The chiral drug Albicar: resolution of its racemate *via* complexation with BINOL†‡

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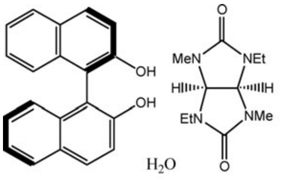
Both enantiomers of the title drug (2,6-diethyl-4,8-dimethylglycoluril; 1) were prepared from their complexes with (*R*)- and (*S*)-BINOL in 59% ((+)-1) and 43% ((−)-1) yield from its racemate. The absolute configuration of (1*R*,5*R*)-(+)-1 was determined by an XRD study of the (*R*)-(+)-BINOL-(+)-1·H_2O complex.

The resolution of chiral drugs is one of the main industrial routes for their production. One of the resolving agents that is gaining increasing importance is BINOL, well-known in asymmetric synthesis as a catalyst.[1] It was found by Toda, co-workers and other researchers, that BINOL forms crystalline hydrogen-bonded diastereomeric complexes with chiral sulfoxides, selenoxides, phosphinates, phosphinoxides, *N*-oxides and phosphonium salts.[2] Recent work has shown the utility of this general method to resolve omeprazol.[3]

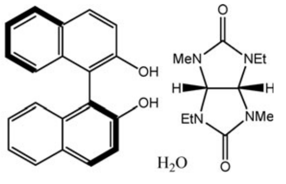
BINOL has also been used in the resolution of the carbonyl compound spiro[4.4]nonane-1,6-dione.[4] However, it has not been used so far to resolve ureas.

Racemic bicyclic bis-urea Albicar (**1**) is an original drug with the properties of a day time tranquillizer and an antidepressant,[5] and its (1*R*,5*R*)-(+)-enantiomer is more active in mice,[6] with an active dose of 75 mg kg^{-1} being two times lower compared to the racemate. Less active achiral prototype Mebicar (**2**) has been produced for a long time by JSC "Olainfarm" (Olaine, Latvia) and sold under the trade name Adaptol®. Previously, **1** was prepared in enantiopure form by the spontaneous resolution of its precursor.[7] Due to the complicated technical implementation of effective spontaneous resolution on a laboratory scale, other efficient methods were needed. Kravchenko *et al.* have developed the enantioseparation of **1** by chromatography on chiral phases.[6,8] However, this method is not cost effective; the reason why we studied the possibility resolving **1** using enantiopure BINOL.

Racemic Albicar, (±)-**1**, was synthesized by the alkylation of its precursor, **3**, with MeI in the presence of NaH in DMF (Scheme 1) in a 70% yield.§ The desired resolution of (±)-**1** was achieved by the formation of diastereomeric complexes **4-R** and **4-S** in an organic solvent in the presence of H_2O (in our case, we used wet ethyl acetate). Thus, (±)-**1** was dissolved in EtOAc and (*R*)-BINOL (99% ee) added to it. Complex **4-R** ((*R*)-BINOL + (1*R*,5*R*)-(+)-**1** + H_2O) immediately started to crystallize, and the mixture was left at 4 °C for a time sufficient to obtain full crystallization of the complex. The mother liquor, **M**, was separated. Thus, the obtained complex, **4-R**, contained (+)-**1** in approximately 90% ee (optical rotation data). It was therefore recrystallized from wet EtOAc to increase the de to >95%. The complex was destroyed by the action of aqueous 15% NaOH, and (+)-**1** was extracted with CH_2Cl_2 in 59% total yield. By the action of HCl on the aqueous layer, (*R*)-BINOL was separated, filtered and recycled. The mother liquor, **M**, was treated in the same way to liberate (−)-**1** in 90% ee, which was purified by the crystallization of **4-S** using (*S*)-BINOL. An alkaline work-up gave (−)-**1** in >95% ee and 43% yield.¶ (+)-**1** and (−)-**1** could also be purified by recrystallization in their uncomplexed form, as the melting point of the enantiomers is >30 °C higher than that of the racemate,[7c] and therefore, outside a certain small eutectic region of the binary phase diagram, mixtures of (+)-**1** and (−)-**1** are optically enriched by recrystallization. The constants of (+)-**1** and (−)-**1** were similar to those previously reported.[7c]



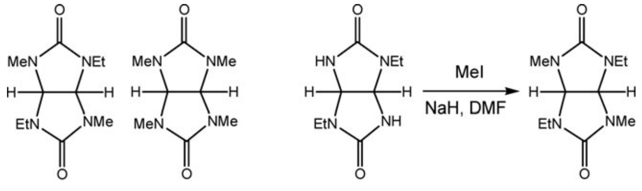
4-R



4-S

Interestingly, in the absence of H_2O (*e.g.* in toluene), no optical resolution occurred; however, the complex between (*R*)-BINOL and (±)-**1** was readily formed.

