THE USE OF THE SCHMIDT REACTION IN THE ELABORATION OF SELECTED ALKALOIDS CONTAINING A SEVEN-MEMBERED RING

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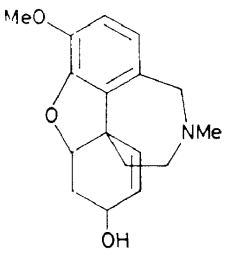
In the past the heterocyclic rings of most alkaloids have been thought to be five- or six-membered, but more recently several examples of bases containing a seven-membered heterocyclic ring have been recognized in nature, *e.g.* in the indole alkaloid field mavacurine-fluorocurine[1] and the iboga bases[2], and among the *Amaryllidaceae* and the *Stemonaceae* alkaloids compounds. The structures of these alkaloids have been derived mainly from degradative studies and by the application of physico-chemical methods. It therefore seemed to us desirable to establish these novel structures more conclusively by synthetic methods. For this purpose we have examined several synthetic approaches and found that the Schmidt reaction[3] is very useful for elaborating a nitrogen-containing seven-membered ring.

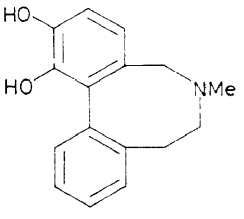
This paper outlines methods by which we have succeeded in synthesizing seven-membered ring heterocyclic compounds closely related to selected alkaloids isolated from the plants of the *Amaryllidaceae* and the *Stemonaceae* growing in the Far East, and emphasizes the value of the Schmidt reaction.

In the course of our studies on the *Amaryllidaceae* alkaloids, it was shown that galanthamine and its congeners such as lycoramine, epigalanthamine, and narwedine, represent the first alkaloids known to contain a seven-membered nitrogenous ring[4]. This conclusion was based on the following evidence.

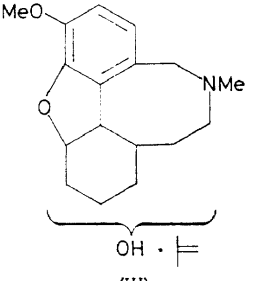
Following Proskurnina and Yakovleva's[5] observation, galanthamine was treated with hydrobromic acid to give apogalanthamine (II), the structure of which was established by degradation and synthesis[6]. From this structure for apogalanthamine, either the formula (I) or (III) had to be assigned to galanthamine depending on whether an acid-catalysed dienone-phenol rearrangement had occurred during the above treatment.



(I)

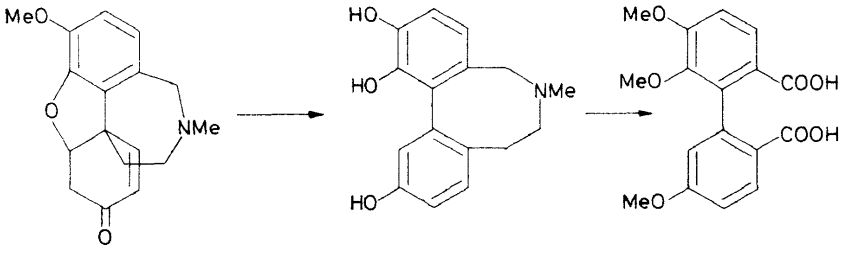


(II)



(III)

Of these two structures we chose structure (I) for galanthamine, and concluded that apogalanthamine must be the product of an acid-catalysed rearrangement, since the structure (I) was consistent with the resistance of galanthamine toward the dehydrogenation. Further support for this structure was provided by the fact that treatment of galanthaminone (narwedine) (IV) with hydrogen iodide afforded hydroxyapogalanthamine, which was shown to be represented by the formula (V), not only by its conversion to the known 5,5′,6-trimethoxydiphenic acid (VI) but also by a synthesis of its trimethyl-derivative[7, 8]. This was accomplished as follows using either the nitrostyrene method or the method which we had developed for the synthesis of apogalanthamine[6].

