STRUCTURE OF NORLOLINE, LOLINE, AND LOLININE

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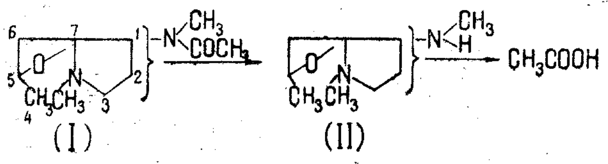
Khimiya Prirodnykh Soedinenii, Vol. 1, No. 4, pp. 262-271, 1965

The production of pyrrolizidine from loline [1] has established the main heterocyclic nucleus of norloline and lolinine.

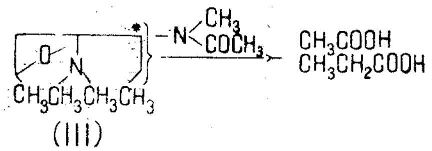
On a basis of the study of the products of the Hofmann degradation of lolinine [2], the formation of two molecules of acetic acid (instead of three) in the chromic anhydride oxidation [3] of tetrahydro-des-N-dimethyl-lolinine (III), and reduction, and also a study of other properties of the alkaloids mentioned, a structural formula has been put forward for them in which the side-chain nitrogen atom is located on C_2 and the ether bridge at C_2-C_5 [2].

In the present paper we give more detailed information obtained in an investigation of the location of the second valency of the oxygen atom and the side-chain nitrogen atom. As we have reported previously [2], the assumption that one valency of the oxygen atom and the side-chain nitrogen atom are on the same carbon atom (in the β position with respect to the tertiary nitrogen atom in $\mathrm{C{-}O{-}\overset{|}{\underset{|}{C}}_2{-}N}\lt$ of the molecule of the three alkaloids) is still completely unproven. To settle this question, we have re-investigated the products of the Hofmann degradation of lolinine [2] and dihydrodeoxyloline [1] with subsequent oxidation by a modified Percheron method [4, 5].

The acetyl residue on the side-chain nitrogen of dihydro-des-N-methyl-lolinine (I) was saponified with 20% hydrochloric acid, giving dihydro-des-N-methyl-loline (II). The latter was oxidized with chromic acid and the volatile acids were collected. On paper chromatography, only acetic acid was detected. Its formation from the des-base (II) confirmed once more that one valency of the oxygen atom is connected to the β carbon atom with respect to the tertiary nitrogen atom of the pyrrolizidine:



The chromic acid oxidation of tetrahydro-des-N-dimethyl-lolinine (III) gave acetic and propionic acids. The formation of propionic acid from the des-base (III) showed that in the second stage of Hofmann degradation it is the bond at the C_3 atom that is ruptured and not that at C_7, as we have previously assumed on the erroneous basis of the production of two molecules of acetic acid from the des-base (III). There are no substituents on the C_2 and C_3 atoms of the lolinine molecule. This is the only way in which it is possible to explain the formation of propionic acid from the des-base (III). Thus, the C_1 position in the lolinine molecule is substituted by the oxygen bridge or by the side-chain nitrogen atom. If C_1 were also free from substituting groups, the oxidation of substance (III) should give not only propionic acid but also butyric acid:

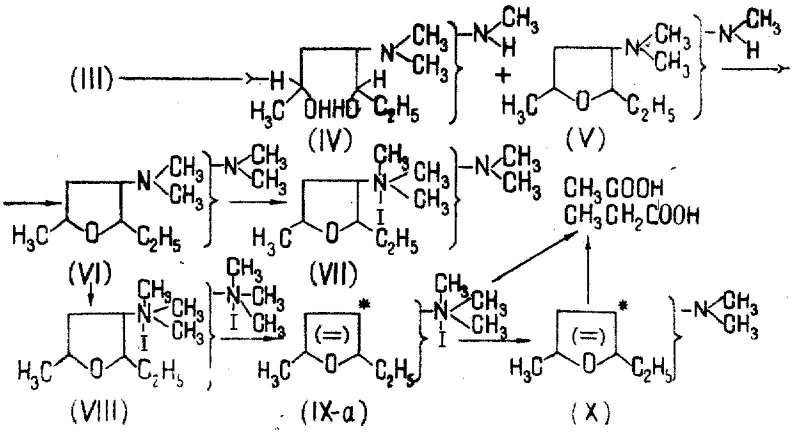


In a further study of this question, the acetyl group of the des-base (III) was saponified with 30% sulfuric acid. Two substances were isolated from the reaction products: dihydroxytetrahydro-des-N-dimethyl-loline (IV) and tetrahydro-des-N-dimethyl-loline (V). Compound (IV) was formed through the saponification of the ether bridge and the acetyl group on the side-chain nitrogen atom, while in the case of compound (V) only the acetyl group was saponified.

