Solid-state properties of 1,2-epoxy-3-(2-cyanophenoxy)propane, a conglomerate-forming chiral drug precursor

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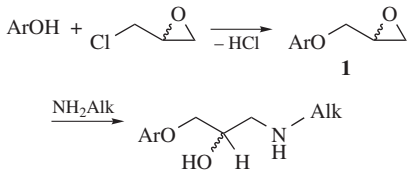
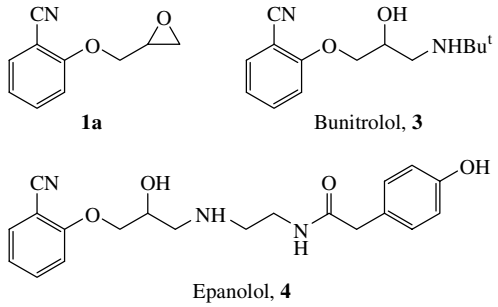
Both enantiomers of 1,2-epoxy-3-(2-cyanophenoxy)propane 1a were obtained and converted into enantiomeric bunitrolol hydrochlorides 3 to confirm the configuration of the formers; racemic 1a undergoes spontaneous resolution upon crystallization and could be resolved into individual enantiomers by a preferential crystallization with low efficiency.

Racemic arylglycidyl ethers **1** are customary intermediates in the industrial production of racemic β-blocker drugs **2** (Scheme 1).



Scheme 1

1,2-Epoxy-3-(2-cyanophenoxy)propane **1a** has an obvious structural similarity with and can be used as an intermediate in the synthesis of β-adrenoblockers bunitrolol **3** and epanolol **4**.[1]



For the family of β-adrenoblockers and for bunitrolol particularly, it has been shown that (*S*)-enantiomers are eutomer components of the racemic drug, whereas (*R*)-enantiomers (distomers) usually display other (often undesirable) activity.[2,3] Therefore, interest in preparative procedures and the properties of scalemic aryl glycidyl ethers as the precursors of single enantiomer drugs is understandable. We have disclosed recently the conglomerate nature of 1,2-epoxy-3-(2-methoxyphenoxy)propane **1b**, another valuable aryl glycidyl ether.[4] Here, we consider the solid-state properties, namely, IR spectra, thermal behaviour, and X-ray structure of epoxide **1a**, as well as some comments on the possibility of spontaneous resolution of racemic **1a**.

Rac-, (*R*)- and (*S*)-**1a** have been prepared uniformly through the reaction of *rac*-, (*S*)- and (*R*)-epichlorohydrin and 2-hydroxybenzonitrile.† Some comments must be done on the configuration ascribing to scalemic **1a** samples. We believe that, in our case, the configuration of resulting epoxides **1a** is predominantly inverted as against the configuration of the starting epichlorohydrine as it has happened to be in a similar reaction with guaiacol.[4] Generally, C(3)-activated 1,2-epoxypropanes do not react with nucleophiles in an unambiguous fashion: alongside the normal attack on the C(3) atom occurs an attack on the C(1) atom with the opening and subsequent closure of the oxirane ring.[7] The first direction is accompanied by conservation of starting material configuration, whereas the other direction leads to an opposite enantiomer as a product, and on the whole the nucleophilic substitution with epichlorohydrine can lead to any stereochemical results.

For (*S*)-**1a**, Nicola *et al.*[6] reported a positive sign for specific rotation in ethanol. Sayyed *et al.*[8] also reported a positive sign for specific rotation for the same enantiomer but in chloroform. We found that epoxide **1a**, as well as *o*-methoxy derivative **1b**, belongs to uncommon compounds changing the sign of rotation with the change of solvent. The sample of (*S*)-**1b** with $[\alpha]_D^{20}$ +13.0 (*c* 0.6, EtOH) manifests $[\alpha]_D^{20}$ –4.9 (*c* 0.6, $CHCl_3$). The sample of **1a** with $[\alpha]_D^{20}$ +18.1 (*c* 1.0, EtOH) simultaneously demonstrates $[\alpha]_D^{20}$ –5.0 (*c* 1.0, $CHCl_3$) or $[\alpha]_D^{20}$ –14.5 (*c* 0.65, CCl_4).

