Mass spectrum: m/e 415 (M^+). IR spectrum, cm^{-1}: 1770, 1745 (2 $OCOCH_3$).

SUMMARY

On the basis of IR, PMR, and mass spectra and chemical transformations, the alkaloid kesselringine isolated from the epigeal parts of Colchicum kesselringii Rgl. has been shown to have the structure of 2,11-dihydroxy-12-methoxyhexahydro-1,12-epoxyhomoproaporphine with the R absolute configuration at the C_{6a} atom.

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THE STRUCTURE OF LUTEIDINE

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The isolation from Colchicum luteum Baker. (yellow autumn crocus) of the nontropolone base luteidine (I) with the composition $C_{20}H_{25}O_4N$ (confirmed by the high-resolution mass spectrum), mp 231-232°C $[\alpha]_D$ −96° (in methanol) had been reported previously [1]. Its UV spectra has absorption maxima at 228 and 272 nm (log ε 3.89 and 4.05). Its IR spectrum contains absorption bands at 1677, 1667, 1617, 1600, and 3535 cm^{-1} showing the presence of an enone grouping [2], an aromatic ring, and a hydroxy group. A color reaction with ferric chloride and a bathochromic shift of the absorption maximum in the UV spectrum in an alkaline medium show the phenolic nature of the hydroxy group.

In the mass spectrum of luteidine, the strongest peak is that of the ion with m/e 244 $(M-99)^+$, and the molecular ion (M^+, 343) has an intensity of 38%. The $(M-1)^+$ ion that is characteristic for many isoquinoline alkaloids with the greatest intensity amounts to only 22%. The PMR spectrum of the base (Fig. 1) has the resonance signals of a N-methyl group (three-proton singlet at 2.37 ppm), two O-methyl groups, one of which is located in an aromatic ring (three-proton singlet at 3.78 ppm) and the other on an olefinic double bond (three-proton singlet at 3.51 ppm). In addition, in the weak-field region there are the singlets of one aromatic proton and one olefinic proton (at 6.46 and 5.79 ppm, respectively). The positive nuclear Overhauser effect (NOE) between the methoxy group (3.78 ppm) and a proton of the aromatic ring (27%) shows that they are in the ortho position with respect to one another. With the aid of an NEO we also showed the position of the other methoxy group and of the proton on the olefinic double bond.

On the basis of the spectral characteristics given, luteidine may belong to the group of alkaloids with the homoproaporphine or androcymbine skeleton [2-4]. The choice of the carbon–nitrogen skeleton for this base was made on the basis of the ^{13}C spectra at the natural content of the isotope. As was to be expected, with complete decoupling from protons the spectrum of luteidine (Fig. 2) consisted of 20 peaks. Below 100 ppm are located

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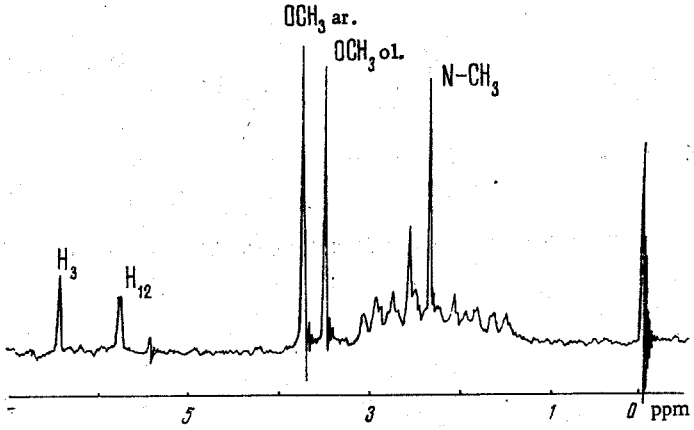


Fig. 1. PMR spectrum of luteidine (in $CDCl_3$).

