NITRATION OF ALKALOIDS FROM Carex parvae

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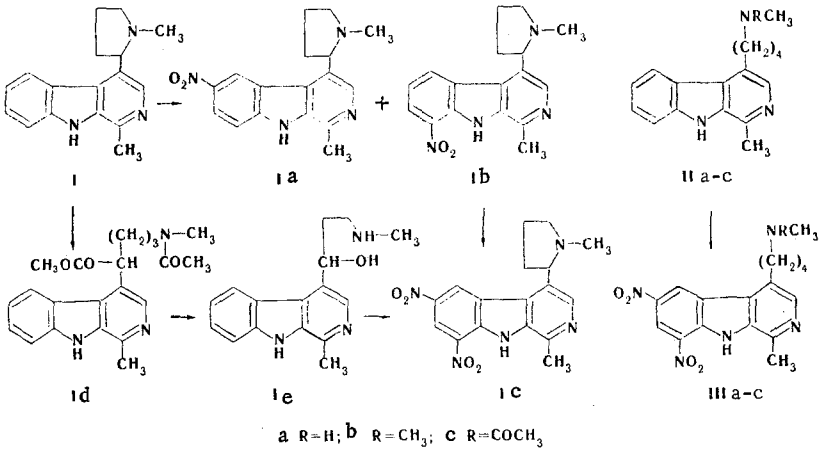
The direct nitration of brevicolline, brevicarine, and methyl-, acetyl-, and hydroxybrevicarine with concentrated nitric acid gave 6- and 8-nitrobrevicolline and 6,8-dinitro derivatives of the enumerated compounds. 6-Nitroharman was obtained by oxidation of 6-nitrobrevicolline to 6-nitroharman-4-carboxylic acid and subsequent decarboxylation.

In order to further study the properties of alkaloids isolated from Carex parvae [1] and to obtain new physiologically active preparations from them, we nitrated the natural bases and some of their derivatives. A limited number of studies have been devoted to the nitration of β-carboline derivatives. However, it has been demonstrated that a mixture of 6- and 8-nitro isomers with quantitative predominance of the 6-nitro-substituted compounds is formed in the reaction of harman and its homologs [2-4]. The 6-nitro derivatives generally have higher melting points than the 8-nitro isomers [4,5], and this property can be used to identify them.

We have accomplished the nitration of brevicolline (I), brevicarine (IIa), methyl- (IIb) and acetylbrevicarine (IIc), and hydroxy derivative Ie, which was obtained from brevicolline.



Depending on the reaction temperature and the amount of nitrating agent, the nitration of brevicolline gives a mixture of 6-nitro- (Ia) and 8-nitrobrevicolline (Ib) or 6,8-dinitrobrevicolline (Ic). Brevicarine and its derivatives form only dinitro compounds IIIa-c (see Table 1). Under milder conditions, for example in acetic acid, the dinitrates of the starting alkaloids are obtained.

In the nitration of hydroxybrevicarine Ie, cyclization with splitting out of water occurs along with the major process, and the reaction product is 6,8-dinitrobrevicolline. In contrast to Ic, the latter is optically inactive.

The nitro compounds of brevicarine and its derivatives are only slightly soluble in alcohols and other organic solvents, but they are soluble in pyridine. The nitrobrevicollines are quite soluble in alcohols, and

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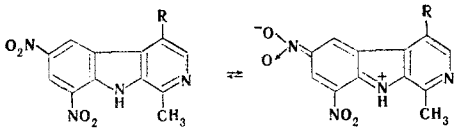
TABLE 1. Characteristics of the Nitro Compounds Obtained

