THE STRUCTURE OF LUTEICINE

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Information has been given previously [1] on the methiodide of luteicine—a base first isolated from the epigeal parts of Colchicum luteum Baker (yellow autumn crocus). By separating a mixture of luteidine, luteine, and this compound [2], we isolated the latter in the form of a crystalline acetate. The free base readily oxidizes in the air and it was impossible to obtain it in the crystalline state.

Luteicine, with composition $C_{20}H_{27}O_4N$ (high-resolution mass spectrum) has absorption maxima in UV light at 215, 237 (inflection), and 287 nm (log ε 4.7, 4.1, 3.5). On the addition of a 0.1 N solution of caustic soda, no bathochromic shift of the absorption maxima was observed, which shows the absence of a phenolic hydroxy group. The IR spectrum of luteicine (Fig. 1) has the absorption bands of a hydroxy group (3370 cm^{-1}), of the C = C bonds of a benzene ring (1600 cm^{-1}), and of methylene groups (1470 cm^{-1}).

The PMR spectrum of the base (Fig. 2) has, in the strong-field region, three-proton singlets at 3.73 and 3.28 ppm due to methoxy groups in benzene and alicyclic rings, and the signals of the protons of a N-methyl group at 2.73 ppm. In the weak-field region there is only a one-proton singlet corresponding to the proton of a benzene ring (6.43 ppm). In its mass spectrum there are the main peaks of ions with m/e 345 (M^+, 50%), 344 $(M-1)^+$ (100%), 330, 328, 314, 302 $(M-43)^+$, 284.

In its spectral characteristics, luteicine is close to the homoproaporphine and proaporphine alkaloids, particularly those with the reduced dienone ring [3-5]. The developed formula of luteicine, $C_{17}H_{17}(OH)(OCH_3)_2(-O-)(NCH_3)$ is similar to that of regeline [6], but it differs somewhat from the latter in its spectral characteristics. One of the methoxy groups of this base is present, as in regeline, in an acetal grouping: it is stable to the action of alkalis and ammonia but is readily hydrolyzed in dilute acid with the formation of norluteicine (II, Scheme 1).

On the basis of the fact that luteicine and regeline are structurally similar compounds, it may be assumed that they differ by the position of the ether bridge, i.e., of the acetal grouping in the spirocyclane ring. A consideration of a model of the luteicine molecule shows that the ether bridge can form preferentially only five- and six-membered rings with the bonds in the C_1-C_{12} or C_1-C_{13} positions [7]. In view of the fact that the structure with the six-membered ring E is that of kesselringine and its analogs [6], the only possible structure for luteicine is that with the attachment of the oxygen bridge in the C_{13} position of ring D. To confirm this hypothesis, we studied the PMR spectrum of the acetyl derivative of luteicine methiodide (III). In the PMR spectrum of

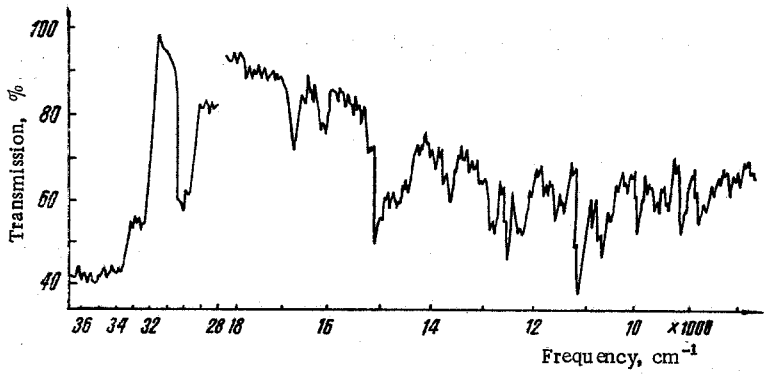

Fig. 1. IR spectrum of luteicine acetate (in KBr).

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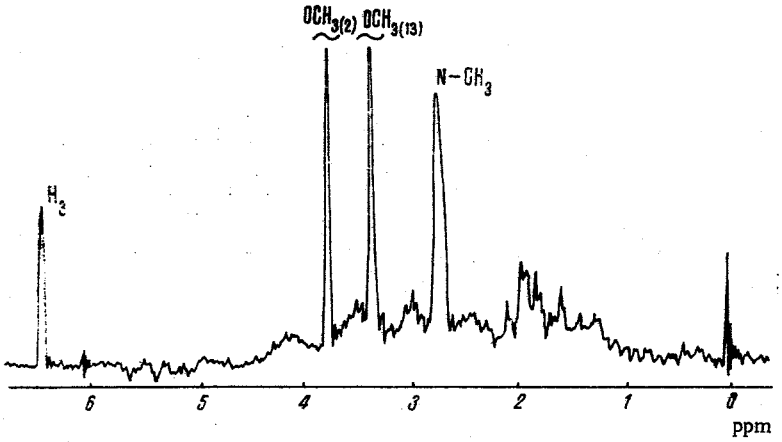
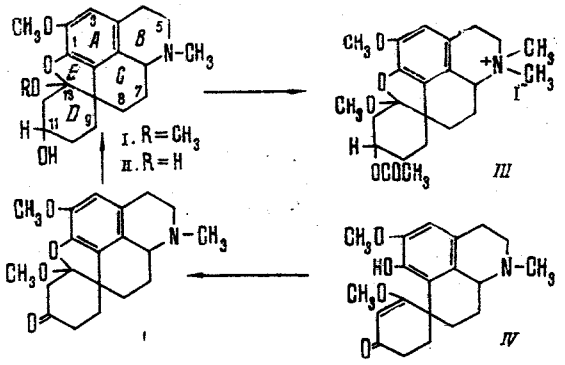


Fig. 2. PMR spectrum of luteicine (in $CDCl_3$).



