STRUCTURE OF VASICOL

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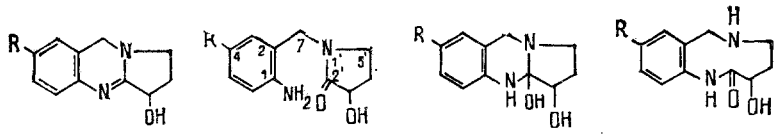
The structure of bromovasicol has been established on the basis of the results of x-ray structural analysis as 4-bromo-2-(3'-hydroxy-2'-oxypyrrolinomethyl)aniline. Vasicol was isolated from the plant Peganum harmala in the form of 2-(3'-hydroxy-2'-oxopyrrolidinomethyl)aniline.

In the process of purifying technical peganina (I) [1], obtained from a mixture of the alkaloids of Peganum harmala [2], we isolated an individual base (II) in the form of an oil; M^+ 204. It formed an O,N-diacetyl derivative, (III), with mp 130°C. The properties of the base isolated (II) and of its diacetate (III) were close to those of vasicol (IV) and its diacetyl derivative (V). Vasicol (IV) had been obtained from the Indian plant Adhatoda vasica and also by heating peganine with water [3]. We repeated the experiment on the conversion of peganine into vasicol (IV). The oily product that we then obtained was identical with the base (II) that had been isolated (TLC, IR spectra, absence of a depression of the melting point of a mixture of the diacetates). This permitted the assumption that base (II) and vasicol (IV) were identical. However, the IR spectrum of (II) had an intense band of an amide carbonyl in the 1660-1690 cm^{-1} region which was not reported by the Indian authors [3] either in the IR spectrum of vasicol (IV) or in the spectrum of its O- and N-methyl derivatives. Considering all the facts given above, we assumed that base (II) should have one of the two isomeric structures (II) and (VI). Thus, we had obtained vasicol not in the form of a carbinolamine (IV) but in an amide form (II) or (VI). The bromine-substituted analog of base (II) – bromovasicol (VIII) – synthesized from bromopeganine (VII) [4], and its O,N-diacetyl derivative corresponded completely in their spectral characteristics with (II) and (III). For bromovasicol, the choice also remained between the alternative formulas (VIII) and (X).



I. R = H
VII. R = Br

II. R = H
VIII. R = Br

IV. R = H
XI. R = Br

VI. R = H
X. R = Br

To solve this problem we carried out the x-ray structural analysis (XSA) of bromovasicol. The results of the analysis showed that bromovasicol had the structure (VIII). Its spatial structure is shown in Fig. 1 in a projection on the plane of the ac axes.

The aminobromobenzyl moiety of the molecule (VIII) has a plane structure; the deviations of the atoms from the plane are not more than 0.05 Å. The other part of the molecule – the pyrrolidone nucleus – assumes an envelope conformation with departure of the C5' atom from the plane of the other four by 0.47 Å. The mutual positions of these two rings (the angle between the mean square planes of the rings is 113°) apparently favored the formation of an intramolecular H-bond of the N–H...O type, as is shown by a N...O1 distance of 2.91 Å.

The geometric parameters (bond lengths and valence angles) of structure (VIII) are given in Fig. 1. The bond lengths in the benzene ring range between 1.37 and 1.43 Å, but

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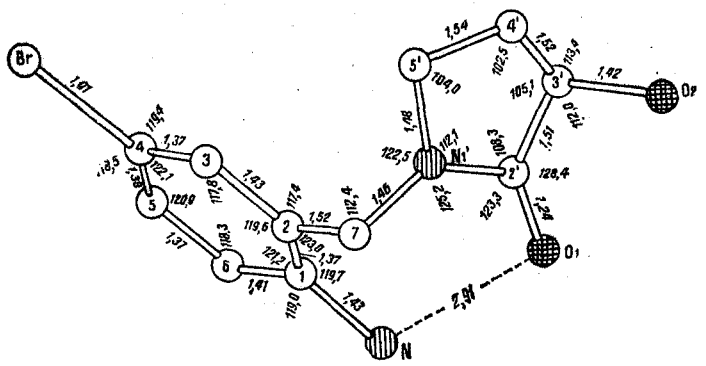