Substance (V) was methylated with formaldehyde and formic acid, giving tetrahydro-des-N-dimethyl-N'-methyl-loline (VI). The product of the methylation of the des-base (VI) formed a monomethiodide (VII) and a dimethiodide (VIII). Hofmann degradation of the monomethiodide (VII) did not take place, while it took place smoothly with the dimethiodide (VIII), the nitrogen atom present in the side chain of lolinine being split off (lolinine ethiodide, which will be discussed below, was used to prove the elimination of the lateral nitrogen atom). The products of the Hofmann degradation of (VIII) yielded tetrahydrohemiloline methiodide (IX) and a small amount of tetrahydrohemiloline (X).

Substance (IX) melted at 133°and was optically active, $[\alpha]_D$ −26.07° (methanol). Compound (X) was a liquid, $[\alpha]_D$ + +16.94° (ethanol).

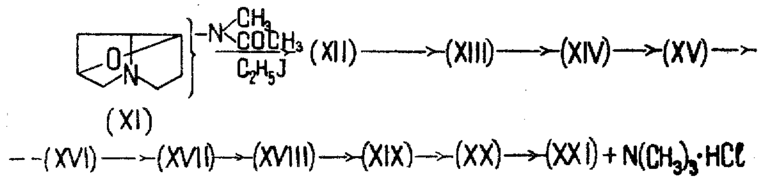
When compound (X) was oxidized with chromic acid, it also gave acetic and propionic acids. The propionic acid formed from tetrahydrohemiloline (X), and the optical activity of this substance, exclude the possibility that the second bond of the oxygen atom and the side-chain nitrogen atom are present on the same carbon atom of the pyrrolizidine. If both functional groups were present at C_1, Hofmann degradation of tetrahydro-des-N-dimethyl-N'-methyl-loline methiodide (VIII) would form optically inactive compounds (IX-a) and (X), or a substance (X), the oxidation of which would not give propionic acid. Consequently, the second bond of the oxygen atom in lolinine must be located in C_1. If position C_1 were completely free from substituents, oxidation would have given butyric acid, in addition to acetic and propionic acids. In no case was butyric acid found on chromic acid oxidation. These properties of substance (VIII) show that the side-chain nitrogen atom must be present on one of the carbon atoms at positions 6 and 7, and the second valency of the oxygen atom must be attached to the carbon atom in position 1. Thus, the oxygen bridge in the lolinine molecule is present between C_1 and C_5:



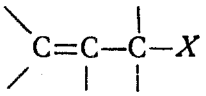
The fact that it was the side-chain nitrogen atom that was eliminated in the Hofmann degradation of the dimethiodide (VIII) was established as follows.

The action of ethyl iodide on lolinine (XI) [2] gave crystalline lolinine ethiodide (XII), the Hofmann degradation of which led to the formation of des-N-ethyl-lolinine (XIII). On catalytic hydrogenation, substance (XIII) absorbed a molecule of hydrogen and was converted into dihydro-des-N-ethyl-lolinine (XIV). With methyl iodide, this base formed dihydro-des-N-ethyl-lolinine methiodide (XV) with mp 218-219° (without decomp.). In the second stage of the Hofmann degradation of compound (XV), dihydro-des-N-methylethyl-lolinine (XVI) was isolated. On catalytic hydrogenation, the latter gave tetrahydro-des-N-methylethyl-lolinine (XVII).