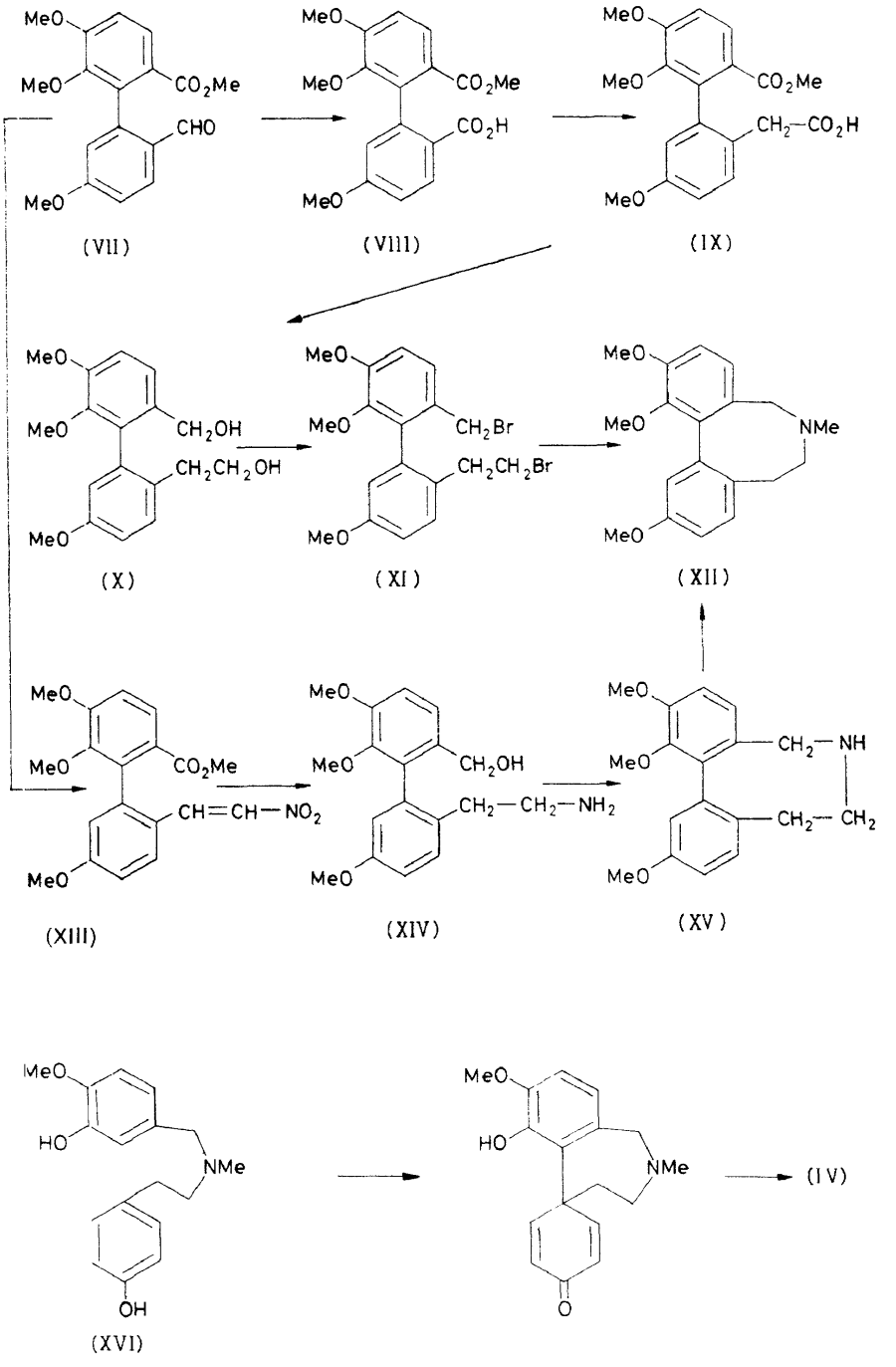


(IV) (V) (VI)

Aldehydo-trimethoxybiphenylcarboxylic ester (VII), which was obtained by the Ullmann condensation of 2-iodo-4-methoxy-benzaldehyde and methyl 2-bromoveratrate, was oxidized to a half ester (VIII), which was converted into the acid chloride, and then into the homologue (IX) by the Arndt-Eistert reaction. Lithium aluminium hydride reduction of (IX) gave a diol (X), which was converted into the dibromide (XI) by treatment with phosphorus tribromide. The desired compound (XII) was obtained by heating (XI) with methylamine in a sealed tube.

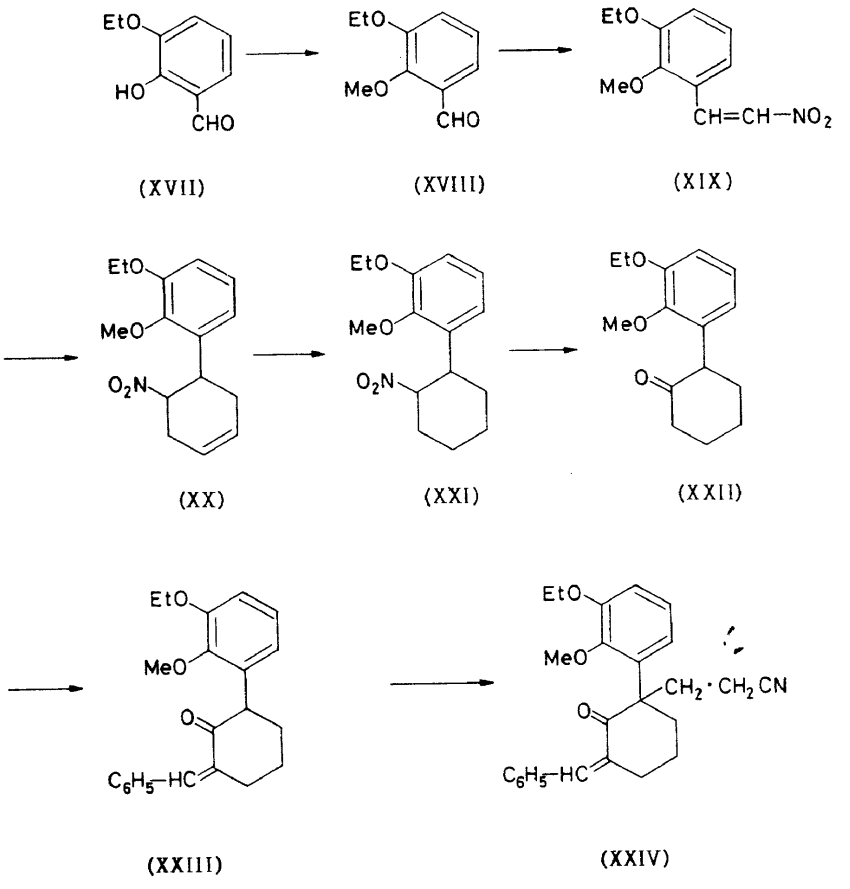
In the second method, the same compound (VII) was used as a starting material and it was converted into the nitrostyrene (XIII) by treatment with nitromethane under drastic conditions. The lithium aluminium hydride reduction of this compound gave an amino-alcohol (XIV), whose hydroxyl group was replaced by a bromine with phosphorus tribromide, and then converted into the secondary amine (XV) by cyclization in an alkaline solution. Methylation of (XV) with formic acid and formaldehyde afforded the compound (XII).

