Crystallization of chiral compounds
2.* Propranolol: free base and hydrochloride

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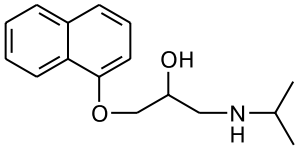
The data from IR spectroscopy, differential scanning calorimetry, and X-ray diffraction analysis are compared for crystalline specimens of homochiral and racemic propranolol and its hydrochloride. The stabilities of the racemates were quantitatively characterized and the factors responsible for the order of their stability are revealed.

Key words: propranolol, chirality, type of crystallization, racemic compound, IR spectroscopy, thermal analysis, X-ray diffraction analysis, crystal packing.

Propranolol, 1-isopropylamino-3-(1-naphthyloxy)propan-2-ol, (**1**) was known for about five decades as a drug regulating human cardiovascular activity.[2]



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Propranolol, primarily as its hydrochloride (**2**), which is known under different trade names, is in general use as a nonselective β-adrenoblocking agent with a broad spectrum of action.[3] Being the oldest drug of this class and having a simple chemical structure, propranolol has been studied in detail. In particular, using this compound as an example, it has been demonstrated for the first time that individual enantiomers of β-adrenoblocking agents differ in physiological activity.[4] Later, it was found that the (*S*) isomer of propranolol is an eutomer (enantiomer causing the desired effect), whereas it distomer, *i.e.*, the (*R*) isomer, stimulates smooth musculature of the uterus and, hence, is responsible for side effects.[5] Consequently, the use of the individual (*S*) enantiomer of propranolol instead of the racemic substance as the β-adrenoblocking agent is an urgent problem.

Beginning with the pioneering study,[4] numerous procedures have been developed for the preparation of propranolol in the enantiopure form. In most cases, the procedures that are offered were developed on the laboratory scale, and their industrial scaling-up presents problems. In this connection, a study is noteworthy[6] in which crystalline racemic propranolol hydrochloride was described as a racemic conglomerate, which was deduced from the results of thermal analysis. Crystallization of a racemic compound as a conglomerate, *i.e.*, as a mechanical mixture of crystals of individual enantiomers, is a prerequisite for the resolution of the racemic compound into enantiomers by entrainment, which is apparently the most efficient procedure for the resolution of racemic mixtures.[7,8]

In addition to the results of thermochemical studies,[6] X-ray diffraction data for this compound were also published.[9,10] It was demonstrated that the unit cell of racemic hydrochloride **2** belongs to the achiral space group $P2_1/c$ or $P2_1/n$. This indicates that the unit cell contains equal amounts of opposite enantiomers, which is incompatible with homochiral crystallization and formation of a racemic conglomerate. This evident inconsistency between the thermochemical and crystallographic data pertaining to the question of fundamental importance and practical significance gave impetus to our investigation. In the present study, specimens of racemic and scalemic (*S*)-propranolol as a free base (*rac*-**1** and *scal*-**1**) and hydrochloride (*rac*-**2** and *scal*-**2**) were investigated by IR spectroscopy and DSC. In addition, crystals of (*S*)-**1** were studied by X-ray diffraction analysis, and the results were compared with the published data for *rac*-**1** [10], *rac*-**2**,[9,10] and (*R*)-**2**.[11]

Experimental

Racemic propranolol and its hydrochloride were synthesized according to known procedures.[12] The preparation of scalemic (*S*)-propranolol hydrochloride has been described by us earlier.[13] Scalemic propranolol was prepared by neutralizing solutions of its hydrochloride with a calculated amount of NaOH. The enantiomeric compositions (optical purities $op = [\alpha_{exp}]/[\alpha_{max}]$) of the samples were monitored by polarimetry. The values $[\alpha]_D^{25} = -9.8$ (*c* 1.6, EtOH)[14] and $[\alpha]_D^{20} = -25.0$ (*c* 1.0, EtOH)[15] were used as $[\alpha_{max}]$ for (*S*)-propranolol and its hydrochloride, respectively.

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The optical rotation was measured on a Perkin—Elmer 341 polarimeter. The IR spectra of crystalline samples of the base, *rac*-**1** and (*S*)-**1**, and hydrochloride, *rac*-**2** and (*S*)-**2**, were recorded on a Bruker IFS-66v Fourier-transform spectrometer in KBr pellets. The melting curves of propranolol and its hydrochloride (15 mg) were measured on a Perkin—Elmer DSC-2 differential scanning calorimeter with a heating rate of 10 °C min^{-1}. The changes in the temperature and heat flux were calibrated against the data for metallic indium.

Single-crystal X-ray diffraction study of (*S*)-**1** was carried out at the Department of X-ray Diffraction Studies of the Center of Collaborative Use of the Russian Foundation for Basic Research on the basis of the Laboratory of X-ray Diffraction Methods of the A. E. Arbuzov Institute of Organic and Physical Chemistry, the Kazan Research Center of the Russian Academy of Sciences. The X-ray data were collected on an automated CAD-4 diffractometer (Nonius B.V.). The crystals of (*S*)-**1**, $C_{16}H_{21}NO_2$, belong to the monoclinic system. At 20 °C, a = 12.03(1), b = 5.146(4), c = 13.00(1) Å, β = 113.1(1)°, V = 740(1) Å^3, Z = 2, d_{calc} = 1.16 g cm^{-3}, space group $P2_1$. The unit cell parameters and intensities of 1773 reflections, of which 1325 reflections were with $I \geq 3\sigma$, were measured at 20 °C (λ(Cu-Kα) = 1.5418 Å, graphite monochromator, ω/2θ scanning technique, $\theta \leq 74.27°$). The intensities of three check reflections showed no decrease in the course of X-ray data collection. The absorption was ignored (μ(Cu) = 5.71 cm^{-1}). The structure was solved by direct methods using the SIR program[16] and refined first isotropically and then anisotropically. Then all H atoms were revealed from difference electron density syntheses. In the final cycles of the refinement, the H atoms were refined isotropically. With the aim of establishing the absolute structure and absolute configuration of molecule (*S*)-**1**, the direct and inverted structures were refined taking into account the anomalous scattering by all nonhydrogen atoms. The reliability factors were as follows: R = 0.052, R_w = 0.062 for the direct structure, and R = 0.053, R_w = 0.063 for the inverted structure based on 1325 reflections with $F^2 \geq 3\sigma$, 255 parameters were refined. According to the Hamilton test,[17] the direct structure corresponds to the absolute structure with the probability of 95%. The final reliability factors were as follows: R = 0.052, R_w = 0.062 based on 1325 independent reflections with $F^2 \geq 3\sigma$. All calculations were carried out using the MolEN program package[18] on an AlphaStation 200 computer. The selected geometric parameters are given in Table 1. The molecules were drawn and the intermolecular interactions in the crystals were calculated using the PLATON program.[19] The atomic coordinates and thermal parameters were deposited with the Cambridge Structural Database.