Scheme 1. Structure and partial synthesis of luteicine.

the latter, the signal of the C_{11} proton, shifted downfield (~ 5.0 ppm) appears in the form of a multiplet, which shows that the C_{10} and C_{12} positions in ring D of luteicine are occupied by methylene groups. We performed a partial synthesis of this base. The cyclization of luteidine (IV) [8] gave the pentacyclic ketone (V), which we have called luteicinone. The latter was reduced with sodium tetrahydroborate, and a compound identical with luteicine was obtained.

On the basis of the facts given above, we have suggested for luteicine the structure of 11-hydroxy-2,13-dimethoxyhexahydro-1,3-epoxyhomoproaporphine (I).

EXPERIMENTAL

The individuality of the substances was checked by paper chromatography in the n-butanol–5% acetic (50:50) system. Radial chromatography of Filtrak No. 1 filter paper was used.

The UV spectra were taken in methanolic solution on a Beckman model 25 spectrophotometer, the IR spectra on a UR-10 double-beam spectrometer, the PMR spectra on an XL-100 instrument, and the mass spectra on an MAT-311 high-resolution mass spectrometer.

Isolation of the Strong-Base Fraction. The leaves and stems of the yellow autumn crocus collected in the fruit-bearing period in the mountains of Bolshoi Chimgan (6.0 kg) were extracted with methanol, and by separating the combined alkaloids into fractions by the method described previously [9], 13.91 g (0.23%) of a mixture of strong bases insoluble in caustic soda was obtained. After crystallization of the luteidine from acetone, the mother liquor contained 6.2 g of a mixture of luteidine (R_f 0.43, luteicine (0.33), and luteinine (0.21). Collutine (R_f 0.47) and a base denoted by the symbols L-8 (R_f 0.54) were present in it only as insignificant impurities.

Luteicine Acetate. The mixture of strong bases remaining after the crystallization of the luteidine (6.0 g) was separated by chromatography on a column containing 600 g of cellulose powder. Elution with n-butanol saturated with 5% acetic acid gave fractions of alkaloids with R_f values of 0.54, 0.47, 0.43, 0.33, and 0.21, respectively.

The eluates containing the luteicine were combined, and the solvent was evaporated off in vacuum. The dry residue was crystallized from acetone, giving 0.262 g of luteicine acetate with mp 210-211°C, $[\alpha]_D$+ 112° (c 1.0; chloroform).

Norluteicine (II). A mixture of 100 mg of luteicine and 15 ml of 6% sulfuric acid was heated to 100°C for 1 h. The acid solution was made alkaline with concentrated ammonia and extracted with chloroform. This yielded 0.92 g of norluteicine, which could not be crystallized; R_f 0.25.

O-Acetylluteicine Methiodide (III). Luteicine methiodide (20 mg) was dissolved in 2 ml of acetyl chloride and the solution was left at room temperature for 10 min. Then the excess of acetyl chloride was evaporated off and the dry residue was treated with ether. Crystals of O-acetylluteicine methiodide with mp 228-230°C and R_f 0.40 separated out.

PMR spectrum, ppm: 2.0 ($OCOCH_3$); 2.09, 2.06 ($2NCH_3$); 3.26; 3.78 ($2OCH_3$); 6.54 (ar. H). IR spectrum: 1750 cm^{-1} ($OCOCH_3$).

Luteicinone (V). Nitrogen was passed into a solution of 80 mg of luteidine in 7 ml of glacial acetic acid for 10 min, and then the solution was saturated with gaseous hydrogen chloride for 30 min. It was left under a current of nitrogen overnight and was then purged with air until the smell of acetic acid had disappeared. When the dry residue was treated with acetone, white crystals of luteicinone hydrochloride deposited with mp 265-267°C, R_f 0.31.

IR spectrum, cm^{-1}: 1730 (CO), 1590 (ar. C=C), 1480 (CH_2); PMR spectrum (D_2O), ppm: 3.24 (NCH_3), 3.51, 3.98 (2 OCH_3), 7.02 (ar. H).

Reduction of Luteicinone to Luteicine (I). A solution of 60 mg of luteicinone in methanol was treated with 80 mg of sodium tetrahydroborate and the mixture was heated on a sand bath for 5 min. Then the solvent was distilled off and the dry residue was dissolved in water and extracted with chloroform. The chloroform was distilled off and a reaction product was isolated the R_f value of which was identical with that of luteicine.

Mass spectrum: m/e 345 (M^+, 52%), 344 $(M-1)^+$ (100%), 330, 328, 302, 284, 244, 242.

SUMMARY

An investigation of the UV, IR, PMR, and mass spectra and chemical transformations of luteicine have established for it the structure of 11-hydroxy-2,13-dimethoxyhexahydro-1,13-epoxyhomoproaporphine.

The structure of the base was confirmed by its partial synthesis from luteidine.

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