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Optical Resolution of $(\pm)$-Fenfluramine and $(\pm)$-Norfenfluramine by Preferential Crystallization

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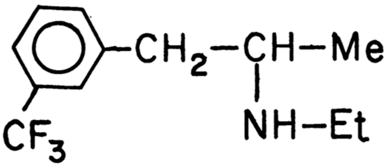
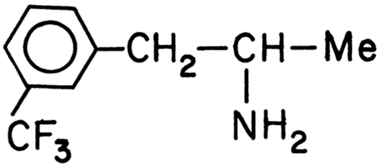
Five salts of $(\pm)$-fenfluramine (**F**) and three salts of $(\pm)$-norfenfluramine (**N**) have been identified as being conglomerates. Six of these salts could be resolved by preferential crystallization.

Fenfluramine (**F**) is useful as an anorectic drug, the activity being predominantly due to the S-(+) enantiomer.[1-3] The racemate can be resolved by recrystallization of diastereomeric salts of d-camphoric acid according to a british patent.[4] In order to set up a more economic process, we investigated an alternative resolution of this compound by the preferential crystallization method (also called resolution by entrainment) which does not require any auxiliary chiral agent. This method, however, is restricted to racemates existing as conglomerates, i.e. as an eutectic mixture of D and L crystals.[5]



F = fenfluramine



N = norfenfluramine

This paper describes several salts of fenfluramine (**F**) and of norfenfluramine (**N**), its synthetic precursor, that are conglomerates. Some preliminary results concerning their resolution by preferential crystallization are also reported.

Racemic and optically active amines **F** and **N** were combined with a large variety of achiral acids (about fifty inorganic or organic acids) to give crystalline salts. Identification of a conglomerate was based on the following criteria: 1. the identity of the IR spectra of the racemic and enantiomeric salts in the solid state (Nujol mull), 2. the agreement (within 1°C) between the melting point of the racemate and the melting point calculated for a conglomerate by using Schröder-Van Laar equation.[5,6]

Among the hundred racemic salts examined, five **F** salts and three **N** salts were identified as being conglomerates. Relevant physical properties are given in Table 1.[7,8] Enantiomers **F1** and **F5** are dimorphous, each form (α or β) giving a conglomerate. In both cases the stable form at room temperature has the lowest melting point. This fact suggests that the solid-solid transitions occur above room temperature. (±)-**F2** crystallizes as an unstable racemic compound and as a stable conglomerate at room temperature. The situation is reversed for (±)-**F4** which gives an unstable conglomerate and a stable racemic compound. The racemate and the enantiomers **F3** decompose on melting.

Table 1. Physical properties of (R)-**F1**-**F5** and (R)-**N1**-**N3**, and of the corresponding conglomerates

		Racemate		Enantiomer			
salt	acid	mp/ °C	ΔH^f/ kJ mol^{-1}	mp/ °C	ΔH^f/ kJ mol^{-1}	$[\alpha]_D^{20}$	solvent
F1	p-Cl-C_6H_4-CH_2-CO_2H	93 (α)	42.1	110 (α) 116 (β)	46.0 43.8	+4.4°	acetone
F2	p-NO_2-C_6H_4-CH_2-CO_2H	103	43.1	122	47.5	+3.7°	acetone
F3	Ph_3C-CO_2H	181 dec	-	196 dec	-	-4.1°	THF
F4	PhO-CH_2-CO_2H	79-81[a)] 93[b)]	29.3 28.1	101	36.4	+8.2°	ether
F5	Ph-CH_2-CH_2-CO_2H	60-62 (β)	34.0	78 (β) 85 (α)	40.4 37.2	+5.1°	acetone
N1	Ph-CH_2-CH_2-CO_2H	65	31.0	85	37.2	-39.1°	acetone
N2	Cl_2CH-CO_2H	117	39.1	138.5	41.3	+48.3°	ethanol
N3	Me-SO_3H	109	22.8	145	25.6	-8.2°	acetone

a) Unstable conglomerate. b) Stable racemic compound, crystallographic parameters : a = 15.34 Å, b = 30.04 Å, c = 8.76 Å, space group Pbca.

