ALKALOIDS OF Colchicum luteum

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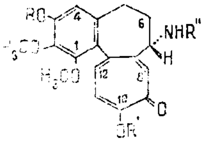
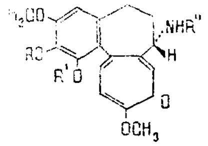
The paper gives a review of the alkaloids of Colchium luteum Baker from various growth sites. The structure of luteidine – one of the main alkaloids of the plant – has been established. In addition, two new alkaloids have been isolated from the plant and the structure of one of them has been established as collutine N-oxide.

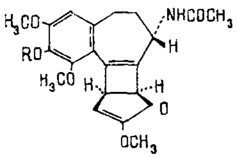
Yellow autumn crocus Colchicum luteum Baker (family Liliaceae) is a widely distributed high-mountain plant of Central Asia and South Kazakhstan [1, 2]. The valuable medicinal properties of this plant were known from the earliest times, and it was imported from India into the Near East and Western Europe [3]. The active principle of the yellow autumn crocus is colchicine – an alkaloid with a tropolone ring C (I) [4]. Colchicine, as a strongly polyploidizing agent, has found use in agriculture [5], and its less toxic basic analog colchamine is used in medicine [6]. Subsequently, this plant growing on the territory of Central Asia was found to have a high content of colchicine, and the new base luteidine [7], which possesses a broad spectrum of physiological activity [8], was discovered.

In 1954-1955, Santavy et al. [9, 10], investigating the corms of yellow autumn crocus growing in India identified colchicine (I), N-formyldeacetylcolchicine (II), 3-demethylcolchicine (III), and β-lumicolchicine (XIII) and established the presence of then unknown tropolone alkaloids. Subsequently [11], cornigerine (VIII) and γ-lumicolchicine (XI) were also isolated from the seeds of this plant and, in addition, the presence of nine bases without a tropolone ring was detected in them. Colchicine, 3-demethylcolchicine, and colchiceine (IV) have also been isolated from this autumn crocus by other authors [12, 13].

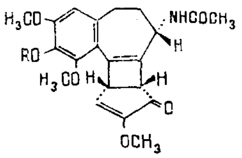




I. $R = R' = CH_3$ $R'' = COCH_3$
II. $R = R' = CH_3$ $R'' = CHO$
III. $R = H$ $R' = CH_3$ $R'' = COCH_3$
IV. $R = CH_3$; $R' = H$ $R'' = COCH_3$
V. $R = R' = R'' = CH_3$
VI. $R = R'' = CH_3$ $R' = H$
VII. $R = R' = H$ $R'' = COCH_3$
VIII. $R + R' = CH_2$ $R'' = COCH_3$
IX. $R = H$ $R' = R'' = CH_3$
X. $R = H$ $R' = CH_3$ $R'' = COCH_3$



XI. $R = CH_3$ XII. $R = H$



XIII. $R = CH_3$ XIV. $R = H$

In 1962, M. K. Yusupov and A. S. Sadykov [7] isolated colchicine, colchiceine, N-formyldeacetylcolchicine, 3-demethylcolchicine, β-luminocolchicine, and the new bases luteidine, luteine, and kesselringine from the epigeal parts of the yellow autumn crocus collected in the Parkent reserve (Tashkent province). These compounds were the first representatives of the isoquinoline bases from plants of the genus Colchicum. A. S. Sadykov et al. [14, 15] then studied the dynamics of the levels and quantitative compositions of the total alkaloids

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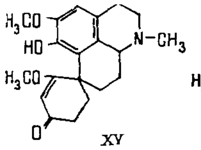
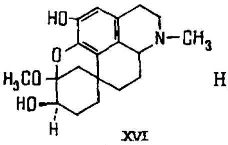
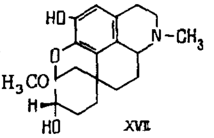
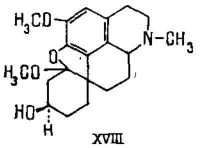
in the individual organs of the plants in various vegetation phases collected in the Sairamskii region (Chimkent province). These authors detected the presence of known alkaloids in the plants – colchamine (V), colchameine (VI), 2-demethylcolchamine (IX), 2-demethylcolchicine (X), and 2-demethyl-β-lumicolchicine (XIV). They revealed a pronounced change both in the qualitative level and in the qualitative composition of the total alkaloids of the autumn crocus in the course of the vegetation period. Furthermore, they isolated and established the structures of two new alkaloids – 3-demethylcolchiceine (VII) [16] and 2-demethyl-γ-lumicolchicine (XII) [17, 18].

