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THE STRUCTURE OF REGELINE

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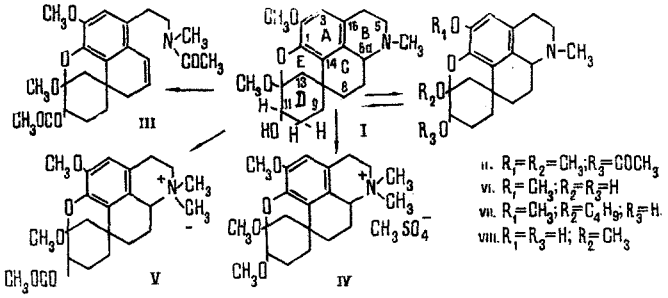
The isolation from the epigeal parts of *Colchicum kesselringii* Rgl. of a new base — regeline — with the composition $C_{20}H_{27}O_4N$, mp 198-200°C, and $[\alpha]_D$ +93° has been reported previously [1]. Its UV spectrum has absorption maxima at 216, 225, and 290 nm (log ε 4.04, 3.96, and 3.37). The IR spectrum of regeline shows absorption bands of a hydroxy group (3200 cm^{-1}), of the C=C bonds of a benzene ring (1600 cm^{-1}), and of methylene groups (1460 cm^{-1}). The mass spectrum of the base has the peaks of ions with m/e 345 (M^+, 65%), 344 $(M-1)^+$ (100%), 330, 326, 302 $(M-43)^+$, 286, 258, 244, 242, 205, 202.

The NMR spectrum of regeline (Fig. 1) shows the signals of a N-methyl group (three-proton singlet at 2.36 ppm), of two O-methyl groups (three-proton singlets at 3.34 and 3.74 ppm) and of a proton in a benzene ring (one-proton singlet at 6.42 ppm).

In the spectral characteristics given, regeline is close to the homoproaporphine and proaporphine bases [2-6]. On the basis of the developed formula, it may be assigned to derivatives of homoproaporphine with a spirocyclohexane ring.

Depending on the conditions, the acetylation of regeline with acetic anhydride led to O-acetyl (II) and O,N-diacetyl (III) derivatives. The formation of the latter shows that the molecule of the base contains a tetrahydroisoquinoline fragment [7], and one of the oxygen atoms is present in the form of a hydroxy group. This hydroxy group possesses an alcoholic nature: it is not methylated by diazomethane nor by methyl iodide in the presence of alkalis. It can be methylated with dimethyl sulfate, which gives N,O-dimethylregeline methosulfate (IV).

The secondary alcohol nature of the hydroxy group of regeline which is probably, by analogy with other alkaloids of this series, located at the C_{11} atom, is confirmed by ready acetylation with acetyl chloride. By acetylating regeline methiodide, we obtained its acetyl derivative (V).



II. $R_1=R_2=CH_3$; $R_3=COCH_3$
VI. $R_1=CH_3$; $R_2=R_3=H$
VII. $R_1=CH_3$; $R_2=C_4H_9$; $R_3=H$
VIII. $R_1=R_3=H$; $R_2=CH_3$

Scheme 1

Regeline is stable to the action of aqueous alkali and ammonia. On being heated with dilute acids, one of its methoxy groups is hydrolyzed with the formation of norregeline (VI). In alcoholic solutions of hydrogen chloride, the base undergoes a transesterification reaction with the formation of the corresponding alkylnorregelines. By heating regeline in n-butanol we isolated O-butylnorregeline (VII). These transformations show that one of the

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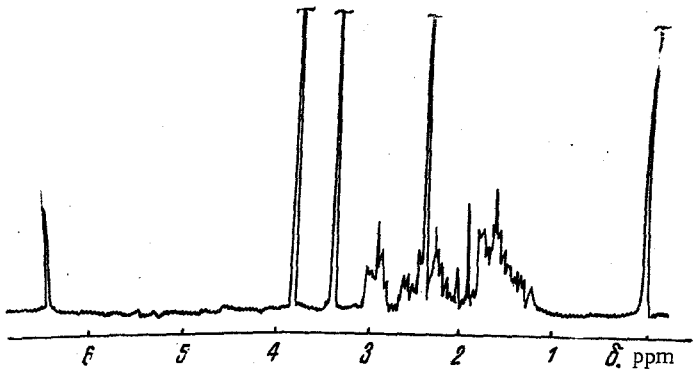


Fig. 1. NMR spectrum of regeline ($CHCl_3$).

