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THE STRUCTURE OF ROEMREFINE

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From Roemeria refracta we have isolated a new quaternary base called roemrefine [1, 2]. The alkaloid contains two methoxy groups and gives a positive reaction for a methylenedioxy group with gallic acid. The UV spectrum of roemrefine has absorption in the 294 mμ region (log ε 3.87). In the Hofmann degradation, an optically active des-base (II) is formed in the first stage which, according to the UV spectrum, is a stilbene derivative. Since the optical activity is preserved in this derivative, benzylisoquinoline and diisoquinoline structures are eliminated for roemrefine. The second stage of the Hofmann degradation leads to the formation of a nitrogen-free product with the composition $C_{19}H_{16}O_4$ (III). The oxidation of roemrefine with potassium permanganate in an aqueous medium has given m-hemipinic acid (IV). Among the oxidation products were found a second acid which, on a paper chromatogram, had the same R_f value as hydrastic (V) and 3, 4-methylene-dioxyphthalic acids.

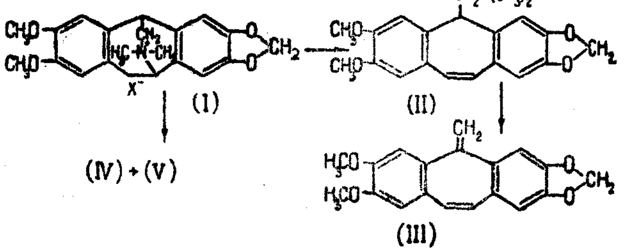
On the basis of what has been said, a pavine or isopavine structure can be put forward for this alkaloid. However, in a consideration of the UV spectra of des-bases of the pavine type [3, 4] [λ_{max} 290 mμ (log ε 3.98)] and the des-isopavine type [5] [λ_{max} 239, 314 mμ (log ε 4.54, 4.15)], it can be seen that the UV spectrum of des-roemrefine [λ_{max} 238, 312 mμ (log ε 4.52, 4.18] almost coincides with the spectrum of des-isopavine and differs fundamentally from that of des-pavine. The absorption curve in the UV region of the nitrogen-free product from roemrefine [λ_{max} 247, 324 mμ (log ε 4.63, 4.10)] also differs strongly from the absorption curve of the corresponding products of the pavine type [3, 4]. The formation in the oxidation of roemrefine of m-hemipinic acid as practically the sole product also indicates its isopavine structure.

Additional data on the structure of the alkaloid roemrefine can be obtained by studying its NMR spectrum. Thus, in the region of aromatic protons there are four one-proton singlets at δ 6.28, 6.67, 7.05, and 7.17, which shows the presence of substituents in the aromatic rings in positions 2, 3, 7, and 8. The $>\overset{+}{N}(CH_3)_2$ group appears in the form of two three-proton singlets at δ 3.38 and 2.9. While the first value is normal for a methyl group on a quaternary nitrogen atom [6], the second is shifted appreciably into the strong-field region. From a consideration of models of the isopavine and pavine structures it can be seen that in the first case when two methyl groups are present on the nitrogen atom one of them is above the plane of the benzene ring coupled to the six-membered ring. This causes the above-mentioned shift of the signal of the methyl group.

The protons of the methylenedioxy group are responsible for the appearance of two one-proton singlets at δ 5.72 and 5.84. The considerable difference in the chemical shifts of the two protons of the methylenedioxy group is apparently due to the fact that the latter is present in a benzene ring coupled with a six-membered ring. In this case the difference in the environments of the two protons will be considerable. Signals in the form of two three-proton singlets at δ 3.83 and 3.88 relate to the protons of the methoxy groups. Thus, roemrefine must have the structure (I).

The proposed structure is confirmed by the NMR spectrum of the nitrogen-free product (III), in which there are signals at δ 6.75 and 6.48 (four aromatic protons), at 6.58 and 6.55 (two protons of a cis-stilbene system [4]), at 5.79 (methylenedioxy group), at 6.06 (exocyclic methylene group), and at 3.81 and 3.76 (methoxy groups).

It is possible that roemrefine is the quaternary form of amurensinine, for which Šantavý et al. have proposed an isopavine structure [7, 8].



Experimental

The NMR spectrum of roemrefine was taken in heavy-water solution (Yu. N. Sheinker, VNIKhFI [Ordzhonikidze All-Union Chemical and Pharmaceutical Scientific-Research Institute]) and that of the nitrogen-free product from roemrefine in deuterochloroform (Yu. A. Ustinyuk, MGU [Moscow State University]). The chemical shifts were identified in millionth parts with respect to the signal of tetramethylsilane taken as zero. The UV spectra were taken in ethanol. The melting points are uncorrected.

Roemrefine (I). The substance, isolated in the form of the chloride, had mp 241–242° C (acetone-ethanol), $[\alpha]_D^{21}$ −147° (c 1.039; water). The melting point of the iodide was 244–245° C (water-methanol).

Des-roemrefine (II). One gram of roemrefine iodide was boiled in 20 ml of 30% methanolic caustic potash for 2.5 hr. After the usual working up, 0.55 g of the oily 1-des-base was obtained. The latter was boiled with 7 ml of methanol and 2 ml of methyl iodide for 1.5 hr. The des-roemrefine methiodide formed melted at 252–253° C (methanol).

Nitrogen-free product from roemrefine (III). Des-roemrefine methiodide was boiled with 30% methanolic caustic potash for 2 hr. The appropriate working up led to a nitrogen-free product with mp 179–181° C (methanol).

Found, %: C 73.50; H 5.30. Calculated for $C_{19}H_{16}O_4$, %: C 74.00; H 5.19.

Oxidation of roemrefine. Potassium permanganate was added to a solution of 0.2 g of (I) in 10 ml of water at 50–60° C until a permanent coloration appeared. After the manganese dioxide had been separated off, the filtrate was evaporated, acidified with concentrated hydrochloric acid, and extracted with ether. The residue from the evaporation of the ether was dissolved in ethanol and treated with a few drops of aniline. This gave the aniline salt of m-hemipinic acid with mp 162-165° C (from ethanol).

Conclusions

Structure (I) has been established for roemrefine on the basis of a study of the products of its Hofmann degradation, oxidation, and spectral characteristics.

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