789. *Resolution of* 1-*Trifluoromethylethanol*

By J. W. C. Crawford

(−)-1-Trifluoromethylethanol has been obtained through resolution of the adduct of the inactive alcohol with acrylic acid, β-(1-trifluoromethylethoxy)propionic acid, and recovery of the active alcohol by fission of the active alkoxy-acid under alkaline conditions.

Attempts to resolve 1-trifluoromethylethanol by the usual acid-ester technique were discouraging. The hydrogen phthalate could readily be prepared, but the solubility and crystallisation-rate characteristics of its salts with the alkaloids normally used were unsatisfactory. Resolution was successfully accomplished using (±)-β-(1-trifluoromethylethoxy)propionic acid, the adduct of the alcohol and acrylic acid. This was separated into its optical isomers through its quinine salt, and active 1-trifluoromethylethanol recovered from the active alkoxy-acid.

The isomeric quinine salts of the alkoxy-acid were preferably separated by fractional solution at room temperature; it was shown that there was some risk of partial fission of the salts into quinine acrylate and 1-trifluoromethylethanol at elevated temperature during resolution by fractional crystallisation from hot solvent. The less soluble quinine salt of the (+)-alkoxy-acid was isolated pure by either method.

1-Trifluoromethylethanol could be recovered from the alkoxy-acid under alkaline conditions. Distillation of the product of 50% over-neutralisation of the acid with 2N-sodium hydroxide yielded the alcohol as a water-azeotrope; condensation of the latter provided an alcohol-rich (94%) layer, in which form the 1-trifluoromethylethanol was obtained in 85—90% yield. Sodium acrylate was formed in an amount equivalent to the alcohol recovered. Alcohol was not obtained from the distillate from alkoxy-acid neutralised to phenolphthalein. Liberation of 1-trifluoromethylethanol in this way from β-(1-trifluoromethylethoxy)propionic acid is regarded as essentially a reversal catalysed by the hydroxyl ion, of the synthesis of the acid from 1-trifluoromethylethanol and acrylic acid:

$$\mathrm{ROCH_2{\cdot}CH_2{\cdot}CO_2^- + OH^- \rightleftharpoons ROCH_2{\cdot}\bar{C}H{\cdot}CO_2^- + H_2O}$$

$$\mathrm{ROCH_2{\cdot}\bar{C}H{\cdot}CO_2^- \rightleftharpoons RO^- + CH_2{:}CH{\cdot}CO_2^-} \qquad [\mathrm{R = CF_3{\cdot}C(Me)H}]$$

$$\mathrm{RO^- + H_2O \rightleftharpoons ROH + OH^-}$$

Distillation tends toward completion of the reactions from left to right, limited by the acidity of the alcohol. The mechanism seems unlikely to give rise to racemisation. The acid-catalysis indicated in the literature [1] for fission of β-alkoxy-propionic acids may be suspected of allowing racemisation of active secondary alcohols.

The above-mentioned decomposition of the quinine salt of β-(1-trifluoromethylethoxy)-propionic acid might occur by a mechanism similar to the alkaline fission of the acid, initiated in this case by formation of an ammonium ion from a proton of the acyloxy-ion and an amino-nitrogen atom of the quinine.

β-s-Butoxypropionic acid,[2] analogous in structure to β-(1-trifluoromethylethoxy)-propionic acid, did not provide identifiable s-butyl alcohol when its similarly over-neutralised solution was distilled, but the butoxypropionic acid recovered from the treatment contained a very small amount of acrylic acid. The n-octyl ether of 1-trifluoromethylethanol, distilled with alkali of a concentration approximately that present in the over-neutralised alkoxy-acid solutions, gave no evidence of formation of 1-trifluoromethylethanol and octylene. The ability of β-(1-trifluoromethylethoxy)propionic acid to split readily under alkaline conditions appears to be due to the concerted effect of the trifluoromethyl group and the carboxy-ion in increasing the acidity of the α-hydrogen atoms of the

---

[1] H. Schulz, U.S.P. 2,341,663 (*Chem. Abs.*, 1944, **38**, 4272).

[2] R. V. Christian and R. M. Hixon, *J. Amer. Chem. Soc.*, 1948, **70**, 1333.

alkoxy-acid. The method of resolution may be restricted to the more acidic alcohols, at least under the conditions of alkaline fission employed in the present case.

(+)-β-(1-Trifluoromethylethoxy)propionic acid gave (−)-1-trifluoromethylethanol with the following values of rotatory power:

λ (mμ)	365	436	546	578	589
$[\alpha]_\lambda^{25}$ (1 dm.)	−10·28°	6·63°	3·93°	3·47°	3·33°
$[\alpha]_\lambda^{25}$	−8·13°	5·25°	3·11°	2·74°	2·63°

The specific rotation of the alcohol at 10% concentration in solvents was as follows:

Solvent	C_6H_6	$CHCl_3$	Bu^{n}OAc	KOH (4N)	H_2SO_4 (98%)
$[\alpha]_D^{25}$	−1·5°	−2·5°	−1·4°	+1·5°	+9·1°

The rotatory power of the alcohol was unchanged after a year's storage. Treatment with deuterium oxide gave no detectable exchange with C–H.

