 15 g (0.11 mol) of 2- Δ^3-cyclopentenyl-2-cyanopropane in 100 ml of dry ether was added dropwise over 30 minutes to a slurry of 10 g (0.26 mol) of lithium aluminum hydride in 100 ml of ether. The resulting mixture was refluxed overnight and then treated with 150 ml of water-saturated ether. The resulting precipitate was filtered off over Celite and the filter cake was washed with two 100-ml portions of ether. The combined ether portions were evaporated to yield 15 g of a residue which was distilled to afford 14.4 g (94%) of the amine (112): bp 102-104° (30 mm); ir 3450, 1640, 1600, 1500, and 1460 cm^{-1}.

Preparation of the Amine (114) --- A mixture of 19.4 g (0.102 mol) of methylindole acetate and 12.9 g (0.093 mol) of the amine (112) was heated at 165-170° for 6 hours. The reaction mixture was then diluted with 250 ml of ether and washed with 10% hydrochloric acid, 5% sodium bicarbonate, and water. Drying and concentration gave 25 g of the crude amide which was chromatographed on 250 g of silicic acid (5% methanol-chloroform elution) to yield 20 g (72%) of pure amide (114): nmr τ 2.3-3.0 (m, 6, aromatic), 4.38 (s, 2,

olefinic), 6.34 (s, 3, OCH_3), 6.80 (s, 2), 7.85 (m, 5), 8.4-8.9 (m, 3), and 9.15 (s br, 3, CH_3).

Selective Hydroxylation of the Amide (114) --- The amide (114) (1.17 g, 3.9 mmol) in 5 ml of dry tetrahydrofuran and 5 ml of dry pyridine were placed in a 300 ml three-necked flask fitted with a mechanical stirrer. The mixture was cooled to -78° and a solution of 1 g of osmium tetroxide in 30 ml of dry tetrahydrofuran was added dropwise with stirring. The solution was stirred for one hour at -78° and then approximately 100 ml of dry ether was added. The precipitate was collected by rapid filtration through Celite. The filter cake was transferred into a flask containing 30 ml of 95% ethanol and 30 ml of chloroform and into this mixture hydrogen sulfide was bubbled at 0° for 15 minutes. The resulting mixture was maintained at 0° overnight before the precipitate was filtered through Celite and the filter cake was washed with 50 ml of chloroform-ethanol (1:1). Evaporation of the solvent gave 1.28 g of the crude diol which was chromatographed on 20 g of silicic acid. Elution with 5% methanol-chloroform afforded 1.2 g (92%) of the diol (115): ir 3330, 1650, and 1525 $cm.^{-1}$.

Preparation of the Trinitrobenzene Derivative of the Diol (115) --- A solution of 62 mg (0.18 mmol) of the diol (115) and 40 mg (0.18 mmol) of trinitrobenzene in

10 ml of chloroform was warmed over a steam bath as hexane was added dropwise until the orange solution became cloudy. The mixture was allowed to stand in a refrigerator for a few hours and then the crystalline precipitate was collected by filtration. The crystals were recrystallized from chloroform-methanol to yield 77 mg of orange crystals: mp 143-144° (reported 145-146°).

Preparation of Dialdehyde (103) --- A 4.6 g (15 mmol) sample of the diol (115) was dissolved in 30 ml of dioxane and 20 ml of water. Then 30 ml of 0.5 M sodium periodate (1:1 water-doxane solution) was added and the mixture was allowed to stand at room temperature overnight. The resulting precipitate was filtered and the filtrate was extracted with 10% acetone-chloroform (4 X 50 ml). The combined organic layers were washed with sodium chloride solution, dried, and evaporated to give 4.13 g (84%) of the dialdehyde (103) as a gum: ir 3350, 1725, 1640, 1525, and 1430 cm^{-1}.

