

Structure of Crociamine

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Abstract: Crociamine is the first homopaporphyrin alkaloid with an open tetrahydroisoquinoline nucleus. Its distant analogues, phenanthrene bases, are isolated from producers of aporphin alkaloids. The structure of crociamine is close to methyl ester of N-methylkesselringin with open ring B, ways of its partial synthesis from kesselringin were studied. Under the influence of methyl iodide on this compound in the presence of potassium carbonate in methanol solution, O-methylkesselringin iodomethylate is formed. Under the action of wet silver oxide, the latter turns into a quaternary base, which turned out to be thermally stable and, when heated, does not decompose into a base. Under the action of methyl iodide, it again passes into iodomethylate. therefore, we studied other ways of opening the heterocyclic ring of kesselringin.

Index Terms: Crociamine, Colchicum, homopaporphin, iodomethylate, N-methylkesselring, O-methylkesselring. structure.

1 INTRODUCTION

Colchicum L. and Merendera ramond plants are widespread in Central Asia and are among the most alkaloid in the liliaceae. Six species of them will grow on the territory of Central Asia - Colchicum kesselring (C. Kesselringii Rgl.), Colchicum yellow (C. luteum Baker), large merendera (M.robusta Bge.), Merendera yolanta (M.jolante E. Czerniak), merendera Hissar (M.hissarica Rgl.) and progeny merendera (M.sobolifera CAM) [1]. The first four were studied as potential sources of valuable antitumor compounds of colchicine and colchamine, as well as new groups of isoquinoline bases. By studying the alkaloids fraction of the main character from the corms of the colchicum Kesselring, along with homopaporphyrin compounds, unknown bases were revealed that manifest themselves with the modified Dragendorff reagent, instead of the usual orange, orange-yellow staining. One of them, m Rf 0.90, was reported earlier in [2]. High Rf values indicated a relatively better solubility of this base in organic solvents. To isolate it, the base mixture is converted by the action of methyl iodide into iodomethylates, after which base iodomethylate with Rf 0.90 is separated from the others by chloroform extraction. According to spectral data, the isolated compound differs significantly from the iodomethylates of other known colchicum bases, and a structure was established for it. The base corresponding to iodomethylate was called crociamine.

2 RESULTS AND DISCUSSION

Crociamine is isolated in the form of iodomethylate, which has the composition $C_{22}H_{33}O_4N + I^-$, t.m.l. 229-230° and $\alpha / D +29$. In the IR spectrum there are absorption bands of the benzene ring (1600 cm^{-1}), methylene and oxymethyl groups (2975-1860, 1490-1450 cm^{-1}), secondary hydroxyl group (3530, 1095 cm^{-1}). The PMR spectrum (CD3OD) shows the signals of three N-methyl groups in the form of a nine-proton singlet (3.22 ppm), two methoxy groups located in alicyclic (3.37 ppm) and aromatic (3.80 ppm) rings. In the weak-field region of the spectrum, signals of three single protons are manifested: H-3 of the aromatic ring (6.80 ppm, p, 1H) and two olefin protons forming the AB system - H α (5.90 ppm, m, 1H) and H β (6.55 ppm, d, 1H) of ring B, indicating the presence of an olefinic bond in the compound.

When heated in dilute acid, one of the oxymethyl groups of the compound located in the alicyclic ring is hydrolyzed. This suggested that, as in the concomitant homopaporphyrin alkaloids [2], it has a ketal character. The presence of a trimethylamine fragment in iodomethylate indicated the presence of a dimethylamino group in the initial base and the alicyclic nature of the base. Based on the above data, structure 1 was assumed for the base, and 2 for its iodomethylate (Fig 1).

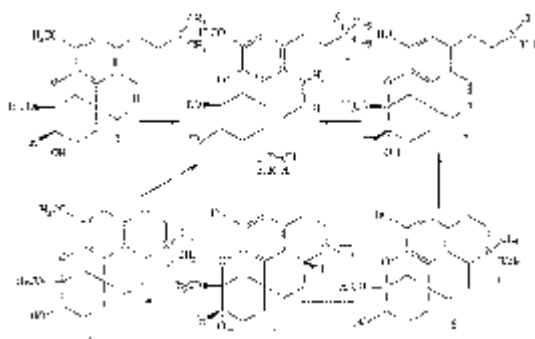


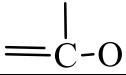
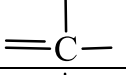
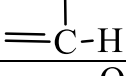
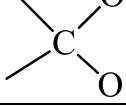
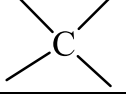
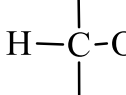
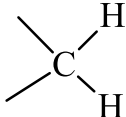
Fig 1. Structure and partial synthesis of crociamine.