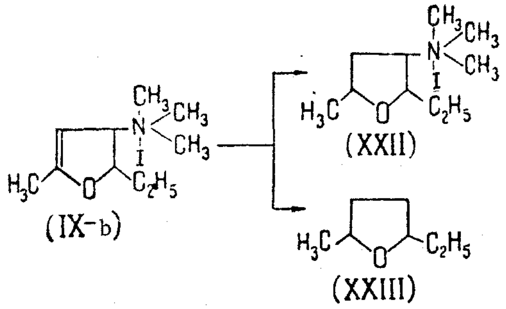
The N-acetyl group in substance (XVII) was saponified, giving tetrahydro-des-N-methylethyl-loline (XVIII). Methylation of compound (XVIII) with formaldehyde and formic acid gave tetrahydro-des-N-methylethyl-N'-methyl-loline (XIX), which, with methyl iodide, formed the dimethiodide (XX). The dimethiodide (XX) was subjected to Hofmann degradation. From the reaction product, trimethylamine was isolated almost quantitatively. The production of trimethylamine shows that in the Hofmann degradation of compounds (VIII) and (XX), only the lateral nitrogen atom is split off. If the nitrogen atom located between the two rings of pyrrolizidine were split off in the decomposition of substance (XX), we should have obtained ethyldimethylamine. In actual fact, the Hofmann degradation of compound (XX) gave not even traces of ethyldimethylamine. Thus, in this case, taking the course of the Hofmann degradation of lolinine [2] into account, this decomposition may be written in shortened form as



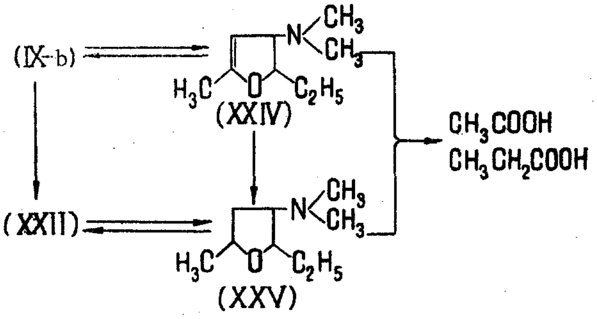
To elucidate the locations of the functional groups further, tetrahydrohemiloline methiodide (IX-a) was hydrogenated over a platinum catalyst. From the mixture of hydrogenation products was isolated hexahydrohemiloline methiodide (XXII) with mp 126°, $[\alpha]_D$ +16° (acetone), and a very small amount of a nitrogen-free substance, α-methyl-α'-ethyl-tetrahydrofuran (XXIII), together with trimethylamine hydriodide. The splitting out of trimethylamine and the formation of the nitrogen-free substance in the hydrogenation of the methiodide of compound (IX-a) shows that an allyl grouping



$>C=C-\overset{|}{\underset{|}{C}}-X$ is located in the molecule of substance (IX-a) in relation to the nitrogen [6-8]. If these properties are brought into consideration as well, the C_6 position in the pyrrolizidine nucleus remains for the lateral nitrogen atom. Consequently, in tetrahydrohemiloline methiodide (IX-b) the double bond must be between carbon atoms $C_5$and C_6:



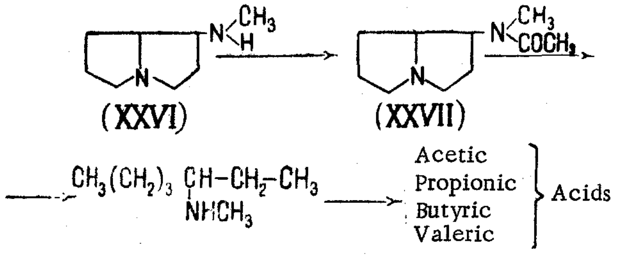
As can be seen from the formulas of substances (IX-b) and (XXII), there is a possibility for the occurrence of Hofmann degradation. Nevertheless, when Hofmann degradation was attempted under the action of freshly-precipitated silver hydroxide, in all cases methyl alcohol was split off from compounds (IX-b) and (XXII) with the formation of tetrahydrohemiloline (XXIV) and hexahydrohemiloline (XXV). This phenomenon is apparently connected with the spatial configuration of compounds (IX-b) and (XXII):



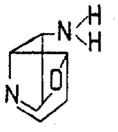
After the location of the oxygen bridge had been established, it remained to ascertain the position of the side-chain nitrogen atom. For this purpose, dihydrodeoxyloline (XXVI) [1] was acetylated with acetyl chloride in order to block the side-chain nitrogen atom. Acetylation took place instantaneously and vigorously with the evolution of heat. The reaction mixture was decomposed with 40% caustic soda, and the N acetyldihydrodeoxyloline (XXVII) was extracted with ether. Hofmann degradation of substance (XXVII) was repeated three times with subsequent hydrogenation. After the elimination of the tertiary nitrogen atom, and the acetyl group on the side-chain nitrogen atom was saponified, and octahydrodeoxyhemiloline (XXVIII) was obtained as the final product.

