MASS-SPECTROMETRIC STUDY OF THE NEW ALKALOIDS FROM PLANTS OF THE FAMILY LILIACEAE

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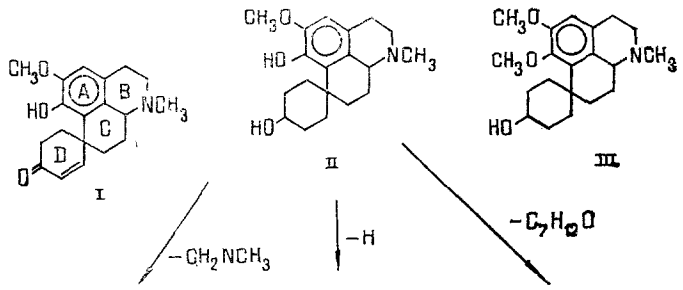
A review is given of the mass spectra of alkaloids isolated from plants of the genera *Colchicum* L., *Merendera ramond*, family Liliaceae that are derivatives of homoproaporphine, homoaporphine, homomorphine, and allochlchiceine. The basic fragmentation pathways and the analytical indications of individual structural types and differences due to the mutual positions of the functional groups, substituents, and the unsaturation of individual rings are given.

As the result of the systematic study of plants of the genera *Colchicum* L. and *Merendera ramond*, family Liliaceae in addition to the tropolone alkaloids and their photochemical isomers, new bases structurally different from known ones have been isolated and studied [1, 2]. The mass spectra of these compounds have been obtained [3-6]. The present review gives their main fragmentation pathways and the analytical indications of individual structural types and differences due to the mutual positions of the functional groups and substituents, and the unsaturation of the individual rings.

Mass Spectra of the Homoproaporphine Alkaloids. Trigamine [7], jolantamine [4, 8], crociflorinine [9], jolantimine [10], leteidine [11], kesselridine [3, 12], kesselringine [3, 13], regelamine [3, 4, 14], regeline [2, 15], and luteicine [2, 16] have been studied.

Bulbocodine (I) [17] and kreysiginone and dihydrokreysiginone [18] underwent retrodiene breakdown with the splitting out of hydrogen and carbon monoxide from ring D and ethylene from ring C. The mass spectrum of bulbocodine contained, in addition, the peaks of ions with m/z 244 and 242 due to the breakdown of ring D [17]. In the mass spectra of trigamine (II) the $(M - H)^+$ ions, the retrodiene fragments, and an ion with m/z 205 were intense. In addition, the $(M - H)^+$ ion and the retrodiene fragment split out water forming ions with m/z 298 and 256, respectively. In the mass spectrum of O-methyltrigamine (III), the product of methylation at the phenolic hydroxyl, all the ions mentioned were shifted in the direction of higher masses by 14 a.m.u..

On the basis of the results of a comparison of these spectra and the spectra of bulbocodine it is possible to arrive at the conclusion that the mass-spectrometric fragmentation of these alkaloids takes place mainly at rings B and D, i.e., with the formation of the $(M - H)^+$ ions and a retrodiene fragment. Ions with m/z 205 (for II) and 219 (for III) are the products of the complete breakdown of rings C and D (Scheme 1).



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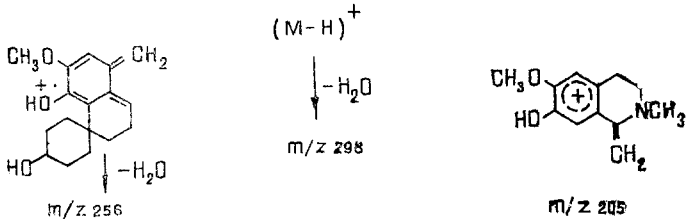
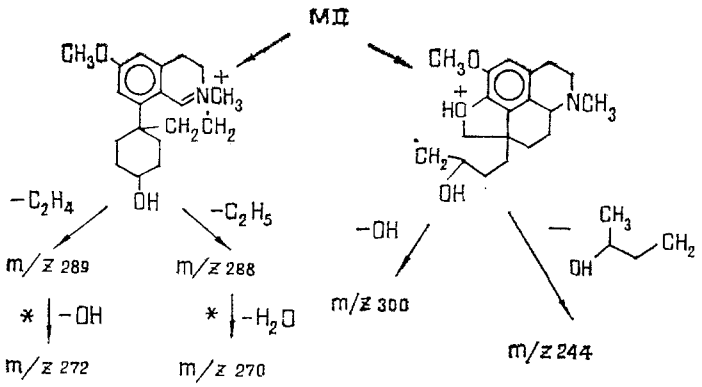


