THE STRUCTURE OF REGALAMINE

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We have previously [1, 2] reported the isolation from the epigeal parts of Colchicum kesselringii Rgl. of a number of new bases. The present paper gives the results of an investigation of the structure of the alkaloid regalamine.

The UV spectrum of regalamine has two absorption maxima [at 218 and 290 nm (log ε 4.34 and 3.59)] which shows the presence of an aromatic ring in its structure. The IR spectrum of the base shows absorption bands of a hydroxy group (3560 cm^{-1}), of the C=C bonds of an aromatic ring (1600 cm^{-1}), and of methylene groups (1480 cm^{-1}).

The NMR spectrum of the alkaloid (Fig. 1) shows the signals of a N-methyl group (three-proton singlet at 2.32 ppm), of an aromatic O-methyl group (three-proton singlet at 3.73 ppm), and of one proton of an aromatic ring (singlet at 6.40 ppm). The mass spectrum of the base shows the peaks of ions with m/e 331 (M^+, 43 %), 330 (M − 1, 100 %), 288 (M − 43), 244, 230, and 202. Such decomposition under the action of electron impact is characteristic for various groups of tetrahydroisoquinoline alkaloids containing N-methyl groups. Since the intensity of the molecular ion in the mass spectrum of regalamine corresponds to approximately half that of the maximum ion $(M-1)^+$, this base can be assigned to the group of homoproaporphine compounds [3-7].

In its composition and spectral characteristics, regalamine is close to homoproaporphine alkaloids of the type of kesselringine [2] in which ring D is completely hydrogenated.

Thus, the further study of the structure of regalamine reduces to establishing the functions and positions of its four oxygen atoms. One of them is present in a methoxy group. The latter is located in the α-position to an aromatic proton of ring A, as is shown by the positive intramolecular nuclear Overhauser effect [8].

Another of the oxygen atoms in regalamine has an inert nature and obviously forms an ether bridge between the aromatic ring A and the saturated ring D. An investigation of the structure of regalamine on a Dreiding model showed that the ether bond can be located only between the C_1 and C_{12} atoms, forming a six-membered ring E. The third oxygen atom has the form of an alcoholic hydroxy group attached to the C_{12}

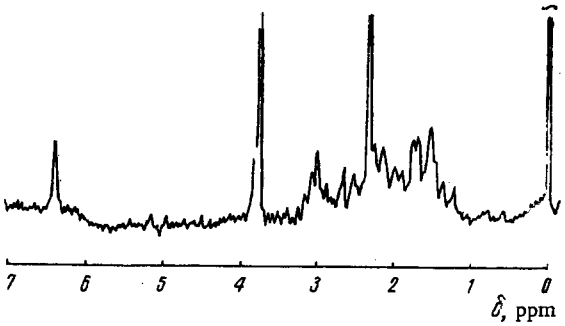

Fig. 1. NMR spectrum of regalamine ($CHCl_3$).

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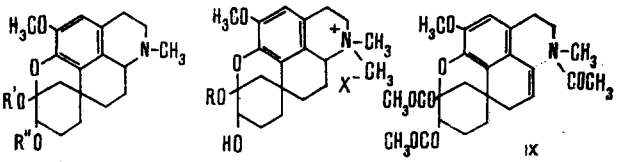
atom. It has been established by etherification reactions that this hydroxy group has a semiacetal nature: methyl (II, Scheme) and n-butyl (III) ethers of the base have been obtained. The later are stable to aqueous solutions of alkalis but are readily saponified in dilute mineral acids to form the initial base.

The action of diazomethane on regalamine also forms the O-methyl derivative (II) through the methylation of the semiacetyl hydroxy group, and a secondary reaction product was also isolated which was identical with the quaternary base of O-methylregalamine (V). The quaternary bases of regalamine (VII) and of O-methylregalamine do not undergo the Hofmann degradation under the usual conditions.

With acetyl chloride regalamine gives a O,O-diacetyl derivative (VIII). This shows that the fourth oxygen atom in it is present in the form of an alcoholic hydroxy group. By analogy with some other proaporphine alkaloids [9], it may be assumed that this hydroxy group is located at the C_{11} atom.

The acetylation of regalamine with acetic anhydride led to the formation of a N,O,O-triacetyl derivative (IX) with the opening of the heterocyclic ring, which is characteristic for tetrahydroisoquinoline derivatives containing a N-methyl group [10].

On the basis of the facts given, we suggest for regalamine the most probable structure 11,12-dihydroxy-2-methoxy-1,12-epoxyhexahydrohomoproaporphine (I). Its transformations are shown below:



I. $R' = R'' = H$
II. $R' = CH_3$; $R'' = H$
III. $R' = C_4H_9$; $R'' = H$
VIII. $R' = R'' = COCH_3$

IV. $R = CH_3$; $X = I$
V. $R = CH_3$; $X = OH$
VI. $R = H$; $X = I$
VII. $R = H$; $X = OH$

IX

EXPERIMENTAL METHOD

The chromatography of the alkaloids was performed on paper of the Volodarskii Leningrad Mill (weight 85 g/cm^2) in the following solvent systems (by volume): 1) n-butanol–water–hydrochloric acid (50 : 13.5 : 7.5) and 2) n-butanol–5% acetic acid (1 : 1). The UV spectra were taken on an SF-4A spectrophotometer (methanol), the IR spectra on UR-10 instrument, the mass spectra on a MKh-1303 mass spectrometer, and the NMR spectra on H-60 and XL-100 spectrometers. Chloroform was used as the solvent.

