Systematic search for conglomerates among glycerol aromatic monoethers: guaifenesin and mephenesin are the cases

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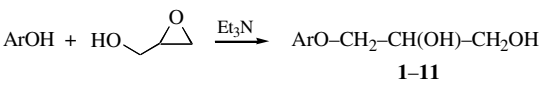
Within the family of biologically active 3-aryloxy-1,2-propanediols, three new conglomerate-forming compounds have been found and resolved into enantiomers using the entrainment procedure.

Louis Pasteur's discovery of spontaneous resolution of Mitscherlich's salt[1,2] has had diverse and far going consequences. The practical use of spontaneous resolution for the efficient production of single enantiomer compounds is an example. Industrial applications of the phenomenon can be illustrated by the Merck process for antihypertensive methyldopa, the Haarmann and Reimer process for *l*-menthol, the Roussel–Uclaf process for chloroamphenicol, and industrial processes for artificial α-amino acids.[3]

However, the potential of spontaneous resolution procedures is restrained by the necessity for a chiral compound subjected to resolution being a conglomerate. It should crystallise as a mechanical mixture of single crystals formed by homochiral molecules. Until now the list of conglomerate-forming chiral substances may number only in hundreds,[4] which is a tiny part of millions of known chemical compounds. The pettiness of this list is a real obstacle for not only fruitful practical use but also theoretical explanations of spontaneous homochiral crystallization. Thus, a search for conglomerates among relatively simple molecules is of practical importance.

During our investigations of synthetic approaches to nonracemic β-adrenoblockers of 3-aryloxy-1-alkylaminopropan-2-ol family,[5] we have obtained a representative set of 3-aryloxypropane-1,2-diols **1**–**11** through the interaction of phenols and glycidol (Scheme 1).



1–11

1 Ar = 2-MeC_6H_4
2 Ar = 2-$MeOC_6H_4$
3 Ar = 2-ClC_6H_4
4 Ar = 1-Naphthyl
5 Ar = Ph
6 Ar = 3-ClC_6H_4
7 Ar = 2-Allyl-C_6H_4
8 Ar = 4-ClC_6H_4
9 Ar = 4-$MeOC_6H_4$
10 Ar = 3-MeC_6H_4
11 Ar = 4-MeC_6H_4

Scheme 1

Dealing with scalemic glycidol of modest enantiomeric purity, we usually have received scalemic aryloxydiols of the same quality. However, in all cases, simple recrystallization was sufficient for producing samples of high optical purity.† This behaviour implies that a zone of racemate formation on the ternary solubility phase diagram (and on the binary melting phase diagram) is relatively narrow for the whole family, and it may be altered to zero width for conglomerate-forming representatives.

On the binary melting phase diagram of a conglomerate-forming chiral substance, the only low-melting eutectic consisting of equal amounts of opposite enantiomers lies between higher fusion temperature regions restricted by mirror-like liquidus curves started from pure enantiomers.[4] Therefore, a necessary (yet not only) attribute for this type of crystallization is the higher melting point for scalemic samples than for racemic ones. Table 1 presents a comparison of fusion temperatures for the pairs of scalemic and racemic polycrystalline samples of diols **1**–**11** and the difference $\Delta T^{f}_{s\text{-}r} = T^{f}_{scal} - T^{f}_{rac}$ for each pair. For 8 from the 11 test compounds, $\Delta T^{f}_{s\text{-}r}$ was positive, and for entries **1**–**6** this value was sufficiently high to suspect conglomerate formation.

Table 1 Fusion temperatures and IR spectra of scalemic and racemic 3-aryloxypropane-1,2-diols $ArOCH_2CH(OH)CH_2OH$ **1**–**11**.