These methods are considered to be generally applicable to the preparation of analogous eight-membered heterocyclic compounds. Establishment of the structure of hydroxyapogalanthamine, and the fact that galanthaminone contains an active methylene group and an unsaturated ketone grouping, confirmed structure (I) for galanthamine. At about the same time as we reached this conclusion, Barton and Cohen[9] independently suggested the same structure based on our previous experiments and their biogenetic considerations.


MeO
MeO
CO2Me
CHO
(VII)
CO2H
(VIII)
CH2—CO2H
(IX)
CH2OH
CH2CH2OH
(X)
CH2Br
CH2CH2Br
(XI)
NMe
(XII)
CH=CH—NO2
(XIII)
CH2—CH2—NH2
(XIV)
CH2—NH
CH2—CH2
(XV)

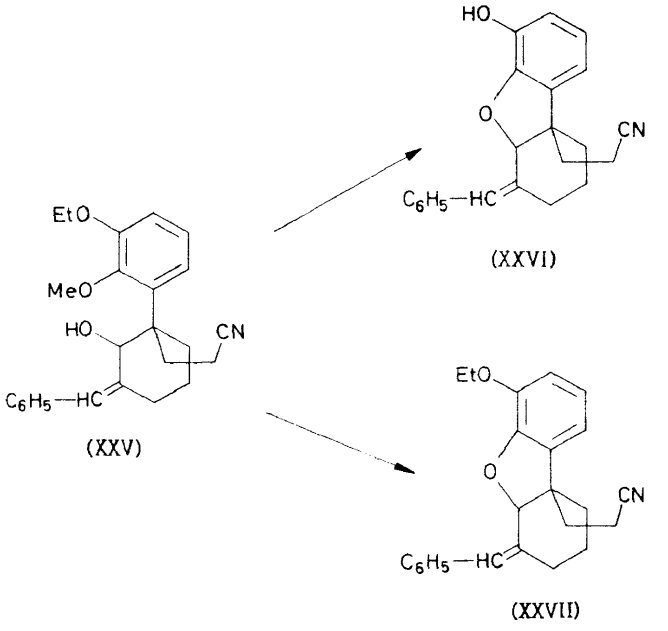
MeO
HO
NMe
OH
(XVI)
O
(IV)

Recently, this proposed biogenetic pathway has been duplicated[10] in the laboratory by an elegant synthesis of galanthamine *via* narwedine (IV) which was obtained by *ortho* and *para* coupling of 4-hydroxy-*N*-(3-hydroxy-4-methoxybenzyl)-*N*-methyl-phenethylamine (XVI), though the yield of the coupling reaction was reported to be very poor. The synthetic steps modelled along the lines of biogenetic hypothesis are few, but a structural proof of this sort is always open to the objection that it is not always easy to show that the reaction path is unique. Prior to the publication of this successful synthesis, we[11] had independently accomplished a synthesis of deoxydemethyl-dihydrogalanthamine by the following unambiguous chemical method and established conclusively that galanthamine has a dihydrofuran and a seven-membered nitrogenous ring.



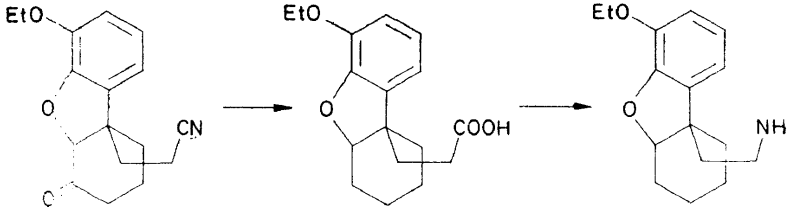
As a starting material we used commercially available 3-ethoxy-2-hydroxybenzaldehyde (XVII) which after methylation was condensed with nitromethane to give the nitrostyrene (XIX). Reaction with butadiene, by the method used by Wildman and Wildman[12], formed the nitrocyclohexene

(XX). The double bond in this compound was reduced, and the product was converted into a cyclohexanone (XXII) by the Nef reaction. Since a preliminary experiment indicated that both positions adjacent to the carbonyl group in (XXII) underwent cyanoethylation, it was necessary to protect the methylene group by converting it into the benzylidene derivative (XXIII) in order to obtain the desired monocyanoethyl product (XXIV) by attack at the benzylic position.



(XXV) (XXVI) (XXVII)

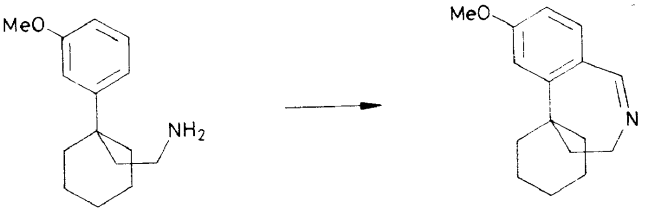
The next step was the reduction of this carbonyl-group with sodium borohydride. The conversion of this hydroxyl group into an oxide ring was achieved in the first instance in only 12 per cent yield by heating the compound with pyridine hydrochloride, but simultaneous dealkylation of the ethoxyl group to give (XXVI) could not be avoided. A better yield of the oxide ring was realized when the hydroxy-compound (XXV) was heated with phosphorus tribromide. In this case the yield of (XXVII) was 51 per cent, and dealkylation of the ethoxyl group was scarcely observed.