Scheme 1. Main ions of trigamine.

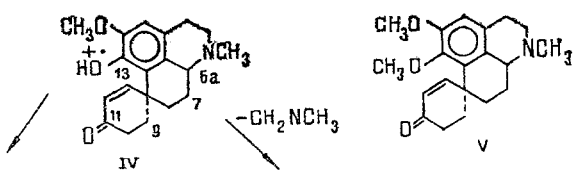
As further investigations showed, the most valuable information on the structure of the alkaloids is given by the weaker ions formed on partial breakdown at rings C and D. For trigamine, these are the fragments M — OH, M — C_2H_4 — OH, M — C_2H_5, and M — C_2H_5 — H_2O and the ions with m/z 244 and 242 (below, ions similar to the last two will be called ions of types *a* and b, respectively). These ions are shown in Scheme 2.

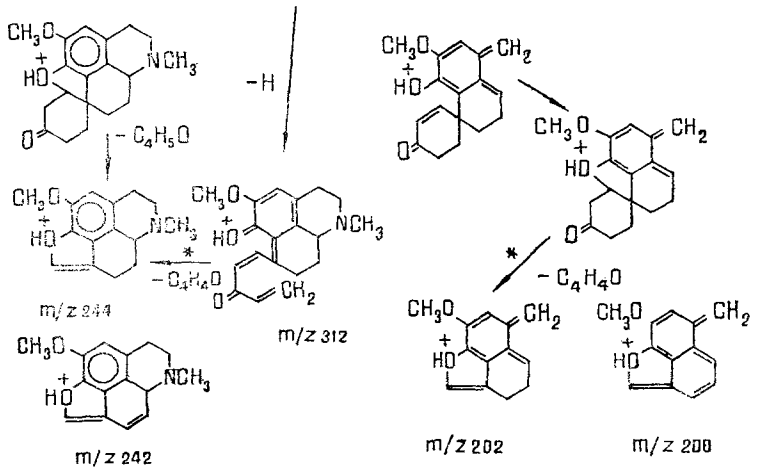
The mass spectrum of jolantamine (IV) differs from that of bulbocodine only by the intensities of certain ions and, in particular, that of the ion with m/z 244. The difference in their structures probably amounts to the positions of the double bond in ring D. The double bond can determine a particular predominant localization of the positive charge on two reaction centers — the aromatic ring or the nitrogen. In bulbocodine, with the double bond in the C_9—C_{10} position, the nitrogen and the carbonyl group conjugated with the double bond are present on the same side of the plane of ring A, which promotes the easy breakdown of ring D. As a result, the ion with m/z 244 is stronger in the spectrum of jolantamine, which has the double bond between carbon atoms 12 and 13 (IV). In this structure, with the same configuration of the asymmetric center 6a as in bublocodine, the nitrogen and the carbonyl group conjugated with the double bond are located on different sides of the plane of ring A. The existence of two reaction centers — the aromatic ring and the nitrogen — is indicated by the fact that on an oscillogram of jolantamine, in addition to the singly charged molecular ions (m/z), the double-ion charged ion (m/2z) is also recorded.



Scheme 2. Trigamine ions having analytical value.

