Chiral drugs *via* the spontaneous resolution

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The psychotropically active drug Albicar 1 has been prepared for the first time in both enantiomerically pure forms starting from the (+)-2 and (–)-2 precursors obtained by spontaneous resolution; the crystal structures of (–)-1 and (±)-1 have been solved by X-ray diffraction study.

A perfect medicine ('the Erlich magic bullet') should match a biological target. The latter is inherently a chiral species; therefore, the racemate and both enantiomers of the medicinal compound may differ strongly in activity, toxicity and side effects (for example, both enantiomers of the chiral drug Thalidomid exhibit sedative action but only one of them is teratogenic).[1] That is why in the last decade the world pharmacy intensively turned to the production of enantiomerically pure medicines.[2]

The simplest ways for obtaining enantiomers are spontaneous crystallization resolution and absolute asymmetric synthesis (*i.e.*, crystallization under conditions of the fast enantiomerization in a solution or melt that gives rise to the complete transformation of a racemate into one enantiomer).[2(b)–(e),3(b)] The ability of a racemate for crystallization in the form of a conglomerate (*i.e.*, a mixture of homochiral crystals of the enantiomers) is a critical requirement in both methods.[3(a)–(d)] Recently, data on the spontaneous crystallization resolution of the pseudo-racemates[3(e)] (in their crystals, the relative positions of the enantiomers are statistically disordered[3(a)]) were reported.

In this work, we describe the synthesis of both enantiomers of the psychotropically active medicine Albicar,[4] 2,6-diethyl-4,8-dimethylglycoluril **1**. Albicar has passed pre-clinical tests and was recommended for clinical tests as a tranquilizer and a remedy for treating vegetative neuroses.

According to the qualitative concepts for constructing conglomerates developed previously,[5] there were the chiral glycolurils that seemed to be the most promising objects. Indeed, whereas the Albicar itself is crystallised as a racemate (space group $P2_1/a$, $Z = 4$)[4(c)] its possible precursors, 2,6-dialkylglycolurils, both do form conglomerates [R = Me (space group $P2_12_12_1$, $Z = 4$),[5(b)] R = Et, **2** (space group $P4_12_12$, $Z = 4$)[6]] and undergo spontaneous resolution by crystallization from water under normal conditions.[5(a),(b)]

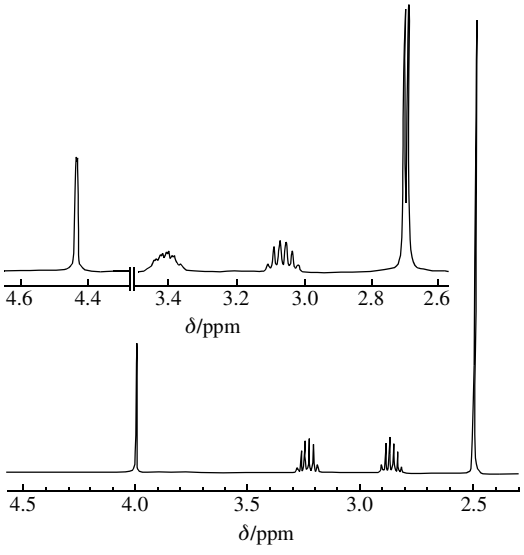
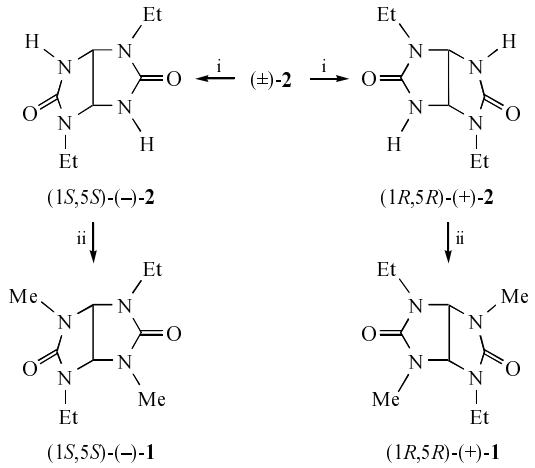


Figure 1 Partial ^{1}H NMR spectra of (±)-**1** (400 MHz) in C_6D_6; below: normal spectrum; above: in the presence of the chiral shift reagent Eu(tfc)$_3$.



Scheme 1 *Reagents and conditions*: i, resolution by an internal entrainment procedure; ii, $(MeO)_2SO_2$ and KOH in H_2O, 3 h at 70–75 °C, neutralization with HCl at 20 °C, extraction with CH_2Cl_2 at 20 °C, chromatography on silica (eluent CH_2Cl_2), and crystallization from Et_2O.