Results and Discussion

The vibrational spectra of *rac*-**1** and (*S*)-**1** (*op* ≈ 90%) recorded in KBr pellets at 100 °C, *i.e.*, at the temperature higher than the melting points of both compounds, are identical. The spectra recorded at room temperature (both of freshly prepared samples and samples pre-heated to 100 °C) have much richer sets of frequencies and are not identical with each other (Fig. 1). There are distinct bands at 501, 915, 927, and 1334 cm^{-1} for *rac*-**1** or at 1174 and 1489 cm^{-1} for (*S*)-**1**, which are much weaker or even absent from the spectrum of another specimen. It should be also noted that the intensities of absorption bands in the regions of 556—571, 998—1216 cm^{-1}, *etc.* are noticeably inverted.

Nevertheless, the spectra of the racemic and scalemic specimens retain the general similarity in both the fingerprint region and the region higher than 2800 cm^{-1} (region of X—H vibrations), which reflects, among other things, the number and character of inter- and intramolecular hydrogen bonds. On the whole, analysis of the IR spectra of propranolol suggests that its racemic specimen crystallizes as a racemic compound (true racemate). However, both the conformation and the system of hydrogen bonds in the crystals of racemic propranolol are similar to those of scalemic propranolol.

The vibrational spectra of *rac*-**2** and (*S*)-**2** (*op* ≈ 95%), which were recorded in KBr pellets at 200 °C, *i.e.*, at the

Table 1. Selected bond lengths (d), bond angles (ω), and torsion angles (φ) in molecule (*S*)-**1**

Bond	d/Å	Bond angle	ω/deg	Torsion angle	φ/deg
O(2)—C(2)	1.422(3)	C(2)—O(2)—H(2)	124.0(3)	H(2)—O(2)—C(2)—C(1)	139(3)
O(3)—C(4)	1.367(4)	C(1)—N(1)—C(12)	113.2(2)	C(3)—O(3)—C(4)—C(5)	−3.1(5)
N(1)—C(1)	1.477(4)	C(12)—N(1)—H(1)	112.0(3)	C(12)—N(1)—C(1)—C(2)	−142.5(3)
N(1)—H(1)	0.84(4)	N(1)—C(1)—C(2)	113.5(2)	C(1)—N(1)—C(12)—C(13)	−68.8(4)
C(2)—C(3)	1.520(5)	O(2)—C(2)—C(1)	111.1(3)	H(1)—N(1)—C(12)—C(13)	174(3)
O(2)—H(2)	0.76(4)	C(1)—C(2)—C(3)	110.7(2)	N(1)—C(1)—C(2)—O(2)	−61.1(4)
O(3)—C(3)	1.423(4)	C(4)—O(3)—C(3)	119.6(3)	O(2)—C(2)—C(3)—O(3)	162.6(3)
N(1)—C(12)	1.470(5)	C(1)—N(1)—H(1)	104.0(3)	O(3)—C(4)—C(5)—C(6)	−178.6(4)
C(1)—C(2)	1.498(5)	N(1)—C(12)—C(13)	109.9(4)	C(3)—O(3)—C(4)—C(11a)	176.9(3)
C(12)—C(13)	1.506(7)	O(3)—C(3)—C(2)	106.5(3)	C(4)—O(3)—C(3)—C(2)	172.9(3)
		O(2)—C(2)—C(3)	109.8(3)	H(1)—N(1)—C(1)—C(2)	−20(2)
		O(3)—C(4)—C(5)	124.7(3)	C(1)—N(1)—C(12)—C(14)	170.5(4)
				H(1)—N(1)—C(12)—C(14)	53(2)
				N(1)—C(1)—C(2)—C(3)	176.7(3)
				C(1)—C(2)—C(3)—O(3)	−74.5(4)
				O(3)—C(4)—C(5)—H(5)	12(3)