Synthesis of the starting material, (±)-β-(1-trifluoromethylethoxy)propionic acid, is best carried out by way of its nitrile, prepared in a slow reaction at room temperature by the addition (shown to be reversible) of 1-trifluoromethylethanol to acrylonitrile, catalysed by the potassium alkoxide. The net yield in this reaction and that in the subsequent hydrolysis of the nitrile are both very high, and contrast favourably with the addition of the alcohol to alkaline acrylate, which is beset with polymerisation difficulties, or the alkoxide-catalysed addition of the alcohol to methyl acrylate, which is accompanied by wasteful transesterification of the ester methyl group.

EXPERIMENTAL

(±)-β-(1-*Trifluoromethylethoxy)propionitrile*.—Potassium (2 g., 0·05 g.-atom) was dissolved under nitrogen in 1-trifluoromethylethanol (690 g., 6·05 moles) and acrylonitrile (318 g., 6 moles) added. The clear mixture was allowed to stand at room temperature for 13 days, and catalyst destroyed by the addition of sulphuric acid (98%; 2·8 ml., 0·05 mole). The filtrate from potassium sulphate was distilled, and unchanged alcohol and acrylonitrile (181 g.), b. p. 44°/170 mm., were collected in a receiver cooled in Drikold. The residue was distilled at 12 mm., and gave alkoxy-nitrile (809 g., 79%; net, 98%), b. p. 78—81°. A sample of redistilled (±)-β-(1-*trifluoromethylethoxy)propionitrile*, b. p. 84°/14 mm., had n_D^{25} 1·3656, d_4^{25} 1·1821 (Found: F, 33·8. $C_6H_8F_3NO$ requires F, 34·1%).

The recovered reactants were treated with 40% potassium hydroxide (1·5 g.), and allowed to stand for 20 days before being worked up as described above. The yield of alkoxy-nitrile, b. p. 82—83°/13 mm., was 85 g. (63%).

Reversibility of Alkoxy-nitrile Synthesis.—Reversibility was demonstrated by treating the pure alkoxy-nitrile with alkoxide catalyst, and analysing the product by gas chromatography. A Pye–Cambridge gas chromatograph was used, with an argon detector. The stationary phase was 10% poly(ethylene adipate) on 85—100 mesh Celite, operated at 75°. The starting material was pure (±)-β-(1-trifluoromethylethoxy)propionitrile, whose chromatogram showed a single peak. The nitrile (16·7 g., 0·1 mole) was treated with potassium 1-trifluoromethylethoxide (0·12 g., 0·0008 mole), made by dissolving potassium in excess of 1-trifluoromethylethanol, and evaporating the solution *in vacuo* at 100° to give the crystalline alkoxide; this dissolved in the alkoxy-nitrile. The solution was allowed to stand for 12 days and the catalyst destroyed by the addition of sulphuric acid (98%; 0·054 g., 0·005 mole). The filtrate from potassium sulphate was submitted to gas chromatography. Acrylonitrile and 1-trifluoromethylethanol were now present in addition to alkoxy-nitrile; the concentration of the latter was 83%. No other substances were detected in the chromatogram.

(±)-β-(1-*Trifluoromethylethoxy)propionic Acid*.—(±)-β-(1-Trifluoromethylethoxy)propionitrile (700 g., 4·2 moles) was added to hydrochloric acid (*d* 1·18; 862 g., 8·4 moles), and the mixture heated under reflux with stirring. From 45°, the heat of reaction carried the temperature to 99°, and this was maintained by external heating for a further hour. When cooled, the mixture deposited ammonium chloride, which was taken up by the addition of water (845 ml.). The lower layer of organic acid was separated, combined with two 250 ml. ether extracts of the aqueous layer, dried (Na_2SO_4), freed from solvent, and distilled. A forerun

(16·1 g.) free from bromine-unsaturation, was followed by alkoxy-acid (742 g., 95%), b. p. 111·5—112·5°/12 mm. (Found: Equiv., 186).

A sample of refractionated (±)-β-(1-*trifluoromethylethoxy*)*propionic acid*, b. p. 114·5—115°/14 mm., had n_D^{25} 1·3731, d_4^{25} 1·2681 [Found: *M* (cryoscopy in benzene), 349; (in ethylene bromide), 319; Equiv., 186. $C_6H_9F_3O_3$ requires *M*, 186·1; Equiv., 186·1].

Methyl Ester.—This was prepared from refractionated acid and acetone dimethyl ketal, according to the method of Lorette and Brown.[3] *Methyl* (±)-β-(1-*trifluoromethylethoxy*)-*propionate*, b. p. 64·3—64·8°/13·5 mm. (corr.), had n_D^{25} 1·3680, d_4^{25} 1·1823 (Found: *M* (Cryoscopy in benzene), 193; (in ethylene bromide), 202; saponificn. value, 274. $C_7H_{11}F_3O_3$ requires *M*, 200; saponificn. value, 280].