No.	T^{f}_{scal}/°C[a]	T^{f}_{rac}/°C	$\Delta T_{s\text{-}r}$/°C	IR spectra[b] of *scal*- *vs.* *rac*-diol
1	91–92	69–70	22	Identical
2	99	79	20	Identical
3	91–92	71–72	20	Similar
4	111–112	99–100	12	Different
5	62–64	51–53	11	Different
6	74–76	64–66	10	Different
7	47–49	43–44	5	Different
8	83	80	3	Different
9	79–80	80–81	–1	Different
10	60–62	67–69	–7	Different
11	64–65	73–74	–9	Different

[a]The enantiomeric purities of scalemic samples are characterised in footnote.† [b]Polycrystalline samples in KBr pellets.

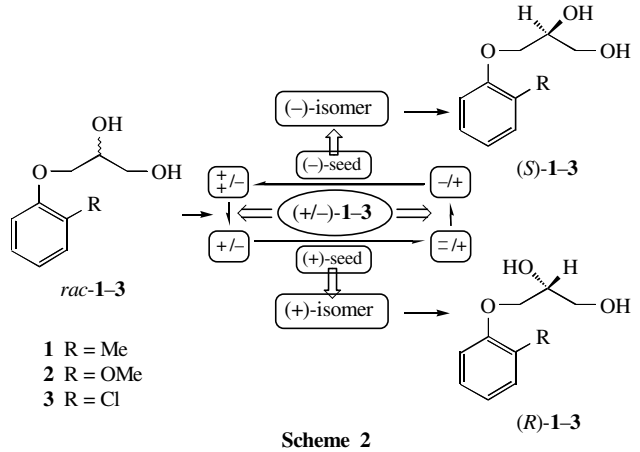
The identity of IR spectra for the pairs of racemic and scalemic polycrystal samples of chiral substances is another diagnostic for conglomerate. We have also done this test, and the results are presented in Table 1. For the upper three members of the column, the IR spectra are identical or closely similar within each pair. The X-ray studies of single crystals picked up from racemic samples of *o*-substituted phenyloxy compounds **1**–**3** have revealed that they all belong to 'chiral' space groups $P2_1$, $P2_12_12_1$ and $P2_12_12_1$, respectively. This can be considered as evidence for the conglomerate nature of solid diols **1**–**3**.

Aromatic monoethers of glycerol (as well as their carbamates) form a family of highly biologically active compounds. Among their number *o*-tolyloxy- and *o*-methoxyphenyloxy-derivatives **1** and **2** are the registered drugs known under the nonproprietary names mephenesin and guaifenesin. In this family, one enantiomer is more active *in vivo* than the other or a racemate.[6] Because of their importance for medicinal chemistry, 3-aryloxypropane-1,2-diols have received much attention from the synthetic standpoint. Among many approaches to single enantiomer glycerol ethers, one can find the 'Chiral Pool' based synthesis,[7] catalytic enantioselective synthesis, especially Sharpless asymmetric dihydroxylation of aryl allyl ethers,[8] biotransformations through the aid of living micro-organisms[9] and the kinetic resolution of racemic derivatives (esters) with the use of natural enzymes.[10]

The crystallization of a chiral substance as a racemic conglomerate makes it possible to resolve it into enantiomers without resort to enantiopure chiral reagents and/or auxiliaries. This problem can be solved, for example, using resolution by the entrainment technique,[4,11] which takes its roots in an early work

