# BROMINATION OF ALKALOIDS OF CAREX PARVAE

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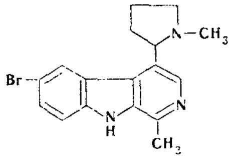
6-Bromobrevicolline, 6,8-dibromobrevicolline, 6,8-dibromobrevicarine, and tribromobrevicarine were obtained by direct bromination of brevicolline and brevicarine. 6-Bromobrevicolline was isolated from the mixture obtained by bromination of brevicarine dihydrochloride.

Little study has been devoted to the bromination of β-carboline derivatives, although the first studies of this sort were accomplished by O. Fischer in the 1930's. In particular, the bromination of harmine was studied, but the position of the bromine in the product was not established [1, 2].

The bromination of brevicolline with bromine in acetic acid gives 6-bromobrevicolline (I, the base) dihydrobromide, the yield of which is raised considerably when brevicolline monohydrochloride is introduced into the reaction instead of the base.

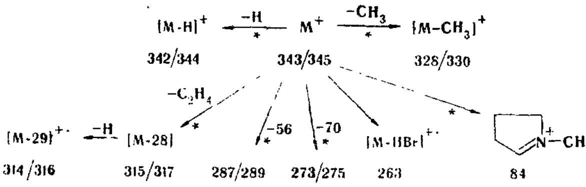


I

The bromination of brevicolline hydrochloride under the conditions of bromination of harmine [2] with an equimolecular amount of bromine in sulfuric acid gives very low yields, and most of the starting alkaloid is regenerated.

The 6-bromobrevicolline (I) formed by direct bromination is identical to the product obtained in [3]. Its IR spectrum contains the absorption band at 605 cm$^{-1}$ that is characteristic for the C–Br bond, but the band at 740 cm$^{-1}$ (substituted benzene rings containing four adjacent CH groups) that is present in the spectrum of the starting alkaloid is absent, and a band at 810 cm$^{-1}$, which corresponds to a 1,2,4-trisubstituted benzene ring [4, 5], appears. The UV spectrum of bromide I differs little from the spectrum of brevicolline itself [6], but two new maxima appear at 203 and 238 nm, and a small bathchromic shift is observed.

The mass spectrum of I is characterized by the presence of molecular ion peaks of equal intensity with m/e 343 and 345; this reflects the natural bromine isotopic ratio and shows that the substance under investigation is a monobromide. Peaks of doubly charged molecular and fragment peaks were also re-



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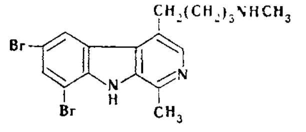
corded. Disintegration of the molecular ion leads to bromine–containing fragments that are formed due to disintegration of the pyrrolidine ring, but, as in the disintegration of brevicolline [6], the ion peak with m/e 84 has the maximum intensity.

The metastable ion peaks confirm the proposed scheme of the transitions.

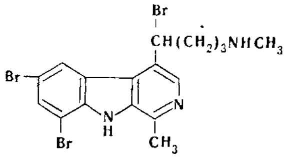
6,8-Dibromobrevicolline is obtained by bromination of the dihydrobromide of I. The IR spectrum of the bromination product contains absorption at 810 and 830 cm$^{-1}$, which is characteristic for a 1,2,3,5-substituted benzene ring, and at 600 and 685 cm$^{-1}$ (C–Br bond). The mass spectrum is characterized by three molecular ion peaks with m/e 421, 423, and 425 in a configuration corresponding to the isotopic bromine composition and by peaks of the corresponding fragments formed via a scheme analogous to the disintegration of I.

The bromination of brevicarine gave a mixture of two products, which were separated by recrystallization from methanol. The compound with a lower chromatographic mobility on paper corresponds to the 6,8-dibromobrevicarine composition (II). Its IR spectrum contains an absorption band at 610 cm$^{-1}$ (C–Br band) and at 850 cm$^{-1}$, which is characteristic for 1,2,3,5-substituted benzenes. A group of molecular ion peaks with m/e 423, 425, and 427 is observed in the mass spectrum of dibromide II; this indicates the presence of two bromine atoms. A maximum intensity peak with m/e 44 ($CH_2=N-CH_3$) is also observed. Just as in the case of brevicarine [6, 7], the molecular ion of 6,8-dibromobrevicarine undergoes fragmentation through the alkylamino chain and gives a set of M-15, M-30, M-44, M-58, M-72, and M-84 fragments containing two bromine atoms in the aromatic portion of the molecule, as well as fragments with one bromine atom, which are formed from the M$^+$–Br ion.