To establish the absolute configuration for **1a**, we transformed both enantiomers of the compound into β-blocker bunitrolol **3** (Scheme 2).‡

Levorotary bunitrolol hydrochloride was obtained from dextrorotary (in ethanol) epoxide, as well as dextrorotary **3**·HCl derives

† Racemic **1a** was prepared from racemic epichlorohydrin and 2-hydroxybenzonitrile by a known procedure,[5] bp 120–122 °C at 0.05 Torr, mp 66–67 °C (colourless needles from diethyl ether) [lit.,[5] mp 65 °C (diethyl ether)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.83 [dd, 1H, C(1)H$_2$, ^2J –4.8 Hz, ^3J 2.7 Hz], 2.92 [dd, 1H, C(1)H$_2$, ^2J –4.8 Hz, ^3J 4.2 Hz], 3.34–3.39 [m, 1H, C(2)H], 4.08 [dd, 1H, C(3)H$_2$, ^2J –11.6 Hz, ^3J 5.4 Hz], 4.37 [dd, 1H, C(3)H$_2$, ^2J –11.6 Hz, ^3J 3.1 Hz], 6.99–7.02 [m, C(4A)H, C(6A)H], 7.44–7.53 [m, C(3A)H, C(5A)H]. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 44.53 [C(1)], 49.89 [C(2)], 69.58 [C(3)], 102.45 [C(2A)], 112.89 [C(6A)], 116.29 [C(4N)], 121.49 [C(4A)], 133.88 [C(3A)], 134.47 [C(5A)], 160.22 [C(1A)].

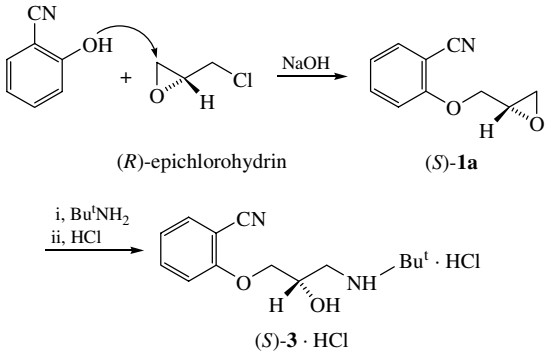
(*R*)-**1a** was obtained from (*S*)-epichlorohydrin {$[\alpha]_D^{20}$ +32.5 (*c* 4.3, MeOH), op 98%; 5.5 g, 0.06 mol} and 2-hydroxybenzonitrile (2.4 g, 0.02 mol) by the same procedure as for the racemic compound.[5] The crude (*R*)-**1a** (3.1 g) was repeatedly crystallised from diethyl ether and a mixture of diethyl ether and methanol to give colourless needles {1.4 g (39%); mp 90–91 °C; $[\alpha]_D^{20}$ –17.5 (*c* 0.8, EtOH), ee 98.0% by d.s.c.} {lit.,[6] $[\alpha]_D^{25}$ –16 (*c* 1, EtOH)}.

(*S*)-**1a** was synthesised analogously from (*R*)-epichlorohydrin. colourless needles; mp 90–91 °C (diethyl ether–methanol), $[\alpha]_D^{20}$ +18.1 (*c* 1.0, EtOH), $[\alpha]_D^{20}$ –5.0 (*c* 1.0, $CHCl_3$), ee 99.92% by d.s.c.; {lit.,[6] mp 88–89 °C, $[\alpha]_D^{25}$ +17.69 (*c* 1, EtOH); lit.,[8] gum, $[\alpha]_D^{25}$ +2.3 (*c* 2.3, $CHCl_3$)}.

The NMR spectra for both enantiomers coincide completely with the spectra for *rac*-**1a**.