† (*R*)-**1**: $[\alpha]_D^{20}$ +19.3 [*c* 1.15, hexane–Pr^iOH (4:1)], lit.,[10] $[\alpha]_D^{20}$ +19.8 [*c* 0.9, hexane–Pr^iOH (4:1), *ee* > 99%]; (*S*)-**2**: $[\alpha]_D^{20}$ +9.4 (*c* 1.0, MeOH), lit.,[13] for (*R*)-**2**: $[\alpha]_D^{20}$ –9.4 (*c* 1.0, MeOH, *ee* 99.4%); (*S*)-**3**: $[\alpha]_D^{20}$ –13.3 [*c* 1.0, hexane–EtOH (4:1)], lit.,[10] $[\alpha]_D^{20}$ –13.4 [*c* 0.9, hexane–EtOH (4:1), *ee* 99%]; (*S*)-**4**: $[\alpha]_D^{20}$ +7.5 (*c* 1.0, MeOH), lit.,[14] $[\alpha]_D^{20}$ +7.6 (*c* 1.0, MeOH); (*S*)-**5**: $[\alpha]_D^{20}$ +9.1 (*c* 1.7, EtOH), lit.,[10] $[\alpha]_D^{20}$ +10.2 (*c* 1.0, EtOH, *ee* 91%); (*S*)-**6**: $[\alpha]_D^{20}$ +11.2 (*c* 1.0, EtOH), lit.,[10] $[\alpha]_D^{20}$ +13.7 (*c* 1.0, EtOH, *ee* 98%); (*S*)-**7**: $[\alpha]_D^{20}$ –2.1 (*c* 2.8, EtOH); (*S*)-**8**: $[\alpha]_D^{20}$ +9.9 (*c* 1.1, MeOH), lit.,[13] for (*R*)-**8**: $[\alpha]_D^{20}$ –10.2 (*c* 1.0, MeOH, *ee* 99.4%); (*S*)-**9**: $[\alpha]_D^{20}$ +7.3 (*c* 1.3, EtOH), lit.,[10] $[\alpha]_D^{20}$ +7.9 (*c* 1.0, EtOH, *ee* 96%); (*S*)-**10**: $[\alpha]_D^{20}$ +8.1 (*c* 0.84, EtOH), lit.,[10] $[\alpha]_D^{20}$ +9.5 (*c* 1.0, EtOH, *ee* 97%); (*R*)-**11**: $[\alpha]_D^{20}$ –8.4 (*c* 1.0, EtOH), lit.,[10] $[\alpha]_D^{20}$ –9.2 (*c* 1.0, EtOH, *ee* 97%).

of Pasteur's student Gernez.[12] Using the procedure, one should seed the oversaturated solution of a racemic or slightly scalemic substrate with the appropriate single enantiomer seed. After a time, the crop of a scalemic product having the configuration of the seed substance is filtered off. Next, the racemic substrate is dissolved in the mother liquor to compensate the removed crystals, and the oversaturated solution of a slightly scalemic substrate is seeded with the single enantiomer seed having an opposite configuration to obtain the new crop of nonracemic crystals of another enantiomer. Theoretically, one can obtain any desirable quantity of both enantiomers with minimal losses and waste products using the above cyclic procedure (Scheme 2).



Scheme 2

We have found that mephenesin, guaifenesin and *o*-chlorophenyl derivative **3** are really capable of spontaneous resolution upon crystallization. Table 2 gives an example of successful resolution by the entrainment of mephenesin **1**. Immediately in the course of spontaneous resolution, only a moderate degree of optical purity can be reached. But the sample of high optical purity can be obtained after single recrystallization of the one-cycle or overall crop of crystals formed by molecules of the same configurations. Similar results have been obtained for guaifenesin **2** and chloro derivative **3**.

Table 2 Resolution by the entrainment of *rac*-mephenesin **1** (165 ml of H_2O; crystallization temperature of 33 °C).

Entry	Additional *rac*-**1**/g	Additional (*R*)-**1**/g	Seed/g	Resolution time/min	(*R*)-**1**		(*S*)-**1**	
					Yield/g	*op* (%)	Yield/g	*op* (%)
1	4.50	0.50	(*R*), 0.025	60	0.86	87.7		
2	0.86		(*S*), 0.025	40			0.82	86.1
3	0.82		(*R*), 0.025	60	0.90	87.3		
4	0.90		(*S*), 0.025	40			0.92	86.3
5	0.92		(*R*), 0.025	50	1.10	80.9		
6	1.10		(S), 0.025	30			0.88	86.1
Overall	9.10	0.50	(*R*), 0.075 (*S*), 0.075		2.86	84.9	2.62	86.2

We hope that our finding will be useful for the large-scale production of this pharmaceutically active single enantiomer substances.

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