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OPTICAL RESOLUTION OF (±)-*N*-ACYLNORFENFLURAMINE DERIVATIVES BY PREFERENTIAL CRYSTALLIZATION

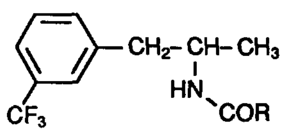
Gérard COQUEREL[§], Roger BOUAZIZ[§], and Marie-Josèphe BRIENNE[‡*]
[§]Chimie Minérale et Structurale, Faculté des Sciences, Université de Rouen, BP 118, 76134 Mont Saint Aignan Cedex, [‡]Chimie des Interactions Moléculaires, ER CNRS 285, Collège de France, 75005 Paris, France.

Three stable and one unstable conglomerates (i. e. eutectic mixtures of D and L crystals) were found among nine synthesized (±)-N-acylnorfenfluramine derivatives. Optical resolution of the stable conglomerates could be achieved by preferential crystallization method only under nonisothermal conditions.

We previously reported[1] that (±)-norfenfluramine [i.e. 1-(3-trifluoromethylphenyl)-2-aminopropane] can be resolved by preferential crystallization of appropriate salts. This method which does not require any auxiliary agent is restricted to racemates existing as conglomerates, i. e. as an eutectic mixture of D and L crystals.[2] The present Note describes some preliminary results concerning the resolution of (±)-*N*-acyl derivatives of norfenfluramine by the same method.

Nine pairs of (±)- and (*R*)-amides were prepared by standard procedures.[3] Four (±)-amides (**1** - **4**, Table 1)[4] were found to be conglomerates, for at least one crystalline form.[5]

Table 1. Physical properties of (*R*)-amides, and of the corresponding conglomerates.[6]

	cpd	R	(±) : mp (ΔH^f)a)	(*R*) : mp (ΔH^f)a)	$[\alpha]_D^{20}$b)
	1	2,4-Cl_2-C_6H_3	108 (30.4)	137.5 (34.9)	+37.9°
	2	*p*-Cl-C_6H_4	118; 120 (33.6)	140; 144 (37.3)	+81.6°
	3	Me_2CH	83.5 (25.5)	111.5 (28.6)	-15.4°
	4	Cl_2CH	65c) (25.1); 79.5d) (28.7)	90 (27.6); 97.5 (24.9)	-11.6°

a) mp/°C and ΔH^f/kJ mol^{-1}. b) EtOH, c = 1. c) Unstable conglomerate. d) Stable racemic compound.

Optical resolution could be achieved in three cases (Table 2).[7] Under usual conditions[2] (isothermal crystallization of a supersaturated solution) the resolution failed primarily due to unfavorable solubility ratios α of the racemate and enantiomer.[8] The degree of supersaturation of the undesired enantiomer rapidly increased during the crystallization of the other and nucleation of the undesired enantiomer could not be avoided. We found that in such unfavorable situations satisfactory results can be obtained under *nonisothermal* conditions. The solutions were seeded when just saturated then gradually cooled while crystallization took place.[9] This technique allows to maintain a degree of supersaturation low enough to prevent the spontaneous crystallization of the nonseeded enantiomer but sufficient to ensure the growth of the seeds of the other enantiomer.

Only single runs were performed to test the feasibility of the method. The efficiency of the resolution is expressed by the Resolution Index (RI)[1] which must be greater than 2 for the alternate crystallization of each enantiomer to be carried out. From this practical point of view, (±)-**2** is the most suitable substrate for this

Table 2. Optical resolution by preferential crystallization.

	operating conditions								amide obtained		
cpd	solv[a)]	T_i-T_f/[b)]	C_i/[c)]	σ[d)]	amide amount/mg			time/[e)]	W/[f)]	op/[g)]	RI[h)]
		°C	g%		Rac	E	seeds	min	mg	%	
1	A	19.8-14.2	12.5	1.31	2411	114	5	3.6	221	85	1.6
2	A	18.2-13.5	12.0	1.40	2292	121	4	5.8	323	87	2.3
3	B	16.5-13.5	15.0	1.29	2933	138	4	3.5	281	88	1.8

a) Solvent: A = EtOH, B = isoamyl acetate. b) Temperature range for the crystallization : at T_i seeds were added and at T_f crystals were collected by filtration. c) Initial concentration in g of solute per 100 g of solution. d) Degree of supersaturation = C_i / racemate solubility at 13 °C. e) Effective duration of the crystallization. f) Weight. g) Optical purity. h) Resolution Index = (W × op - seeds) / E.

process. The RI values are comparable to those previously observed for norfenfluramine salts.[1] The allowable supersaturations σ, however, are considerably lower resulting in lower global yields. Nevertheless, since optical resolution by preferential crystallization is inherently less easy for covalent compounds than for salts[8], the simple solution presented above may be of general utility when conventional conditions fail.

References and Notes

1. G. Coquerel, R. Bouaziz, and M.-J. Brienne, *Chem. Letters*, 1988, 1081.

2. J. Jacques, A. Collet, and S. Wilen "*Enantiomers, Racemates, and Resolutions*", J. Wiley, New York, 1981; A. Collet, M.-J. Brienne, and J. Jacques, *Chem. Rev.*, 1980, **80**, 215.

3. Condensation of the appropriate acid chlorides or anhydrides and amines were effected at room temperature either in aqueous NaOH (Schotten-Baumann conditions) or in pyridine.

4. Other crystalline amides prepared : R = H, Me, $ClCH_2$, Ph, o-NO_2-C_6H_4.

5. Identification of a conglomerate was based on the following criteria: a. the identity of the IR spectra of the racemate and enantiomers in the solid state (Nujol mull), b. the agreement (within 1°C) between the mp of the racemate and the mp calculated for a conglomerate by using Schröder-Van Laar equation (see ref. 2).

6. Melting points and enthalpies of fusion (ΔH^f) were measured by microcalorimetry on a Perkin-Elmer DSC2 instrument connected to a HP86 calculator for data acquisition and processing. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

7. Attempts to resolve (±)-**4** have failed. At room temperature or above, the stable crystalline modification is the racemic compound.

8. α = racemate solubility / enantiomer solubility, expressed in mole fraction. The resolution is the easier as the ratio α is low. In theory, $\alpha = 2$ for covalent compounds and $1.4 < \alpha < 2$ for dissociable compounds (see ref. 2). Ratios α for **1** - **3** are respectively 2.21, 2.10 and 2.15 (measured in solvents of Table 2).

9. Typical procedure : a mixture of (±)-**2** (2.292 g) and (+)-**2** (0.121 g) was dissolved in EtOH (17.7 g) at 23 °C then cooled at the following rate : (T/°C-t/min) = (23-0), (19-1), (16.5-2), (15-3), (14.5-4), (13.75-6), (13-11). The supersaturated solution was magnetically stirred and seeded 1.25 min (18.2 °C) after the beginning of the cooling by finely ground (+)-**2** (4 mg). The precipitated crystals were collected at t = 7 min (13.5 °C). The weight of the dried crystals was 0.323 g (op 87%).

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