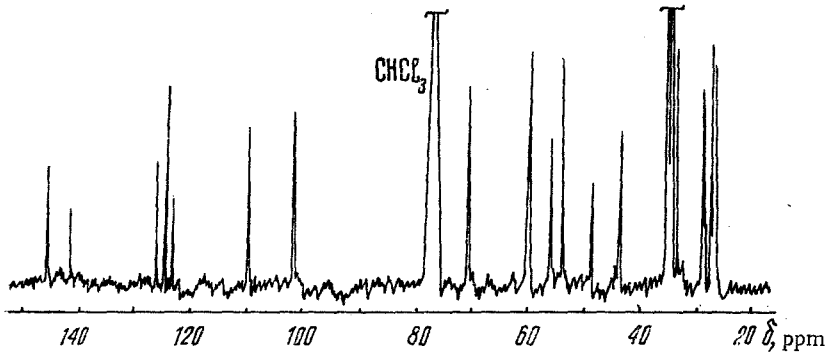
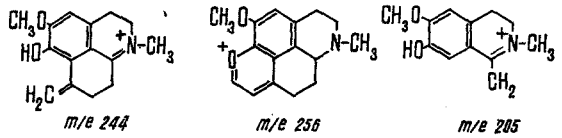


Fig. 2. ^{13}C NMR spectrum of regeline ($CHCl_3$).

methoxy groups of the base has an acetal nature. The fourth of the oxygen atoms in regeline forms an ether bond between the aromatic ring A and the spirocyclohexane ring D, forming the six-membered ring E. The existence of an ether bridge in the molecule of the base is confirmed by the presence in its mass spectrum of the peaks of ions with m/e 256, 244, and 205, which show the position of its bond in the aromatic ring (C_1) and the spirocyclohexane ring (C_{12}) of the base [8, 9].



Scheme 2

A comparative analysis of the spectral characteristics and properties of regeline and the known alkaloids of *Colchicum kesselringii* has shown that it must be similar in structure to regelamine (VI) [10] and to kesselringine (VIII) [11]. On comparing the developed formulas and NMR spectra (ppm) of these three compounds (Table 1) we concluded that regeline is an O-methyl ether both of regelamine and of kesselringine.

To confirm this, we methylated kesselringine with diazomethane and obtained a methyl ether of this base that was identical with regeline. Simultaneously, norregeline was identified with regelamine, which contains a semiacetal hydroxy group.

On the basis of the facts presented, for regeline we have proposed the structure of 11-hydroxy-2,12-dimethoxy-1,12-epoxyhexahydrohomoproaporphine (I).

We have studied the ^{13}C NMR spectrum of regeline, which, from the nature of the C atoms, simultaneously confirms the homoproaporphine skeleton and the complete structure of this base. The spectrum of regeline (Fig. 2) is formed by the signals of 20 carbon atoms, 13 of which are located in the high-field section and relate to carbons with saturated bonds. Information from powerful nonresonance irradiation shows the presence of three methyl substituents in the regeline molecule. On the basis of their chemical shifts, the signal at 43.6 ppm (δ scale) can be assigned to a N-methyl group and signals at 48.9 and 56.0 ppm to O-methyl groups.

TABLE 1

Compound	Developed formula	OCH_3	OCH_3	$N-CH_3$	H_{ar}
I	$C_{17}H_{17}(OH)(OCH_3)_2(-O-)(N-CH_3)$	3,74	3,34	2,36	6,42
VI	$C_{17}H_{17}(OH)_2(OCH_3)(-O-)(N-CH_3)$	3,73	—	2,32	6,40
VIII	$C_{17}H_{17}(OH)_2(OCH_3)(-O-)(N-CH_3)$	—	3,32	2,32	6,42

The methylene carbons are represented in the spectrum by six signals (26.4, 27.0, 28.8, 33.0, 34.2, and 53.6 ppm), the signal at 34.2 ppm corresponding to two methylene carbons. Two signals — at 60.0 and 70.5 ppm — relate to tertiary carbons attached to nitrogen and oxygen. The quaternary carbon of the spiro center of the molecule resonates at 34.6 ppm.

The low-field part of the spectrum is represented by seven signals. A signal at 101.9 ppm is due to a carbon atom attached to two oxygen atoms. The remaining six signals correspond to the carbons of the aromatic ring of the molecule. A CH carbon resonates at 110.2 ppm. Carbons attached to oxygen show signals at 142.1 ppm and 145 ppm. Three signals (123.8, 124.6, and 126.4 ppm) relate to the C_{14}, C_{15}, and C_{16} carbons of the aromatic ring.

By analogy with other similar homoproaporphine and proaporphine alkaloids, regeline may be assigned the R configuration at the C_{6a} atom. On the basis of information for regelamine [12] and kesselringine [11] it may be assumed that the acetal methoxy group of regeline corresponds to an equatorial, and the secondary alcohol group to an axial, orientation in the spirocyclohexane ring D.

EXPERIMENTAL

The individuality of the substances was checked by radial paper chromatography in the following solvent systems: 1) n-butanol—5% acetic acid (50:50); and 2) n-butanol—hydrochloric acid—water (40:7.5:15). The R_f values of the substances are given in system 1.