‡ *(*R*)-(+)-1-(2-Cyanophenoxy)-3-*tert*-butylaminopropan-2-ol hydrochloride; (*R*)-bunitrolol hydrochloride; (*R*)-**3**·HCl.* (*R*)-**1a** {0.76 g, 4.3 mmol, $[\alpha]_D^{20}$ –17.0 (*c* 0.5, EtOH)} and 4.6 ml (43 mmol) of Bu^tNH_2 were heated under reflux for 5–7 h. The reaction was monitored by TLC. After disappearance of the starting epoxide, the mixture was evaporated to dryness and the residue was dissolved in diethyl ether; dry HCl was passed through the solution until saturation. The solid hydrochloride was filtered off (yield 87%); after two successive crystallizations from EtOH (*R*)-**3**·HCl was isolated in 66% yield, mp 188–191 °C, $[\alpha]_D^{20}$ +29.1 (*c* 0.9, EtOH). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.54 (s, 9H, Me), 3.29 (dd, 1H, CH$_2$N, ^2J –18.5 Hz, ^3J 9.5 Hz), 3.40 (dd, 1H, CH$_2$N, ^2J –18.5 Hz, ^3J 8.6 Hz), 4.25 (dd, 1H, CH$_2$O, ^2J –9.5 Hz, ^3J 5.1 Hz), 4.29 (dd, 1H, CH$_2$O, ^2J –9.5 Hz, ^3J 4.0 Hz), 4.72 (m, 1H, CH), 5.50 (s, 1H, OH), 7.03–7.06 [m, C(4A)H, C(6A)H], 7.53–7.56 [m, C(3A)H, C(5A)H], 8.29 (s, 1H, NH), 9.62 (s, 1H, NH). ^{13}C NMR (150.864 MHz, $CDCl_3$) δ: 25.91 (Me), 45.28 (NCH$_2$), 58.01 (*C*Me$_3$), 65.58 (CHOH), 70.82 (OCH$_2$), 102.36 [C(2A)], 113.04 [C(6A)], 116.27 (CN), 121.50 [C(4A)], 133.43 [C(3A)], 134.50 [C(5A)], 160.14 [C(1A)]. The numbering of atoms in the aromatic part is shown in Figure 3.

(*S*)-**3**·HCl was obtained from (*S*)-**1a** and Bu^tNH_2 following the above procedure; mp 188–191 °C, $[\alpha]_D^{20}$ –29.2 (*c* 0.7, EtOH).



Scheme 2

from levorotary **1a**. For the (+)-**3**·HCl *R* configuration was established unambiguously by the Bijvoet method.§ The revealed correspondence between the sign of optical rotation and the absolute configuration is typical of the family of aryloxypropanolamine β-blockers where (*S*)-isomers both as free base and especially as salts with achiral acids always dispose negative rotation in proton solvents.[9]

Figure 1 shows the IR spectra of both racemic and highly enantiomerically enriched crystalline samples¶ of **1a** in KBr pellets, along with the normalised difference curve between individual spectra. Excepting very minor discrepancies, the spectra are identical. This is a good but not definitive diagnostic for racemic conglomerate formation.

Valuable information on a chiral substance can be obtained by differential scanning calorimetry (d.s.c.). With a knowledge of the temperature and enthalpy of fusion for racemic and enantiopure samples, it is possible to calculate (for enantiomeric

§ *X-ray diffraction data for* (+)-**3**·HCl: $C_{14}H_{21}ClN_2O_2$, $M = 284.78$, orthorhombic, space group $P2_12_12_1$, $a = 8.815(2)$, $b = 12.510(3)$ and $c = 13.750(3)$ Å, $V = 1516.3(6)$ Å^3, $Z = 4$, $d_{calc} = 1.25$ g cm^{-3}; 1773 independent reflections (1501 with $I \geq 2\sigma$); $T = 20$ °C. The final residuals were $R_{(obs)} = 0.046$ and $R_{w(obs)} = 0.113$, $R_{(tot)} = 0.059$ and $R_{w(tot)} = 0.123$, GOF = 1.021. Flack parameter –0.07(3) (absolute structure was established as *R*).

For **1a**: $C_{10}H_9NO_2$, $M = 175.18$, at 20 °C, orthorhombic, space group $P2_12_12_1$, $a = 4.245(1)$, $b = 7.834(2)$ and $c = 26.989(6)$ Å, $V = 897.4(4)$ Å^3, $Z = 4$, $d_{calc} = 1.30$ g cm^{-3}; 1000 independent reflections (825 with $I \geq 2\sigma$). The final residuals were $R_{(obs)} = 0.031$ and $R_{w(obs)} = 0.070$, $R_{(tot)} = 0.049$, and $R_{w(tot)} = 0.077$, GOF = 0.999. Flack parameter –0.1(5) (absolute structure was not established).

Cell parameters and intensities for single or single like crystals were measured on an Enraf-Nonius CAD-4 diffractometer in the $\omega/2\theta$-scan mode, $\theta \leq 74.9°$, using CuKα radiation with a graphite monochromator. Absorption correction was not applied for **1a** and was applied for **3**·HCl [μ(Cu) = 22.3 cm^{-1}]. The structures were solved by a direct method using the SIR[15] program and refined by the full matrix least-squares using the SHELXL97 program.[16] All non-hydrogen atoms were refined anisotropically. The positions of the hydrogen atoms at OH and NH_2 groups were located from difference Fourier maps and refined isotropically, at C atoms were idealised. All calculations were performed on a PC using the WinGX program.[17] Cell parameters, data collection and data reduction were performed on an Alpha Station 200 computer using the MolEN program.[18] The figure was made using the PLATON program.[19]

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference numbers 606995 and 613539 for **1a** and **3**·HCl, respectively. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2006.