The compound with higher chromatographic mobility contains three bromine atoms – tribromobrevicarine (III). Its IR spectrum contains two absorption bands at 620 and 635 cm$^{-1}$ (C–Br band) and an intense band at 860 cm$^{-1}$, which is characteristic for 1,2,3,5-substituted benzene derivatives. The UV spectrum of tribromobrevicarine differs from the spectrum of 6,8-dibromobrevicarine; this is due to the effect of the side-chain bromine.



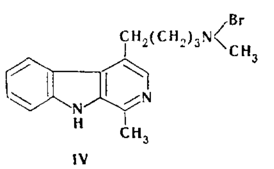
II



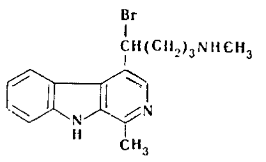
III

The mass spectrum of tribromide III contains four molecular ion peaks with mass numbers 500-505 and fragment–ion peaks each containing three bromine atoms and associated with cleavage of the alkylamino chain. The presence of a peak with m/e 429 ([M–72]$^+$) proves that the third bromine atom is attached to the α-carbon atom of the aliphatic chain. Cleavage with the loss of a bromine atom in the first step occurs simultaneously with the fragmentation path described above; the most typical fragment recorded at different temperatures (even at 0°) is a group of peaks with m/e 421, 423, and 425.

Compounds I-III were isolated chromatographically in the bromination of brevicarine dihydrochloride under similar conditions. The formation of 6-bromobrevicolline (I) from brevicarine might have been represented as proceeding through bromoamine IV or bromide V with subsequent closing of the aliphatic chain to a pyrrolidine ring with subsequent bromination of the resulting brevicolline.



IV



V

However, we were unable to record intermediates IV or V.

We observed similar cyclization in the nitration of hydroxybrevicarine [8]. The direct transition from brevicarine to brevicolline by means of microorganisms was recently accomplished.

## EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-10 spectrophotometer. The UV spectra of ethanol solutions were recorded with a Specord UV-vis spectrophotometer. The mass spectra were obtained with an MS-1302 mass spectrometer with direct introduction of the samples into the ionization chamber at a heater temperature of 100-150°, an emission current of 20 mA, an accelerating voltage of 3 kV, and an ionizing voltage of 40 eV. The $pK_a$ values were determined by potentiometric titration of 0.01 M solutions of the substances with 0.1 N hydrochloric acid in 67% dimethylformamide (DMFA) with a pH-340 pH-meter-millivoltmeter. Chromatography was accomplished with activity III aluminum oxide in columns and on plates with a loose layer of activity III $Al_2O_3$ (the solvent for the plates was chloroform containing 5% methanol). Ascending chromatography on paper (Leningrad slow filtering) was accomplished with n-butanol–acetic acid–water (10 : 1 : 5), organic phase.

6-Bromobrevicolline (I). A 1-g (3.3 mmole) sample of brevicolline monohydrochloride was dissolved in 25 ml of 50% acetic acid, and 0.4 ml (7.3 mmole) of bromine was added to its dropwise with vigorous stirring. The resulting brick-red precipitate of the dihydrobromide of I was removed by filtration and recrystallized from methanol to give 1.4 g (83.4%) of a product with mp 270-272°.

Base I was obtained by treatment of an aqueous alcohol solutions of the salt with 25% ammonium hydroxide. The yield of shiny colorless crystals with mp 240-242° (from methanol) was quantitative. A mixture of this product with 6-bromobrevicolline obtained by the method in [3] melted without depression at 240-243°.

The samples were identical with respect to their chromatographic mobilities ($R_f$) on paper (0.58) and on plates (0.67) and with respect to their IR spectra. UV spectrum, $\lambda_{max}$: 203, 240, 248, 258, 285, 294, 350, and 364 nm (log $\varepsilon$ 4.15, 4.58, 4.58, 4.42, 3.75, 3.08, 3.60, and 3.66, respectively). $pK_{a1}$ 6.64 ± 0.02, $pK_{a2}$ 3.54 ± 0.03 [9].

Similarly, 0.38 g (45.5%) of 6,8-dibromobrevicolline hydrodromide, with mp 254-256°, was obtained from 1 g (2 mmole) of the dihydrobromide of I in 25 ml of 50% acetic acid by bromination with 0.3 ml (5.5 mmole) of bromine. Found: N 8.4%. $C_{17}H_{17}Br_2N_3 \cdot HBr$. Calculated: N 8.3%. $R_f$ 0.62 ($Al_2O_3$). IR spectrum: 600, 685 (C–Br), 810, and 830 $cm^{-1}$ (1,2,3,5-substituted benzene). UV spectrum, $\lambda_{max}$: 205, 238, 247, 258, 286, 294, 350, and 364 nm (log $\varepsilon$ 3.96, 4.40, 4.38, 4.26, 4.11, 4.31, 3.93, and 3.98, respectively). $pK_{a1}$ 6.05 ± 0.02, and $pK_{a2}$ 3.46 ± 0.03.