(XXVIII) (XXIX) (XXX)

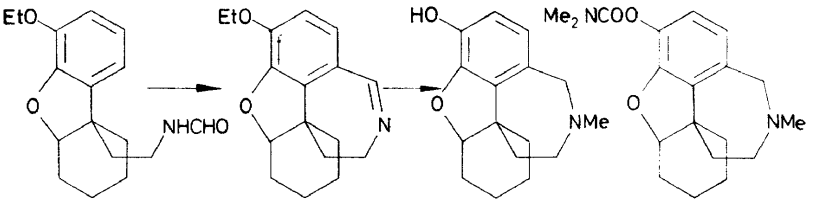
The benzylidene derivative (XXVII) was oxidized by potassium permanganate to the ketone (XXVIII) which was reduced by the Wolff-Kishner method to give a carboxylic acid (XXIX) as a result of concomitant saponification of the cyano group in the alkaline medium. The carboxylic acid was converted into the amine (XXX) by the Curtius reaction.

For the next step, namely the ring-closure of this amine to a seven-membered ring, the Pictet-Spengler and the Bischler-Napieralski reactions were tried. Since no precedent was found in the literature for the preparation of a seven-membered heterocyclic ring by means of these reactions, we first of all examined the preparation of some model compounds.



(XXXI) (XXXII)

Using 3-(*m*-methoxyphenyl)-3,3-pentamethylene propylamine (XXXI) as a model compound, we compared these two reactions and found, under the conditions used by us, that the Pictet-Spengler reaction was not successful, but that the Bischler-Napieralski reaction afforded the desired seven-membered ring compound (XXXII) although the yield was only 12·3 per cent.

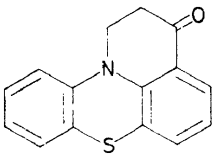


(XXXIII) (XXXIV) (XXXV) (XXXVI)

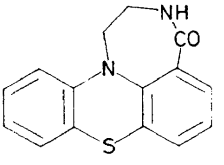
Under analogous conditions, application of the Bischler-Napieralski reaction to the formamide (XXXIII) gave a basic substance (XXXIV) in 20 per cent yield. The crystalline methiodide of this base was reduced by sodium borohydride, and the product was de-ethylated with 48 per cent hydrobromic acid. In this way a compound, m.p. 225–226°, was obtained which was identical in all respects with the corresponding compound (XXXV) derived from (±)-narwedine.

Thus, we have been able to prove that galanthamine has a spiro-structure and a seven-membered heterocyclic ring. If we could improve some stages of the synthesis, especially the ring closure, by adopting the Schmidt reaction

as discussed below, this sequence of reactions might afford a practical method for the synthesis of a compound such as (XXXVI) which has strong anti-choline-esterase activity[13].



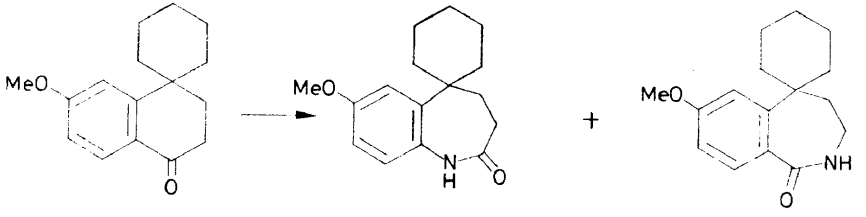
(XXXVII)



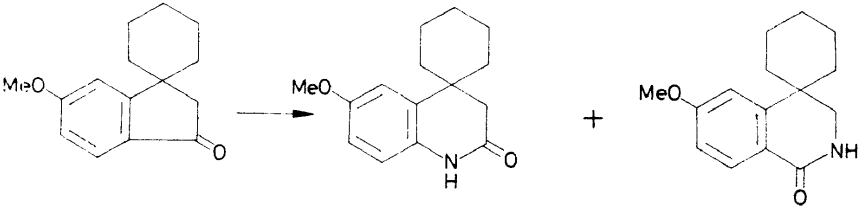
(XXXVIII)

Towards the end of this synthetic study, Ichii[14] showed that the Schmidt reaction on 1,2-dihydro-3*H*-pyrido [3,2,1-*kl*] phenothiazine-3-one (XXXVII) afforded, contrary to his initial expectation, compound (XXXVIII) in which the nitrogen atom introduced was not adjacent to a benzene ring. Although Smith[15] reported that the Schmidt reaction with tetraline gave homodihydrocarbostyril, we considered that the formation of a homodihydroisocarbostyril was possible with a substituted tetralone possessing an electron releasing group (*e.g.* alkoxyl) in the position *ortho* or *para* to the carbonyl group.

In order to confirm this idea, we undertook several experiments using a tetralone (XXXIX) and an indanone (XLII). We found that the tetralone gave a normal product, homocarbostyril (XL), in 38 per cent yield and an abnormal product, homoisocarbostyril (XLI), in 28 per cent yield. The nature of the remaining products still remains to be elucidated. In the case of the indanone (XLII), the carbostyril (XLIII) was obtained in only 7



(XXXIX) (XL) (XLI)



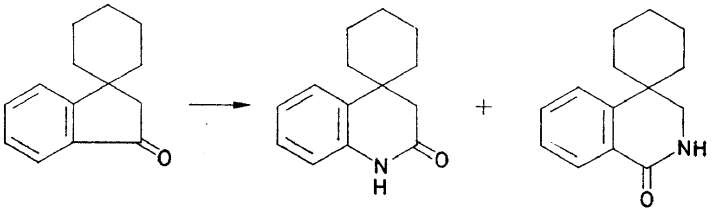
(XLII) (XLIII) (XLIV)

U

per cent yield, while the yield of the isocarbostyril (XLIV) was as high as 71 per cent.