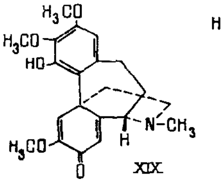
Later, A. S. Sadykov et al. [19, 20] isolated from yellow autumn crocus growing in the Parkent region and in Bolshoi Chimgan (Tashkent province) the isoquinoline alkaloids luteicine, luteinine, and collutine. At the present time, the structures of all the isoquinoline alkaloids of the plant have been established. Of them, luteidine (XV) [21] belongs to the dehydrohomoproaporphine bases, luteine (XVI) [22], kesselringine (XVII) [23], luteicine (XVIII) [24] to the hexahydrohomoaporphine bases, and collutine (XIX) [20] to the homomorphinandienone bases. A probable structure with a modified homoproaporphine carbon-nitrogen skeleton (XX) has been proposed for luteinine [25].

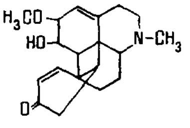

XV


XVI

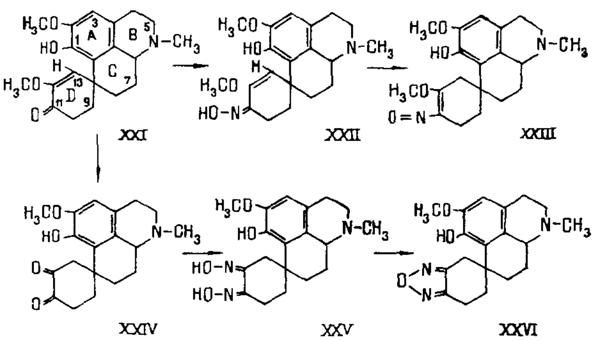

XVII


XVIII


XIX

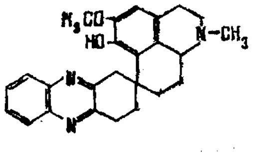

XX

The structures of two bases – luteidine and luteicine – have not been strictly demonstrated. On the basis of UV, IR, PMR, and ^{13}C NMR spectra and chemical transformations, the structure of 1-hydroxy-2,13-dimethoxyhomoproaporphine (XV) has been proposed for the first of them. In spite of the large amount of information obtained, the position of the methoxy group at the olefinic bond of ring D has not yet been definitively determined, and we have therefore continued the search for methods to demonstrate the structure of ring D of luteidine completely. In a study of the PMR spectrum of the oxime of this base (XXII) it was found that part of the substance underwent a rearrangement. The spectrum of the compound formed, unlike that of (XXII), had no signal of an olefinic proton in ring D, but the signal of the hydroxymethyl group at an olefinic bond (3.45 ppm) was retained. From this, the conversion of part of (XXII) into the nitroso derivative (XXIII) was suggested.

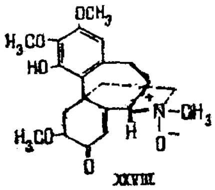


It can be seen from a comparison of the structural formulas of (XV), (XXI), (XXII), and (XXIII) that if the olefinic methoxy group were present at C_{13}, then, after the migration of the double bond, the signal of the olefinic proton at C_{12} would be retained but the methoxy group would prove to be in the saturated chain of the molecule with a chemical shift in the $\sim$3.30 ppm region of the spectrum [23, 26].

Considerable difficulties arise in the deciphering of the structure of luteinone — a hydrolysis product of luteidine. According to some statements it may be regarded as a β-diketone [21] or as a saturated ketone. However, from the formation of the dioxime (XXV), which is converted by the splitting out of a molecule of water into the anhydride (XXVI), luteinone is an α-diketone. Furthermore, with o-phenylenediamine, luteinone, as an α-diketones, forms the quinoxaline derivative (XXVII) [27]. The IR spectrum of luteinone also shows the presence of an α-diketone grouping in it (1735 cm^{-1}) [28]. According to the facts given above, luteidine is represented by the structure of 1-hydroxy-2,12-dimethoxyhomoproaporphine (XXI).