In the mass spectrum of jolantamine there are also the peaks of the retrodiene fragment and of ions with m/z 202 and 200. The structures of the ions with m/z 202 and 200 have been interpreted on the basis of the results of a study of the spectra of metastable transitions and a determination of compositions. These ions are formed from the retrodiene fragment by a scheme similar to the formation of the ions with m/z 244 and 242 from the molecular ion. The fragmentation of jolantamine is shown in Scheme 3.





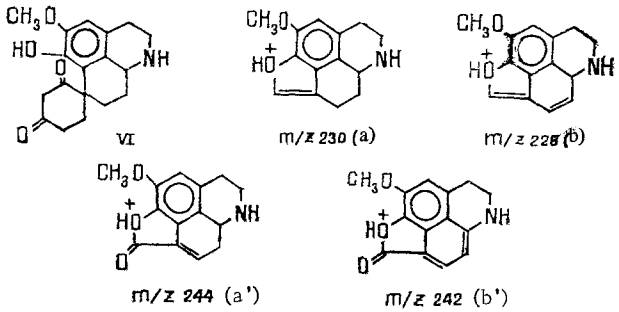
Scheme 3. Fragmentation of jolantamine.

The spectrum of trigamine also contains ions with m/z 202 and 200. To these correspond ions with m/z 216 and 214 in the mass spectrum of O-methyltrigamine.

The given structures of jolantamine and of the ions formed from it have been confirmed by the deuterium-exchange reaction and by a study of the mass spectrum of the deuterium analog — M 317. In this spectrum, the peak of the $(M - 43)^+$ ions is shifted by 4 a.m.u. — m/z 274 — and the peaks of the ions of types *a* and b are shifted by only one unit — m/z 245 and 243. Ions with m/z 289 (M — 28) and 288 (M — 29) of the same spectrum confirm the scheme of breakdown of ring C in their formation. It must be added that these ions are stronger in the spectrum of jolantamine and its deuterium analog than in the spectrum of trigamine and O-methyltrigamine.

The mass spectrum of crociflorinine (V, Scheme 3) is analogous to that of jolantamine, but all the peaks of the ions are shifted in the direction of higher masses by 14 a.m.u.

The mass spectra of jolantimine (VI) [10] and its deuterium analog — M 321 — gave confirmation of the secondary nature of the nitrogen (elimination of $CH_2{=}NH$ and $CH_2{=}ND$, respectively), and of the position of the secondary ketone group. In these spectra, in addition to the ions of types *a* and b (m/z 230 and 228; in the spectrum of the deuterium analog, m/z 232 and 230), there were the peaks of ions with m/z 244 and 242 in the spectrum of jolantimine and m/z 246 and 244 in the spectrum of the deuterium analog (Scheme 4). The latter ions we shall call ions of types *a'* and b'.



Scheme 4. Analytical ions of jolantamine.

A mass-spectrometric structural analysis permitted the structure of luteidine (VII) [11] to be refined and differences in the mass-spectrometric fragmentation of alkaloids of the luteicinone and the kesselridine subgroup to be revealed.

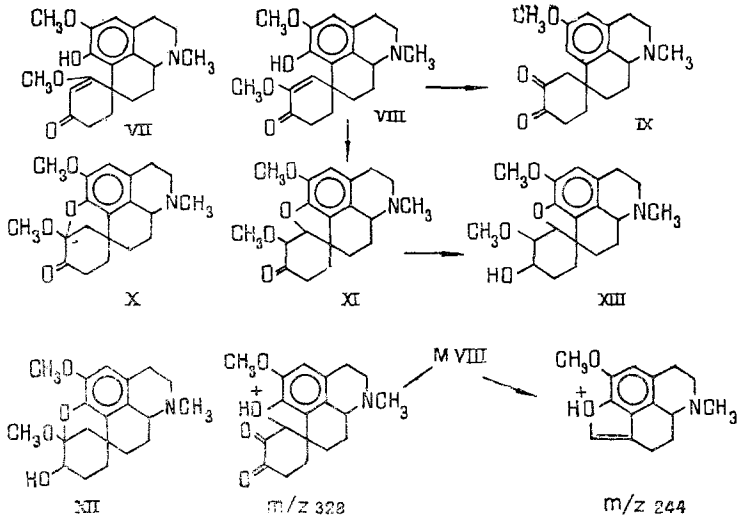
In contrast to the mass spectrum of jolantamine, in the spectrum of luteidine the strongest peaks are those of the ions with m/z 328 (M — 15) and 244. The splitting out of a methyl radical is included in the general scheme of fragmentation of the alkaloids under consideration only if the methoxy group in luteidine is present not in position 13 (VII) but 12 (VIII). Of the other ions, only the molecular ion and the retrodiene fragment are of high intensity.

