Resolution of 1-Trifluoromethylethanol. Part II[1]

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The diastereoisomeric quinine salts of (±)-β-(1-trifluoromethylethoxy)propionic acid, deposited from aqueous solvents as monohydrates, were separated by crystallisation to yield, by methods already described,[1] (−)-1-trifluoromethylethanol, $[\alpha]_D^{25}$ −5·65°.

Part I of this study[1] described the resolution of (±)-1-trifluoromethylethanol by way of the quinine salt of its adduct with acrylic acid, (±)-β-(1-trifluoromethylethoxy)propionic acid. The active alkoxy-acid yielded (−)-1-trifluoromethylethanol, $[\alpha]_D^{25}$ −2·6°. It has since been calculated by Feigl and Mosher[2] from the results of gas chromatographic separation of the diastereoisomeric (−)-*O*-methylmandelic esters of partially active 1-trifluoromethylethanol that the fully active alcohol should have $[\alpha]_D^{27}$ 5·6°.

In further examination of the resolution by way of the alkoxy-acid, it appeared that, since heating the alkaline solution of the active acid for one day under reflux before distilling out the 1-trifluoromethylethanol yielded alcohol of the same rotatory power as that produced under normal conditions,[1] the low activity of the alcohol was not due to racemisation during its formation, but was probably the result of ultimate deposition of solid solutions of the quinine salt isomers in the resolution of the alkoxy-acid. Other active bases commonly used in resolution gave salts with the alkoxy-acid which were deposited as oils from their solutions, but the quinine salt could be crystallised from water, or, better, 20% aqueous n-propanol, as a monohydrate. Repeated crystallisation of this gave a product from which was recovered, by the methods previously described,[1] (−)-1-trifluoromethylethanol, $[\alpha]_D^{25}$ −5·65°. The melting point of the quinine salt was an insufficiently sensitive guide to the degree of resolution of the alkoxy-acid, and the optical purity of the 1-trifluoromethylethanol was controlled by Feigl and Mosher's method,[2] which indicated that the active alcohol still contained about 1% of the (+)-enantiomer, and that the fully active material would have $[\alpha]_D^{25}$ 5·8°.

The lengthy nature of the Feigl–Mosher method for control inspired unsuccessful attempts to simplify enantiomer analysis of the alkoxy-acid or alcohol. For example, Pirkle's[3] fluorine magnetic resonance analysis with this alcohol dissolved in active 1-phenylethylamine, at frequencies of 56 and 94 Mc./sec., indicated that any difference between the chemical shifts of the enantiomers was less than 0·5 c./sec. Also, the 60 Mc./sec. proton magnetic resonance spectrum of the hydrated quinine salt of the alkoxy-acid dissolved in deuteriochloroform showed only one doublet, assigned to *C*-methyl, irrespective of the degree of resolution of the acid (the salt contains one such methyl- in the alkoxy-group next to the asymmetric carbon atom).

The optical rotatory power of homogeneous (−)-1-trifluoromethylethanol has been measured over the range 600—220 mμ, and that of its 10% solution in isopropyl chloride over the range 600—230 mμ. The plots of $1/\alpha$ against λ^2 were linear, and the dispersion ratios $\alpha_{436}/\alpha_{546}$ 1·65 and 1·69, respectively. Single term Drude equations employing constants derived in each case from terminal data gave dispersion constants from which were derived wave-lengths of maximum rotation of 169 and 174 mμ. These rotatory dispersion properties are similar to those of the saturated unsubstituted aliphatic alcohols.[4]

EXPERIMENTAL

Resolution of 1-*Trifluoromethylethanol.*—A mixture of 1 mole of each of (±)-(1-trifluoromethylethoxy)propionic acid (186 g.) and anhydrous quinine (324 g.) was stirred with boiling 20% (v/v) aqueous n-propanol (7 l.), the solution was cooled in water to 50—60°, and crystallisation was induced by scratching or seeding. The crop of quinine salt was allowed to develop slowly, with natural cooling, to avoid deposition of oil. The filtered salt, m. p. 150° (dehydration *ca.* 100°), was recrystallised six times. The sixth and seventh crops melted at 159°. The air-dried seventh crop, plus a further 26 g. of salt obtained by systematic processing of the mother-liquors, weighed 164 g. (62%) (Found: N, 5·4; H_2O loss in vacuo at 100°, 3·5. Calc. for $C_{26}H_{33}F_3N_2O_5,H_2O$: N, 5·3; H_2O, 3·4%). This quinine salt (135 g.), converted into (±)-β-(1-trifluoromethylethoxy)propionic acid by the procedure already given,[1] yielded 43 g. (90%) of acid, b. p. 114°/12 mm. (corr.), d_4^{25} 1·2705, n_D^{25} 1·3724, $[\alpha]_D^{25}$ +3·56° (Found: Equiv., 187. Calc. for $C_6H_9F_3O_3$: Equiv., 186·1). The methyl ester, b. p. 64·4°/14 mm. (corr.), had $[\alpha]_D^{25}$ +3·40°. Alkaline fission[1] of the acid yielded (−)-1-trifluoromethylethanol, d_4^{25} 1·264, n_D^{25} 1·3137, $[\alpha]_D^{25}$ −5·36°.

