STRUCTURE OF DELPHATINE

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The alkaloid delphatine, $C_{26}H_{43}O_7N$, (I), isolated from Delphinium biternatum Huth. and consisting of an amino alcohol derivative of delbine contains five methoxyl, two hydroxyl, and one N-ethyl groups [1–3]. The empirical formula and the functional composition are confirmed by its mass and NMR spectra. The mass spectrum of the base is characteristic for alkaloids with a lycoctonine skeleton [4].

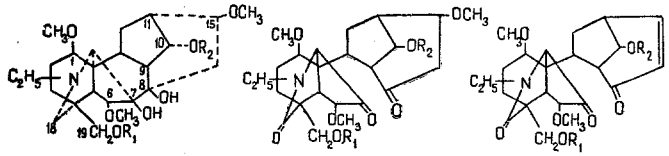
On oxidation with potassium permanganate solution in aqueous acetone, a product $C_{26}H_{41}O_8N$ (II) was obtained which had a lactam carbonyl in a six-membered ring (ν_{max}^{KBr} 1620 cm^{-1}). The mass spectrum of the lactam is characteristic for 18-oxo compounds with the lycoctonic skeleton [4]. The oxidation of oxodelphatine with periodic acid led to a tricarbonyl compound (oxosecodelphatine), $C_{26}H_{39}O_8N$ (III), the IR spectrum of which (ν_{max}^{KBr} 1640, 1700, and 1753 cm^{-1}) shows the position of one carbonyl group in a five-membered ring and another in a six-membered or larger ring. The presence of an aldehyde group is excluded by the NMR spectrum.

Consequently, in delphatine both hydroxyl groups are tertiary and they are present on neighboring carbon atoms. One of them belongs to a five-membered ring and the other to a six-membered or a larger ring. Treatment of the tricarbonyl compound with H_2SO_4 gives oxosecodehydromethoxydelphatine, $C_{25}H_{35}O_7N$ (IV), which is an α,β-unsaturated ketone, $\lambda_{max}^{C_2H_5OH}$ 225 and 322 mμ ($\log\varepsilon$ 4.04 and 2.55). The ready elimination of a molecule of methanol shows that one of the methoxy groups is in the position β to a keto group. According to the IR spectrum (ν_{max}^{KBr} 1660, 1680, and 1760 cm^{-1}), this keto group is present in a six-membered ring.

If, as a working hypothesis, we adopt the lycoctonine skeleton for delphatine, the two tertiary hydroxyl groups may be located at C_7 and C_8 or at C_8 and C_9. The mass spectra of oxosecodehydromethoxydelphatine and the analogous products from lycoctonine and browniine (V and VI, respectively) show that all three compounds are very similar. If the diol system occupies the C_7–C_8 position, one of the methoxyl groups must be present at C_{15}. An analysis of the NMR spectra of a series of compounds with an α-hydroxyl group at C_{10} shows that when there are no substituents at C_9 and C_{11} a proton in this position is always found at about 4.10 ppm in the form of a poorly-resolved triplet with $J \approx 5$ Hz. In the NMR spectrum of delphatine, a poorly-resolved one-proton triplet with $J \approx 5$ Hz is found at 3.52 ppm. The replacement of a hydroxyl group in delphatine by a methoxy group correspondingly shifts the signals from the C_{10} proton in the strong-field direction. In the mass spectrum of delphatine, the M – 31 peak has the maximum intensity while in the spectrum of oxodelphatine it is extremely small. This fact shows that the third methoxyl group is at C_1 [4]. A comparative analysis of the mass spectra of delphatine and its derivatives together with the spectra of lycoctonine (VII) and browniine (VIII) and their corresponding derivatives are good reasons for placing the two other methoxyl groups at C_6 and C_{19}. The formation of oxodelphatine on potassium permanganate oxidation shows the β-orientation of the methoxy group at C_6 [5]. Thus, structure I may be proposed for delphatine.

To confirm the presence of methoxy groups at C_6 and C_{19}, we heated oxodelphatine with zinc chloride and HCl. Compounds with the methoxyl groups in these positions are demethylated under similar conditions and form internal ethers. Thus, N-acetyl-N-desethylisopyrochasmanine gave the corresponding product IX [6]. In all compounds with which this reaction has been performed, there was an α-oriented methoxyl group at C_6. In the reaction with delphatine, we isolated two products. The first, according to the UV spectrum ($\lambda_{max}^{C_2H_5OH}$ 245 mμ, $\log\varepsilon$ 3.98) is an α,β-unsaturated ketone. The carbonyl group is present in a six-membered or larger ring (IR spectrum: 1615, 1675, 3068, 3105, and 3403 cm^{-1}). A functional analysis shows that only three methoxyl groups are present in the compound obtained. In view of what has been said, and also of the increase in the molecular weight by 64 amu, we came to the conclusion that the reaction led to the elimination of a molecule of water and one of methanol, and to the demethylation of one of the

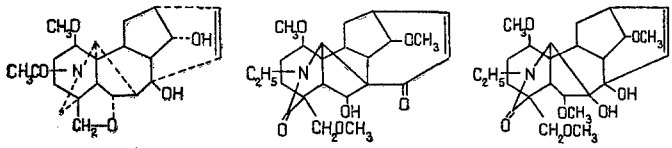
methoxyl groups. This is possible only in a pinacolin rearrangement, and the resulting product must have structure X.