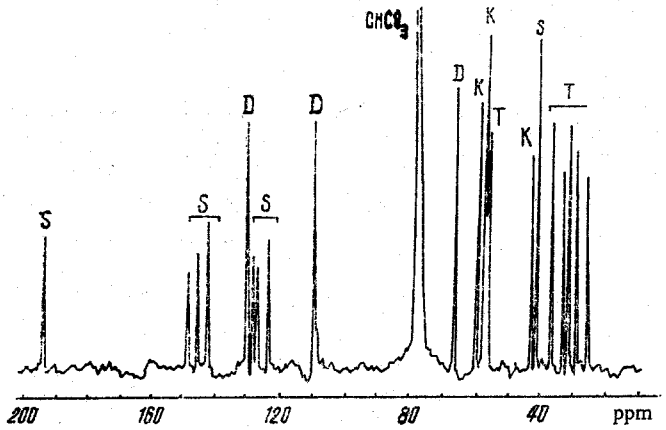
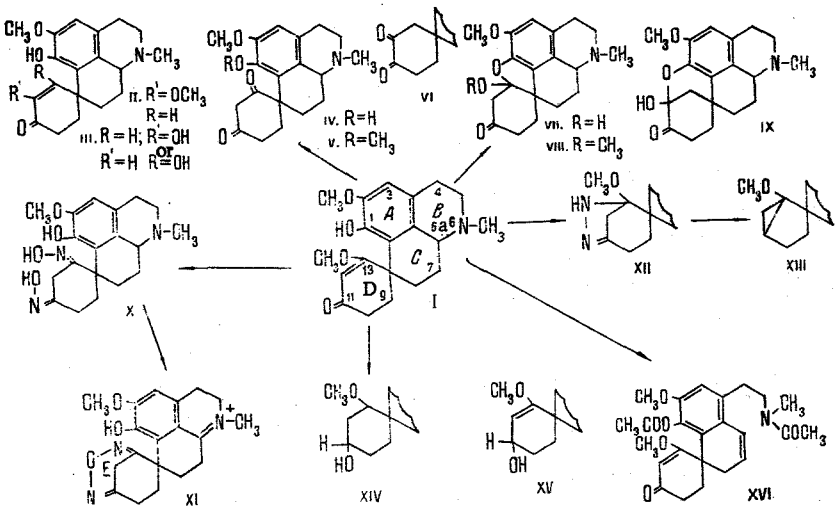


Fig. 2. ^{13}C NMR spectrum of luteidine (in $CHCl_3$).

the signals of the carbon atom with the sp^2 hybridization of the atomic orbitals, and above there are 11 signals of sp^3-hybridized carbon atoms. Such a distribution of the signals is characteristic for the types of alkaloids mentioned. It was established by powerful nonresonance irradiation [5] that luteidine contains the following types of carbon atoms (the numbers of C atoms are given in parentheses): $=\overset{|}{\underset{|}{C}}$ (7), $=\overset{|}{\underset{|}{CH}}$ (2), $-\overset{|}{\underset{|}{C}}-$ (1), $-\overset{|}{\underset{|}{CH}}$ (1), $\overset{|}{CH_2}$ (6), $-CH_3$ (3). They may form a molecule with a homoproaporphine skeleton and do not correspond to a molecule of the androcymbine series $=\overset{|}{\underset{|}{C}}$ (6), $=\overset{|}{\underset{|}{CH}}$ (3), $-\overset{|}{\underset{|}{CH}}$ (2) $\overset{|}{CH_2}$ (5), $-\overset{|}{\underset{|}{C}}-$ (1), $-CH_3$ (3) (the assignment of the lines of the luteidine spectrum will be reported later).

At the same time, the ^{13}C NMR spectrum confirms the presence in luteidine of a spirocarbon atom (C_{8a}) (38.8 ppm).