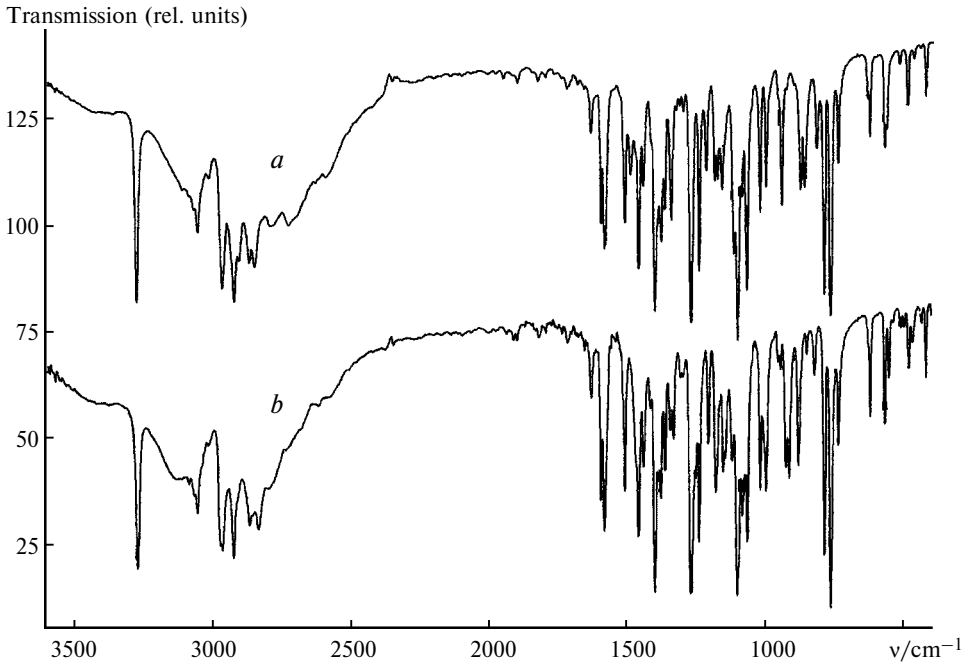


Fig. 1. IR spectra of crystalline specimens of *rac*- (*a*) and (*S*)-propranolols **1** (*b*).

temperature higher than the melting points of both compounds, are identical. In contrast, substantial differences are observed in the spectra recorded at room temperature (Fig. 2). As in the above-described case, the bands at 670, 900, 927, 1143, 2710, 2924, 3226, 3282, and 3326 cm^{-1} in the spectrum of *rac*-**2** and the bands at 477, 833, 911, 992, 1350, 2723, and 3342 cm^{-1} in the spectrum of (*S*)-**2** should be noted. These bands are either very weak or absent from the spectrum of another specimen. In addition, virtually any group of bands, even if they are characterized by identical or similar frequencies, has its own configuration of intensities in the IR spectra of *rac*- and (*S*)-**2**. This character of vibrational spectra, first, indicates that racemic propranolol hydrochloride crystallizes as the true racemate and, second, provides evidence for substantial differences in the structure (conformation) of molecules **2**

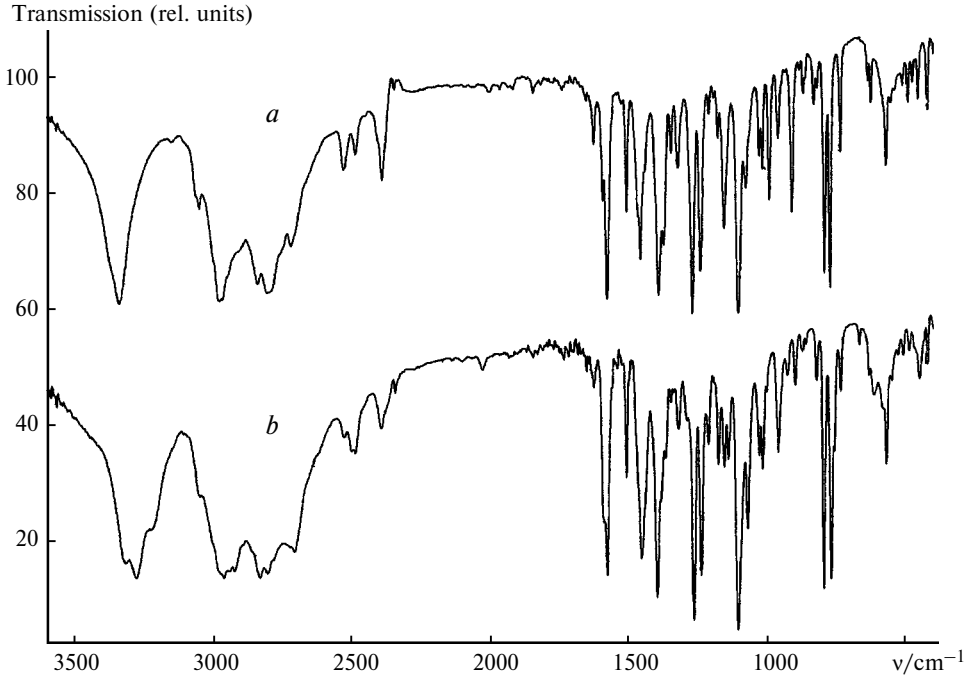


Fig. 2. IR spectra of crystalline specimens of *rac*- (*a*) and (*S*)-propranolol hydrochlorides **2** (*b*).

and in the system of inter- and intramolecular hydrogen bonds in the homo- and heterochiral crystals.

According to the DSC data, melting of racemic propranolol is characterized by m.p. 95.4 °C and the enthalpy of melting ΔH_m = 38329 J mol^{-1}. Based on these data and using the Prigogine—Defay ratio[8]

$$\ln 4x(1-x) = (2\Delta H^R{}_m/R)(1/T^R{}_m - 1/T_m), \quad (1)$$

where x is the mole fraction of one of the enantiomers in the mixture (the mole fraction of another enantiomer $x' = (1-x)$), $\Delta H^R{}_m$ and $T^R{}_m$ are the enthalpy and temperature of melting of the racemic compound, respectively, and R is the universal gas constant (R = 8.3170 J K^{-1} mol^{-1}), one can construct a curve whose central region describes the liquidus line of the melting diagram of propranolol on the "enantiomeric composition—absolute temperature" coordinates, if this chiral substance forms a racemic compound with a 1 : 1 composition. Figure 3 shows this theoretical curve *DCD′* along with the experimental points *1—6* corresponding to the completion of melting of samples of **1** with different enantiomeric compositions. All these experimental points fit well the curve thus confirming the IR spectroscopic data, which indicate that propranolol forms a solid racemic compound. The melting curves of samples of *scal*-**1** with intermediate enantiomeric purities, *viz.*, points *3—5* in Fig. 3, are described by two separate peaks, the first of which (points *3′—5′*) characterizes melting of an eutectic. The solidus line passing through these points parallel to the horizontal axis at T = 69.3 °C intersects the curve *DCD′* at the points *B* and *B′*, which correspond to samples with an enantiomer ratio of 0.038 : 0.962, *i.e.*, *op* ≈ 92%. It is known that the binary melting phase diagram is similar in shape (two minima corresponding to eutectics and a maximum corresponding to a racemic compound) and some metric characteristics (composition of the eutectic) to an isothermic cross-section of a ternary solubility phase diagram of a chiral compound. This provides an explanation why attempts to increase the optical purity of samples of propranolol with the initial *op* ≤ 90% by recrystallization failed. Since the starting sample is intermediate in composition between eutectics, each next recrystallization affords crystals whose composition approaches that of the racemate rather than that of an enantiopure compound.