It should be noted that in some instances crystallization in the form of a conglomerate occurs only under high pressures or elevated temperatures;[3(a)–(c)] sometimes, the conglomerates do not undergo spontaneous resolution due to epitaxy.[5(b)]

By a comparative analysis of the crystal properties of Albicar precursors, the advantage of **2** was shown;[5(b)] therefore, its spontaneous resolution into enantiomers was completed using an internal entrainment procedure (the novel method including applying a single crystal as the seed from primary racemic conglomerate;[7] early resolution by mechanical sorting of crystals was described[5(a)]). Among the known methods for the N-alkylation of glycolurils,[4(b),8–11] we have selected the simplest one[7] and found conditions to provide quantitative yields of the product.

The obtained enantiomers of **1** have been purified by crystallization from diethyl ether until the constancy of melting points and optical rotation angles, and characterised by ^{1}H NMR (Figure 1) and CD spectra (Figure 2).† The absolute configuration of the enantiomers of **1** is apparent from those established earlier[5(a)] for precursors **2** (Scheme 1). The purity of (–)-**1** exceeds 95% as it is evident from the absence of the signals due to MeN, CH_2O, and HC relating to another enantiomer and observed for the racemate in ^{1}H NMR spectrum in the presence of the chiral shift reagent Eu(tfc)$_3$ (Figure 1). It should be noted that the melting points of the enantiomers are higher than that of the racemate by 25 °C.† This uncommon case[3,12] may indicate to a metastable state of the racemate.[3] However, crystallization of (±)-**1** from toluene at an elevated temperature (80–100 °C)

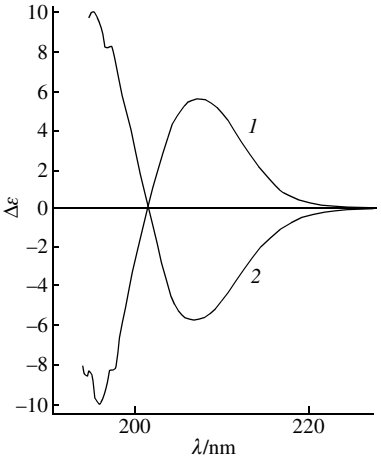


Figure 2 CD spectra (MeOH) of (*1*) (1*S*,5*S*)-(–)-**1** and (*2*) (1*R*,5*R*)-(+)-**1**.

led to lower melting racemic crystals. In order to compare the peculiarities of the crystal structures of enantiomerically pure and racemic **1**, the X-ray investigation of both crystals (grown from Et_2O at 20 °C) was carried out.‡ The geometries of **1** in homo- and heterochiral crystals are similar (Figure 3). The conformations of the five-membered rings are slightly different. Thus, in (–)-**1** both five-membered rings are characterised by the envelope conformation with the deviations of the N(2) and N(4) by 0.11 and 0.13 Å, respectively, while in (±)-**1** the maximum

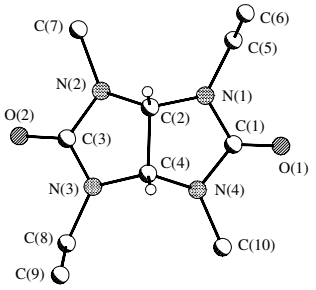


Figure 3 The general view of (–)-**1**.

† The NMR spectra were measured on a Bruker WM-400 spectrometer (400.13 MHz for ^{1}H), optical rotation was measured on a Polamat A polarimeter, and CD spectra were recorded on a JASCO-J500A instrument with a DP-500N data processor.

(±)-**1**, obtained from (±)-**2** by Scheme 1, mp 112–114 °C (Et_2O) (lit.,[4(b)] mp 108–110 °C). ^{1}H NMR (C_6D_6) δ: 0.85 (t, 6H, 2$MeCH_2$, ^3J 7.4 Hz), 2.5 (s, 6H, 2MeN), 3.05 (m, 4H, 2CH_2N, ABX_3 spectrum, $\Delta\nu$ 152 Hz, ^2J –14.8 Hz, ^3J 7.4 Hz), 3.99 (s, 2H, 2HC). When adding the chiral shift reagent in the molar ratio **1**/Eu(tfc)$_3$ = 20 a low-field shift of all the signals and splitting some of the signals of the enantiomers are observed ($\Delta\nu$/Hz), ^{1}H NMR [C_6D_6 + Eu(tfc)$_3$] δ: 0.99, 2.69 (4.4), 3.07, 3.42 (2.8), 4.3 (1.2), upon adding an amount of Eu(tfc)$_3$ the signal of MeN moves to 2.8 ppm ($\Delta\nu$ 23.1 Hz), and the signal of HC, to 4.58 ppm ($\Delta\nu$ 12.7 Hz).