The mass spectrum of the deuterium analog of luteidine with M 346 has been studied. In luteidine, there are three mobile hydrogen atoms and not four as is envisaged by structure (VII). The peaks of the M − 15, M − 28, and M − 43 ions are also shifted by three a.m.u. The peaks of the ions with m/z 244 and 242 are shifted by only one unit.

In the mass spectrum of the product of the hydrolysis of luteidine — luteinone (IX) — the ion $(M - H)^+$ and the retrodiene fragment with m/z 286 are strong. The peaks of types *a* (m/z 244) and b (m/z 242) are weaker and there are no peaks with m/z 258 and 256.

Ions should be recorded at these mass numbers if structure (VII) is correct. Furthermore, the mass spectrum of the β-diketone expected from structure (VII) should be similar to that of jolantimine. However, no such similarity exists. The facts given above have been confirmed by the mass spectra of luteidine derivatives. In the mass spectrum of luteidine oxime, the maximum ion peak is that with m/z 244. There are also peaks of methyl-elimination ions and of the retrodiene fragment. In the mass spectrum of acetylluteidine, likewise, the maximum ion peak is that of type *a* — m/z 284.

The structure of luteidine and its main ions are shown in Scheme 5.



Scheme 5. Structure of luteidine.

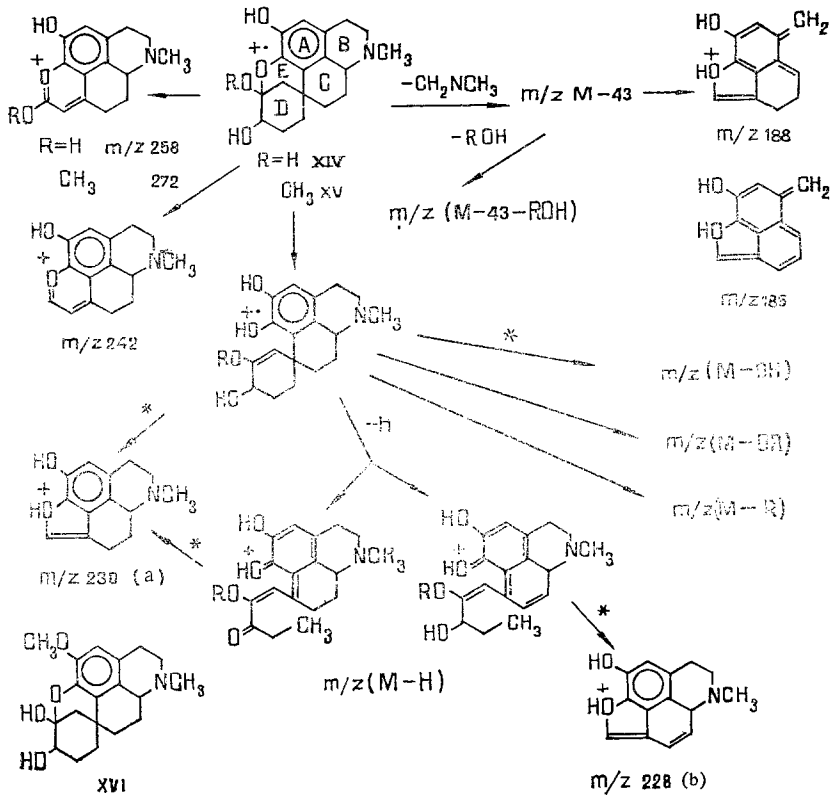
Luteidine gives an isomerization product — luteicinone. Its mass spectrum (M 343) contains, in addition to strong peaks of ions formed by the splitting out of methyl and carbon monoxide (m/z 315.1812; calc. 315.1821) the peaks of ions with m/z 286 and 272. The latter ion then, as is shown by the spectrum of its daughter ions, splits out methyl, methoxyl radicals, and methanol. The mass spectrum of the product of the reduction of luteicinone — luteicinol (M 345) — has the peaks of the fragments M − H, M − OCH_3, M − OH, M − H_2O, M − H − H_2O, and M − CH_2NCH_3, and of ions with m/z 288, 244, and 242. A number of structures for luteicinone "fit" these facts, including the most probable ones (X) and (XI). The first structure fails since in this case the mass spectra of luteicinol and of regeline (XII) should be identical or close if they are epimers. However, these spectra differ considerably in the intensities of the peaks with m/z 330 (M − 15), 328 (M − 17), and 284 (M − CH_2NCH_3 − H_2O).