Regalamine (I) has mp 225-226° C (from acetone), $[\alpha]_D$ +33° (c 1.93; methanol), R_f 0.31 (1), 0.28 (2). Soluble in methanol and chloroform, sparingly soluble in acetone and water, insoluble in ether and petroleum ether. Solutions in concentrated sulfuric acid are not colored.

O-Methylregalamine (II). A mixture of 100 mg of regalamine and 10 ml of a 7% methanolic solution of hydrogen chloride was boiled for 2 h. The solvent was distilled off, the residue was dissolved in water, and the solution was made alakline with ammonia and extracted with chloroform. The solvent was distilled off, giving compound (II) with mp 199-200° C (from acetone), R_f 0.43 (1), 0.46 (2).

O-Methylregalamine Methiodide (IV). It was isolated by heating an acetone solution of O-methylregalamine with methyl iodide. mp 249-250° C (from acetone), R_f 0.47 (1), 0.45 (2).

Quaternary Base of O-Methylregalamine (V). Freshly precipitated moist silver oxide (from 50 mg of silver nitrate) was added to a solution of 70 mg of O-methylregalamine methiodide in 5 ml of methanol. The mixture was shaken for 30 min, and then the solid matter was filtered off and washed with methanol, and, after being dried over sodium sulfate, the filtrate was evaporated in vacuum. The residue consisted of (V) with mp 235-236° C (from acetone), R_f 0.48 (1), 0.39 (2).

Regalamine Methiodide (IV). It was obtained by mixing a methanolic solution of the base and methyl iodide. The mixture was boiled for 1 h and the solvent was distilled off. The residue consisted of (VI) with mp 279-280° C (from acetone), R_f 0.30 (1), 0.28 (2).

The quaternary base of regalamine (VII) was isolated by the method used for the quaternary base of O-methylregalamine. This gave orange crystals with mp 202-205° C (from acetone), R_f 0.30 (1), 0.28 (2).

O-Butylregalamine (III). A solution of 60 mg of regalamine in 8 ml of n-butanol containing 5% of

hydrogen chloride was boiled for 1 h. The solvent was evaporated off in vacuum and the reaction product was isolated as in the methanolysis reaction. The O-butylregalamine did not crystallize; R_f 0.78 (1), 0.72 (2).

Hydrolysis of O-Methyl- and O-Butylregalamines. In each case, a 50-mg sample was heated with 6 ml of 10% hydrochloric acid at 100° C for 2 h. Then the solution was made alkaline with ammonia and extracted with chloroform. Evaporation of the chloroform extract yielded regalamine.

Methylation of Regalamine with Diazomethane. An excess of diazomethane in petroleum ether was added twice to a solution of 120 mg of regalamine in 2 ml of methanol. The solvent was distilled off, the residue was dissolved in chloroform, and the solution was washed twice with water. Then the solvent was evaporated; the residue consisted of O-methylregalamine (II).

The wash-waters were evaporated in vacuum and the residue was chromatographed on a column of alumina. Compound (V) was isolated from an acetone–methanol (1 : 1) eluate.

O,O-Diacetylregalamine (VIII). A solution of 100 mg of regalamine in 2 ml of acetyl chloride was left for 2 h. Then the excess of the reagent was carefully evaporated off, the residue was dissolved in water, and the solution was made alkaline with ammonia. This gave substance (VIII) with mp 167-169° C; R_f 0.64 (1), 0.66 (2).

IR spectrum: ν_{max} 1750, 1730 cm^{-1} (2 $OCOCH_3$); NMR spectrum: 2.05, 1.99 ppm (2 $OCOCH_3$).

N,O,O-Triacetylregalamine (IX). To a solution of 100 mg of regalamine in 2 ml of acetic anhydride was added 1 g of freshly fused sodium acetate, and the mixture was heated at 45-50° C for one day. Then 3 ml of methanol was added and the mixture was evaporated to dryness. The residue was dissolved in water, and chloroform then extracted N,O,O-triacetylregalamine with mp 140-142° C (from acetone); R_f 0.93 (1), 0.90 (2).

IR spectrum: ν_{max} 1635 cm^{-1} ($NHCOCH_3$), 1750 cm^{-1} ($OCOCH_3$). NMR spectrum: 2.05, 2.05, 1.98 ppm (3 $COCH_3$).

SUMMARY

On the basis of UV, IR, NMR, and mass spectra and chemical transformations the structure of 11,12-dihydroxy-2-methoxy-1,12-epoxyhexahydrohomoproaporphine has been proposed for regalamine.

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