Formic Acid Cyclization of Dialdehyde (103) --- The dialdehyde (103) (4 g, 12 mmol) and 2 g of sodium carbonate were dissolved in 80 ml of 88% formic acid and 20 ml of water. The mixture was heated on a steam bath for one hour and after cooling, the mixture was made basic (pH 10) with 50% sodium hydroxide and extracted with four 50-ml portions of dichloromethane. The extract was

washed with sodium chloride solution, dried, and evaporated to give 3 g of crude material which was chromatographed on 80 g of silicic acid. Elution with chloroform afforded 2.2 g of the cyclized compound (118): ir 2710, 1720, 1680, 1600, 1490, and 1360 cm^{-1}(reported 1680 and 1730 cm^{-1}).

Sodium Borohydride Reduction of (118) --- Sodium borohydride (1 g, 26 mmol) was added in small portions to a solution of 2 g (5.7 mmol) of the cyclized aldehyde (118) in 40 ml of methanol. After stirring the mixture overnight the methanol was evaporated and the residue was diluted with 100 ml of water. The aqueous solution was extracted with five 50-ml portions of chloroform. The chloroform solution was then extracted with three 50-ml portions of 10% sulfuric acid; the acidic solution was immediately made basic (pH 10) with 10% sodium hydroxide. The basic solution was extracted with five 50-ml portions of chloroform and the organic layer was washed with water, dried, and evaporated to give 0.9 g of a crude residue which was chromatographed on 30 g of neutral alumina (12% water by weight). Elution with 5% methanol-dichloromethane afforded 0.79 g (42%) of the product (119) which was sublimed at 150° and 0.02 mm to give 420 mg of a crystalline alcohol: mp 55-58°; ir 3350, 1680, 1610, 1490, 1440, 1410, 1315, and 1290 cm^{-1}; mass spectrum exhibited M^+ at m/e 314.1909 with that

calculated for $C_{19}H_{26}N_2O_2$ 314.1951. Reported values are: mp 53-56°; uv (ethanol) λ_{max} 243 (logϵ 3.99) and 295 mμ (logϵ 3.54).

Acetylation of Alcohol (119) --- A 416 mg (1.29 mmol) sample of the alcohol (119) was dissolved in 2 ml of acetic anhydride and 2 ml of pyridine. The mixture was allowed to stand at room temperature overnight and then the solvents were evaporated at reduced pressure yielding 493 mg of a residue which was chromatographed on 10 g of silicic acid. Chloroform containing 1% methanol served to separate the residue into two components in the ratio of 3:1, (121a) and (121b) respectively. Spectral properties of (121a): ir 1725, 1690, 1600, 1490, 1430, 1400, 1375, 1340, 1275, 1245, and 1025 cm^{-1}; nmr τ 2.58-2.78 (m, 4, phenyl), 5.90 (s, 2), 6.35 (m, 2, CH_2-O), 7.25 (d), 7.70 (s, 3, N-Ac), 8.0 (s, 3, O-Ac), 8.2 (t), 8.65 (m), 8.95 (m); uv (ethanol) λ_{max} 2.52 (logϵ 4.117), 279 (logϵ 3.37), and 288 mμ (logϵ 3.24); mass spectrum showed a peak at m/e 398.2270, calculated m/e for $C_{22}H_{30}N_2O_4$ is 398.2206.

Hydrolysis of the O-Acetyl Group in (121a) --- A mixture of 102 mg (0.256 mmol) of the compound (121a) in 10 ml of absolute methanol and 0.56 ml (0.22 mmol) of 0.4 M sodium methoxide was warmed at 50-60° for one hour. After cooling, a few drops of water were added and carbon dioxide was bubbled through the solution until

neutralization. The solvent was evaporated and the residue was diluted with 5 ml of water and 50 ml of dichloromethane. The separated organic layer was dried and evaporated to give 115 mg of crude alcohol (122) which was sublimed at 150° (0.02 mm) to yield crystals of the product: mass spectrum showed a peak at m/e 356.2101, calculated m/e is 356.2099.