Substance (XXVIII) was oxidized with chromic acid. In the volatile acids produced, acetic, propionic, butyric, and valeric were identified by paper chromatography. The formation of valeric acid from compound (XXVIII), and also the results of a study of the other properties mentioned above indicate that the lateral nitrogen atom is present on the sixth carbon atom in dihydrodeoxyloline (XXVI).

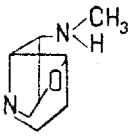
Taking all the properties found in the investigation of the structure of lolinine into account, the course of the decomposition of dihydrodeoxyloline (XXVI) can be represented in shortened form as follows:



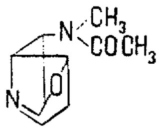
Thus, the alkaloids norloline (XXIX), loline (XXX), and lolinine (XXXI) must have the following structural formulae:



(XXIX)



(XXX)



(XXXI)

Experimental

Saponification of (I) with 20% hydrochloric acid. A mixture of 300 mg of the des-base (I) and 1.5 ml of 20% hydrochloric acid was heated for 6 hr in a sealed tube at 100°. Then the tube was opened. The excess of acid was evaporated off on a water bath. The residue crystallized. After recrystallization from a mixture of methanol and acetone, the hydrochloride of (II) melted at 260-262° (decomp). Yield 260 mg.

150 mg of the hydrochloride of (II) was decomposed with ammonia, and exhaustively extracted with ether. The residue was distilled under vacuum. The yield of substance (II) was 60 mg.

Chromic acid oxidation of (II). 25 mg of compound (II) was oxidized with 4 ml of chromic acid mixture [9]. The experiment was carried out by the modified Percheron method [4, 5]. The residue was chromatographed on paper in parallel with a standard. No higher acids than acetic were found. For acetic acid, R_f 0.25.

Chromic acid oxidation of (III). 25 mg of compound (III) was oxidized with 4 ml of chromic acid mixture. The experiment was carried out as in the case of (II). Of the volatile acids, acetic acid with R_f 0.25 and propionic acid with R_f 0.37 were identified.

Saponification of (III) with 30% sulfuric acid. A mixture of 2 g of substance (III) and 20 ml of 30% sulfuric acid was heated on a boiling water bath for 2 hr. Then the reaction mixture was made alkaline with 40% caustic soda and was extracted with ether. The reaction product was distilled. Two fractions were obtained. The low-boiling fraction consisted of compound (V). Yield 900 mg, bp 90° (2 mm), $[\alpha]_D^{25}$ −21.79° (c 5.74; methanol). The second fraction (350 mg) consisted of substance (IV), bp 136-138° (2 mm), $[\alpha]_D$ +1.81° (c 4.97; methanol).

Methylation of (V). Formaldehyde and formic acid (equimolar amounts) were added to a solution of 1 g of substance (V) in 1.5 ml of water. The mixture was heated for 10 hr on a boiling water bath under reflux, and then the reaction mixture was acidified with sulfuric acid and was washed several times with ether. The acid solution was neutralized with 40% caustic soda and the methylation product was extracted with ether. The yield of compound (VI) was 920 mg, bp 93° (2 mm), $[\alpha]_D^{29}$ +16.4° (c 3.828; methanol).

Monomethiodide of (VII). A solution of 250 mg of substance (VI) in 1.5 ml of methanol was treated with methyl iodide (equimolar amount). The reaction mixture was boiled in a flask with a reflux condenser for 5 min. Yield 420 mg. After recrystallization from a mixture of acetone and ether, the monomethiodide (VII) melted at 128-129°, $[\alpha]_D^{18}$ +15.77° (c 3.3; acetone).

Found, %: I 37.1. Calculated for $C_{12}H_{27}N_2OI$, %: I 37.08.

The Hofmann degradation of substance (VII) did not take place in a 30% methanolic solution of caustic potash. The initial methiodide (VII) was recovered.