I, $R_1 = R_2 = CH_3$
Ia, $R_1 = H$; $R_2 = CH_3$
II, $R_1 = R_2 = CH_3$; $C_{18} = CO$
VII, $R_1 = H$; $R_2 = CH_3$
VIII, $R_1 = CH_3$; $R_2 = H$

III, $R_1 = R_2 = CH_3$
IIIa, $R_1 = H$; $R_2 = CH_3$
IIIб, $R_1 = CH_3$; $R_2 = H$

IV, $R_1 = R_2 = CH_3$
V, $R_1 = H$; $R_2 = CH_3$
VI, $R_1 = CH_3$; $R_2 = H$



IX X XI

Another rearrangement route is excluded, since only in the given case does the rearrangement product contain in the position β to the carbonyl group a methoxyl group capable of being eliminated in the form of methanol and thus forming an α,β-unsaturated ketone.

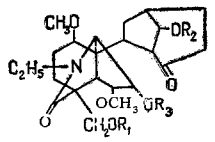
The corresponding series of reactions carried out with oxolycoctonine gave an analogous product (ν_{max}^{KBr}: 1600, 1653, 3053, 3090, 3280, 3400, and 3550 cm^{-1}), which excluded the demethylation of the methoxy group at C_{19}. The mass spectra of the two substances were similar. Therefore, on the bases of the IR spectra of the rearrangement products, it was probably the methoxyl group at C_6 that was demethylated. In these compounds, $\nu_{C=O}$ is low, because of a hydrogen bond between the hydroxyl and the carbonyl groups, which, as models show, is possible only when the hydroxyl group is present at C_6.

This second reaction product (XI), according to its mass spectrum and its functional analysis, was formed by the elimination of a molecule of methanol from oxodelphatine. In order to establish the structure of this compound, we oxidized it with periodic acid. We obtained an α,β-unsaturated ketone. Its UV, IR, and mass spectra were very similar to the corresponding spectra of oxosecodehydromethoxydelphatine (IV). Thus, the elimination of a molecule of methanol led to the appearance of a double bond between C_{15} and C_{16}.

The spectra of XI are similar to those of IV, but XI is not identical with IV. On this basis, we assume that under the reaction conditions the configuration of one of the methoxyl groups changed. It was impossible to detect a substance analogous to IX among the reaction products. This is apparently due to the β-orientation of the methoxyl group at C_6 in delphatine. A consideration of models confirms this hypothesis, since the formation of an internal ether is possible only when this methoxyl group has α-orientation.

We see from a comparison of structure I, which we propose for delphatine, with the structure of lycoctonine that the two compounds differ by the presence in delphatine of a methoxyl group at C_{19}, while in lycoctonine there is a hydroxyl group in this position. We methylated oxosecolycoctonine (IIIa) with methyl iodide in the presence of sodium hydride. Instead of the expected five methoxyl groups, the resulting compound had six. The methylation of oxosecodehydromethoxylycoctine (V) with methyl iodide in the presence of silver oxide also lead to the appearance of an additional methoxyl group.

In order to correlate delphatine with lycoctonine, we hydrogenated oxosecodehydromethoxydelphatine by Adams' method. A tetrahydro product $C_{25}H_{39}O_7N$ (XII) was formed which had neither a double bond nor a carbonyl group in a five-membered ring ($\nu_{max}^{CHCl_3}$ 1630, 1700, and 3450 cm^{-1}). When this compound was methylated with methyl iodide in the presence of sodium hydride, a methyl ether identical with the corresponding product XIII that we synthesized from lycoctonine was obtained.



XII, $R_1=R_2=CH_3$; $R_3=H$

XIII, $R_1=R_2=R_3=CH_3$

XIV, $R_1=R_3=H$; $R_2=CH_3$

This correlation confirms structure I proposed for delphatine and the configurations of the substituent at C_6 and C_{10}, and also establishes the β-orientation of the methoxyl group at C_1. The configuration of the methoxyl group at C_{15} is apparently the same as in lycoctonine, which is confirmed by the ease of formation of IV.

EXPERIMENTAL

The homogeneity of the substances was checked by chromatography in a thin layer of ShSK silica gel in a benzene–methanol (5 : 1) system. The NMR spectra were taken on a JNM-4H-100/100 MHz instrument in deuterochloroform with HMDS as internal standard (the values are given in the δ scale); the mass spectra were taken on an MKh-1303 instrument fitted with a glass system for direct introduction of the sample into the ion source.

