LITERATURE CITED

1. V. G. Kharchenko, I. A. Markushina, T. I. Gubina, and S. P. Voronin, USSR Inventor's Certificate No. 595961; Izobret. SSSR Rubezhom, 55, No. 5, 1 (1981).
2. V. G. Kharchenko, I. A. Markushina, and T. I. Gubina, Dokl. Akad. Nauk SSSR, 255, 1144 (1980).
3. Yu. K. Yur'ev, Zh. Obshch. Khim., 16, 851 (1946).
4. N. A. Chumaevskii, V. M. Tataevskii, and Yu. K. Yur'ev, Opt. Spektrosk., 6, 45 (1959).
5. B. A. Arbuzov and E. G. Kataev, Dokl. Akad. Nauk SSSR, 96, 983 (1954).

SATURATED NITROGEN-CONTAINING HETEROCYCLES.

9.* SYNTHESIS AND STUDY OF OPTICALLY ACTIVE PYRROLIDINYLALKANOLS AND THEIR TARTRATES

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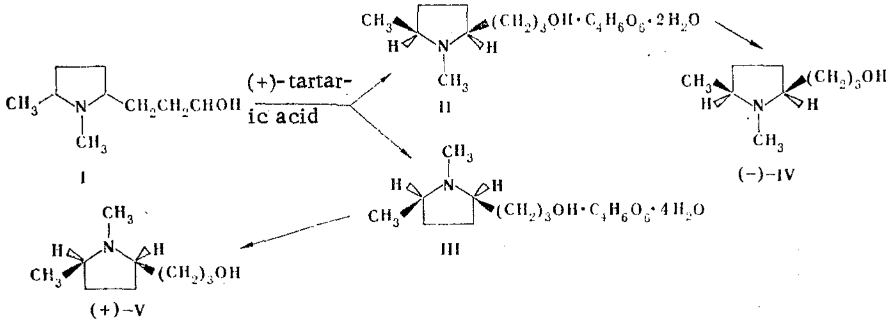
Optically active 3-(5-methyl-2-pyrrolidinyl)-1-propanols and their tartrates were synthesized. The stereochemical structures of the latter were established by x-ray diffraction analysis and PMR and IR spectroscopy. The absolute configuration was determined for (–)-cis-3-(1,5-dimethyl-2-pyrrolidinyl)-1-propanol (+)-bitartrate dihydrate, and the conformational and structural peculiarities of the pyrrolidinium cation and the tartrate anion were studied.

We have previously reported a new reaction involving the formation of alkyl- and aryl-substituted 3-(2-pyrrolidinyl)-1-alkanols by catalytic hydrogenation of the corresponding amines of the furan series in acidic solutions [1]. It was established that the reaction is stereospecific and that the degree of realization of the principal geometrical form is 80-90% when two or more substituents are present in the pyrrolidine ring.

Pyrrolidinylalkanols are biologically active compounds [2, 3], and the study of their three-dimensional structure is therefore of practical value. Since this problem cannot be solved by PMR spectroscopy, we used x-ray diffraction analysis.

On the basis of the racemate of the geometrical isomer of 3-(1,5-dimethyl-2-pyrrolidinyl)-1-propanol (I) and (+)-tartaric acid we synthesized two hydrates (II and III) of diastereomeric bitartrates, from which optically active alcohols (–)-IV and (+)-V were isolated by treatment with alkali.



Bitartrate dihydrate II, which was obtained in the form of well-formed crystals, was subjected to x-ray diffraction analysis. The geometries of the pyrrolidinium cation and the bitartrate anion (in the absolute configuration) with the bond lengths and torsion angles in

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*See [1] for communication 8.

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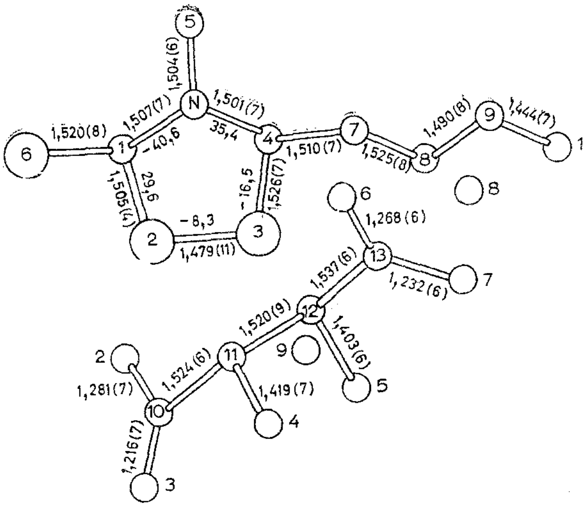