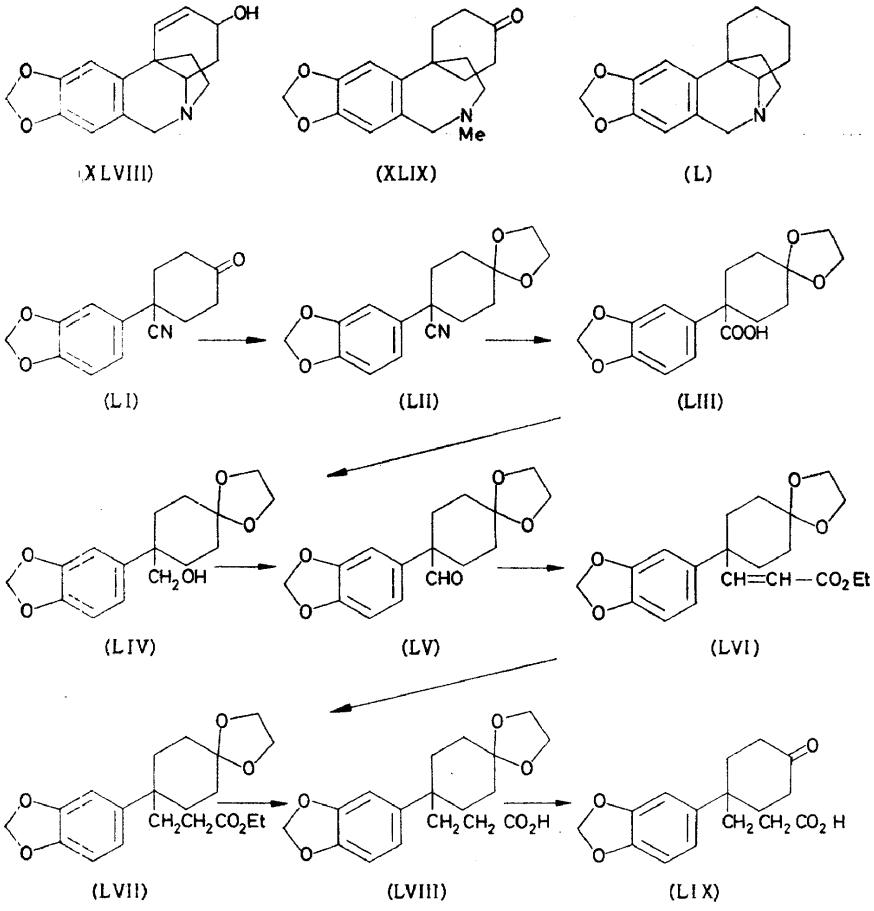
To confirm the structures assigned to these products, direct reduction of the lactams with lithium aluminium hydride and comparison of the ultraviolet light absorption spectra of the resulting amines is possible, but this is best done after *N*-methylation, since (XLI), for example, reduces very poorly compared with (XL).

In contrast to the above results we ascertained that when the compound (XLV), containing no methoxyl group in the benzene ring, was subjected to the Schmidt reaction the carbostryil (XLVI) was obtained in 54 per cent yield and the isocarbostyril (XLVII) in 5 per cent yield.



(XLV) (XLVI) (XLVII)

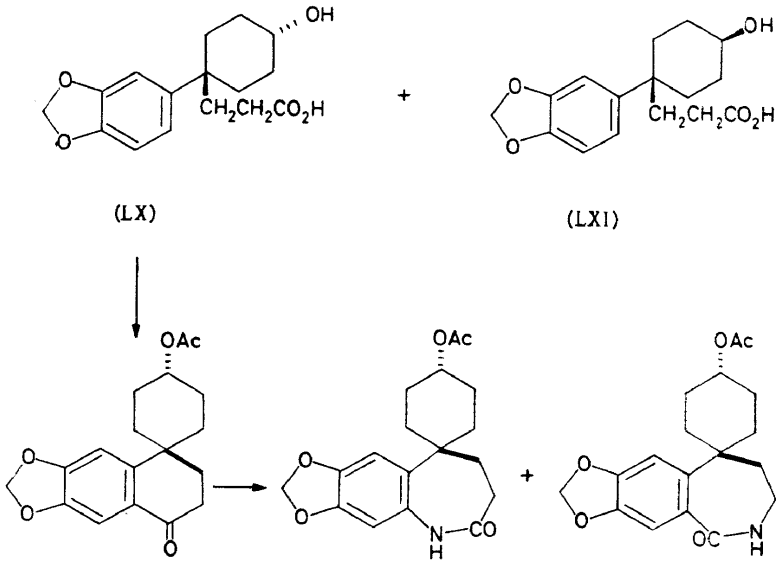
From the above experiments, it became clear that the methoxyl group located at the *p*-position to a carbonyl group plays an important rôle in determining the direction of this reaction. These discoveries found an application in the synthesis of tetrahydro-oxocrinine methine (XLIX) which represents another example of a base containing a seven-membered heterocyclic ring. The structure (XLVIII) has been proposed for crinine, and the synthesis of its skeleton, crinane (L), was accomplished by Wildman[16], but the position of the original hydroxyl group in the molecule was assigned only from the fact that tetrahydro-oxocrinine methine was optically inactive and hence had a plane of symmetry. It was felt, therefore, that a synthesis of this methine would be of use in establishing unequivocally the location of the hydroxyl group, and thus the structure of crinine itself. Furthermore, it would be a test case to show the usefulness of the Schmidt reaction as a synthetic approach to such natural products, thereby making them readily accessible. As a starting material for this synthesis, we selected the cyanoketone (LI) which we had already prepared[17] in the course of our synthesis of a degradation product of the alkaloid tazettine. After many unsuccessful attempts to lengthen the carbon chain of this cyano group by two units, we found that we were able to achieve our aim by the following sequence of reactions. After masking the ketone function with ethylene glycol to give the ketal (LII), the cyano group was hydrolysed with alkali. The carboxyl group in the product (LIII) was reduced with lithium aluminium hydride to give an alcohol (LIV), which was oxidized with chromic acid to give the aldehyde (LV) in 30 per cent over-all yield. The Wittig reaction was then used in the next step. Other well-known reactions, such as those of Cope,



Knoevenagel, and Reformatsky did not work smoothly. However, we obtained the acrylate (LVI) in excellent yield by the Wadsworth and Emmons[18] modification of the Wittig synthesis.