Comp.	mp, °C	Empirical formula	Found, %			Calc., %			λ_{max}, nm (lg ε)	Yield, %
			C	H	N	C	H	N		
Ia	251—253	$C_{17}H_{18}N_4O_2$	65,8	5,9	18,5	65,8	5,8	18,1	232; 270; 290; 350 (4,49; 4,33; 4,18; 4,07)	86
Ib	217—218	$C_{17}H_{18}N_4O_2$	65,8	6,0	17,8	65,8	5,8	18,1	231; 297; 400 (4,73; 3,93; 3,94)	5,1
Ic	94—96	$C_{17}H_{17}N_5O_4$	57,1	4,8	19,5	57,4	4,8	19,7	221; 250; 297; 388 (4,49; 4,19; 4,17; 3,87)	90
Id	139—140	$C_{17}H_{21}N_3O \cdot 0{,}25H_2O$	70,8	7,6	14,5	71,0	7,5	14,6	—	—
IIc	154	$C_{19}H_{23}N_3O$	73,4	7,4	13,8	73,8	7,4	13,6	—	53
IIIa*	187—188	$C_{17}H_{19}N_5O_4$	57,2	5,2	19,1	57,1	5,3	19,6	222; 250; 296; 390 (4,58; 4,29; 4,23; 3,91)	87
IIIb	257—259	$C_{18}H_{21}N_5O_4 \cdot HNO_3$	49,6	5,3	18,9	49,7	5,3	19,0	220; 250; 295; 392 (4,60; 4,26; 4,19; 3,85)	93
IIIc	255—257	$C_{19}H_{21}N_5O_5$	57,2	5,8	16,8	57,1	5,3	17,5	221; 250; 296; 390 (4,22; 3,98; 3,91; 3,59)	90

*The nitrate was obtained as yellow crystals with mp 224-225° (from methanol). Found: C 48.7; H 4.8; N 20.1%. $C_{17}H_{19}N_5O_4 \cdot HNO_3$. Calculated: C 48.6; H 4.7; N 20.0%.

the 8-nitro compounds are much more soluble than the 6-nitro compounds. Alkaline solutions of them are cherry-red, which is apparently associated with the development of a quinoid structure [6,7].



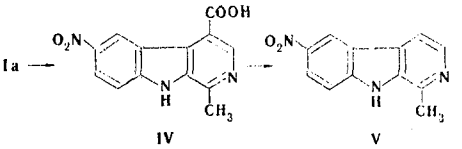
The structures of the nitro compounds obtained were confirmed by their spectral characteristics. The electronic spectra of 6- and 8-nitrobrevicolline differ substantially. The spectrum of 6-nitrobrevicolline is characterized by four maxima, while that of 8-nitrobrevicolline has three maxima. As compared with the UV spectra of the mononitro compounds, four maxima, which are shifted to the short-wave region, are observed in the UV spectra of the dinitro derivatives, which is in agreement with the data presented for 6- and 8-nitroharmans [4] and 6,8-dinitroharman [8].

Absorption bands at 1530-1540 cm^{-1} are observed in the IR spectra of all of the nitro compounds. An intense band at 1325 cm^{-1} is characteristic for 6-nitrobrevicolline, while, as for the dinitro derivatives, the presence of doublet absorption bands at 1310 and 1340 cm^{-1} is characteristic for 8-nitrobrevicolline. All of the bands are specific for the symmetrical and asymmetrical vibrations of the nitro group [9].

The PMR spectra* confirm the structures of the nitro derivatives of brevicolline, since the chemical shifts of the major portion of the protons coincide with the proton signals of the starting alkaloid [10]. However, in the case of 6-nitrobrevicolline, the signals of the aromatic protons in the 5 and 7 positions are shifted to lower field (δ 9.57 and 8.32 ppm) due to the effect of the nitro group. Only the signal of the aromatic proton in the 7 position (δ 8.94 ppm) is shifted in the spectrum of 8-nitrobrevicolline. The more pronounced shift of the aromatic protons in the 5 and 7 positions (10.10 and 9.08 ppm) is a consequence of the introduction of two nitro groups into the brevicolline molecule. The magnitudes of the shift correspond to those presented for substituted nitrobenzenes [11].

In addition, the 6-nitrobrevicolline structure was confirmed by its oxidation and subsequent decarboxylation to 6-nitroharman (V).

*The PMR spectra of dimethyl sulfoxide solutions of the compounds were recorded in the laboratory of S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical Chemistry Institute with a JNM-4H-100 spectrometer with hexamethyldisiloxane as the internal standard. The authors thank Yu. N. Sheinker and N. Kostyuchenko for recording the spectra and aiding us in their interpretation.