The UV spectra were taken in methanolic solution on a SF-4A spectrophotometer, the IR spectra on a UR-10 double-beam spectrometer, the NMR spectra on an XL-100 instrument, and the mass spectra on an MKh-1303 spectrometer with direct introduction of the sample.

Regeline (I) has mp 198-200°C (from acetone), $[\alpha]_D$ +93° (c 1.5; methanol). It is readily soluble in methanol and chloroform, soluble in acetone and water, and insoluble in ether, and it dissolves in concentrated sulfuric acid with no coloration. R_f 0.36.

Hydrochloride, mp 237-238°C (from acetone).

Methiodide, mp 249-250°C (from acetone).

O-Acetylregeline (II). With stirring, one drop of concentrated sulfuric acid was added to a solution of 100 mg of regeline in 2 ml of acetic anhydride. The reaction mixture was left for 1 h, and then the O-acetylregeline was isolated in the usual way. It could not be crystallized. R_f 0.67; M^+ 387.

IR spectrum: 1750 cm^{-1} ($OCOCH_3$).

O,N-Diacetylregeline (III). A mixture of 60 mg of regeline, 100 mg of freshly fused sodium acetate, and 2 ml of acetic anhydride was heated at 50-60°C for 56 h. Then the mixture was cooled, and the excess of acetic anhydride was evaporated off with the addition of methanol. The dry residue was dissolved in water and the reaction product was extracted with chloroform. O,N-diacetylregeline was isolated with R_f 0.84; M^+ 429.

IR spectrum: 1650, 1750 cm^{-1} ($NCOCH_3$, $OCOCH_3$).

N,O-Dimethylregeline Methosulfate (IV). Dimethyl sulfate (0.5 ml) was added to a solution of 60 mg of regeline in 5 ml of 3% caustic soda, and the mixture was shaken until the layer of dimethyl sulfate had disappeared. The acid solution after the reaction was made alkaline with ammonia and evaporated to dryness.

Two substances were found in the reaction product — with R_f 0.39 (the main spot) and 0.48 — and these were separated by chromatography on cellulose using water-saturated n-butanol as eluent. The compound with R_f 0.48 was crystallized from acetone, mp 232-233°C; M^+ 373. Its structure was not studied.

The substance with R_f 0.39 (IV) could not be crystallized; M^+ 359.

NMR spectrum of (IV): 1.76 (6 H, s), 2.08 (3 H, s), 3.31 (6 H, s), 3.74 (3 H, s), 6.48 (1 H, s).

O-Acetylregeline Methiodide (V). A solution of 70 mg of regeline methiodide in 1 ml of acetyl chloride was kept at room temperature for 20 min. Then the acetyl chloride was evaporated off and the dry residue was treated with acetone, which led to the isolation of O-acetylregeline methiodide.

IR spectrum: 1750 cm^{-1} ($OCOCH_3$).

NMR spectrum, ppm: 2.00; 2.04 (NCH_3; $OCOCH_3$); 3.28; 3.73 (2 OCH_3).

Norregeline (VI). A mixture of 80 mg of regeline and 5 ml of 3% sulfuric acid was heated at 100°C for 2 h. Then the solution was cooled, make alkaline with aqueous ammonia, and extracted with chloroform. The solvent was distilled off and norregeline was obtained with mp 233-234°C (from acetone); R_f 0.25.

Mass spectrum: m/e 331 (M^+), 330 $(M-1)^+$ (100%).

NMR spectrum: 3.71 ppm (arom. OCH_3).

O-Butylnorregeline (VII). A solution of 60 mg of regeline in 5 ml of n-butanol containing 7% of hydrogen chloride was boiled on the sand bath for 2 h. Then the solvent was distilled off, the residue was dissolved in water, and the solution was made alkaline with ammonia and was extracted with chloroform. After the drying and distillation of the solvent, an amorphous powder of O-butylnorregeline was obtained with R_f 0.61.

Mass spectrum: m/e 387 (M^+, 48%), 386 $(M-1)^+$ (100%).

O-Methylkesselringine was obtained by methylating kesselringine with diazomethane by the method described previously [5]: mp 196-198°C (from acetone); R_f 0.36; M^+ 345.

NMR spectrum: 3.35 and 3.75 ppm (2 OCH_3).

SUMMARY

On the basis of a study of spectra and chemical transformations the structure of 11-hydroxy-2,12-dimethoxy-1,12-epoxyhexahydrohomoproaporphine has been proposed for regeline — a base from *Colchicum kesselringii* Rgl.

The homoproaporphine carbon–nitrogen skeleton and the complete structure of regeline have been confirmed by a study of its ^{13}C NMR spectrum.

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