(1*S*,5*S*)-(–)-**2** and (1*R*,5*R*)-(+)-**2**, upon complete crystallization of (±)-**2** from H_2O, a racemic mixture of the well-formed crystals was obtained; two crystals of the opposite optical rotation signs were selected, rubbed to powder and used as seeds for resolution of (±)-**2** by an internal entrainment procedure.[7] Repeated crystallization of the enantiomerically enriched products resulted in preparing enantiomerically pure samples [*cf.* ref. 5(*a*)]. Starting from 5 g of (±)-**1**, 2.3 g of (–)-**2** (91.4%) and 2.1 g of (+)-**2** (84%) were obtained.

(1*S*,5*S*)-(–)-**1**, obtained from (1*S*,5*S*)-(–)-**2**[5(a)] (Scheme 1), yield 96%, mp 137.5–139 °C (Et_2O). ^{1}H NMR spectrum (C_6D_6) is similar to that for (±)-**1**; when adding Eu(tfc)$_3$ gradually until the low-field shift of the signals at 2.74 (MeN) and 4.5 ppm (HC) the splitting was not observed; $[\alpha]^{20}_{578}$ –17.3°, $[\alpha]^{20}_{546}$ –20.9°, $[\alpha]^{20}_{436}$ –40.8°, $[\alpha]^{20}_{406}$ –47.1° (*c* 0.38, MeOH); CD spectrum (*c* 3.76×10^{-3} M MeOH), $\Delta\varepsilon$ (λ/nm): 5.8 (207.5), 0.0 (202), –10.0 (196).

(1*R*,5*R*)-(+)-**1**, obtained from (1*R*,5*R*)-(+)-**2**[5(a)] (Scheme 1), yield 96.5%, mp 137.5–138 °C (Et_2O). ^{1}H NMR spectrum (C_6D_6) is similar to those for (±)-**1**; $[\alpha]^{20}_{578}$ +18.3°, $[\alpha]^{20}_{546}$ +21.0°, $[\alpha]^{20}_{436}$ +39.3°, $[\alpha]^{20}_{406}$ +44.5° (*c* 0.38, H_2O); CD spectrum (*c* 9.3×10^{-3} M MeOH), $\Delta\varepsilon$ (λ/nm): –5.8 (207.5), 0.0 (202), +10.0 (196).

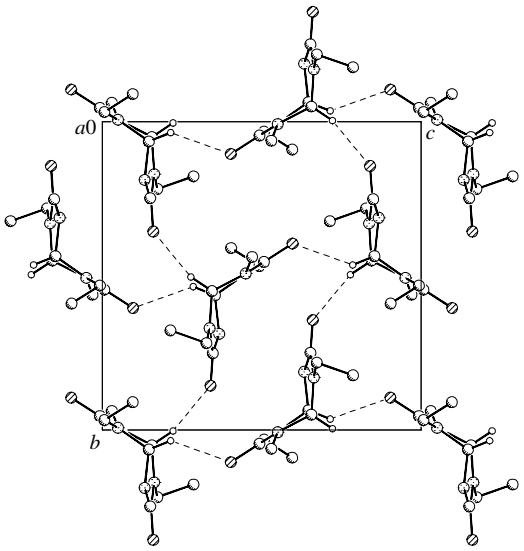


Figure 4 The intermolecular C–H···O contacts in (–)-**1**. The parameters of the C–H···O contacts are: C(2)–H(2)···O(1′) (–*x*, –$^1/_2$ + *y*, $^1/_2$ – *z*) {H(2)···O(1′) 2.43 Å, ∠C(2)H(2)O(1′) 155°, C(2)···O(1′) 3.435(6) Å}; C(4)–H(4)···O(2′) ($^1/_2$ – *x*, –*y*, $^1/_2$ + *z*) {H(4)···O(2′) 2.41 Å, ∠C(4)H(4)O(2′) 141°, C(4)···O(2′) 3.309(6) Å}. C–H distances in (–)-**1** are normalised to the ideal values 1.07 Å.

deviations of atoms from the mean square planes are less than 0.05 Å. The angles between planes in both structures are similar and, in average, equal to 121°.