Structure (XI) for luteicinone and, consequently, structure (XIII) for luteicinol (Scheme 5) are confirmed by a comparison with the spectra of the alkaloids of the kesselridine and luteicine subgroups.

The structure of kesselridine (XIV) was shown mainly by mass-spectrometric methods. The presence in the mass spectrum of the base of the main ions $(M - H)^+$ and $(M - CH_2NHCH_3)^+$ showed that it belonged to the tetrahydroisoquinoline derivatives containing a N-methyl group. At the same time, the intensity of the peak of the molecular ion was approximately half that of the maximum — the $(M - H)^+$ — ion. Such spectra are characteristic for homoproaporphines. The presence of ions with m/z 230 (type *a*) and 228 (b) simultaneously excludes an aporphine skeleton.

The mass numbers of the ions of types *a* and b, and also analogies with known structures indicate that a hydroxyl is present at the second carbon atom. A comparison of this spectrum

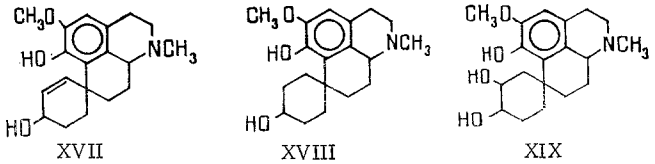
with that of kesselringine (XV) gave confirmation of the position of linkage of rings D and E (ion with m/z 242), of a second hydroxyl group in kesselridine (ion with m/z 258) and of a methoxy group in ring D of kesselringine (ion with m/z 272). The ions formed by the splitting out of a hydroxy radical and water indicate that there is also a hydroxy group close to the reaction center, i.e., at carbon atom 11. The fragmentation pathways of kesselridine and kesselringine are shown in Scheme 6.



Scheme 6. Fragmentation of kesselridine and kesselringine.

The fragmentation pathways of regeline (XII) and regelamine (XVI) are similar. The compositions of the regelamine ions the structures of which are shown in Scheme 6 have been determined.

The mass spectra of the reduction products of regelamine and of jolantamine have been studied. On reduction, jolantamine forms jolantaminol (XVII) and tetrahydrojolantamine (XVIII). Regelamine also forms two reduction products, one of which is dihydroregelamine (XIX), while the other is identical with tetrahydrojolantamine.



XVII XVIII XIX

The mass spectrum of dihydroregelamine is similar to that of trigamine. The molecular ion is strong and the maximum ion is $(M - H)^+$. The m/z 244 and 205 ions are also strong. There are ions formed on the decomposition of the retrodiene fragment — m/z 272 (M — 43 — 18) and 202. There are no peaks of ions — in particular, of an ion with m/z 256 — confirming the presence of ring E in regelamine.