Successive reactions, *viz.* reduction of the double bond, hydrolysis of the ester and of the ketal group, and reduction of the ketone group to the alcohol had to be carried out before cyclization of the carboxylic acid to the tetralone, since the ketal would not be stable enough under the acidic conditions used in this reaction, and it was necessary to control the Schmidt reaction so that it took place at only one position and not at two. The sodium borohydride reduction of ketocarboxylic acid (LIX) gave two stereoisomers (LX and LXI) of the hydroxycarboxylic acid, of which the *trans*-isomer (LX) was the predominant product. This may be due to the bulkiness of the three carbon chain which prefers the equatorial orientation. The *trans*-compound (LX) was used for the next step. After acetylation of its hydroxyl group, it was converted into the acid chloride with phosphorus pentachloride, and cyclized with stannic chloride to furnish the tetralone (LXII).

Application of the Schmidt reaction to this compound using sodium azide in trichloroacetic acid afforded two isomeric lactams in almost equal amounts. For positive identification of the desired compound, comparison of the ultraviolet spectra of the two reduced compounds (obtained by reaction with lithium aluminium hydride) was preferred to direct comparison

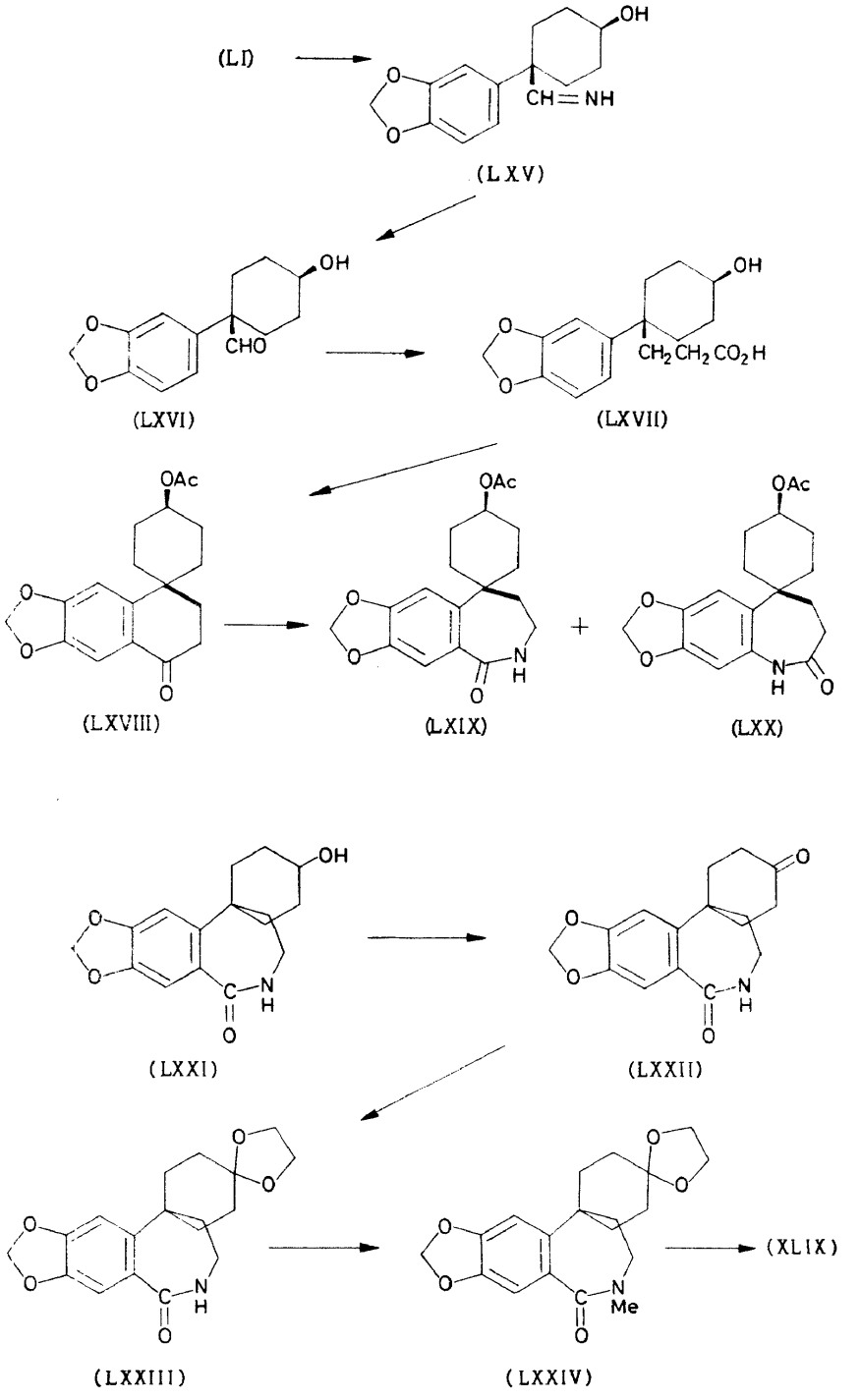


(LX) (LXI)

(LXII) (LXIII) (LXIV)

of the infrared and ultraviolet spectra of the lactams, since the ultraviolet spectrum of the reduction product of the desired compound (LXIV) should remain essentially unaltered in both acid and alkaline media, and thus allow a clear differentiation to be made.