XXVII



XXVIII

In a further investigation of the total alkaloids of the yellow autumn crocus collected on the slopes of Bolshoi Chimgan, we isolated two new compounds: the first, (XXIX), with the composition $C_{19}H_{23}O_4N$, mp 237-238°C, and the second, (XXVIII), with the composition $C_{21}H_{25}O_6N$, mp 217-219°C (decomp.), and $[\alpha]_D$ −204°. We have established the structure of the second of them. Its UV spectra contains absorption maxima at 240 and 277 nm, and its IR spectrum the absorption bands of a hydroxy group (3300 cm^{-1}), of a carbonyl group conjugated with a double bond (1680, 1656, 1618 cm^{-1}), and the C=C bonds of a benzene ring (1600 cm^{-1}). The PMR spectrum of the substance exhibits the signals of three aromatic protons in the form of one-proton singlets (6.72, 6.32, and 6.26 ppm), of three O-methyl groups (4.00, 3.71, and 3.57 ppm), and of one N-methyl group (3.24 ppm). From the combination of spectral characteristics, this compound has been assigned to the group of homomorphinandienone bases of the autumn crocus. In actual fact, when it was reduced with zinc dust, two compounds were formed one of which was chromatographically identical with collutine (1-hydroxy-2,3,10-trimethoxyhomomorphinandienone) [20]. On the basis of the facts given, it may be concluded that this compound is collutine N-oxide (XXVIII). No N-oxides of homomorphinandienones have been described in the literature before, and collutine N-oxide is their first representative.

EXPERIMENTAL

Luteidine Oxime (XXII). A solution of 0.5 g of luteidine and 0.4 g of hydroxylamine hydrochloride in a mixture of 10 ml of dry pyridine and 20 ml of ethanol was boiled for 3 h. The solvent was distilled off, the residual substance was dissolved in water, and the solution was extracted with chloroform.

Compound XXII was isolated, with mp 169-171°C (from acetone), R_f 0.46 (chromatography on Filtrak No. 1 paper in the n-butanol—water (1:1) system, Luetidine has R_f 0.43.

IR spectrum (cm^{-1}): 1700, 1600, 1463, 1370, 1310, 1280, 1253.

PMR spectrum (in CD_3OD, ppm): 6.51 (H_3), 5.05 (H_{13}), 3.74 (ar. OCH_3), 3.50 (al. OCH_3), 2.43 ($N-CH_3$).

Mass spectrum (m/z): 358 (M^+), 343, 325, 315, 298, 287, 270, 250, 244, 242.

The nitroso derivative (XXIII) was isolated from the acetone mother liquor from (XXII) by repeated recrystallization. R_f 0.40.

PMR spectrum (in CD_3OD, ppm): 6.57 (H_3), 3.71 (ar. OCH_3), 3.45 (al. OCH_3), 2.34 ($N-CH_3$).

The quinoxaline (XXVII) was obtained in usual ways by heating an alkaline aqueous solution of luteinone and o-phenylenediamine.

Leuteinone Dioxime (XXV). A solution of 0.1 g each of luteinone and hydroxylamine hydrochloride in a mixture of 2 ml of dry pyridine and 6 ml of ethanol was boiled for 2 h. Compound (XXV) was isolated, with mp 212-213°C (from acetone), R_f 0.38. Luteinone has R_f 0.20.

Mass spectrum, (m/z): 359 (M^+), 341 (50%), 340 (100), 326, 296, 284, 244, 242.

The isolation of the bases (XXVIII) (composition $C_{21}H_{25}O_6N$, mp 217-219°C (from acetone), $[\alpha]_D$ −204° (c 0.36; chloroform), R_f 0.51 (n-butanol—5% acetic acid (1:1) system) and (XXIX) (composition $C_{19}H_{23}O_4N$, mp 237-238°C, R_f 0.28) was carried out from the luteidine (R_f 0.42) mother solution by a procedure described previously [8].

Compound (XXIX). IR spectrum (cm^{-1}): 3690-3050, 2960, 2945, 2930, 2920, 1735, 1650, 1640, 1600.

PMR spectrum (in $CDCl_3$, ppm): 6.43 (ar. H), 4.90 (1 H), 3.71 (ar. OCH_3), 2.34 ($N-CH_3$).

Mass spectrum (m/z): 329 (M^+), 328 (100%), 287, 244, 242.

The reduction of (XXVIII) to (XIX) with zinc dust was performed in 10% acetic acid with heating. Ths formed compounds with R_f 0.44 and 0.53, the first of which was identified chromatographically as collutine (XIX).

SUMMARY

1. A number of reactions of luteidine and its hydrolysis product luteinone have been studied. A corrected structure of this base is proposed as 1-hydroxy-2,12-dimethoxyhomoproaporphine.

2. Two new bases have been isolated from yellow autumn crocus: with the composition $C_{19}H_{23}O_4N$, mp 237-238°C, and with the composition $C_{21}H_{25}O_6N$, mp 217-219°C, $[\alpha]_D$ −204°. The structure of collutine N-oxide is proposed for the second of them.

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