Fig. 1. Spatial structure of the molecule of VIII (the errors in the determination of the valence bonds and angles do not exceed 0.013 Å and 0.8°, respectively.

agree within the 3σ limits with the generally adopted 1.40 Å. The lengths of the other types of bonds are close to the standard values [5]. The tendency observed to a lengthening of the C2'=O bond and to a shortening of the C2'—N1' bond from the generally accepted values can be explained by the conjugation of the π-electronic system of the C=O with the free electron pair of the N1' atom. No anomalies are observed in the values of the valence angles of the (VIII) molecule.

Analysis of the crystal structure of (VIII) show the existence of intermolecular H-bonds of the —N—H...O2=C— (3.04 Å) type along the 2_1 axis [x; 0; 1/4] and also of the

O2—H...N (2.93 Å) type along with translation axis *a*.

Thus, the structure of 4-bromo-2(3'-hydroxy-2'-oxopyrrolidinodimethyl)aniline has been established for bromovascol (VIII). It follows from this that the vasicol from Peganum harmala has the structure of 2-(3'-hydroxy-2'-oxopyrrolidinomethyl)aniline (II).

In the PMR spectra of O,N-diacetylvasicol (III) and O,N-diacetylbromovasicol (IX) a characteristic paramagnetic shift by 0.7-1.0 ppm of one aromatic proton having an ortho-coupling constant is observed. Such an effect has been reported for aniline and indoline acetates [6] and is due to the spatial influence of the carbonyl group on the neighboring aromatic proton. There is an ortho-proton with respect to the acetamido group in structures (II) and (VIII) but the possibility is not excluded that, on acetylation, vasicol and bromovasicol pass into the carbinolamine forms (IV) and (XI). In the latter there is also the possibility of the appearance of an ortho-effect of the carbonyl group in the diacetate. To examine this question we recorded the ^{13}C NMR spectra of vasicol and bromovasicol diacetates. Three singlet signals in the 170 ppm region from the three carbonyl groups were evidence in favor of structures (III) and (IX). Thus, vasicol and bromovasicol diacetates exist in solution in the same amide form as the initial bases (II) and (VIII).

The diacetyl derivatives of vasicol and of bromovasicol underwent saponification differently: while (IX) partially re-formed the initial base (VIII) under very mild conditions, and in an acid medium bromopeganine (VII) as well, under far more severe conditions compound (III) gave only N-monoacetylvasicol (XII).

Tetrahydropyridoquinazoline and hexahydrobenzodiazecine (XIII) have been isolated from plants of the genus Mackinlaya [7]. In the light of the results that we have obtained for peganine-vasicol the structure of 2-(2'-oxopiperidinomethyl)aniline is not excluded for (XIII).

According to our observations and literature information [3, 8], bases of the vasicol type are present in freshly obtained extracts of plants in small amounts and are, apparently, native alkaloids. When the combined alkaloids are stored for several years their amount increases appreciably.

TABLE 1. Coordinates ($\times 10^4$) of the Basis Atoms of (VIII) Molecule

Atom	x	y	z
Br	48 3 (2)	73 (1)	5823 (1)
O1	6074 (9)	7267 (5)	6122 (3)
O2	12753 (10)	6975 (6)	6579 (3)
N	5578 (11)	6513 (7)	5426 (4)
C1	5487 (9)	4904 (8)	5514 (4)
C2	6046 (11)	4366 (7)	6232 (4)
C3	5764 (14)	2858 (7)	6547 (5)
C4	5131 (13)	2 094 (7)	5717 (4)
C5	45 5 (12)	2730 (8)	5 03 (4)
C6	4736 (12)	4194 (9)	4887 (4)
N1′	8750 (10)	5241 (7)	6853 (3)
C2′	9720 (12)	6216 (7)	6467 (4)
C3′	11581 (13)	5806 (8)	6491 (5)
C4′	11719 (15)	4745 (9)	7208 (6)
C5′	9884 (15)	4106 (8)	7239 (5)

EXPERIMENTAL

PMR spectra were obtained on a JNM-C-60-HL/60 MHz spectrometer in $CDCl_3$ or, for (VIII), in CF_3COOH, with O-HMDS, and ^{13}C NMR spectra on a BS 567A instrument (Tesla) at a frequency of 25.142 MHz in $CDCl_3$ (for the diacetyl derivatives (III) and (IX)) and in DMSO-d_6 O-TMS, under conditions of complete and incomplete decoupling from protons.