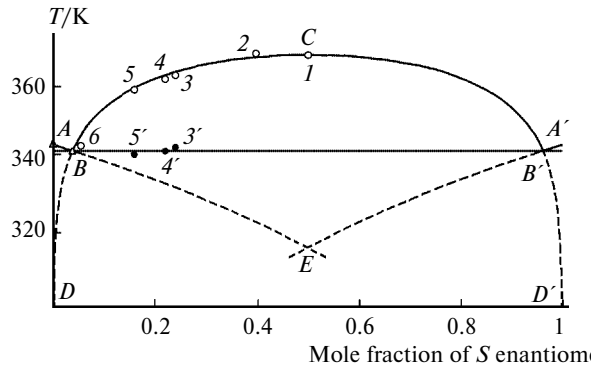


Fig. 3. Theoretical melting phase diagram of propranolol **1** calculated from experimental data (see comments in the text).

Since we had no way of direct measuring the melting enthalpy of an enantiopure sample of **1**, we estimated this value by an indirect route. The region of the liquidus line between an enantiopure sample and an eutectic is described by the Schröder—Van Laar equation:[7,8]

$$\ln x = (\Delta H^A{}_m/R)(1/T^A{}_m - 1/T_m), \quad (2)$$

where $\Delta H^A{}_m$ and $T^A{}_m$ are the enthalpy and temperature of melting of enantiopure compounds, respectively. Substituting the composition and melting point of the eutectic, which we have evaluated above, in Eq. (2), this equation can be solved for $\Delta H^A{}_m$, if the melting point of the enantiopure sample is known. For propranolol with a high (but not quantitatively characterized) enantiomeric purity, the melting points of 71 °C [14] and 73 °C [4] were reported. The corresponding calculated values of $\Delta H^A{}_m$ are 22.4 and 10.3 kJ mol^{-1}. Apparently, the first values, *viz.*, 71 °C and 22.4 kJ mol^{-1}, are closer to the true values. The corresponding calculated branches of the curves *AE* and *A′E* described by Eq. (2) are shown in Fig. 3. It should be noted that the enthalpies of melting of homochiral crystals of **1** are always much smaller (by 10—20 kJ mol^{-1}) than those of heterochiral crystals.

In the case of propranolol hydrochloride, DSC measurements of a sample of *rac*-**2** gave $T^R{}_m$ = 163.7 °C and $\Delta H^R{}_m$ = 33631 J mol^{-1}. For a sample of (*S*)-**2** (*op* > 98%), $T^A{}_m$ = 197.2 °C and $\Delta H^A{}_m$ = 31652 J mol^{-1}. Figure 4 shows the curves, which were constructed based on these data and correspond to solutions of Eqs. (1) and (2), *viz.*, *DCD′* and *AE* and *EA′*, respectively. The line *BB′* passing through the points of their intersections corresponds to the calculated solidus line, and the solid curve *ABCB′A′* corresponds to the liquidus line of the binary melting phase diagram of compound **2**.

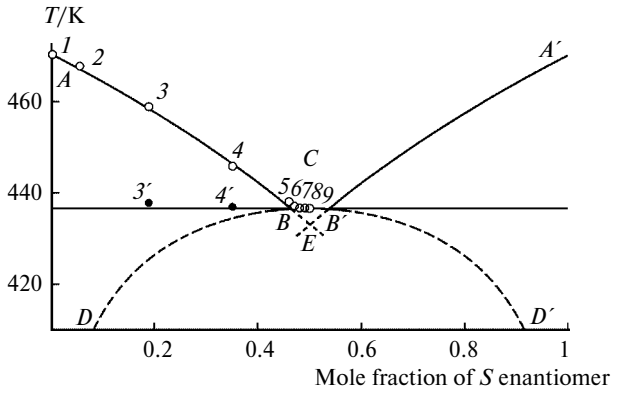


Fig. 4. Theoretical melting phase diagram of propranolol hydrochloride **2** calculated from experimental data (see comments in the text).

The general character of the melting diagram of chiral hydrochloride **2** demonstrated the formation of the racemic compound with a 1 : 1 composition, which agrees with the data from IR spectroscopy. However, the region of its existence is very narrow, the difference between the experimental temperature T_m = 163.7 °C of the racemic compound and the theoretical temperature T_m = 160.1 °C calculated for a racemic conglomerate (point *E* in Fig. 4) is also small. In this case, small and generally insignificant errors of the determination of the experimental values (T_m, ΔH_m, *op*) can influence the general character of the phase diagram. Probably, this may account for the incorrect identification of the type of crystallization of **2** reported in the earlier study.[6] We additionally investigated the melting of samples of **2** with different enantiomeric purities. The results of this investigation are presented in Fig. 4. When the melting peaks of an eutectic of hydrochloride **2** were recorded separately (points *3′* and *4′*), the temperatures T^E_m determined for these points fit well the theoretical solidus line. The temperatures at which melting of all samples is over are also consistent with the theoretical liquidus line. In this case, the values for the points with low enantiomeric purities (points *6—9*) form a plateau rather than a minimum typical of a racemic conglomerate. Therefore, the experimental thermal analysis unambiguously demonstrated that molecules **2** formed the racemic compound. Simultaneously, thermal analysis showed that the enthalpies of melting of the racemic compound and homochiral crystals differ by only 1.98 kJ mol^{-1}, which is substantially smaller than the corresponding difference for compound **1**.