The mass spectrum of tetrahydrojolantaminol is identical with that of trigamine. The peaks of the ions of jolantaminol (M 315) with m/z greater than 250 are shifted by two units in comparison with the spectrum of trigamine (M 317).

The mass spectrum of luteine has also been studied [19]. It differs from the spectrum of kesselringine. The retrodiene fragment of luteine splits out water, while the corresponding

fragment of kesselringine splits out methanol. On the other hand, the mass spectrum of luteine is similar to the spectra of luteicine and regilinine [2], but the peaks of its ions are shifted by 14 a.m.u. in the direction of smaller masses. From this it is possible to draw the conclusion that luteine, luteicine, and regilinine belong to the same subgroup — with a five-membered ring E.

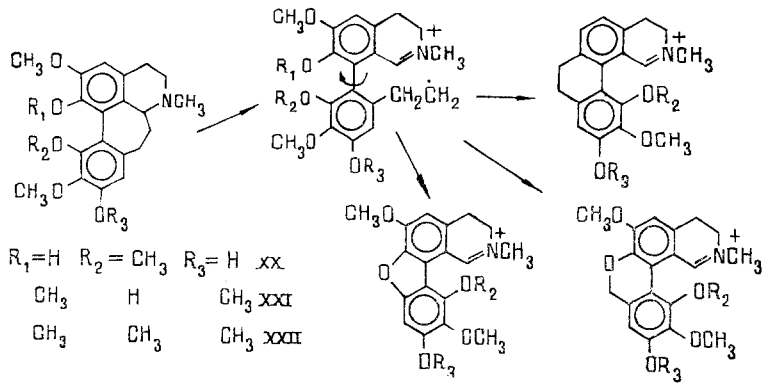
The mass spectrum of methylluteine is identical with the spectra of luteicinol (XIII, Scheme 5) and regilinine. Consequently, luteine is 2-demethylregilinine.

On the basis of a comparison of the characteristics of the mass spectra of the homoproaporphine alkaloids it is possible to arrive at the following conclusion. For compounds with a saturated ring D and with a hydroxy or methoxy group in this ring (trigamine, tetrahydrojolantamine, dihydroregelamine, kesselridine, kesselringine, regeline, regelamine, and luteicine) intense peaks of the $(M - H)^+$ ions and the retrodiene fragments are characteristics. Subsequently, these ions split out water or methanol from ring D at the expense of the substituent from position 12 (kesselridine and its analogs) or 11 (the luteicine subgroup). The ions formed as the result of breakdown at ring D — in particular, those of types *a* and b — are less intense. For alkaloids containing a six-membered ring E, i.e., an acetate bridge (the kesselridine subgroup) pairs of ions with m/z 188 and 191 (ring A with two hydroxy groups) or 202 and 205 (ring A with one hydroxy and one methoxy group) are specified. Characteristic for alkaloids for the luteicine subgroup are isolated ions with m/z 188 or 205. In the spectra of compounds of the trigamine type a solitary ion with m/z 205 or 219 is intense.

For compounds with one double bond in ring D (jolantamine, crociflorine, jolantaminol), the $(M - H)^+$ ions are also intense. But the mass spectrum of each of these contains the peak of an ion formed by the elimination of ethylene from ring C. The intensity of this ion is greater than that of the retrodiene fragment.

The alkaloids of the luteidine subgroup form — together with intense $(M - H)^+$ ions and the retrodiene fragments — ions involving the breakdown of ring D. Ions formed by the splitting out of methyl from ring D and ions of types *a* and b are intense.