¶ The IR spectra of the polycrystalline samples of *rac*-**1a** and (*R*)- or (*S*)-**1a** in KBr pellets were recorded on a Bruker IFS-66v Fourier transform spectrometer. The NMR spectra were recorded on Bruker MSL-400 and Avance-600 spectrometers in $CDCl_3$ with TMS or the solvent as an internal standard. Optical rotations were measured on a Perkin-Elmer model 341 polarimeter (concentration *c* is given as g per 100 ml). Melting points for general purposes were determined using a Boëtius apparatus and are uncorrected.

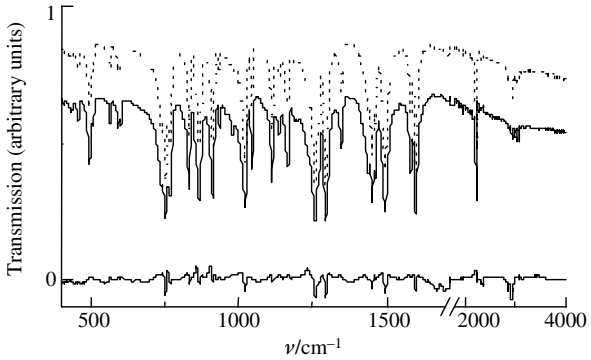


Figure 1 Experimental IR spectra of racemic (solid line) and scalemic (dotted line) 1,2-epoxy-3-(2-cyanophenoxy)propanes **1a** as well as difference curve (beneath).

1a) the entropy of mixing in the liquid state ΔS_l^m and the free energy of formation ΔG^0 of racemic compound in the solid state.[10,11] Table 1 represents experimental†† and calculated thermodynamic parameters for epoxide **1a**. The calculated entropy of mixing is equal to 5.32 J K^{-1} mol^{-1}, which is very close to an ideal value of 5.77 J K^{-1} mol^{-1} (Rln2) for conglomerates. The near-zero value of ΔG^0 points to the same crystallization peculiarity.

From the d.s.c. data for samples of different enantiomeric purity the melting temperature against composition diagram (binary phase diagram) was drawn (Figure 2). Experimental points in Figure 2 form an obvious single eutectic V-shape curve typical of a racemic conglomerate.[10] Figure 2 also presents the theoretical liquidus curve (dashed line) deduced for conglomerate from the simplified Schröder–Van Laar equation $\ln x = (\Delta H_A^f/R)(1/T_A^f - 1/T^f)$. Both experimental and theoretical sets correlate quite well, and the calculated eutectic melting point ($T_{eu} = 64.9$ °C) is very close to the experimental value of T_R^f.

The above evidences that epoxide **1a** crystallises as a conglomerate. Thus, the resolution of the racemic mixture *via* a classical entrainment procedure has been tested.‡‡

Nominally, such a resolution takes place, *i.e.,* the weight of individual (*R*)- or (*S*)-**1a** obtained after two beginning cycles was more than common weight of initial excess of corresponding

Table 1 D.s.c. measured melting point T^f and enthalpy of fusion ΔH^f of racemic (subscript R) and (*S*)-**1a** (subscript A), as well as calculated thermodynamic characteristics of 1,2-epoxy-3-(2-cyanophenoxy)propane.

Parameter	Value
T_A^f/°C	90.5
T_R^f/°C	65.7
ΔH_A^f/J mol^{-1}	27665
ΔH_R^f/J mol^{-1}	25392
ΔG^0/J K^{-1} mol^{-1}	–68
ΔS_l^m/J K^{-1} mol^{-1}	5.32

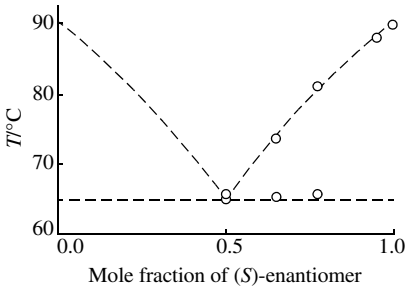


Figure 2 Experimental (circles) and calculated (dashed lines) melting point phase diagram of epoxide **1a**.