Preparation of the p-Nitrobenzoate of Alcohol (122) --- A 52 mg (0.28 mmol) sample of p-nitrobenzoyl chloride was added to a solution of alcohol (122) (70 mg, 0.20 mmol) in 1 ml of pyridine at 0°. The mixture was stirred for 30 minutes and then the solvent was evaporated. The residue (85 mg) was chromatographed on 5 g of silicic acid. Elution with 5% methanol-chloroform afforded 80 mg of the benzoate (123): nmr τ 2.9 (m, phenyl), 5.7 (m, 2, O-CH_2-), 5.9 (s, 2, N-CH_2-), 7.23 (d, 2, -CH_2CO), 7.78 (s, 3, CH_3-CO), and 9.02 (t, 3, CH_3); ir 1720, 1670, 1600, 1530, 1480, 1400, 1340, 1275, 1100, and 1010 cm^{-1}.

Hydrolysis of Ethyl 2-(Δ^3-Cyclopentenyl)cyanoacetate --- A mixture of 4.5 g (0.028 mol) of ethyl 2-(Δ^3-cyclopentenyl)cyanoacetate and 32.6 ml (0.028 mol) of 0.87 M potassium hydroxide was refluxed for one hour. After cooling, the reaction mixture was diluted with 50 ml of water and extracted with 100 ml of ether. The aqueous layer was acidified with 50% sulfuric acid as it was

cooled. The acidic solution was extracted with three 100-ml portions of dichloromethane. The dichloromethane solution was washed with brine, dried, and evaporated to give 4.02 g of crystals: mp 74-78°; ir 2250 and 1720 cm^{-1}.

Decarboxylation of 2-(Δ^3-Cyclopentenyl)cyanoacetic Acid --- A solution of 4.0 g (28 mmol) of 2-(Δ^3-cyclopentenyl) cyanoacetic acid in 25 ml of quinoline was heated at 180° until gas evolution ceased. The reaction mixture was poured into 100 ml of cold 10% sulfuric acid and then extracted with three 100-ml portions of ether. The ether was removed by evaporation and the residue was dissolved in 50 ml of dichloromethane, dried, and evaporated to give 2.77 g of a crude residue which was distilled to yield 1.91 g (63%) of cyanomethylcyclopentene: bp 100-102° (30 mm); ir 2250 cm^{-1} (CN) and no carbonyl absorption.

Reduction of Cyanomethylcyclopentene (124) --- A solution of 1.91 g (17.8 mmol) of cyanomethylcyclopentene (124) in 10 ml of ether was added to 30 ml of a 0.84 M lithium aluminum hydride solution in ether and the mixture was refluxed overnight. The reaction mixture was decomposed with 50 ml of water-saturated ether and the precipitate was filtered through Celite. The filter cake was washed with ether several times and the combined ether solution (200 ml) was evaporated. The residue was

diluted with 100 ml of dichloromethane, dried, and evaporated to give 1.9 g of a crude residue which was distilled using a molecular distillation apparatus to give 1.52 g of the amine (125): bp 100-120° (30 mm); ir 3340 cm^{-1}; nmr τ 4.35 (s, 2, olefinic), 7.3 (t, 2, $N-CH_2-$), 7.5-8.6 (m, 7, methylene), and 8.8 (s, 2, NH_2).

Condensation of Amine (125) with Methylindole acetate --- A mixture of 1.52 g (0.014 mol) of the amine (125) and 3.8 g (0.014 mol) of methylindole acetate was heated at 180° for 6 hours. The resulting oil was diluted with 100 ml of ether and washed with dilute hydrochloric acid, 5% sodium bicarbonate, and water and then dried and evaporated to give 5.04 g of crude amide which was chromatographed on 80 g of silicic acid. Chloroform served to elute a crystalline amide which was recrystallized from ethyl acetate to give 2.21 g (57%) of the pure amide (126): mp 79-80°; ir 3400, 3250, 1655, 1525, 1460, 1415, 1340, and 1090 cm^{-1}.