We have studied a number of transformations of luteidine, which have enabled its structure to be established. From its physical constants and spectral characteristics, luteidine is very similar to dihydrokreysiginone (II) [6]. A comparison of the features of the PMR spectra of these two compounds showed that they differ by the position of the methoxy group in the enone grouping of ring D: in luteidine it must be in the β position with respect to the carbonyl group. We made a number of investigations to confirm the presence of the enone system in luteidine. In the isoquinoline bases [7, 8] and, in particular, in the known proaporphine and homoproaporphine alkaloids [2, 3], two oxygen-containing substituents in ring D are located on the neighboring C_{11} and C_{12} atoms.



Structure and transformations of luteidine.

In view of the absence of an authentic sample of dihydrokreysiginone we studied the transformations of luteidine that could show the position of the enone methoxy group. Leuteidine was readily hydrolyzed when it was heated in dilute mineral acids, giving a compound which we have called luteinone. Since the unsaturated alcohol formed in this reaction is unstable, four possible structures can be proposed for luteinone – α- and β-diketonic structures (IV, VI) or cyclic structures (VII, IX); in the presence of hydrogen ions, cyclization of an unsaturated alcohol of type (III) could take place.

Luteinone forms a dioxime (X), (M^+, 359), which shows its diketone nature. Under the conditions of mass spectrometry, the latter readily splits out a molecule of water, and strong ions with m/e 341 and 340 (XI) appear in the mass spectrum, showing the formation in them of a stable six-membered ring E.

The retention of the phenolic hydroxy group in luteinone is confirmed by its methylation with diazomethane. In the NMR spectrum of the methyl ether obtained (V) there are two three-proton singlets corresponding to methoxy groups in an aromatic ring.

α-Diketones are colored substances [9], but luteinone forms colorless crystals, and it gives a copper complex, which is characteristic for β-diketones [10]. These facts permit the assumption for it of structure (IV), which is explained by the β position of the methoxy group with respect to the carbonyl group in luteidine (I). Furthermore, in the ^{13}C NMR spectrum of luteidine there are two signals of =CH carbon atoms: at 109.4 ppm there is the signal of the C_3 atom and at 129.2 ppm the =CH of the enone grouping of ring D. The chemical shift of the latter shows its ortho position in relation to the carbonyl group and the meta position of the substituent [11].

The reduction of luteidine with sodium tetrahydroborate led not to the expected luteidinol (XV) but to a tetrahydro derivative (XIV). We also obtained the latter by the hydrogenation of (I) in the presence of Raney nickel.

When compound (I) was reduced to the Kizhner [Wolff–Kishner] method, a reaction took place which is characteristic for unsaturated compounds containing a carbonyl group conjugated with a double bond [12]: as a result of a pyrazole rearrangement in ring D, compound (XII) was formed which was converted on catalytic decomposition into the cyclopropane derivative (XIII). This is confirmed by the absence of the signal of an olefinic proton in the PMR spectrum and by the correspondence of its molecular weight with that of deoxyluteidine (M^+, 329).

To determine the position of the double bond in ring D (at the C_9-C_{10} or $C_{12}-C_{13}$ atoms) we cyclized luteidine under conditions close to those described in the literature [13, 14]. The substance isolated contained no olefinic bond or phenolic hydroxy groups, which shows the formation of the heterocyclic E, and the substance can be ascribed the structure (VIII). In acid solutions, the acetyl compound is readily hydrolyzed and is converted into the hemiacetal (VII). According to the literature [15], compound (VIII) can be formed only if the double bond is present in the $C_{12}-C_{13}$ position.

The facts given fully show the structure of ring D of luteidine. The presence of the tetrahydroisoquinoline fragment is confirmed by the opening of the nitrogen-containing heterocyclic ring on the acetylation of the base

with acetic anhydride (16) with the formation of the O,N-diacetyl derivative (XV). In the latter substance, in spite of the disappearance of the optical center at the C_{6a} atom, a low degree of optical activity is retained, which can be ascribed to the spirocarbon atom (C_{8a}) [17].

The action of methyl iodide and potassium acetate on (I) gave O-methylluteidine methiodide, the quaternary base of which did not undergo the Hofman degradation under the usual conditions.