Towards the end of our many experiments to obtain a sufficient amount of this compound, we noticed that mild lithium aluminium hydride reduction of the keto-nitrile (LI) gave an aldimine (LXV) which was readily hydrolysed with acid to give the hydroxy-aldehyde (LXVI) in good yield. The *cis*-configuration of the hydroxyl group and the aldehyde group in this compound (LXVI) was proved by the fact that the corresponding hydroxy-carboxylic acid formed a lactone. A Wittig reaction on this compound, using conditions identical with those described above, hydrogenation of the resulting double bond, and Friedel-Crafts cyclization of the saturated carboxylic acid (LXVII) gave the tetralone (LXVIII). A Schmidt reaction with this compound gave two seven-membered ring lactams which were not identical with those obtained before because of the difference in configuration of the hydroxyl group, but the desired homoisocarbostyril (LXIX) could be characterized by the method described above. Since direct reduction of this lactam, gave an amine in a poor yield, the procedure used by Gates and Tschudi[19] in the synthesis of morphine was adopted. Thus, after deacetylation, the resulting hydroxy compound was oxidized to the

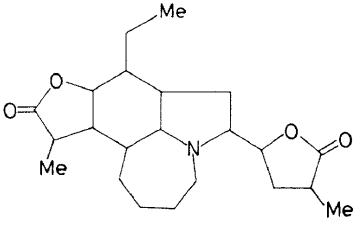

(LI)
OH
CH=NH
(LXV)
OH
CHO
(LXVI)
OH
CH2CH2CO2H
(LXVII)
OAc
(LXVIII)
OAc
N
H
(LXIX)
+
OAc
N
H
(LXX)
OH
(LXXI)
(LXXII)
(LXXIII)
N
Me
(LXXIV)
(XLIX)

ketone (LXXII) which was then protected by converting it into the ketal (LXXIII). The latter was *N*-methylated with sodium hydride and methyl iodide, and the product (LXXIV) was reduced with lithium aluminium hydride. Extraction with acid caused hydrolysis of the ethylene ketal group, and the product isolated after basification was a crystalline compound. This derivative was identical in every respect with an authentic sample of tetrahydro-oxocrinine methine (XLIX) kindly furnished by Professor Wildman of the Iowa State University.

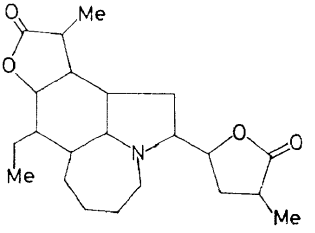
This synthesis adds further support to the structure of crinine, and could conceivably be extended to the total synthesis of the alkaloid.

An additional example of a nitrogen-containing seven-membered heterocyclic compound is the alkaloid tuberostemonine which was isolated from the roots of *Stemona tuberoso*, *Stemonaceae*. So far, four species belonging to this family have been investigated. As early as 1889 Inoko[20] began studies on the constituents of a species of this family. From 1911 onwards Suzuki[21] carried out the isolation and structural investigation of at least four alkaloids without making any notable contribution to their chemistry. In 1936 Schild[22] reported chemical studies on one of the alkaloids which was probably identical with Suzuki's tuberostemonine.

About this time, Kondo[23] took up the problem. He studied mainly the dehydrogenation of the base, and identified some of the functional groups in the molecule, *viz.* a pyrrolidine ring, two lactone rings, and ethyl and methyl side chains. In 1959 we joined the research group and started an investigation of this base. Early last year, we became acquainted with the paper of Götz, Bögri and Gray[24] who proposed two alternative structures (LXXV and LXXVI) for tuberostemonine mainly on the results of a nuclear magnetic resonance study of this alkaloid and some of its degradation products. This prompted us to submit a communication[25] in which we reported that we had also come to the same conclusions concerning the structure of the alkaloid. In marked contrast to the work conducted in



(LXXV)

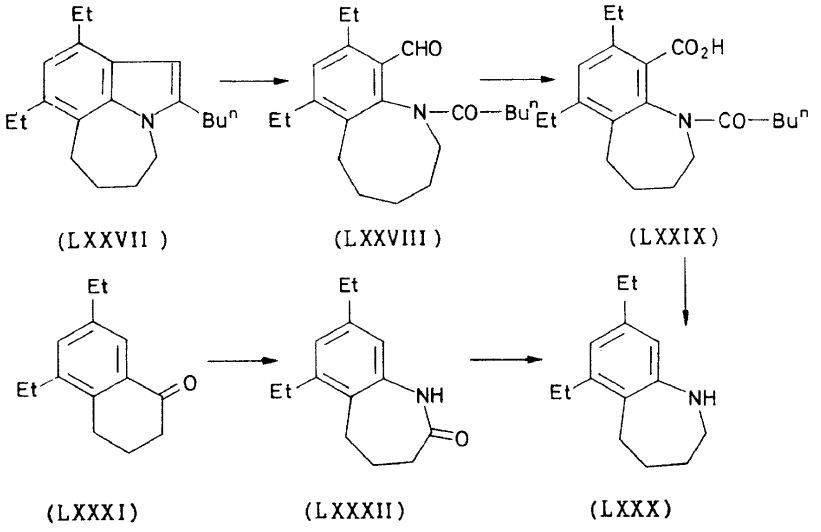


(LXXVI)

New Brunswick, our work was concerned primarily with the dehydrogenation of tuberostemonine with the purpose of elucidating the skeleton of this alkaloid by synthetic means. The results obtained by us gave strong support to the heterocyclic moiety proposed by the above authors, *viz.* the azepino-[3,2,1-*hi*]-indole system.