For further resolution, the above alkoxy-acid (16 g.) and quinine (30 g., 1 mol.) were dissolved in boiling 20% aqueous n-propanol (650 ml.), and the crop of salt was recrystallised twice. The air-dried product (35 g.), m. p. 159°, was converted into the alkoxy-acid, and the latter was freed from ether and almost neutralised with 2N-sodium hydroxide. The solution was boiled to remove the last of the solvent, over-neutralised to the usual extent, and 1-trifluoromethylethanol was distilled out. The purified alcohol, b. p. 77·8—77·9°/761 mm. (corr.), had d_4^{25} 1·263, n_D^{25} 1·3140, α_D^{25} (1 dm.) −7·14°, $[\alpha]_D^{25}$ −5·65°.

(−)-O-*Methylmandelic Esters.*— The (−)-*O*-methylmandelic acid used had $[\alpha]_D^{20}$ −150° (*c* 0·5, ethanol) and, from Neilson and Peters' data,[5] contained *ca.* 0·3% of (+)-isomer. The acid (1 mol.) was set aside overnight with

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[1] Part I, J. W. C. Crawford, *J. Chem. Soc.*, 1965, 4280.
[2] D. M. Feigl and H. S. Mosher, *Chem. Comm.*, 1965, 615.
[3] W. H. Pirkle, *J. Amer. Chem. Soc.*, 1966, **88**, 1837.
[4] T. M. Lowry, 'Optical Rotatory Power,' Longmans Green and Co., London, 1935, p. 123.
[5] D. G. Neilson, D. A. V. Peters, *J. Chem. Soc.*, 1962, 1519.

thionyl chloride (10 mol.); excess of the latter was removed *in vacuo* and the remainder was evaporated off twice *in vacuo* with benzene. The residual methylmandelyl chloride was mixed with 1-trifluoromethylethanol (0·5 mol.), pyridine (6·5 mol.), and benzene (6·5 mol.), and the mixture was set aside for 3 hr. at room temperature. It was worked-up for ester, which was short-path distilled (bath *ca.* 60°, pressure 0·25 mm.) (Found: OMe, 11·6. Calc. for $C_{12}H_{13}F_3O_3$: OMe, 11·8%). Gas chromatographic separation of the diastereoisomeric esters was performed at 130° in a 24 ft. column of 0·07 in. bore, packed with Carbowax 20M on kieselguhr. Nitrogen carrier flow was 10 ml./min., and the sample, about 0·05 μl., was injected as 10% (v/v) solution in benzene. The ester from the final alcohol was treated with known small amounts (6—15%) of (+)-ester, added as (±)-ester. This gave well shaped (+)-component peaks and better consistency of data in estimation of the small proportion of (+)-enantiomer in the alcohol. Results: for alcohol of $[\alpha]_D^{25}$ −5·36°, 5·1 and 5·4 (average 5·3%) (+)-enantiomer; for alcohol of $[\alpha]_D^{25}$ −5·65°, 1·0, 1·3, and 1·3 (average 1·2%).

Rotatory Power of (−)-1-*Trifluoromethylethanol*.—The alcohol used had $[\alpha]_D^{25}$ −5·36°, d_4^{31} 1·255. Measurements were made with a Perkin-Elmer P22 polarimeter. The Table gives values of α_λ^{31} (*m*°, 0·02 dm.) for homogeneous alcohol (A), and α_λ^{30} (*m*°, 0·1 dm.) for solution in isopropyl chloride (*c* 9·4) (B). Constants for single term Drude equations were based on values of α at wavelengths 600 and 220 (230) mμ. Values of 100 $(\alpha_{obs.} - \alpha_{calc.})/\alpha_{obs.}$ are given (D)

λ (mμ) ...	600	550	500	450	400
A (*m*°) ...	134	161	197	252	335
D (%) ...		−0·6	−1·5	−0·6	−0·9
λ (mμ) ...	350	300	250	230	220
A (*m*°) ...	469	725	1341	1855	2255
D (%) ...	−1·3	+0·3	+1·9	+1·2	

B (*m*°)	64	77	97	122	164	227	350	652	928
D (%)		−0·6	+1	0	+0·6	−0·9	−1	−0·2	

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