Oxodelphatine (II). A solution of 0.25 g of delphatine in 15 ml of 80% aqueous acetone was added to 0.25 g of potassium permanganate in 200 ml of 50% aqueous acetone. The reaction mixture was shaken for 10 min. The excess potassium permanganate was decomposed with sodium sulfite, and the manganese dioxide was separated off. The acetone was distilled off on a water bath, and the residual solution was acidified with H_2SO_4 and repeatedly extracted with chloroform. The residue, after distillation of the chloroform, was dried and treated with hexane. This gave 0.22 g of a product with mp 94–95° C (ether). NMR spectrum: 1.03 ppm (CH_3CH_2, triplet), mol wt 495.

Oxosecodelphatine (III). A solution of 0.15 g of II and 0.15 g of periodic acid in 10 ml of distilled water was left at 20° C for 2 days. The reaction product was extracted with chloroform. The residue, after the distillation of the chloroform, was dried and treated with ether. The yield of product was 90 mg, mp 187–189° C (cyclohexane), mol wt 493.

Dehydromethoxy-III (IV). A solution of 0.3 g of III in 30 ml of chloroform was shaken with 10 ml of 10% H_2SO_4 for 5 hr. The chloroform layer was separated off, washed with water, dried over sodium sulfate, and distilled. The dark-red resinous product was chromatographed on a column of alumina. The amorphous mass, eluted by a chloroform–ether mixture (1 : 1), was treated with ether. This gave 0.25 g of crystals with mp 142–144° C (cyclohexane), mol wt 461.

Tetrahydro-IV (XII). A 0.2-g quantity of IV in 10 ml of methanol was hydrogenated over a platinum catalyst for 25 hr. The catalyst was separated off and the solution was evaporated. This gave a white amorphous substance, mol wt 465.

Methylation of XII. Sodium hydride, 0.25 g, was added to 0.13 g of XII in 8 ml of dry dioxane, and the mixture was stirred at 60–70° C. After 30 min 1 ml of methyl iodide was added, and the resulting mixture was stirred at 80–90° C for 8 hr. An additional 1 ml of methyl iodide was added, and after 10 hr the reaction mixture was cooled and filtered. The filtrate was evaporated and dried in vacuo. According to a chromatogram, the product XIII was homogeneous, mol wt 479. The IR spectrum was identical with that of the corresponding product obtained from lycoctonine.

Reaction of II with zinc chloride. A mixture of 0.17 g of II, 7 g of zinc chloride, and 3 ml of 5% HCl was heated in a water bath for 1 hr. The cooled dark-red solution was diluted with 20 ml of water and extracted with chloroform. The chloroform extract was washed with 4% aqueous caustic potash and then with water. The residue, after the distillation of the chloroform, was chromatographed on a column of alumina (3 g) and eluted with ether. The first two fractions (5 ml each) gave 10 mg of X with mp 220–230° C (cyclohexane–ether), mol wt 431. The subsequent fractions contained XI, mol wt 463.

Oxidation of XI with periodic acid. A mixture of 45 mg of XI and 45 mg of periodic acid in 5 ml of methanol–

water (1 : 5) was left at 20° C for 2 days. The reaction product was extracted with chloroform and the white amorphous substance remaining after the distillation of the chloroform (40 mg) was dried in vacuo; according to a chromatogram, it was homogeneous, mol wt 461.

Oxosecobrowniine (IIIb). A mixture of 0.1 g of oxobrowniine obtained in a manner similar to II and 0.1 g of periodic acid in 7 ml of distilled water was left at 20° C for two days. The reaction product was extracted with chloroform. After the chloroform had been distilled off, the product was shown by chromatography to be uniform, mol wt 479.

Dehydromethoxy-IIIb (VI). A solution of 0.7 g of IIIb in 1 ml of ethanol was added to 5 ml of 30% H_2SO_4, and the mixture was heated in a steam bath for 7 hr. The cooled solution was extracted with chloroform. After the distillation of the chloroform, a homogeneous substance with mol wt 447 was obtained.

Methylation of oxosecolycoctonine. Compound IIIa (0.18 g) was methylated by the method described for XII. The reaction product was chromatographed on a column of alumina. Elution with an ether–chloroform mixture (5 : 1) gave 0.13 g of a homogeneous white pulverulent substance with mol wt 507.

Dehydromethoxy-IIIa (V), obtained in a manner similar to VI, had mp 197–201° C (benzene), mol wt 447.

Tetrahydro-V (XIV), with mp 283–285° C (methanol) is formed in the same way as XII. IR spectrum: 1642 and 1688 cm^{-1}, mol wt 451.

Methylation of XIV. Compound XIV (0.32 g) was methylated by the method described for XII. This gave 0.28 g of XIII in the form of a white amorphous powder, mol wt 479. The IR spectrum was identical with that of the corresponding product obtained from XII.

Reaction of oxolycoctonine with zinc chloride. Oxolycoctonine (0.6 g) was treated with zinc chloride by the method described for II. The resinous product was treated with acetone. This gave 20 mg of a substance with mp 212–220° C (acetone), mol wt 417, $\lambda_{max}^{C_2H_5OH}$ 248 mμ (log ε 3.96). A mixture with X melted at 190–200° C.

CONCLUSIONS

The structure of the alkaloid delphatine has been established on the basis of chemical reactions and spectral characteristics. A correlation of delphatine with lycoctonine has been carried out.

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