The comparison of the crystal packings has revealed that in accordance with the greater value of the mp of (–)-**1** its density (1.217 g cm^{-3}) at room temperature is slightly higher than the corresponding value in (±)-**1** (1.188 g cm^{-3}). However, the C–H···O contacts (*cf.* ref. 13), which are observed in both crystals, are shorted in (±)-**1**. In (–)-**1**, the C–H···O contacts of the hydrogen atoms attached to the C(2) and C(4) atoms assemble molecules into a three-dimensional framework and with the C···O distances from 3.309(6) to 3.435(6) Å (Figure 4). While in (±)-**1** the molecules are assembled into layers with hydrophobic coatings (Et groups) parallel to the *bc* crystallographic plane by the C–H···O contacts with the C···O distances varying in a range of 3.214(4)–3.345(4) Å (Figure 5). Taking into account that the C–H···O contacts play a great role in the formation of crystals, the above shortening of the C–H···O contacts can be responsible

‡ *Crystallographic data for* (–)-**1** *and* (±)-**1**: at 295 K, the crystals of $C_{10}H_{18}N_4O_2$ (–)-**1** are orthorhombic, space group $P2_12_12_1$, a = 9.460(3) Å, b = 11.225(4) Å, c = 11.626(4) Å, V = 1234.6(7) Å^3, Z = 4, M = 226.28, d_{calc} = 1.217 g cm^{-3}, μ(MoKα) = 0.87 cm^{-1}, F(000) = 488; (±)-**1** monoclinic, space group $P2_1/c$, a = 10.042(2) Å, b = 11.022(2) Å, c = 11.950(2) Å, β = 106.963(4)°, V = 1265.1(4) Å^3, Z = 4, M = 226.28, d_{calc} = 1.188 g cm^{-3}, μ(MoKα) = 0.85 cm^{-1}, F(000) = 488. Intensities of 6917 and 12096 reflections were measured with a Smart 1000 CCD diffractometer at 295 K [λ(MoKα) = 0.71073 Å, ω-scans with a 0.3° step in ω and 30 and 15 s per frame exposure, $2\theta < 50°$, $2\theta < 60°$ for (–)-**1** and (±)-**1**, respectively], and 2123 and 3627 independent reflections were used in a further refinement. The structures were solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. Due to high libration of the ethyl group C(5)–C(6) in (–)-**1**, it was refined with the constrained bond lengths (C–C of 1.55 Å and N–C of 1.44 Å). Hydrogen atoms were located from the Fourier synthesis and refined using a riding model in (–)-**1** and an isotropic approximation in (±)-**1**. The refinement converged to wR_2 = 0.1218 and GOF = 1.006 for all independent reflections [R_1 = 0.0625 was calculated against F for 799 observed reflections with $I > 2\sigma(I)$] for (–)-**1** and to wR_2 = 0.1101 and GOF = 0.957 for all independent reflections [R_1 = 0.0465 was calculated against F for 1399 observed reflections with $I > 2\sigma(I)$] for (±)-**1**. All calculations were performed using SHELXTL PLUS 5.1 on IBM PC AT. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2002. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/103.

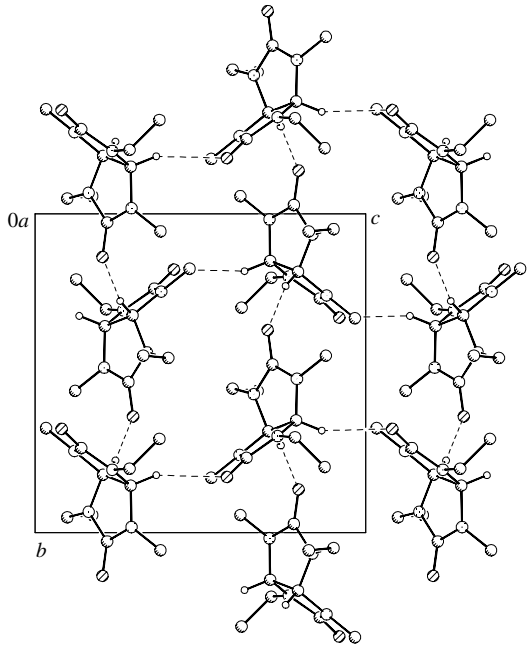


Figure 5 The intermolecular C–H···O contacts in (±)-**1**. The parameters of the C–H···O contacts are C(2)–H(2)···O(1′) (x, $^1/_2 - y$, $-^1/_2 + z$) {H(2)···O(1′) 2.34 Å, ∠C(2)H(2)O(1′) 155°, C(2)···O(1′) 3.3452(4) Å}; C(4)–H(4)···O(2′) ($2 - x$, $-^1/_2 + y$, $^1/_2 - z$) {H(4)···O(2′) 2.17 Å, ∠C(4)H(4)O(2′) 165°, C(4)···O(2′) 3.213(4) Å}. C–H distances in (±)-**1** are normalised to the ideal values 1.07 Å.

in part for the metastable formation of a racemic crystal upon the crystallization of a racemic solution.

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