The relative stability of a racemic compound can be evaluated based on the melting phase diagram of a chiral compound in arbitrary dimensionless units *i* according to Pettersson's equation[8,20]

$$i = (T^R_m - T^E_m)/(T^A_m - T^E_m), \quad (3)$$

where T^E_m is the melting temperature of the eutectic. According to Pettersson, the values $i < 0.5$ characterize unstable racemic compounds, $0.5 \leq i \leq 1.5$ are indicative of their moderate stability, and $i > 1.5$ are typical of chiral compounds that form stable racemic compounds with a 1 : 1 composition. The *i* values for base **1** and hydrochloride **2** calculated from the melting diagrams (see Figs. 3 and 4) according to Eq. (3) are $i_1 \approx 15.3$ and $i_2 \approx 0.01$, respectively. Consequently, according to this criterion, the racemic compound is extremely stable for the base and is very unstable in the case of its hydrochloride. The reasons for this fact should be searched for in the characteristic features of the molecular packings in the homo- and heterochiral crystals of **1** and **2**.

The structure and molecular packing of *rac*-**1** have been established by X-ray diffraction analysis earlier.[10] X-ray diffraction analysis of scalemic (*S*)-**1** was carried out in the present study. The structure of molecules (*S*)-**1** in the crystal is shown in Fig. 5. This figure gives also the numbering scheme of the nonhydrogen atoms in the propranolol molecule, which is used for all compounds under consideration. The selected structural parameters of molecule (*S*)-**1** in the crystal are listed in Table 1. Since the bond angles and bond lengths both in molecule (*S*)-**1** (according to our results) and molecules *rac*-**1** (see

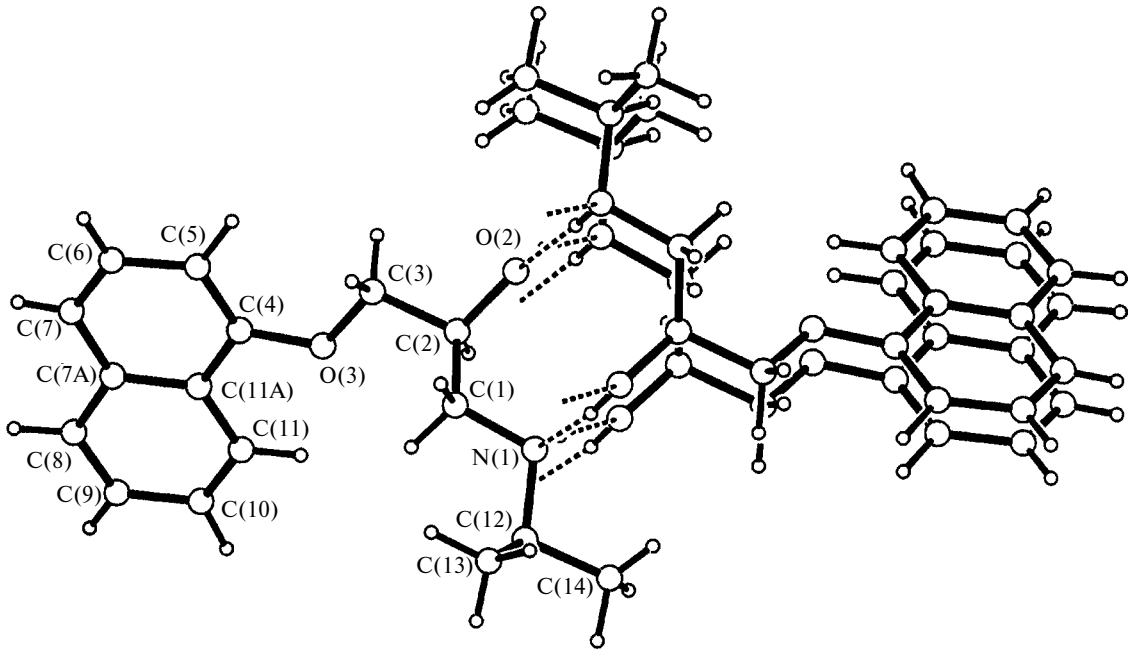
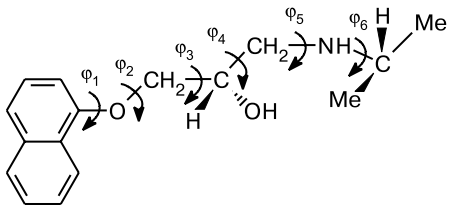


Fig. 5. System of hydrogen bonds, structure, and atomic numbering scheme in the crystal structure of propranolol (*S*)-**1**.

Ref. 10) have values typical of crystalline organic compounds, they are not discussed. The principal torsion angles characterizing the conformation of the propranolol molecules are shown below.



The φ_1 angle corresponding to C—C—O—C is measured from the C(11A) atom in the naphthalene ring located at the junction, and the φ_2, φ_3, φ_4, φ_5, and φ_6 angles correspond to C—O—C—C, O—C—C—C, C—C—C—N, C—C—N—C, and C—N—C—H, respectively. The numerical values of these torsion angles in the crystals of compounds *rac*-**1** and (*S*)-**1** are given in Table 2. For *rac*-**1**, the data for the (*S*) isomer are given for comparison.