6,8-Dibromobrevicarine (II). A 0.38-ml (7 mmole) sample of bromine was added dropwise to a solution of 1 g (3.3 mmole) of brevicarine in 25 ml of 50% acetic acid, and the mixture was allowed to stand in a refrigerator. The resulting precipitate of gold-yellow needles was removed by filtration and recrystallized three times to give 1.46 g (66.7%) of white crystals of 6,8-dibromobrevicarine dihydrobromide with mp 269-270°. Found: N 7.2%. $C_{17}H_{19}Br_2N_3 \cdot 2HBr$. Calculated: N 7.2%. UV spectrum, $\lambda_{max}$: 203, 242, 248, 282, 293, 350, and 364 nm (log $\varepsilon$ 4.33, 4.57, 3.92, 4.01, 3.79, and 3.77, respectively).

The action of a concentrated alkali solution on a hot aqueous alcohol solution of the salt gave a greenish resin; the solution was decanted from it, and it was washed thoroughly with distilled water and treated with ether. White crystals of II with mp 153-155° precipitated from the ether solution. Found: C 48.1; H 4.8; Br 36.8; N 10.2%. $C_{17}H_{19}Br_2N_3$. Calculated: C 48.0; H 4.5; Br 37.6; N 9.9%. UV spectrum, $\lambda_{max}$: 205, 242, 249, 283, 293, 350, and 366 nm (log $\varepsilon$ 4.45, 4.48, 3.88, 3.96, 3.78, and 3.85, respectively). $pK_{a1}$ 9.58 ± 0.01, $pK_{a2}$ 4.93 ± 0.02.

Tribromobrevicarine (III). The methanol mother liquor from the recrystallization of II was evaporated, and the resulting precipitate was dissolved in water and treated with concentrated sodium hydroxide solution. The resin that formed was extracted with hot benzene to give 0.18 g (10%) of colorless crystals with mp 187-188°. Found: C 41.1; H 3.4; Br 47.6; N 8.8%. $C_{17}H_{18}Br_3N_3$. Calculated: C 40.5; H 3.6; Br 47.6; N 8.3%. UV spectrum, $\lambda_{max}$: 253, 286, 295, 357, and 371 nm (log $\varepsilon$ 4.13, 3.52, 3.42, and 3.48, respectively).

A 1-g (2.7 mmole) sample of brevicarine dihydrochloride was brominated with excess bromine as in the case of I-III. The reaction product was separated, recrystallized from methanol, dissolved in a small amount of water, and treated with concentrated alkali solution. The resulting resin was washed with water, dried on a watch glass, and dissolved in a small amount of alcohol. Aluminum oxide (1 g) was added, and the methanol was evaporated. The residual mixture was transferred to a column filled with 10 g of the same adsorbent and eluted with benzene containing 1% methanol to give 0.4 g (39%) of 6,8-bromobrevicarine

0.3 g (24%) of 6,8-dibromobrevicarine (II) and 0.3 g (20%) of tribromobrevicarine (III). The isolated bromides were identified from their melting points, chromatographic mobilities, and UV and IR spectra.

## LITERATURE CITED

1. R. A. Abramovitch and I. D. Spenser, Advances in Heterocyclic Chemistry, Vol. 3 (1964), p. 79.
2. D. Barcovic and T. Bican, Ark. Kem., 20, 135 (1948); Chem. Abstr., 44, 5884 (1950).
3. T. I. Shirshova and I. V. Terent'eva, Khim. Geterotsikl. Soedin., 952 (1973).
4. L. Bellamy, Infrared Spectra of Complex Molecules, Methuen (1958).
5. K. Nakanishi, Infrared Spectroscopy, Practical, Holden–Day, San Francisco (1962).
6. Collection: Brevicolline [in Russian], Kishinev (1969), pp. 5, 36.
7. I. V. Terent'eva, G. V. Lazur'evskii, and T. I. Shirshova, Khim. Prirod. Soedin., 397 (1969).
8. T. I. Shirshova, I. V. Terent'eva, P. A. Vember, and G. V. Lazur'evskii, Khim. Geterotsikl. Soedin., 987 (1972).
9. T. I. Shirshova and I. V. Terent'eva, Izv. Akad. Nauk Moldav. SSR, Ser. Biol. i Khim. Nauk, 76 (1973).