Due to the fact that crociamine is close in structure to methyl ester of N-methylkesselring with open ring B [3], ways of its partial synthesis from kessselringin were studied. Under the action of methyl iodide on this compound in the presence of potassium carbonate in a methanol solution, O-methylkesselringin iodomethylate is formed (4). Under the action of wet silver oxide, the latter turns into a quaternary base, which turned out to be thermally stable and, when heated, does not decompose into a base. Under the action of methyl iodide, it again passes into iodomethylate. therefore, we studied other ways of opening the heterocyclic ring of kesselringin. The use of caustic soda instead of potassium carbonate in the reaction with methyl iodide leads to the formation of a mixture of two compounds of kesselring, one of which is identical in value to Rf (0.85) and the color of the manifestation (orange) with O-methylkesselring iodine, and three times more Rf (0.94) and appears with an orange-yellow stain. Modifying this experiment, we subsequently treated Kesselringin iodomethylate (6) sequentially with a 30% methanol solution of alkali and methyl iodide. In this case, a quantitative formation of only one compound with rf 0.94 from kesselringin iodomethylate, identical with crociamine amine

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iodide, is achieved; in terms of the value of R_f and the PMR spectrum, they turned out to be the same. In order to fully confirm the structure 2 for crociamine amine iodide, we recorded its ^{13}C -NMR spectrum in which the signals of carbon atoms (CD_3OD) were detected:

Table 1. Carbon Atoms

Carbon atom type	number	Chemical shifts in ppm
	2	147,6; 143,4
	3	123,8; 123,2x2
	3	125,9; 122,8; 113,4
	1	103,2
	1	36,0
	1	70,8
	6	37,3; 34,5; 30,5; 27,8; 27,0; 67,9
$\text{N}(\text{CH}_3)_3$	(3)	54,0; 53,8; 53,7
OCH_3	2	57,0; 49,4

The number and types of carbon atoms in the spectrum fully correspond to the structure of 2 crociamine amine iodide. Based on this, it was concluded that crociamine - the base has a structure of 1 [4]. Crociamine is the first homoporphyrin alkaloid with an open tetrahydroisoquinoline nucleus. Its distant analogues, phenanthrene bases, were isolated from producers of aporphin alkaloids [5]. According to spectral data and chemical transformations, crociamine is close to homoporphyrin alkaloids of regecolin and 12-demethylutein [6-7].

3 EXPERIMENTATION

UV spectra were recorded in a solution of methanol or water on a Bekman spectrometer (model 25). IR spectra - on a double-beam spectrometer UR-10 paraffin oil, tablets of potassium bromide or on a thin layer of the substance. ^1H and ^{13}C NMR spectra were recorded on a VXR-400 instrument in a solution of CDCl_3 and D_2O , and mass spectra were recorded on a Varian MAT-311 spectrometer. The individuality and authenticity of the substances was controlled by BH and TLC methods. Radial BC was carried out on Filtrak paper using mobile phases n-butyl alcohol - hydrochloric acid - water, 50: 7.5: 13, and n-butyl alcohol-5% acetic acid 50:50, and TLC on glass plates with fixed 15% 3: 3: 3: 1 chloroform-isopropyl alcohol-acetone-benzene 25% aqueous ammonia

layer of silica gel LS 5/40 C grade 13% gypsum with mobile phases : 4: 4: 5: 1. The stain of substances showed a modified Dragendorff reagent and iodine vapor. Hydrolysis of crociamine iodomethylate (2) to the 12-demethyl derivative (3). 0.03 g of base iodomethylate in 3 ml of 5% sulfuric acid was heated at 100° for two hours. After completion of the reaction, the solution was made basic, evaporated in vacuo, and the residue was extracted with heating with chloroform. A 12-demethyl derivative of crociamine iodomethylate was isolated. PMR spectrum: the absence of a proton signal from an alicyclic methoxy group (3.37 ppm). Reactions of kesselringin (5) with methyl iodide (partial synthesis of crociamine amine iodide, 2).

1. A mixture of 0.1 g of kesselringin, 1 ml of methyl iodide and 0.1 g of anhydrous potassium carbonate in 5 ml of methanol was boiled for 2 hours. The solvent was distilled off and the residue was repeatedly extracted with warm dry chloroform. O-methylkesselringin iodomethylate was isolated (4). Mp $249-250^\circ$ (from acetone).
2. To a solution of 0.20 g of kesselringin in 5 ml of methanol was added 1 ml of methyl iodide and the mixture was boiled for one hour. The solvent was distilled off, and Kesselringin iodomethylate (6) was crystallized from acetone. Mp $236-237^\circ$.
3. 0.10 g of kesselringin, 0.50 g of potassium hydroxide and 0.5 ml of methyl iodide in a solution of 5 ml of methanol were boiled for one hour. The solvent was distilled off and the residue was removed with dry warm chloroform. Mixtures of iodomethylates of O-methylkesselringin (4) and crociamine (2) were isolated.
4. To a solution of 0.15 g of kesselringin iodomethylate in 3 ml of methanol, a solution of 0.50 g of potassium hydroxide in 3 ml of methanol was added with stirring. After 3 hours, 1 ml of methyl iodide was added to the solution, and the reaction mixture was left until the next day. The solvent was distilled off and the residue was repeatedly extracted with warm chloroform.

Crociamine iodomethylate (2) was isolated with mp. $229-230^\circ$ (from acetone), which, unlike iodomethylates of homoporphyrin bases, appears as a modified Dragendorff reagent on yellow stained paper.

4 CONCLUSION

1. Crociamine is the first homoporphyrin alkaloid with an open tetrahydroisoquinoline nucleus.
2. According to spectral data and chemical transformations, crociamine is assigned to a number of homoporphyrin alkaloids and its structure has been established.

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