On the basis of the facts given, we propose for luteidine the structure of 1-hydroxy-2,13-dimethoxy-11-oxo-9,10-dihydrohomoproaporphine (I).

EXPERIMENTAL

The UV spectra were taken on a Beckman model 25 spectrophotometer, the IR spectra on a UR-10 double-beam spectrometer, and the PMR spectra on a Varian XL-100 spectrometer. The mass spectra were obtained on MKh-1303 and Varian MAT-311 instruments.

The individuality of the compounds obtained was checked by paper chromatography [in the n-butanol–water (1:1) and n-butanol–5% acetic acid (1:1) systems] and by TLC on silica gel [chloroform–benzene–methanol–ammonia (20:5:6:2) system].

Luteinone (IV). A solution of 200 mg of luteidine in 6 ml of 12% hydrochloric acid was heated to 100°C for 2 h. Then the reaction mixture was made alkaline with ammonia to pH 8 and was extracted with chloroform. The solvent was distilled off and the luteicine was crystallized from acetone. Mp 234-235°C, $[\alpha]_D^{20}$ + 325°C (c 1.0; chloroform). IR spectrum, cm^{-1}: 1735 (CO), 3220 (OH). PMR spectrum, ppm: 2.35 (NCH_3), 3.71 (OCH_3), 6.44 (ar. H). Mass spectrum, m/e: 329 (M^+, 50%), 328 $(M-1)^+$ (100%), 287, 244, 242.

Luteinone Methiodide, mp 253-255°C (from a mixture of acetone and methanol).

Luteinone Dioxime (X). A solution of 50 mg of luteinone in 3 ml of absolute ethanol was treated with 1 ml of pyridine and 50 mg of hydroxylamine hydrochloride. The mixture was heated on a sand bath for 2 h. The solvent was distilled off and the dry residue was treated with a mixture of chloroform and methanol. White crystals precipitated with mp 210.211°C. IR spectrum, cm^{-1}: 3200 (OH), 1600 (C=C), 1470 ($-CH_2$). Mass spectrum, m/e: 359 (M^+), 341 (52%), 340 (100%) 326, 298, 296, 289, 284, 274, 264, 256, 244, 242, 205.

O-Methylluteinone (V). A petroleum ether solution of diazomethane was added to a methanolic solution of 150 mg of luteinone. The solvent was distilled off, and the dry residue was dissolved in chloroform. The chloroform solution was washed with water, and the solvent was distilled off, giving O-methylluteinone with mp 178-180°C (from acetone).

PMR spectrum, ppm: 2.38 (NCH_3), 3.74, 3.71 (2 OCH_3), (6.46 ar. H).

Hydrogenation of Luteidine. In the presence of Raney nickel catalyst, 100 mg of luteidine dissolved in 7 ml of abs. methanol were hydrogenated for 4 h, with magnetic stirring. The catalyst was separated off and washed with methanol, and the solvent was distilled off, giving tetrahydroluteidine (XIV) as an oily product with $[\alpha]_D$ + 13.2° (c 1.14); chloroform). IR spectrum, cm^{-1}: 3400-3200 (OH); 1600 (C=C); M^+ 347. PMR spectrum, ppm: 2.86 (NCH_3), 3.28, 3.74 (2 OCH_3), 6.42 (ar. H).

Reduction of Luteidine with Sodium Tetrahydroborate. A methanolic solution of 60 mg of luteidine was treated with 80 mg of sodium tetrahydroborate. The mixture was heated for 10 min, the solvent was distilled off, and the dry residue was dissolved in water; the solution was acidified with hydrochloric acid (pH 1) and was then made alkaline with ammonia and extracted with chloroform. This gave tetrahydroluteidine (XIV), identical with the product of hydrogenation of (I) in the presence of Raney nickel.