X-Ray Structural Analysis. The space group and the parameters of the elementary cell were determined from precession photographs and were refined in a Sintex $P2_1$ diffractometer using CuK_α radiation: a = 7.633(1), b = 9.361(2), c = 16.330(3) Å; d_{calc} = 1.614 g/cm^3; space group $P2_12_12_1$; z = 4. A complete set of experimental results was obtained on the diffractometer mentioned. The calculations made use of 917 reflections with intensities exceeding 2σ. The structure was interpreted by the direct method using programs of the Rentgen-75 complex [9] in the automatic regime and was refined by the method of least squares in the anisotropic approximation to R = 0.080. An electron-density difference synthesis did not permit the positions of the H atoms to be determined. The coordinates of the basis atoms from the last stage of MLS are given in Table 1.

Isolation of (II). A. Technical peganine (I) (100 g), obtained as described in [2] was dissolved in 10% H_2SO_4. The acid solution was treated with chloroform and the chloroform was evaporated to give vasicinone [1]. Then the acid solution was made alkaline with concentrated NH_4OH and the peganine that deposited was filtered off. The filtrate was treated with chloroform. This gave 25 g of a dark resin which was placed in a column containing 500 g of Al_2O_3. Elution with chloroform led to the isolation of 4.24 g of a fraction enriched with compound (II). This fraction was chromatographed on a column containing 100 g of SiO_2. Elution with $CHCl_3$–CH_3OH (100:3) gave 1.73 g of (II) in the form of a light yellow oil, M^+ 206. UV spectrum ($\lambda_{max}^{C_2H_5OH}$, nm): 240, 293 (lg ε, 3.89; 3.53). IR spectrum: (ν_{max}^{film}, cm^{-1}): 3240-3450, 1660-1690, 1612. PMR spectrum: 6.57 (4H, m, Ar–H), 4.22 (3H, m, H-7, H-3'), 3.12 (2H, m, H-5'), 2.02 (2H, m, H-4'), ^{13}C NMR spectrum: 174.27 (s, C-2'), 146.48 (s, C-1), 130.12 (d, C-5), 128.62 (d, C-3), 118.77 (s, C-2), 115.78 (d, C-6), 114.81 (d, C-4), 69.02 (d, C-3'), 43.25 (t, C-5'), 42.50 (t, C-7), 28.01 (t, C-4'). The value of the chemical shift for C-2' corresponded to the literature figure [10].

B. Peganine (0.5 g) was heated with H_2O under the conditions of [3]. The yield of vasicol in the form of an oil was 0.31 g. Its IR spectrum was identical with that of the base (II) isolated in experiment A. On acetylation, vasicol gave a diacetate with mp 130°C. Under similar conditions, deoxypeganine [1] did not change while peganol [1] was converted into deoxyvasicinone.

Diacetyl Derivative of Vasicol (III). A mixture of 0.39 g of base (II), 4 ml of $(CH_3CO)_2O$, and 1 ml of pyridine was heated in the water bath for 2 h and it was then evaporated and the residue was crystallized from ether–acetone (3:1). The yield of (III) was 0.15 g, mp 130°C (it gave no depression of the melting point with the diacetate obtained in