Reaction of Osmium Tetroxide with Amide (126) --- To a solution of 1.1 g (3.9 mmol) of the amide (126) in 5 ml of pyridine and 5 ml of tetrahydrofuran was added 1.1 g (4.4 mmol) of osmium tetroxide in 50 ml of tetrahydrofuran at -80° with stirring. After stirring for one hour, 100 ml of dry ether was added and the precipitated solid was filtered through Celite. The filter cake was transferred into 30 ml of chloroform-ethanol(1:1)

and then hydrogen sulfide was passed into the solution at 0° for 15 minutes. The reaction mixture was maintained at 0° overnight, filtered through Celite and the filtrate was evaporated to leave 1.51 g of crude residue which was chromatographed on 20 g of silicic acid. Elution with 5% methanol-chloroform afforded 1.06 g of the diol: ir 3330 and 1650 cm^{-1}.

Preparation of Dialdehyde (127) --- A 34 ml solution of 0.1 M sodium metaperiodate in water-dioxane (1:1) was added to a 1.06 g (3.4 mmol) sample of the above diol. The mixture was maintained at room temperature overnight before the precipitate was filtered and the filtrate was extracted with three 50-ml portions of 30% acetone-chloroform. The solvents were evaporated and the residue (980 mg) was the dialdehyde (127): ir (thin film) 3300 (OH), 1710 (aldehyde), and 1630 cm^{-1} (amide).

Formic Acid Cyclization of Dialdehyde (127) --- A solution of 895 mg (28.7 mmol) of the dialdehyde (127) in 30 ml of tetrahydrofuran was added to a mixture of 60 ml of 88% formic acid, 15 ml of water, and 1.5 g of sodium carbonate over a period of one hour on a steam bath. After heating for an additional hour, the solution upon cooling was diluted with water and the tetrahydrofuran was evaporated. The residual aqueous solution was extracted with four 50-ml portions of chloroform and the organic layer was washed with 100 ml of 5% sodium

bicarbonate and 100 ml of brine solution and then dried and evaporated to give 763 mg of the crude cyclized product which was used for the next reaction without further purification: ir 2710, 1725, 1680, 1600, 1490, 1420, 1360, and 1290 cm^{-1}.

Sodium Borohydride Reduction of the Cyclized Aldehyde

Sodium borohydride (0.6 g, 15 mmol) was added to a solution of the cyclized aldehyde (760 mg, 2.5 mmol) in 15 ml of methanol at 0°. After stirring for one hour at 0°, carbon dioxide was bubbled through the reaction mixture at room temperature for 15 minutes. Evaporation of the solvent yielded a residue which was diluted with 50 ml of dichloromethane and then washed with brine, dried, and evaporated to give 694 mg of the crude alcohol. Chromatography twice on 20 g of silicic acid gave, upon elution with 5% methanol-chloroform, 340 mg of the pure alcohol: ir 3350, 1650, and 1429 cm^{-1}.

Acetylation of the Alcohol --- A solution of 340 mg (1.12 mmol) of the alcohol prepared above in 3 ml of pyridine and 3 ml of acetic anhydride was maintained at room temperature overnight. The solvents were evaporated with the aid of xylene and the residue was chromatographed on 25 g of silicic acid. Elution with 2% methanol-chloroform afforded 412 mg of pure compound (128), sublimable at 150° (0.02 mm): ir 1735, 1680, 1600, 1490, 1400, 1240, and 1030 cm^{-1}; uv (ethanol)

λ_{max} 255 mμ (log ε 3.78); mass spectrum showed a peak M^+ at m/e 370.1895, calculated for $C_{21}H_{25}N_2O_4$ is 370.1893; thin layer chromatography on silica gel with 5% methanol-ethyl acetate as solvent showed a single spot.

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