The dimethiodide (VIII). This compound was formed instantaneously from (VII), and also from the des-base (VI) when 2 moles of methyl iodide was added. After recrystallization from ethanol, (VIII) melted at 194°;

Found, %: I 51.8. Calculated for $C_{13}H_{30}N_2OI_2$, %: I 52.42.

Hofmann degradation of (VIII). A mixture of 2 g of substance (VIII) and 40 ml of 30% methanolic caustic potash was heated on a boiling water bath for 4 hr. The trimethylamine was collected in 2% aqueous hydrochloric acid. The methanol was eliminated completely in vacuum (distillate A). The residue was dissolved in a small amount of water and the reaction product was extracted with chloroform. The yield of substance (IX) was 820 mg, mp 134° (from a mixture of ether and acetone).

Found, % : I 42.6. Calculated for $C_{10}H_{20}NOI$, %: I 42.70.

Distillate A was acidified with 2% hydrochloric acid and the methanol was evaporated off at room temperature. The residue was neutralized with caustic potash and was extracted with ether. The yield of compound (X) was 260 mg, mp 84-85° (5 mm) $[\alpha]_D^{20}$ +16.94° (c 2.36; ethanol).

Chromic acid oxidation of (X). 25 mg of substance (X) was oxidized with 4 ml of chromic acid mixture. The subsequent operations were carried out by a published method [4, 5]. The concentrate was chromatographed with standard substances on paper. Of the volatile acids, CH_3COOH with R_f 0.25 and CH_3CH_2COOH with R_f 0.37 were identified.

The ethiodide (XII). By the usual method, 4 g of substance (XI) gave the ethiodide (XII) with mp 117-118° (from a mixture of acetone and methanol). Yield 7 g.

Hofmann degradation of (XII). A solution of 7 g of compound (XII) in 100 ml of methanol was treated with freshly-precipitated silver hydroxide (from 2.4 g of $AgNO_3$). The solvent was distilled off completely. The residue was dissolved in 200 ml of ether. The des-base (XIII) passed into the ether. Yield 3.4 g.

The dihydro-des-base (XIV). 3.4 g of the des-base (XIII) was hydrogenated over a platinum catalyst, 1 mole of hydrogen being absorbed. Yield of substance (XIV) 3.4 g.

The methiodide (XV). A solution of 3.4 g of substance (XIV) in 10 ml of methanol was treated with 4 ml of methyl iodide. The mixture was boiled for 6 hr. Yield of (XV), 5.42 g, mp 218-219° (without decomp; ethanol).

Found, %: I 34.3. Calculated for $C_{14}H_{25}N_2O$, %: I 34.48.

Hofmann degradation of (XV). A solution of 5.42 g of the methiodide (XV) in methanol was treated with freshly precipitated silver hydroxide in the usual way. After the appropriate working up, compound (XVI) was isolated. Yield 2.8 g.

The tetrahydro-des-base (XVII). 2.8 g of the des-base (XVI) was hydrogenated with freshly-prepared platinum black, 1 mole of hydrogen being absorbed. The yield of substance (XVII) was 2.8 g.

Saponification of (XVII). A solution of 2.8 g of substance (XVII) in 28 ml of 20% sulfuric acid was heated on a boiling water bath for 4 hr and was then neutralized with 40% caustic soda and treated with ether. The yield of compound (XVIII) was 2.1 g.

Methylation of (XVIII). 2.1 g of the des-base (XVIII) was methylated with formaldehyde and formic acid (equimolar amounts). The mixture was heated until the evolution of carbon dioxide had ceased completely. Then the reaction mixture was neutralized with 40% caustic soda and was extracted with ether. Yield of (XIX) 2.08 g.

The dimethiodide (XX). A solution of 2.08 g of substance (XIX) in 5 ml of methanol was treated with 2 ml of methyl iodide. The mixture was boiled for 6 hr. The methanol and the excess of methyl iodide were eliminated completely. It was impossible to crystallize the residue. The yield of compound (XX) was 4.7 g.

Hofmann degradation of (XX). A solution of 2.5 g of the dimethiodide (XX) in 25 ml of 30% methanolic caustic potash was boiled for 6 hr. The volatile amine was collected in 2% aqueous hydrochloric acid. The acid solution was evaporated on a water bath and was then dried in vacuum. The residue crystallized, mp 271-274°. Yield of trimethylamine hydrochloride, 430 mg.