experiment B), M^+ 290. UV spectrum: ($\lambda_{max}^{C_2H_5OH}$, nm): 242 (lg ε 2.71), IR spectrum: (ν_{max}^{KBr}, cm^{-1}): 3335, 3330, 1760, 1680-1670. PMR spectrum: 8.12 (1H, d, J = 8 Hz), 7.10 (3H, m, Ar—H), 5.17 (1H, t, H-3'), 4.14 (2H, q, H-7), 3.27 (2H, m, H-5'), 2.05 (2H, m, H-4'), 2.00 (3H, s, AcO-3'), 2.10 (3H, s, Ac—N-1). ^{13}C NMR spectrum: 171.20 (s, C-2'), 170.08 (s, N—$COCH_3$), 169.49 (s, $OCOCH_3$), 137.29 (s, C-1), 130.94 (d, C-5), 129.52 (d, C-3), 124.74 (s, C-2), 123.92 (d, C-6), 123.17 (d, C-4), 71.04 (d, C-3'), 44.74 (t, C-5'), 43.77 (t, C-7), 25.85 (t, C-4'), 24.35 (q, $NCOCH_3$), 20.77 (q, $OCOCH_3$).

Saponification of the Diacetyl Derivative (III). A mixture of 0.15 g of the diacetate and 20 ml of a 20% solution of KOH in CH_3OH was heated in the water bath for 3 h. The CH_3OH was evaporated off, the residue was treated with 20 ml of H_2O, and the reaction product was extracted with chloroform. This gave N-monoacetylvasicol (XII) in the form of an oil. M^+ 248. IR spectrum (ν_{max}^{film}, cm^{-1}) 1670-1690.

Bromovasicol (VIII). 6-Bromopeganine (VII) (9.5 g) [4] was passed through a column containing 250 g of Al_2O_3. On elution with chloroform, 5.67 g of (VIII) with mp 146-147°C was isolated. UV spectrum: ($\lambda_{max}^{C_2H_5OH}$, nm): 250, 312 (lg ε 4.10; 3.49). IR spectrum: (ν_{max}^{KBr}, cm^{-1}): 3330, 3200, 1680. PMR spectrum: 7.07 (3H, m, Ar—H), 4.25 (3H, m, H-7, H-3'), 3.37 (2H, m, H-5'), 2.01 (2H, m, H-4'). ^{13}C NMR spectrum: 174.49 (s, C-2'), 145.95 (s, C-1), 132.00 (d, C-5), 131.01 (d, C-3), 121.15 (s, C-2), 116.67 (d, C-6), 106.15 (s, C-4), 69.70 (d, C-3'), 42.65 (t, C-5'), 28.03 (t, C-4').

Diacetyl Derivative of Bromovasicol (IX). A mixture of 0.45 g of (VIII), 4 ml of $(CH_3CO)_2O$, and 1 ml of pyridine was left at 20°C for six days. After the elimination of the excess of reagents, the residue was crystallized from acetone—hexane (1:3). The yield of (IX) was 0.33 g, mp 108°C, M^+ 368/370. UV spectrum: ($\lambda_{max}^{C_2H_5OH}$, nm): 250 (lg ε 4.07). IR spectrum: (ν_{max}^{KBr}, cm^{-1}): 1680-1710, 1750. PMR spectrum: 8.20 (1H, d, J = 9 Hz, H-6), 7.48 (1H, dd, J = 9 Hz, J = 1.5 Hz, H-5), 7.48 (1H, overlaps the H-5 signal, H-3), 5.32 (1H, t, H-3'), 4.34 (2H, q, H-7), 3.40 (2H, m, H-5'), 2.12 (2H, m, H-4'), 2.20 (3H, s, Ac—N-1), 2.02 (3H, s, AcO-3'). ^{13}C NMR spectrum: 171.43 (s, C-2'), 170.01 (c, N—$COCH_3$), 169.49 (s, $OCOCH_3$), 136.54 (s, C-1), 133.41 (d, C-5), 132.36 (d, C-3), 126.68 (s, C-2), 124.67 (d, C-6), 116.15 (s, C-4), 70.89 (d, C-3'), 44.3 (t, C-5'), 43.85 (t, C-7), 25.77 (t, C-4'), 24.35 (q, $COCH_3$), 20.77 (q, $NCOCH_3$).