Mass Spectra of the Homoaporphine and Homomorphinan (Anhydrocymbine) Bases. Merenderine (XX) [20], szovitsamine (XXI) [21], and O-methylkreysigine (XXII [22] have been studied. The mass spectra of the homoaprophines differ completely from the spectra of the homoproaporphines [30]. In their mass spectra the main peak in each case is that of the ion formed by the splitting out of the substituent at the third carbon atom. The localization of the positive charge on nitrogen leads to the breakdown of the seven-membered ring, and as the result of an attack of the radical so formed there is a splitting out of OR_1, CH_2R_1, and $CH_2CH_2R_1$ radicals. The splitting out of the R_2 and the OR_2 substituents takes place in parallel. The main ion $(M - OR_1)^+$ partially eliminates hydrogen (Scheme 7).

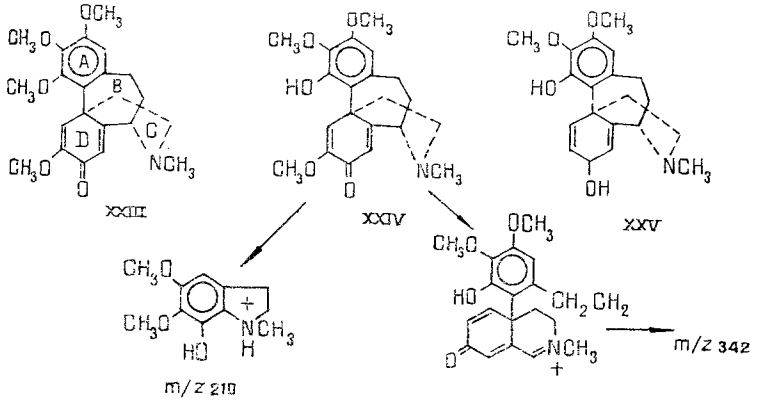


Scheme 7. Fragmentation of the homoaporphine alkaloids.

This scheme is confirmed by the mass spectra of 3,6-dideuterooxymerenderine, di-O-methylmerenderine, and di-O-acetylmerenderine. The compositions of the merenderine ions have also been determined.

In the mass spectra under consideration, the $(M - 43)^+$ ion is a doublet. One member of the doublet in the case of szovitsamine, for example, corresponds to the splitting out of a propyl radical, and the other to the elimination of CH_2NCH_3. But the retrodiene fragment is uncharacteristic for the homoaporphines and its peaks do not exceed 1-2% of the total current.

Of the homomorphinan bases, anhydrocymbine [23, 24], kreysiginine [25], O-methylanhydrocymbine (XXIII) [24, 26], collutine (XXIV) [27], and szovitsidine (XXV) [28] have been studied. Characteristic for them is a high yield of molecular ions — 35-40% of the total current. At the same time, the ions resulting from retrodiene decomposition are weak. The breakdown of the seven-membered ring forms ions by the splitting out of an ethyl radical. The fragmentation of the same molecular radical ions leads to the formation of isoquinoline fragments hydrogenated to different degrees; for O-methylanhydrocymbine and collutine this is an ion with m/z 190 and for szovitsidine one with m/z 192. This is the main difference of the mass spectra of the homomorphinans. The mass spectra each contain a fairly strong peak of a fragment containing ring A (Scheme 8).



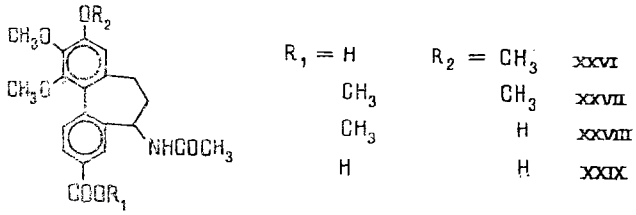
Scheme 8. Homomorphinan bases and fragmentation of collutine.

Biogenetically close to the homomorphinan alkaloids are allocholchiceine (XXVI) and its derivatives — allocolchicine (XXVII), 3-demethylallocolchicine (XXVIII), and 3-demethylallocolchiceine (XXIX) [6].

Characteristic for the mass spectra of allocolchicine and of 3-demethylallocolchicine is a high intensity of the peaks of the molecular ions and the peaks of ions produced by the elimination of acetamide. Subsequently, these fragments split out methyl and methoxy radicals. A methoxy radical and methanol and methoxyl are also split out successively from the molecular ion in each case.