The crystal structure of complex **4-R** was elucidated by XRD (Fig. 1).‖ Besides the molecules of BINOL and Albicar,



Scheme 1

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‡ CCDC reference number 712625. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b9nj00701f

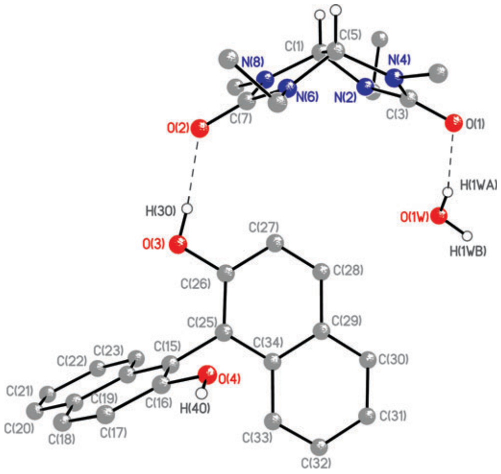

Fig. 1 A general view of **4-R**.

the crystal also contains one molecule of H_2O per unit cell. The absolute configuration of (1*R*,5*R*)-(+)-**1** was deduced from the known absolute configuration of *R*-(+)-BINOL. Previously, the absolute configuration of (1*R*,5*R*)-(+)-**1** was determined by a covalent diastereomeric derivative of its precursor with a chiral auxiliary of known configuration.[7a]

Thus, an efficient method for resolving **1** has been developed. The more active (+)-enantiomer of **1** is now easily accessible on a large scale for biological and clinical studies.

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§ Compound (±)-**1**: (±)-**3** (25.75 g, 0.13 mol) was dissolved in DMF (400 ml) and NaH (60% suspension; 12.6 g, 0.315 mol) carefully added. After stirring for 1 h, MeI (65 ml, 150 g, 1.05 mol) was slowly added, the temperature rising to 80 °C. At this temperature, the mixture was stirred for 3 h. The DMF was then evaporated *in vacuo*, and the residue dissolved in H_2O (100 ml) and extracted with chloroform (4 × 100 ml). The organic phase was dried and evaporated. The residue was recrystallized from EtOAc–Et_2O (1 : 1) to give (±)-**1** (20.5 g, 70%). mp 114–116 °C.

¶ **4-R** (>95% de): mp. 147–162 °C; $[\alpha]^{20}$ (λ) (*c* 1, MeOH): +20 ± 2 (578), +27 ± 2 (546), +108 ± 2 (436) and +196 ± 2 (406).

4-S (>95% de): mp. 145–161 °C; $[\alpha]^{20}$ (λ) (*c* 1, MeOH): −19 ± 2 (578), −26 ± 2 (546), −111 ± 2 (436) and −195 ± 2 (406).

^{1}H NMR of **4-R** (CD_3OD): 1.15 (t, 6H, $2CH_2Me$, ^3J = 7 Hz), 2.89 (s, 6H, 2Me), 3.27, 3.42 (m, 4H, $2CH_2$), 5.15 (s, 2H, 2CH), 7.00 (d, 2H, H_{Ar}, ^3J = 8 Hz), 7.14 (t, 2H, H_{Ar}, ^3J = 8 Hz), 7.23 (t, 2H, H_{Ar}, ^3J = 8 Hz), 7.27 (d, 2H, H_{Ar}, ^3J = 8 Hz), 7.81 (d, 2H, H_{Ar}, ^3J = 8 Hz) and 7.85 (d, 2H, H_{Ar}, ^3J = 8 Hz). ^{13}C NMR: 13.28, 29.9, 37.44, 69.59, 115.44, 118.57, 122.13, 124.55, 125.63, 127.74, 128.19, 128.51, 134.25, 153.03 and 158.14.

‖ X-Ray diffraction analysis at 100 K of crystals of **4-R**: $C_{30}H_{34}N_4O_5$, triclinic, space group *P*1, a = 9.0758(5), b = 9.2281(5), c = 9.3635(5) Å, α = 64.225(1), β = 81.697(1), γ = 70.4350(1)°, V = 665.42(6) Å^3, Z = 1, (Z' = 1), FM = 530.61, d_c = 1.324 g cm^{-3}, μ(Mo-K$_\alpha$) = 0.91 m^{-1}, F(000) = 282. The intensities of 8160 reflections were measured with a Bruker Smart APEX II CCD diffractometer (λ(Mo-K$_\alpha$) = 0.71072 Å, $2\theta < 58°$) and 3554 independent reflections (R_{int} = 0.0193) were used in the further refinement. The structure was solved by direct methods and refined using the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. The hydrogen atoms were located from a Fourier density synthesis. The refinement converged to wR_2 = 0.0864 and GOF = 1.021 for all independent reflections (R_1 = 0.0321 was calculated against F for 3478 observed reflections with $I > 2\sigma(I)$). All calculations were performed using SHELXTL PLUS 5.0.‡

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