Molecules of β-adrenoblocking agents are conformationally labile due to the presence of a large number of potential axes of internal rotation. About 9000 local minima of the potential energy were found in the multidimensional conformational space of the model β-adrenoblocking agent by molecular mechanics.[21] Nevertheless, the general structural features of this class of compounds were rather well studied for both solid and liquid phases. In most of experimental studies and calculations (see Ref. 21 and references cited therein), the O—C—C—C fragment has a synclinal conformation ($\varphi_3 = \pm 60 \pm 30°$), whereas other heavy atoms in the aliphatic chain of the molecule are in nearly antiperiplanar orientations. As can be seen from Table 2, molecules *rac*-**1** and (*S*)-**1** have analogous structures in the crystals. However, although being conformationally similar, the molecules in the homo- and heterochiral crystals differ in the configuration. In each individual propranolol molecule, crystallization fixes one of two possible (which undergo rapid inversion at standard temperatures in the gas and liquid phases) configurations of the unsymmetrically substituted pyramidal N atom. In the homochiral crystals, this atom adopts the configuration identical with that of the chiral carbon center. In the crystals, molecules (*S*)-**1** occur only as the ($S_C S_N$) diastereomer. Crystallization of racemic propranolol is accompanied by fixation of the N atoms in configurations opposite to those of the C atoms. The heterochiral crystals contain both the ($S_C R_N$) diastereomers and their centrosymmetrical equivalents, *i.e.*, the ($R_C S_N$) diastereomers.

Let us emphasize this important feature once again. If individual molecules in samples of racemic and scalemic propranolol in the gas phase, solutions, and melts possess equal thermodynamical characteristics, including free energies, each molecule of the racemic sample in crystals appears to be a diastereomer with respect to each molecule of the scalemic sample. The differences in the inner energies of macroscopic samples are determined already on the molecular level. It was of interest to estimate the relative energies of these diastereomeric molecules.

A search for conformers corresponding to the global minima on the potential energy surface (PES) of these stereoisomers was beyond the scope of our study. At the same time, it is incorrect to compare the calculated energies of the molecules with the fixed experimental geometric parameters. In this case, insignificant differences in "rigid" characteristics, such as bond lengths (which depend strongly on the quality of X-ray diffraction data), will make the major contribution to the calculated energies. Hence, we proceeded as follows. We used the geometries of the ($S_C S_N$) and ($S_C R_N$) diastereomers, which were determined by X-ray diffraction analysis of (*S*)-**1** and *rac*-**1**, respectively, as the starting points in PM3 quantum-chemical calculations with full geometry optimization. The conformers corresponding (according to the results of calculations) to the minima on PES nearest to the starting points are characterized by the torsion angles

Table 2. Experimental (I) and calculated (II) torsion angles (φ) and calculated enthalpies of the individual molecules of propranolol (**1**) and propranolol hydrochloride (**2**) in crystals

Molecule	$-\Delta H_f$ /kJ mol^{-1}	φ/deg											
		φ_1		φ_2		φ_3		φ_4		φ_5		φ_6	
		I	II	I	II	I	II	I	II	I	II	I	II
rac-**1**[a]	216.75	177.6	−167.9	−179.7	172.8	−68.8	−82.4	175.7	166.0	−173.0	−171.1	68.2	−49.9
scal-**1**[b]	211.85	175.9	169.9	173.0	152.8	−74.5	−84.3	176.6	156.1	−142.6	173.1	43.3	32.1
rac-**2**[a]	342.10	−172.0	−130.9	174.7	166.8	−58.0	−76.6	−176.0	157.3	−82.2	−78.1	51.5	51.5
scal-**2**[c]	346.21	171.9	169.5	−174.7	−173.4	−174.6	−170.9	162.2	166.4	170.6	169.4	54.7	56.4

[a] For the experimental data, see Ref. 10.
[b] The experimental data were obtained in the present study.
[c] For the experimental data, see Ref. 11.

given in Table 2. These values differ only slightly from those found experimentally. The structure occurring in the homochiral crystals is energetically less favorable than that in the heterochiral crystals by ~4.9 kJ mol^{-1}. Thermochemical experiments showed that the difference in the enthalpies of melting of the racemic and scalemic specimens has the same sign but is substantially larger in the magnitude.

In searching for additional stability factors of the racemic compound for base **1**, let us turn our attention to cooperative effects of the packing and consider a system of hydrogen bonds in the homo- and heterochiral crystals of propranolol. The system of hydrogen bonds in the crystal of (*S*)-**1** is shown in Fig. 5. Each molecule is involved in four intermolecular hydrogen bonds (two bonds as a donor and two bonds as an acceptor). The H atom at the O(2) atom forms a bond with the N(1´) atom of another molecule related by the symmetry operation ($1 - x$, $-1/2 + y$, $2 - z$). The parameters of the hydrogen bond are as follows: O(2)—H(2), 0.76(4) Å; H(2)...N(1´), 2.11(5) Å; O(2)...N(1´), 2.791(3) Å; O(2)—H(2)...N(1´) angle, 149(5)°. The H atom at the N(1) atom forms a bond with the O(2´) atom of the molecule related by the symmetry operation ($1 - x$, $-1/2 + y$, $2 - z$). The parameters of the hydrogen bond are as follows: N(1)—H(1), 0.85(4) Å; H(1)...O(2´), 2.43(4) Å; N(1)...O(2´), 3.274(3) Å; N(1)—H(1)...O(2´) angle, 170(4)°. The principal characteristic features of the graph of the hydrogen bonds in the crystal lattice of (*S*)-**1** are described by the formulas[22] C 1,1(5)*a*; C 1,1(5)*b*; C 2,2(4) > *a* > *b*; R 2,2(10) > *a* < *b*. The hydrogen bonds involving the OH and NH groups form infinite tubes along the *y* axis. These tubes are linked to each other only by lipophilic interactions between the peripheral hydrocarbon naphthyl and isopropyl fragments (Fig. 6).