Saponification of the Diacetate (IX). A. A mixture of 0.85 g of the diacetate and 10 ml of 5% KOH was left at room temperature for 12 h. After the usual working up, 0.44 g of the monoacetyl derivative (XII) was obtained with mp 206°C (chlf), M^+ 326/328. IR spectrum: (ν_{max}^{KBr}, cm^{-1}): 3340, 1688.

B. A mixture of 0.2 g of the substance and 4 ml of 1% HCl was heated in the water bath for 1.5 h. After the reaction mixture had cooled, 0.08 g of a precipitate deposited with mp 206°C which was identical with the monoacetyl derivative described above. The acid solution remaining after the separation of the precipitate was washed with chloroform and was made alkaline, and the reaction product was extracted with chloroform. This gave 0.07 g of a substance with mp 206-207°C (decomp.), M^+ 266/268, identical with (VII).

C. Under the conditions for the saponification of (III), 1.2 g of the diacetate (IX) gave 0.8 g of bromovasicol (VIII).

SUMMARY

Bromovasicol has been synthesized from 6-bromopeganine. An x-ray structural analysis has established its structure as 4-bromo-2-(3'-hydroxy-2'-oxopyrrolidinomethyl)aniline.

Vasicol has been isolated from the plant Peganum harmala in the form of 2-(3'-hydroxy-2'-oxopyrrolidinomethyl)aniline.

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ALKALOIDS OF Haplophyllum bungei

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The alkaloids dictamnine, skimmianine, folimine, robustinine, and 4-methoxy-2-quinolone, found for the first time in plants of the genus Haplophyllum and the new alkaloid haplobungine, for which the structure of 4,7,8-trimethoxy-2-quinolone has been established, have been isolated from the epigeal part of the plant Haplophyllum bungei Trautv. growing in the Moiynkumy desert, Chimkent province, Kazakh SSR.

Continuing a systematic study of plants of the genus Haplophyllum [1] we have subjected to chemical investigation the epigeal part of H. bungei Trautv, collected in the flowering period in the Moiynkumy desert, Chimkent province, Kazakh SSR. The plant H. bungei grows in Central Asia in sandy deserts [2] and belongs to the Haplophyllum species with low levels of alkaloids [3]. Skimmianine, dictamnine, robustinine and an unidentified base with mp 83°C have been isolated previously from this plant gathered on the territory of the Karakalpak Ust-Urt [5], where it forms pure thickets [4].

The comminuted raw material was extracted with methanol. The total alkaloids were obtained by the method generally adopted, these making up 0.08% of the mass of the dry epigeal part. Column chromatography of the mixture of alkaloids gave dictamnine, skimmianine, robustinine, folimine, a base with the composition $C_{12}H_{13}NO_4$, mp 174-175°C (I), and a substance with mp 254-255°C which was identified by spectral characteristics as 4-methoxy-2-quinolone.

Alkaloid (I) was new and was given the name haplobungine. Its UV spectrum had absorption maxima in the 219, 231, 251 (inflection), 288, 313, and 323 nm regions and did not change on acidification and alkylinization – properties characteristic for alkaloids of the 4-alkoxy-2-quinolone series. In the IR spectrum, a broad maximum was observed at 3175 cm^{-1} (NH) and intense absorption at 1660 cm^{-1} (amide carbonyl of a 2-quinolone). The NMR spectrum of haplobungine confirmed that it was a 4-alkoxy-2-quinolone derivative, since the spectrum contained the one-proton singlet at 5.74 ppm from H-3 that is characteristic for this group of substances [6]. The other signals – a one-proton broad signal at 8.65 ppm (NH), two doublets at 7.50 and 6.78 ppm with an ortho-splitting constant (J = 9 Hz), and two singlets at 3.90 (3 H) and 3.87 (6 H) – permitted the proposal of the structure of 4,7,8-trimethoxy-2-quinolone for the alkaloid isolated (see scheme on following page).

The results obtained do not exclude the alternative 4,5,6-trimethoxy-2-quinolone structure for haplobungine, and we therefore methylated (I) and obtained the N-methyl derivative (II), the spectral characteristics and melting point of which were identical with those published for 4,7,8-trimethoxy-N-methyl-2-quinolone isolated from Spathelia sorbifolia [7].

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