Fig. 1. Geometry of a fragment of the structure of bitartrate dihydrate II [the $O_{(8)}$ and $O_{(9)}$ atoms belong to the water molecules]. The bond lengths and torsion angles (only in the heteroring) are presented. The numbers in the circles are the numbers of the carbon atoms, while the numbers adjacent to the circles are the numbers of the oxygen atoms. This numbering of the atoms differs from the generally accepted chemical numbering.

the heteroring are shown in Fig. 1.

The average lengths of the N^+—C and C—C bonds in the pyrrolidinium cation are in agreement with the values found for an analogous structure [4].

The conformation of the five-membered heteroring is intermediate between a half chair and an envelope, as is apparent from a comparison of the torsion angles presented in Table 1. If the conformation of the heteroring is assumed to be an envelope, bending is realized along the $C_{(1)}$—$C_{(4)}$ line with 0.58 Å deviation of the nitrogen atom from the middle of the plane of the remaining ring atoms; this value is comparable to the previously found value (0.54 Å) in a similar cation [5]. The substituents attached to the $C_{(1)}$, $C_{(4)}$, and N atoms occupy a pseudoequatorial position; the first two are located on one side relative to the middle of the plane of the heteroring, i.e., in the cis position.

The average lengths of the C—C and C—O bonds in the γ-hydroxypropyl substituent are close to the standard values [7].

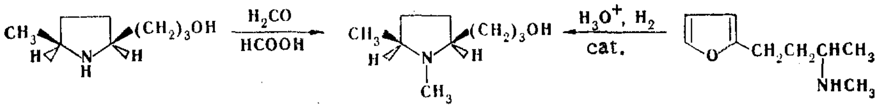
The lengths of the $C_{(10)}$—$O_{(2)}$ and $C_{(13)}$—$O_{(6)}$ bonds in the anion differ appreciably from the standard value for C—OH [1.358(5)Å] in carboxylic acids [7]; this is explained by participation of the $O_{(2)}$ and $O_{(6)}$ atoms in the formation of a very strong hydrogen bond with a length of 2.451 Å between the anions. The "acidic" hydrogen atom of the anion, which participates in the formation of the indicated $O_{(2)}...H^+...O_{(6)}$ hydrogen bond, evidently belongs to these atoms to virtually the same extent, i.e., it is statistically disordered, and this explains our failure to reveal it in differential synthesis of the electron density. In the crystal the cations form helixes about the 2_1 helical axes parallel to the C axis due to N—H...$O_{(1)}$ hydrogen bonds with a length of 2.755(7) Å. The $O_{(3)}$ and $O_{(7)}$ atoms of the carboxy groups of the anion and both of its hydroxy groups, as well as the hydroxy group of the cation, participate in hydrogen bonds with water molecules; the geometrical parameters of these bonds, particularly the O...O distances (2.8-2.9 Å), differ little from the accepted standard values [8].

The absolute configuration of the carbon atoms of the pyrrolidine ring was determined unambiguously on the basis of the known absolute configuration of (+)-tartaric acid, which is included in the composition of salt II. The asymmetric carbon atoms in tartrate II and, consequently, in alcohol (—)-IV have the following configuration: S for $C_{(1)}$ and R for $C_{(4)}$ (see Fig. 1).

TABLE 1. Experimental and Calculated [6] Torsion Angles ψ (deg) in the Five-Membered Rings

Angle	Cation of II	Ideal envelope	Ideal half chair
$C_{(4)}NC_{(1)}C_{(2)}$	−40,6	−60	−60
$NC_{(1)}C_{(2)}C_{(3)}$	29,6	36,5	50
$C_{(1)}C_{(2)}C_{(3)}C_{(4)}$	−8,3	0	−19
$C_{(2)}C_{(3)}C_{(4)}N$	−16,5	−36,5	−19
$C_{(3)}C_{(4)}NC_{(1)}$	35,4	60	50

Optically active alcohol (+)-V has PMR and IR spectra and physical constants that are identical to those of alcohol (−)-IV, on the basis of which it is an enantiomer of the latter, i.e., it has the (1R, 4S) configuration. The data obtained from x-ray diffraction analysis provided the basis for the assignment of the cis configuration of alcohol VI, by methylation of which, i.e., by alternative synthesis, alcohol I was obtained:



VI I

Tartrates VIII and IX, which give the same dextrorotatory alcohol VII, were obtained from VI. Data from the tartrates and optical isomers obtained are presented in Table 2.