The scheme of hydrogen bonds in the racemic crystal of propranolol constructed based on the data published earlier[10] is shown in Fig. 7. In this case, each molecule is also involved in four intermolecular hydrogen bonds (two as a donor and two as an acceptor). The H atom at the O(2) atom forms a bond with the N(1´) atom of the molecule related by the symmetry operation ($-x$, $-y$, $-z$). The parameters of the hydrogen bond are as follows: O(2)—H(2), 0.79 Å; H(2)...N(1´), 2.10 Å; O(2)...N(1´), 2.82 Å; O(2)—H(2)...N(1´) angle, 151°. The H atom at the N(1) atom forms a bond with the O(2″) atom of the molecule related by the symmetry operation ($-x$, $-1 - y$, $-z$). The parameters of the hydrogen bond are as follows: N(1)—H(1), 0.83 Å; H(1)...O(2″), 2.44 Å; N(1)...O(2″), 3.17 Å; N(1)—H(1)...O(2″) angle, 146°. In the racemic crystal, the propranolol molecule has one intramolecular hydrogen bond with the following parameters: N(1)—H(1), 0.83 Å; H(1)...O(2), 2.59 Å; N(1)...O(2), 2.92 Å; N(1)—H(1)...O(2) angle, 105°. In sum, the graph of the system of hydrogen bonds is described by the formulas C 2,2(4) > *a* > *b*, R 2,2(10)*a*, R 2,2(10)*b*, S 1,1(5)*c*. The packing of *rac*-**1** is, on the whole, similar to that of *scal*-**1**. The hydrogen-bonded pairs of enantiomers form infinite columns, which, in turn, are held together by lipophilic interactions between peripheral groups.

Although the conformations of the molecules and characteristic features of their packings are similar (both these facts are supported by the similarity of the IR spec-

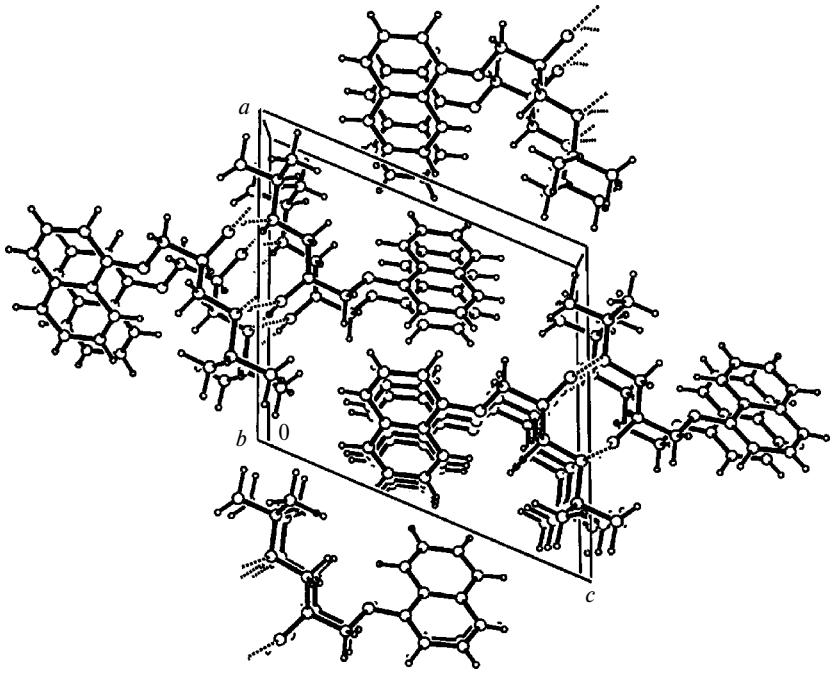


Fig. 6. Molecular packing (projection along the *y* axis) in the crystal of (*S*)-**1**.

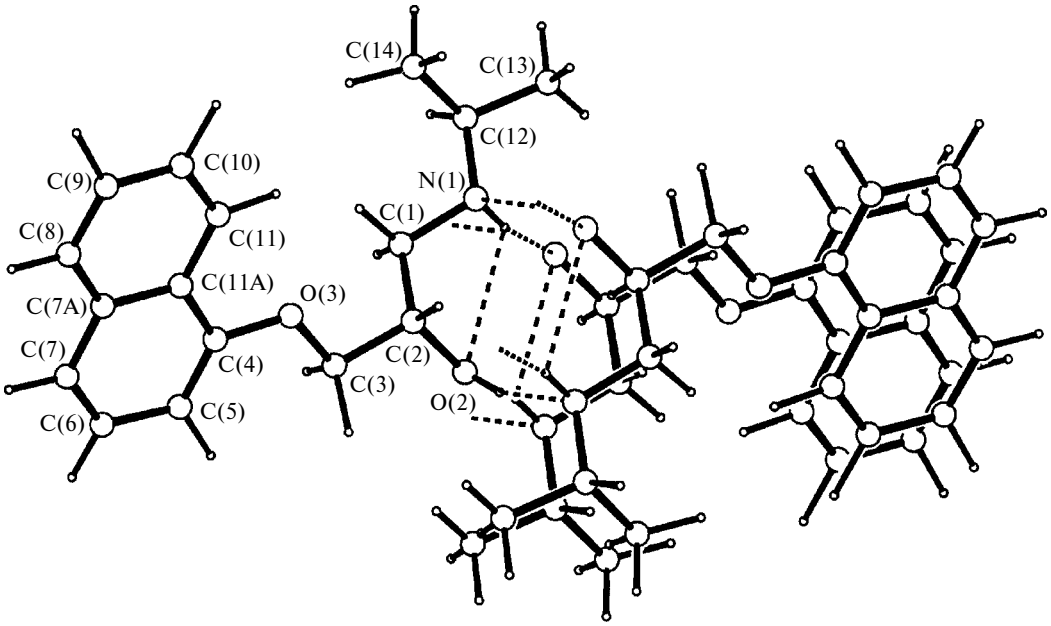


Fig. 7. System of hydrogen bonds in the crystal structure of propranolol (*rac*)-**1** according to the published data.[10]