Hydrogenation of (IX-b). A solution of 2 g of the methiodide (IX-b) in 10 ml of ethanol was treated with 200 mg of platinum black. The mixture was shaken under a current of hydrogen for 6 hr, more than 1 mole of hydrogen being absorbed. The alcohol was evaporated off. The residue partially crystallized. Yield 720 mg (mother liquor A), mp 254-255° (ethanol). The crystals were identified as trimethylamine hydriodide.

The mother liquor A remaining after the separation of the trimethylamine iodide was treated with fresh ether. The highly volatile nitrogen-free substance (X) passed into the ether, and the trimethylamine hydriodide and the methiodide (XXII) remained partially in insoluble form. The yield of substance (X) was 60 mg.

The residue after the removal of the nitrogen-free substance was neutralized with 40% caustic soda and extracted with chloroform. Yield 940 mg. After recrystallization from a mixture of acetone and ether, compound (XXVII) melted at 125-126° (without decomp), $[\alpha]_D^{24}$ +16° (c 4; acetone).

Found, % : I 42.23. Calculated for $C_{10}H_{22}NOI$, %: I 42.41.

Hofmann degradation of (IX). A solution of 1 g of substance (IX) in 20 ml of methanol was treated with freshly-precipitated silver hydroxide (equimolar amount). The mixture was shaken until the iodide ion had been completely precipitated. The silver iodide which had been deposited was filtered off and the methanol was distilled off. The residue was insoluble in petroleum ether, ether, benzene, and acetone. It was readily soluble in methanol, ethanol, and water, which is characteristic for quaternary ammonium compounds. The reaction mixture was distilled in vacuum. Bp of the substance 84-85° (5 mm). Yield 420 g, $[\alpha]_D$ +16.94° (c 2.36; ethanol).

Found, %: N 8.93. Calculated for $C_{19}H_{17}NO$, %: N 9.02.

The methiodide (IX). A solution of 200 mg of substance (X) in 2 ml of methanol was treated with 0.5 ml of methyl iodide. The mixture was boiled for 1 hr and then the methanol and the excess of methyl iodide were evaporated off. The methiodide (IX-b) crystallized, mp 134°.

Chromic acid oxidation of (IX). 25 mg of substance (IX) was oxidized with 4 ml of chromic acid mixture. The whole operation was carried out exactly as described in the literature [5, 6]. In the oxidation products, CH_3COOH with Rf 0.25 and CH_3CH_2COOH with Rf 0.37 were identified with standard samples.

Hexahydrohemiloline (XXV). A solution of 1 g of substance (XXII) in 20 ml of methanol was treated with silver hydroxide. The silver iodide was filtered off and the methanol was distilled off. The residue, a quaternary ammonium base, was subjected to vacuum distillation. At 97-98° (5 mm), compound (XXV) distilled over with a yield of 240 mg, $[\alpha]_D^{29}$ −23.33° (c 3; ether).

The methiodide (XXII). A solution of 250 mg of substance (XXV) in 2 ml of methyl alcohol was treated with 0.5 ml of methyl iodide. The mixture was boiled for 1 hr. The yield of (XXII) was 460 mg, mp 125-126° (from a mixture of acetone and ether). A mixture with the methiodide obtained from substance (IX) by hydrogenation gave no depression of the melting point.

Chromic acid oxidation of (XXV). 25 mg of substance (XXV) was oxidised with 4 ml of chromic acid mixture. In the oxidation products, CH_3COOH with Rf 0.25 and CH_3CH_2COOH with Rf 0.37 were identified with standard samples.

Acetylation of (XXVI). With cooling, 4 g of the base was treated in drops with 8 ml of acetyl chloride. Acetylation took place very vigorously and rapidly with the evolution of heat. The yield of (XXVII) was 3.8 g.

Methiodide of N-acetyldihydrodeoxyloline. A solution of 3.8 g of the base (XXVII) in 10 ml of methanol was treated with 6 ml of ethyl iodide. The reaction took place instantaneously. A non-crystalline methiodide was obtained. Yield 6.54 g.