EXPERIMENTAL

The II crystals were monoclinic with the following parameters: a = 7.1149(5), b = 10.579(1), c = 11.708(1) Å, γ = 100.02(1), V = 867.8(3) $Å^3$, M = 343.45, d_{calc} = 1.31 g/cm^3, space group $P2_1$. The cell parameters and intensities of 1117 independent reflections with I ⩾ 2σ were measured with a Hilger–Watts automatic four-circle diffractometer regulated by a PD P-8/1 minicomputer. The structure was decoded by the direct method by means of the MULTAN program and was refined by the method of least squares within the fully matrix anisotropic approximation to R = 0.040.

The IR spectra of suspensions of the crystalline substances in mineral oil and hexachlorobutadiene and of microlayers of the liquid substances were recorded with a UR-20 spectrometer. The PMR spectra of solutions of CCl_4 and $CDCl_3$ were obtained with a Varian HA-100 spectrometer with tetramethylsilane as the internal standard. The optical rotation was measured with an SPU-E spectropolarimeter.

3-(1,5-Dimethyl-2-pyrrolidinyl)-1-propanol (I) and 3-(5-methyl-2-pyrrolidinyl)-1-propanol (VI) were obtained by the methods in [9, 10].

(−)-cis-3-(1,5-Dimethyl-2-pyrrolidinyl)-1-propanol (+)-Bitartrate Dihydrate (II) and (+)-cis-3-(1,5-Dimethyl-2-pyrrolidinyl)-1-propanol (+)-Bitartrate Tetrahydrate (III). A hot solution of 2.4 g (0.015 mole) of (+)-tartaric acid in 20 ml of ethanol was added to a solution of 2.36 g (0.015 mole) of alcohol I in 15 ml of ethanol, and the mixture was stirred and allowed to stand at room temperature. After 4 h, the precipitated crystals (2.3 g), with mp 84°C, were separated and crystallized three times from ethanol to give 2 g (40%) of salt II. Ether (1 ml) was added to the filtrate, and the crystals that formed after 24 h were removed to give 2.75 g of a product with mp 73-74°C. Four recrystallizations from ethanol gave 1.5 g (57%) of salt III.

(+)-cis-3-(5-Methyl-2-pyrrolidinyl)-1-propanol (+)-Bitartrate (VIII) and (+)-cis-3-(5-Methyl-2-pyrrolidinyl)-1-propanol (+)-Bitartrate Hydrate (IX). A hot solution of 3.0 g (0.02 mole) of (+)-tartaric acid in 22 ml of ethanol was added to a solution of 2.8 g (0.02 mole) of alcohol VI in 8 ml of ethanol, and the mixture was allowed to stand for 12 h. The resulting crystals were removed by filtration and recrystallized from alcohol to give 3.2 g (55%) of salt VIII. Ether (5 ml) was added to the filtrate, and the crystals that formed after 2 h were separated to give 1.8 g (31%) of salt IX.

(2R,5S)-3-(1,5-Dimethyl-2-pyrrolidinyl)-1-propanol (IV). A saturated solution of alkali was added to a solution of 2 g (0.015 mole) of tartrate II in 4 ml of water until an oily