tra of crystalline *rac*-**1** and *scal*-**1**), there are differences associated with changes in the configuration of the N atom. On the macroscopic level, it can be noted that the calculated density of the centrosymmetrical crystals of the racemate is somewhat higher than that of the chiral crystals of (*S*)-**1** (1.167 and 1.163 g cm^{-3}, respectively). Formally, propranolol follows Wallach's rule, according to which crystals of racemates have a higher density than crystals of individual enantiomers (this rule and modern analysis of its applicability have been discussed[23]). At the same time, the relative difference between the densities is very small (less than 0.5%). The difference between the unit cell volumes is of the same order of magnitude (1476.2 and 1481.4 Å^3, respectively; $\Delta V = 5.2$ Å^3 with respect to an equal number of molecules per unit cell). The difference between the packing coefficients of these crystals calculated according to Kitaigorodsky is larger (0.69 for *rac*-**1** and only 0.65 for (*S*)-**1**). The latter value corresponds to a loose crystal packing. It can be assumed that the denser packing of racemic **1** is favored by the intramolecular hydrogen bond present in the (S_CR_N)- and (R_CS_N)-propranolol molecules (this bond is absent from molecules (S_CS_N)-**1**). An increase in the density of the packing is manifested in the changes in the same interatomic distances for *rac*-**1** and (*S*)-**1**, the crystal structures being similar. For example, the distances between the N atoms of the molecules located one above the other in the stacks formed by translations are 4.80 Å for *rac*-**1** and 5.15 Å for (*S*)-**1**. A change in the density of the packing caused by the above-mentioned factors along with a higher stability of the individual molecules leads finally to an increase in stability of the racemic crystals compared to the enantiopure crystals.

The crystal structure of propranolol hydrochloride has been studied earlier for both racemic samples[9,10] and scalemic (*R*)-**2**.[11] In molecules **2**, the quaternary N atom loses chirality and, hence, the diastereomeric differences between individual molecules in the crystalline samples disappear. On the molecular level, the difference in the inner energy is determined by the conformational factor. As can be seen from Table 2, the conformations of the individual molecules in the crystal lattices of *rac*-**2** and *scal*-**2**, first, differ from those of *rac*-**1** and *scal*-**1** and, second, differ from each other. We evaluated the inner energy of isolated conformers **2** analogously to **1**, *i.e.*, calculated this energy by the PM3 method with full geometry optimization using the experimental geometries as the starting points. The calculated torsion angles, which characterize local minima on PES, differ insignificantly from the starting values (see Table 2). According to the quantum-chemical estimates, conformer *scal*-**2** in which all heavy atoms of the aliphatic fragment adopt anticlinal conformations is energetically more favorable by ~4.1 kJ mol^{-1}. As mentioned above, the difference between the enthalpies of melting of *rac*-**2** and *scal*-**2**, *i.e.*, the relative stability of their crystal lattices, is ~2.0 kJ mol^{-1}, *rac*-**2** being more favorable. It is reasonable to relate the reverse order of stability as compared with that obseved for the isolated molecules to the cooperative effects of the packing.

Analysis of the three-dimensional crystal packing of hydrochlorides **2** based on the published data[9–11] enables one to reliably establish that the formation of infinite structures is determined primarily by interactions of the positively charged regions adjacent to the ammonium ni-

trogen atom with the Cl^- anions. Unfortunately, the quality of the X-ray diffraction data does not allow one to judge the fine details of the formation of these structures. In the earlier studies,[9,11] the H atoms of the hydroxy and amino groups were not located, and, consequently, it is impossible to analyze the motif of hydrogen bonds. In the crystals of *rac*-**2**, substantial disorder was revealed[10] in the vicinity of the secondary hydroxy group of the independent molecule, which also hinder the location of the H atom of the OH group. Moreover, disorder in the vicinity of the chiral center of molecule **2** makes it impossible to reliably identify whether the character of infinite fragments in the crystal lattice is homochiral or heterochiral.

There are reasons to believe that in the crystal of *rac*-**2**, the molecules adopting the same configuration are linked in infinite stacks by Coulomb interactions and strong intermolecular hydrogen bonds. Within the symmetry of the crystal lattice, these homochiral fragments located around the screw axes 2_1 are related by inversion centers with the columns of the molecules adopting the opposite configuration. The physical relation between the enantiopure stacks occurs through hydrophobic interactions between the peripheral isopropyl and naphthyl groups. If this assumption is true, the enantiomers in the crystals of *rac*-**2** are to a large extent resolved. The racemic compound detected by thermal analysis is stabilized only by dispersion forces, which accounts for its instability. A high-precision X-ray diffraction study can prove these assumptions.

Therefore, racemic propranolol forms a stable racemic compound upon crystallization from a melt or solutions. The stability of the homochiral crystals is associated with both a higher stability of the diastereomeric form of the individual molecules and a change in the character of intra- and intermolecular hydrogen bonds. In the case of propranolol, both factors act in the same direction.

Racemic propranolol hydrochloride also forms a racemic compound, which is, however, unstable. In this case, the individual conformers that form the homochiral crystal packing are more stable than those forming the racemic compound. Consequently, in the case of propranolol hydrochloride, the factors associated with the stability of the individual molecules and their cooperative formation (crystal lattice) act in opposite directions. Apparently, in the crystal packing of *rac*-**2**, it is the homochiral molecules that are linked by Coulomb forces and hydrogen bonds. In turn, their supramolecular ensembles are held in the crystal by much weaker short-range hydrophobic interactions. In this case, one would expect that an insignificant directed change in the molecular structure of **2** could destroy the unstable racemic compound and gives rise to crystallization of such a modified structure as a racemic conglomerate.

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