Our re-investigation of the dehydrogenation of the alkaloid carried out by Kondo, furnished five crystalline compounds in minor yields and one oily compound in a yield as high as 70 per cent. The good yield of the oil, together with our finding that it was in all respects homogeneous, led us to pursue the structure of this compound which was named tuberostemonane (LXXVII).

Tuberostemonane was analysed for $C_{20}H_{29}N$, and exhibited the ultraviolet light absorption bands characteristic of an indole. On the basis of this finding, and a positive Ehrlich test, we assumed that tuberostemonane was an indole derivative and subjected it to ozonolysis in order to cleave the indole ring by the standard method. As expected, the crystalline compound thus obtained was found to be an amido-aldehyde (LXXVIII) as shown by the infrared and the ultraviolet light absorption spectra. This amido-aldehyde was oxidized to an amido-carboxylic acid (LXXIX) by potassium permanganate or nickel peroxide. As the carboxyl band in the



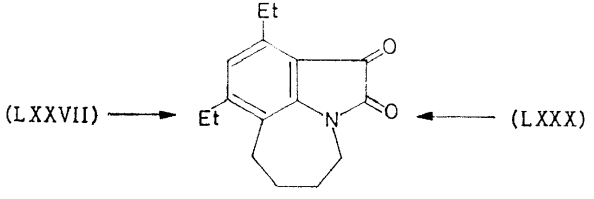
infrared spectrum of this acid was at a higher frequency than expected, it was assumed to be sterically hindered. The nuclear magnetic resonance spectrum showed two methyl groups present in ethyl side chains, and one hydrogen in the benzene ring.

These very useful findings made it possible for us to write down a structure (LXXIX) for this amido-carboxylic acid. In order to establish this structure with certainty, cleavage of the amide linkage was attempted, but without much success. In most instances, the starting material was recovered unchanged on treatment with acids or alkalies. Alkaline fusion afforded an amino-acid, but the yield was so poor that the procedure was not practical. A successful hydrolysis of the amide linkage was finally achieved by heating

it with concentrated hydrochloric acid in acetic acid in a sealed tube. This gave an amine by hydrolysis of the amide linkage and subsequent decarboxylation. The acid portion of the amide was identified as n-valeric acid by gas–liquid chromatography. The amine was an oil, characterized as its styphnate; its infrared light absorption indicated the presence of a 1,2,3,5,-tetrasubstituted benzene ring and the ultraviolet light absorption spectrum resembled that of 2,3,4,5-tetrahydro-1*H*-1-benzazepine rather than that of tetrahydroquinoline.

In good agreement with these findings, it resisted dehydrogenation over palladium–carbon, but under drastic conditions it was possible to obtain a compound which showed the ultraviolet light absorption bands characteristic of quinoline. Thus, this compound must be diethyl-tetrahydrobenzazepine as represented by the formula (LXXX), and this was proved by the following synthesis.

The commercially available 1,3-diethylbenzene was converted into a ketocarboxylic acid by a Friedel-Crafts condensation with succinic anhydride. After Clemmensen reduction of this ketone, the product was converted into the tetralone (LXXXI) using again the Friedel-Crafts reaction. As expected, the Schmidt reaction afforded in this case a compound (LXXXII) of the homoquinoline type in which the nitrogen atom is adjacent to the benzene ring. The lithium aluminium hydride reduction of this lactam readily gave an amine (LXXX), identical in all respects with the compound derived from the natural sources as stated above. Thus the structure of tuberostemonane was established as (LXXVII).



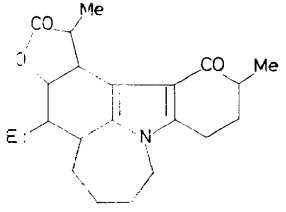
(LXXXIII)

Further treatment of the amine (LXXX) thus obtained with chloralhydrate, hydroxylamine and anhydrous sodium sulphate in hydrochloric acid by Sandmeyer's method gave the isatin (LXXXIII) which was shown to be identical with a permanganate oxidation product of tuberostemonane. This provided conclusive proof that tuberostemonane possessed an indole ring.

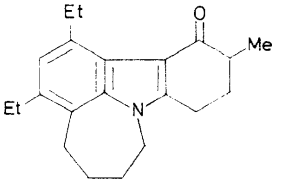
In conjunction with the earlier findings of Kondo and his collaborators, and especially of Edwards, Feniak and Handa[26], there is no doubt that our results represent alternative evidence for the structure (LXXV) or (LXXVI) for tuberostemonine, as advanced by the Canadian authors, if we rule out the possibility of a rearrangement during the initial dehydrogenation over palladium–carbon.

It should be added that very recently Edwards and Feniak[27] have favoured the structure (LXXVI) rather than (LXXV) on the bases of their nuclear magnetic resonance studies.

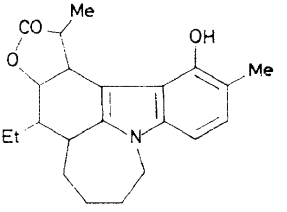
As to the crystalline dehydrogation products mentioned above, we have arrived at the conclusion that three of them should be represented by the formulae (LXXXIV), (LXXXV) and (LXXXVI).



(LXXXIV)



(LXXXV)



(LXXXVI)

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