TABLE 2. 3-(2-Pyrrolidinyl)propanols and Their Tartrates

Compound	R	mp or bp, °C (hPa)	n_D^{20}	$[\alpha]_{579}^{20}$ (water)	Found, E			Empirical formula	Calc., %		
					C	H	N		C	H	N
I[a]	CH_3	113 (8,0)	1,4680	0	68,3	12,2	8,9	$C_9H_{19}NO$	68,8	12,1	8,9
II[b,c]	CH_3	90—91	—	−8,0	45,4	8,6	4,4	$C_9H_{19}NO \cdot C_4H_6O_6 \cdot 2H_2O$	45,5	8,4	4,1
III[b,d]	CH_3	61—62	—	+30,0	41,3	8,1	3,7	$C_9H_{19}NO \cdot C_4H_6O_6 \cdot 4H_2O$	41,2	8,2	3,7
IV[a]	CH_3	103 (8,0)	1,4650	−45,0	68,7	12,1	9,1	$C_9H_{19}NO$	68,8	12,1	8,9
V[a]	CH_3	103 (8,0)	1,4650	+38,0[e]	68,2	12,2	9,0	$C_9H_{19}NO$	68,7	12,1	8,9
VI[f]	H	116 (9,3)[g]	1,4750[h]	0	67,2	12,3	9,5	$C_8H_{17}NO$	67,2	12,0	9,7
VII[f]	H	121 (9,3)[i]	1,4732[h]	+2,25	67,0	12,0	9,8	$C_8H_{17}NO$	67,2	12,0	9,7
VIII[b]	H	159	—	+10,0	49,0	8,0	5,3	$C_8H_{17}NO \cdot C_4H_6O_6$	49,0	7,8	4,8
IX[b,j]	H	57—58	—	+4,8	44,3	8,5	4,4	$C_8H_{17}NO \cdot C_4H_6O_6 \cdot H_2O$	44,4	8,3	4,6

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[a] IR spectrum: 3380 (O—H); 2985, 2870 (C—H); 2780 (N—CH_3); 1470, 1380 (CH_3); 1310, 1265, 1080 cm^{-1} (O—H). PMR spectrum, δ: 1.12 (3H, d, CH_3), 2.25 (3H, s, CH_3—N), 2.18 (1H, m, 2-H), 2.37 (1H, m, 5-H), 1.66 (4H, m, CH_2), and 3.58 ppm (2H, m, CH_2—O). [b] IR spectrum: broad band at 2500-3600 cm^{-1} with maxima at 3500 (H_2O); 3320-3380 (O—H); 2840-2980 (CH); 2500-2730 ($\overset{+}{N}H$); 1700-1720 (C=O); 1550-1660 (CO_2^-); 1310, 1140, 1075 cm^{-1} (O—H). [c] Dihydrate. [d] Tetrahydrate. [e] Contains 15% racemate. [f] IR spectrum: 3360 (O—H); 3260 (NH); 2985, 2875 (CH); 1600 (NH); 1470, 1380 (CH_3); 1310, 1260, 1000 cm^{-1} (OH). [g] This compound had mp 20-21°C. [h] For the supercooled liquid. [i] This compound had mp 39-40°C. [j] Monohydrate.

layer separated, after which it was extracted with ether. The extract was dried with potassium hydroxide and distilled *in vacuo* to give 0.6 g (60%) of IV. (2S,5R)-3-(1,5-Dimethyl-2-pyrrolidinyl)-1-propanol (V) and cis-(+)-3-(5-methyl-2-pyrrolidinyl)-1-propanol (VII) were similarly obtained (see Table 2).

LITERATURE CITED

1. M. V. Noritsina, I. N. Klochkova, and T. S. Bykovskaya, Khim. Geterotsikl. Soedin., No. 2, 186 (1976).
2. W. Rost, B. Sutton, B. Frank, F. Pfeiffer, W. Holmes, N. Ditullio, and E. Ongram, J. Pharm. Sci., 56, 1958 (1967).
3. I. N. Klochkova, M. V. Noritsina, and L. K. Kulikova, Khim.-farm. Zh., No. 9, 63 (1977).
4. K. Coughenour and D. Dennis, Acta Cryst., B, 31, 1229 (1975).
5. P. J. Clarke, P. J. Pauling, and T. J. Petcher, J. Chem. Soc., Perkin Trans. I, No. 7, 774 (1975).
6. J. C. P. Schwarz, Chem. Commun., No. 14, 505 (1973).
7. L. E. Sutton (editor), Tables of Interatomic Distances and Configurations in Molecules and Ions, London (1968).
8. W. C. Hamilton and J. A. Ibers, in: Hydrogen Bonding in Solids, New York (1968), p. 77.
9. A. A. Ponomarev, A. P. Kriven'ko, and M. V. Noritsina, USSR Inventor's Certificate No. 158277; Byull. Izobret., No. 21, 15 (1963).
10. A. A. Ponomarev, M. V. Noritsina, and A. P. Kriven'ko, Khim. Geterotsikl. Soedin., No. 6, 923 (1966).