The mass spectra of the deuterium analogs show that the methoxyl radical is split out both at the expense of the phenolic methoxyl and at the expense of the methoxycarbonyl group. Methanol is eliminated by the ions exclusively at the expense of the phenolic methoxyl.

Allocolchiceine and 3-demethylallocolchiceine decompose analogously.



Scheme 8. Hemomorphinan bases and fragmentation of collutine.

The following generalization can be made concerning the mass spectra of the new alkaloids of *Colchicum* L. and *Merendera ramond*. The main peaks in the mass spectra of the homoproaporphine alkaloids are those of the $(M - H)^+$ ions and the retrodiene fragments. Alkaloids containing no ring E, furthermore, split out ethylene and an ethyl radical through the breakdown of ring C. The differences in their spectra relate to the peaks of the ions formed in the breakdown of ring D. In addition to the M^+ and $(M - H)^+$ ions, the retrodiene fragment also undergoes decomposition in ring D.

Characteristic for the homoaporphines is the splitting out of substituent at position 3 in ring A following the breakdown of ring C at the nitrogen reaction center. The peak of the ion formed by the splitting out of the substituent from position 4 is also strong. The

nature of the remaining substituents of the homoaporphine alkaloids is readily determined from the difference in the mass numbers of peaks of the fragments given above. The intensity of the retrodiene fragment is low.

The homomorphinan alkaloids form the most stable molecular ions. The intensities amount to 35-40% of the total ion currents. The decomposition of the seven-membered ring forms a tetrahydroisoquinoline fragment. From the mass numbers of this fragment and the product of its transformations it is easy to determine the presence, the position, and nature of substituents in ring D. The main differences in the mass spectra of the homomorphinans relate to the peaks of the ions formed on fragmentation with respect to ring D. The nature and position of the substituents in ring A can be determined by comparing the mass numbers of the strong peak of a rearrangement fragment — a benzopyrrole.

The allocolchiceine derivatives break down mainly in relation to the substituents of ring B (elimination of acetamide) and ring C (breakdown at the carboxy and methoxycarbonyl groups).

Thus, in spite of the structural diversity of the alkaloids of *Colchicum* L. and *Merendera ramond* forming derivatives of homoproaporphine, homoaporphine, and homomorphinan that have been isolated in recent years, together with the tropolone bases studied previously, the mass-spectrometric method can be used successfully for determining both structural type and the individual elements of their structure.

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DEGRADATION OF CARBOXYMETHYLSTARCH UNDER THE ACTION OF γ-RADIATION

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It has been shown that the main process in the radiolysis of carboxymethylstarch (CMS) is the degradation of the polysaccharide accompanied by a contraction of the MWD. Conditions have been developed for obtaining sodium-CMS with given molecular-weight and hydrodynamic parameters.

The main aim of this work was to obtain products with different molecular-weight and hydrodynamic parameters for their subsequent medicobiological investigations as polymeric carriers for drugs.

Sodium carboxymethylstarch (CMS) was obtained by the mechanochemical method [1]. The change in the supermolecular structure of the CMS in the dispersion process permits it to be irradiated in solution under dynamic conditions at a controlled pH, i.e., permits the degradation of the polymer to be carried out uniformly throughout its bulk and the depth of oxidative transformations to be lowered.

The radiolysis of aqueous solutions of CMS was accompanied by falls in the molecular weight of the polysaccharide and in the viscosity of the solutions (Table 1), i.e., the process of degradation was predominating. A comparison of these parameters with the analogous parameters for the hydroxyethylstarch (HES) used in clinical practice, which includes acid hydrolysis as a stage in production [2], permitted the conclusions that the viscosities and molecular weights of the CMS and the HES of equal degrees of substitution were close (Table 2), while the molecular weight of clinical dextran with the same characteristic

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