EXPERIMENTAL

6-Nitrobrevicolline (Ia). A 1-g (3.8 mmole) sample of I in 10 ml of concentrated nitric acid (sp. gr. 1.52) cooled to 0° was stirred at this temperature for 1 h. While maintaining the reaction mixture at ~0-5°, the excess acid was neutralized with 25% ammonium hydroxide to precipitate a mixture of Ia and Ib. Crystallization from methanol yielded the bulk of Ia as pale-yellow crystals.

8-Nitrobrevicolline (Ib). The methanol mother liquor, which contained about 0.1 g of a mixture of Ia and Ib, was applied to 1 g of aluminum oxide, and the mixture was transferred to a column containing 10 g of the same adsorbent. A benzene–methanol mixture (24 : 1) eluted Ib as bright-yellow crystals (from methanol).

6,8-Dinitrobrevicolline (Ic). A. A 1-g (3.2 mmole) sample of Ia or Ib (or a mixture of them) was nitrated with 10 ml of concentrated nitric acid at 45° in the course of 1 h. The solution was cooled to 0° and treated with 25% ammonium hydroxide to precipitate shiny orange crystals of Ic (from methanol).

B. A 1-g (3.6 mmole) sample of Ie was nitrated with 20 ml of concentrated nitric acid at 0° to give shiny yellow crystals with mp 94-96°. According to the results of elementary analysis, chromatographic characteristics, and PMR spectra, the product was identical to Ic obtained above. It did not depress the melting point of a sample of Ic obtained by method A (mp 94-96°).

Hydroxybrevicarine (Ie). A 10-g (3.8 mmole) sample of I was heated for 3 h with 15 ml of acetic anhydride. At the end of the heating period, the mixture was diluted with 150 ml of water and allowed to stand overnight with charcoal. The solution was filtered and treated with alkali. The resinous precipitate was dried on a watch glass in a desiccator and dissolved in 40 ml of methanol. Finely ground NaOH (10 g) and 20 ml of water were added to the resulting solution, and the mixture was heated on a boiling-water bath for 6 h. The solution was decanted from the dark-brown oil, and the oil was washed with cold water. Compound Ie was recrystallized from a large amount of methanol. A second recrystallization gave colorless shiny crystals.

6,8-Dinitrobrevicarine (IIIa). A 2.5-g (9.3 mmole) of IIa was added in small portions with vigorous stirring to 35 ml of heated (to 35°) concentrated nitric acid, and the mixture was stirred at this temperature for 1-1.5 h. It was then cooled with an ice–salt mixture, and the excess acid was neutralized with 25% ammonium hydroxide to precipitate IIIa. Crystallization from pyridine gave a cherry-red powder.

Acetylbrevicarine (IIc). A 3.6-g (0.013 mole) sample of IIa was heated with 23 ml of acetic anhydride for 1 h, and the excess acetic anhydride was removed by vacuum distillation. The oil solidified on standing in a refrigerator and was dissolved in acetone. The precipitated colorless crystals were recrystallized from acetone.

6,8-Dinitroacetylbrevicarine (IIIc). This compound was obtained by the method used to prepare IIIa. In addition, IIIc was obtained by acylation of IIIa in excess acetic anhydride as bright-yellow crystals (from methanol).

6,8-Dinitromethylbrevicarine Nitrate (IIIb). This compound was obtained by nitration of IIb by the method used to prepare IIIa. In addition, it can be obtained by Wallach methylation of IIIa to give shiny orange-yellow crystals (from pyridine).

6-Nitroharman-4-carboxylic Acid (IV). A 10-g (0.03 mole) sample of Ia dissolved in 700 ml of 5% sulfuric acid was oxidized with 10.5 g (0.1 mole) of chromic anhydride via the method in [10]. The flocculent yellow precipitate was insoluble in water and alcohols and soluble in alkalis and concentrated ammonium hydroxide. The melting point was indistinct at about 254°. The UV spectrum was similar to that of 6-nitroharman and had four maxima: 230, 272, 288, and 335 nm. The yield was 7.7%.

6-Nitroharman (V). Acid IV was decarboxylated in vacuo in a sublimation apparatus. The sublimate was resublimed and crystallized from alcohol to give pale-yellow crystals with mp 300-301°. A comparison of the V obtained with an authentic sample of 6-nitroharman confirmed that they were identical. The chromatographic and spectral characteristics were in complete agreement [4]. The product did not depress the melting point of the authentic sample (mp 299-300°).

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