Optical resolution by preferential crystallization could be achieved in six cases (Table 2). Only single runs were performed to test the feasibility of the method and experimental conditions were not optimized.[9)] The efficiency of the process was expressed by a Resolution Index (RI) defined by the ratio of the amount of pure enantiomer obtained to the initial excess of this enantiomer. RI = 1 means that exactly the initial excess of the enantiomer crystallized, and hence that the entrainment of the seeded enantiomer did not occur. RI should be greater than 2 for the alternate crystallization of each enantiomer to be carried out efficiently. Clearly this condition could be readily secured for salts **F1** and **F2** and could probably be attained for the other salts in Table 2 with appropriate adjustments of the conditions. Survey has been made earlier of the factors that control the crystallization rate.5) The choice of the correct initial composition (i.e. the degree of supersaturation σ and the initial excess E of enantiomer) is of great importance to ensure a relatively rapid growth of the seeded enantiomer and to minimize the spontaneous crystallization of the other. In view of the relatively high supersaturation levels used in this study, an increase in the RI value and in the optical purity of the crystals are most likely to be achieved by simply decreasing the supersaturation and by adjusting the stirring rate. For large-scale production, one ought also to consider other variables such as nature of the solvent, crystallization temperature and so on.

Table 2. Optical resolution by preferential crystallization

	operating conditions								salt obtained		
salt	solva)	T/ °C	C_i/b) g%	σc)	salt amount/mg Rac	E	seeds	time/ min	W/d) mg	ope) %	RIf)
F1	A	13	8	4.2	1654	106	7	65	270	84	2.1
F2	B	13	8	4.7	1301	83	10	35	325	75	2.8
F3	C	13	12	1.85	3393	217	5	10	435	83	1.6
F5	D	13	18	1.94	3605	190	6	235	400	71	1.5
N1	A	10	14	3.93	2171	139	6	250	361	70	1.8
N3	A	12	8	4.0	2120	88	4	17	182	82	1.7

a) Solvent: A = acetonitrile, B = azeotrope mixture of 1-propanol and cyclohexane, C = THF, D = diisopropylether. b) Initial concentration in g of solute per 100 g of solution. c) Degree of supersaturation = C_i / racemate solubility. d) Weight. e) Optical purity. f) Resolution Index = (W x op - seeds) / E.

Only two salts, **F4** and **N2**, could not be resolved by this technique. This failure is not surprising in the former case because of the existence of a stable racemic compound at the crystallization temperature. The behavior of **N2** is more unusual. Evidence was found that growth of a single crystal of an enantiomer is strongly perturbed in the presence of the racemic solution. Some crystal faces act as seeds for the other enantiomer which grows onto these faces to eventually provide composite crystals of very low optical purity.10)

The resolution of fenfluramine reported here may constitute an alternative to the classical diastereomer method. The above preliminary results suggest that salts **F1** and **F2** are the most suitable substrates for an industrial development.

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7) 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 micropolarimeter at concentrations = 1%.
8) Crystallographic parameters of the enantiomers (single crystal). Are given successively salt number, a/Å, b/Å, c/Å, β°, space group : **F1**, 14.25, 18.0, 8.60, 90, $P2_12_12_1$ or $P2_12_12$; **F2**, 13.90, 17.80, 8.40, 90, $P2_12_12_1$ or $P2_12_12$; **F3**, 15.052, 8.872, 11.298, 111.33, $P2_1$; **F4**, 19.33, 12.53, 8.54, 90, $P2_12_12_1$ or $P2_12_12$; **F5**(β), 16.36, 8.40, 16.36, 90, $P4$ or $P4_2$; **N1**, 24.50, 13.04, 6.02, 90, $P2_12_12_1$ or $P2_12_12$; **N2**, 13.359, 6.81, 8.447, 107.55, $P2_1$; **N3**, 7.50, 18.10, 44.10, 93.3, $P2_1$.
9) A typical procedure is as follows : a mixture of (±)-**F1** (1.653 g) and (+)-**F1** (0.106 g) was dissolved in acetonitrile (20.22 g) at 50 °C then cooled to 13 °C (15 min). The supersaturated solution was seeded with (+)-**F1** (7 mg, finely ground) and magnetically stirred for 65 min. The precipitated crystals were collected by filtration and were not washed. The weight of the dried crystals was 0.270 g, op 84%.
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