†† The melting curves of the samples of 1,2-epoxy-3-(2-cyanophenoxy)-propane were measured on a Setaram DSC-111 differential scanning calorimeter in stainless steel cells with the rate of heating of 1 K min^{-1}. The mass of samples amounted to approximately 2.5 mg. Temperature scale and heat flux were calibrated against the data for α-corundum (sapphire), phenol and naphthalene. Experimental DSC curves were treated according to Gallis *et al.*[12]

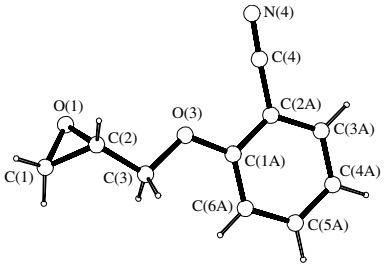


Figure 3 Molecular structure of epoxide **1a** in a crystal.

enantiomer in mother liquor and seed added. But the general degree of resolution is rather low. Furthermore, the investigation of the alterations in mother liquor optical rotation during single enantiomer seed induced crystallization reveals that after sign inversion this value never amounts to absolute magnitude of starting solution. In practice, after the second run, the mother liquor becomes racemic.

The existence of a stable conglomerate is a necessary but insufficient condition for a practical entrainment effect. An obstacle for the efficient resolution is the existence of a metastable racemic compound.[13] Another possible reason for a feebly marked entrainment effect is the lamellar racemic twinning of nascent crystals.[14] We studied the crystals of **1a** by XRD. Diffraction experiments showed that for particularly all tested crystals picked from racemic samples automatic indexation gives unrealistic cell parameters (very high or very low cell volume, large experimental errors of the cell parameters). Only manual selections of registered reflections led to realistic values. This means that the test crystals are epitaxies or random joint of crystals of the individual crystal components, contrary to lamellar twinning with ideal overlapping crystallographic axes of individual components, discussed previously.[14] The absence of the lamellar twinning can be confirmed by visual control of small racemic sample fusion. Whereas druses and large crystals melt near 65 °C, tiny splinters having no contacts with bulk melt fuse at 90 °C, the melting point of enantiopure sample. The last observation implies that when crystal aglomerate grows from the racemate solution its components consist of enantiomerically individual material, though the particle as such can be racemic or near racemic.

The cell parameters of crystals belonged to racemic crop were measured, the useful array of reflection intensities was obtained, and the structure of **1a** was solved and refined. Single crystals picked up from a racemic sample of **1a** belong to the 'chiral' space group $P2_12_12_1$, $Z = 4$. This fact confirms that, in general terms, epoxide **1a** crystallises as a racemic conglomerate. Another experiment was conducted with a single crystal of enantiopure dextrorotary (in ethanol) **1a** in an effort to establish absolute configuration of this compound. It turned out that enantiopure crystals are also joint of crystals or twins, but required reflects can easily be sorted out during the procedure of indexing of the crystal. The general experimental parameters for racemic sample are just worse but similar to parameters for scalemic one. Thus, only the last set was further used.[§] Cell parameters for the crystal of (+)-**1a** are identical to the cell parameters of single crystals picked up from a racemic sample. The molecular structure of **1a** is shown in Figure 3.

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[‡‡] Racemic **1a** (1.32 g) and (*R*)-**1a** {0.14 g, $[\alpha]_D^{20}$ –16.9 (*c* 1.0, EtOH), op 94%} was dissolved in 48 ml of CCl_4 at 40 °C. The solution was cooled to 25 °C and seeded with finely pulverised (*R*)-**1a** {7 mg, $[\alpha]_D^{20}$ –17.5 (*c* 0.8, EtOH)}. After stirring the mixture for 60 min at 24–25 °C, precipitated (*R*)-**1** was collected by filtration {0.21 g after drying; $[\alpha]_D^{20}$ –16.1 (*c* 0.6, EtOH), op 89%}. The extra portion of *rac*-**1a** (0.21 g) was then dissolved in the mother liquor at 40 °C; the resulting solution was cooled to 25 °C. After addition of (*S*)-**1a** {7 mg, $[\alpha]_D^{20}$ +18.1 (*c* 1.0, EtOH)} as seed crystals to the solution, and stirring the mixture for 70 min at 24 °C, (*S*)-**1a** {90 mg after drying; $[\alpha]_D^{20}$ +10.7 (*c* 0.6, EtOH), op 59%} was collected by filtration.

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