Hofmann degradation of N-acetyldihydrodeoxyloline methiodide. A solution of 6.54 g of the methiodide in 300 ml of methanol was treated with freshly-precipitated silver hydroxide. The des-base was separated from the quaternary ammonium compound by treatment with ether. Yield 2.9 g, $[\alpha]_D^{26}$ +34.47° (c 4.38; methanol).

Hydrogenation of the des-base. A solution of 2.9 g of the des-base in 30 ml of ethanol was treated with 0.3 g of freshly-prepared platinum black. The mixture was shaken under a current of hydrogen, 1 mole of hydrogen being absorbed. The yield of tetrahydro-des-N-methyl-N-acetyldeoxyloline was 2.9 g, $[\alpha]_D^{27}$ 15.11° (c 4.3; methanol).

Tetrahydro-des-N-methyl-N'-acetyldeoxyloline methiodide. The methiodide was obtained from 2.9 g of the tetrahydro-des-base by the usual method. Yield 4.53 g, mp 185-186° (from a mixture of ether and methanol).

Found, %: I 36.94. Calculated for $C_{12}H_{25}N_2O_2I$, %: I 37.30.

Hofmann degradation of the methiodide of the tetrahydro base. A solution of 4.53 g of the methiodide in 250 ml of methanol was treated with freshly-precipitated silver hydroxide. The silver iodide was separated off and the methanol was distilled off. The residue was heated in a glycerol bath at 100-110° for 6 hr. The reaction mixture was treated with dry ether. The tetrahydro-des-N-dimethyl-N'-acetyldeoxyloline passed into the ether. The yield of des-base was 2.25 g.

Hydrogenation of tetrahydro-des-N-dimethyl-N'-acetyldeoxyloline. A solution of 2.25 g of the des-base in 30 ml of ethanol was treated with 0.3 g of freshly prepared platinum black. The mixture was shaken under a current of hydrogen for 30 min, 1 mole of hydrogen being absorbed. The yield of hexahydro-des-N-dimethyl-N'-acetyldeoxyloline was 2.25 g.

Hexahydro-des-N-dimethyl-N'-acetyldeoxyloline methiodide. A mixture of 2.25 g of the hexahydro-des-base, 20 ml of methanol, and 4 ml of methyl iodide was boiled for 3 hr. The hexahydro-des-N-dimethyl-N'-acetyldeoxyloline could not be crystallized. Yield 3.72 g.

Hofmann degradation of hexahydro-des-N-dimethyl-N'-acetyldeoxyloline methiodide. A solution of 3.72 g of the methiodide of the hexahydro base in 50 ml of methanol was shaken with freshly precipitated silver hydroxide. The methanol was distilled off and the residue was subjected to distillation. On vacuum distillation, water and trimethylamine were split out. The trimethylamine was collected in 80% sulfuric acid. The yield of hexahydro-N-acetyldeoxyhemiloline was 1.85 g.

Saponification of hexahydro-N-acetyldeoxyhemiloline. 1.85 g of the hexahydro hemi product was heated with 30% sulfuric acid at 95-100° for 3 hr. Then the acid solution was made alkaline and was exhaustively extracted with ether. The yield of hexahydrohemiloline was 1.31 g.

Hydrogenation of hexahydrodeoxyhemiloline. On catalytic hydrogenation, 1.31 g of hexahydrodeoxyhemiloline absorbed 1 mole of hydrogen. The octahydrodeoxyhemiloline boiled at 85-87° (2 mm). Yield 630 mg.

Oxidation of octahydrodeoxyhemiloline (XXVIII). 25 mg of the substance was oxidized with 4 ml of chromic acid mixture. In the oxidation products, the following acids were identified with authentic samples by paper chromatography: acetic with Rf 0.25, propionic with Rf 0.37, butyric with Rf 0.52, and valeric with Rf 0.64.

Summary

On the basis of a study of the oxidation products, the course of the Hofmann degradation, the reduction of tetrahydrohemiloline methiodide, and other properties of the alkaloids investigated, it has been established that norloline has the structure of 6-amino-1, 5-oxypyrrolizidine, loline that of N-methyl-6-amino-1, 5-oxypyrrolizidine, and lolinine that of N-acetyl-N-methyl-6-amino-1, 5-oxypyrrolizidine.

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18 March 1965

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