Reduction of Luteidine by the Kizhner [Wolff–Kishner] Method. A solution of 50 mg of luteidine in 6 ml of diethyleneglycol was treated with 4 ml of hydrazine hydrate and 10 ml of caustic potash. The reaction mixture was heated on a sand bath for 3 h, and then 10 ml of water was added and it was acidified with hydrochloric acid (pH 1). Then the solution was made alkaline with ammonia (pH 8) and extracted with chloroform. The solvent was distilled off, giving an amorphous substance–the cyclopropane derivative (XIII). IR spectrum, cm^{-1}: 3350 (OH), 1600 (C=C, ar.), 1460 (CH_2). PMR spectrum, ppm: 2.40 (NCH_3), 3.30, 3.72 (2 OCH_3), 6.38 (H, ar.). Mass spectrum, m/e 329 (M^+), 328, 314 (M–15), 256 (M–43).

Cyclization Reaction. Gaseous hydrogen chloride was passed into a solution of 100 mg of luteidine in 7 ml of glacial acetic acid for 30 min. Then the solution was left overnight under a current of nitrogen. White crystals of the hydrochloride of the acetal compound (VIII) deposited. The crystals were filtered off with suction

and washed with acetone. Mp 265-267°C. IR spectrum, cm^{-1}: 1730 (CO), 1590 (C=C), 1480 (CH_2). PMR spectrum (D_2O), ppm: 3.24 (NCH_3), 3.51, 3.98, (2 OCH_3), 7.02 (H, ar.). Mass spectrum, m/e: M^+ 343 (40%), (M−1) (100%), 328, 314, 300, 286, 272, 244.

Hydrolysis of the Cyclic Compound (VII). A solution of 80 mg of the acetal compound in 10 ml of 5% hydrochloric acid was heated at 100°C for 3 h. The reaction mixture was made alkaline with ammonia and extracted with chloroform. After the solvent had been distilled off, the reaction product (VII) was isolated, with mp 108-110°C (from acetone), $[\alpha]_D$ + 91.7° (c 1.3; water). IR spectrum, cm^{-1}: 3580 (OH), 1730 (CO), 1600, 900-800 (ar. ring). PMR spectrum (D_2O), ppm: 3.34 (NCH_3), 4.11 (OCH_3), 7.08 (ar. H). Mass spectrum, m/e: 329 (M^+) (41%), 328 (M−1) (100%).

N,O-Diacetylluteidine (XVI). A solution of 100 mg of luteidine in 2 ml of acetic anhydride was treated with 1 g of freshly fused sodium acetate. The mixture was heated at 40-50°C for 24 h, and then methanol was added and it was evaporated to dryness. The residue was dissolved in water and extracted with chloroform. Distillation of the solvent yielded amorphous N,O-diacetylluteidine. mp 198-200°C; $[\alpha]_D$ −5.6° (c 1.79; chloroform), M^+ 427. IR spectrum, cm^{-1}: 1645 ($NCOCH_3$), 1740 ($OCOCH_3$).

O-Methylluteidine Methiodide was obtained by heating a methanolic solution of the base with methyl iodide and freshly fused potassium acetate. mp 263-265°C (from a mixture of chloroform and acetone).

Quaternary Base of O-Methylluteidine. A solution of 50 mg of O-methylluteidine methiodide in 5 ml of methanol was treated with moist freshly precipitated silver oxide obtained from 50 ml of silver nitrate. The mixture was shaken for 30 min, the precipitate was filtered off and washed with methanol, and, after being dried over sodium sulfate, the filtrate was evaporated under vacuum. The quaternary base obtained was crystallized from acetone. Mp 208-210°C. PMR spectrum (D_2O), ppm: 3.08, 3.48 (2 NHC_3), 3.76 3.90, 4.00 (3 OCH_3), 6.32 (ol. H), 7.10 (ar. H).

SUMMARY

On the basis of UV, ^{13}C NMR, and mass spectra, it has been established that luteidine belongs to the group of homoproaporphine alkaloids.

The IR, PMR, and ^{13}C NMR spectra of luteidine and the products of its transformations have permitted the structure of 1-hydroxy-2,13-dimethoxy-11-oxo-9,10-dihydrohomoproaporphine to be proposed for this base.

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