Resolution of (±)-β-(1-*Trifluoromethylethoxy*)*propionic Acid*.—*Preparation of quinine salt*. (±)-β-(1-Trifluoromethylethoxy)propionic acid (558 g., 3 moles), dissolved in carbon tetrachloride (6 l.), was heated to 60°, and dehydrated quinine (924 g., 2·85 moles) added, with stirring at such a rate as to keep the liquid boiling. The resulting solution was cooled quickly in water, and the *quinine salt* that crystallised was separated in a basket centrifuge and air-dried (1090 g., 75%) (Found: N, 5·4. $C_{29}H_{33}F_3N_2O_5$ requires N, 5·5%).

Separation of isomeric quinine salts. The air-dried salt was treated with chloroform–carbon tetrachloride (1 : 3; 2·7 l.), and the whole equilibrated by being tumbled slowly for 3 days at room temperature. The residual salt was filtered in the centrifuge, and washed in the basket with carbon tetrachloride (300 ml.); the air-dried salt weighed 766 g. The series of fractional solutions was continued by using *ca*. 2·5 ml. mixed solvent, with 0·3 ml. carbon tetrachloride for washing, per g. of salt treated. Progress of the solution was followed from measurements of the specific rotation, in solution in n-butyl acetate, of the alkoxy-acid liberated from samples of residual salt and the corresponding extraction liquid. The specific rotations converged after seven extractions. The final residue, the *quinine salt* of (+)-β-(1-*trifluoromethylethoxy*)*propionic acid* (205 g., 27%), had $[\alpha]_D^{25}$ −129·8° (*c* 5, in MeOH) (Found: N, 5·4%).

(+)-β-(1-*Trifluoromethylethoxy*)*propionic Acid*.—The (+)-quinine salt (200 g., 0·39 mole) was stirred with 8% hydrochloric acid (500 ml., 1·1 mole) until it had decomposed. The alkoxy-acid was extracted with ether, the extract freed from quinine by washing it with acid (2N) and water, dried (Na_2SO_4), the solvent removed, and the residue fractionated. (+)-β-(1-*Trifluoromethylethoxy*)*propionic acid* (64·4 g., 89%) distilled steadily at 111·2°/11 mm. (corr.). It had n_D^{25} 1·3727, d_4^{25} 1·2705, $[\alpha]_D^{25}$ +1·70° (homogeneous), +1·85° (*c* 10, in n-butyl acetate, $\lambda_{max.}$ (cyclohexane) 213 mμ (ε 40) (Found: Equiv., 186. $C_6H_9F_3O_3$ requires Equiv., 186·1).

Methyl Ester.—This was prepared from the (+)-acid, in the same way as the ester of the (±)-acid. The *ester* distilled at 63·5°/12·5 mm. (corr.), and had n_D^{25} 1·3676, d_4^{25} 1·1830, $[\alpha]_D^{25}$ +1·63°, $\lambda_{max.}$ (cyclohexane) 218 mμ (ε 55) (Found: saponificn. value, 282. $C_7H_{11}F_3O_3$ requires saponificn. value, 280).

(−)-1-*Trifluoromethylethanol*.—(+)-β-(1-Trifluoromethylethoxy)propionic acid (40·1 g., 0·22 mole) was dissolved in sodium hydroxide (2N; 165 ml.), and the solution distilled through a 12-in. glass spiral-packed column, fitted with an automatic separator to remove the lower layer of the condensed water-azeotrope. The reflux ratio was *ca*. 10 : 1. Over 2·5 hr., the azeotrope distilled at 76·9°, giving 22·3 g. of lower layer containing 6% water (Karl Fischer) (equiv. anhydrous alcohol, 21 g., 86%). The alcohol was dried by successive treatments with calcium chloride and distilled, to minimum refractive index. (−)-1-Trifluoromethylethanol, b. p. 77·7—77·9°/752 mm. (corr.), had n_D^{25} 1·3130, d_4^{25} 1·2634. The proton magnetic resonance spectrum, measured at 60 Mc./sec., showed bands at τ 8·62 (doublet, 3 protons, J = 7 c./sec.); 7·28 (broad, 1 proton); 5·86 (quartet, 1 proton), 6 [assigned to CH_3, OH, and CH, respectively, in the formula $CF_3CH(Me)OH$]. Measurement of the rotatory power of the homogeneous alcohol was made in a Perkin-Elmer polarimeter, type 141.

A sample of (±)-1-trifluoromethylethanol, prepared in the same way from (±)-β-(1-trifluoromethylethoxy)propionic acid, had n_D^{25} 1·3130, d_4^{25} 1·2632.

The extent of formation of acrylic acid in the alkaline fission was studied with the (±)-alkoxy-acid. This (8·96 g., 0·049 mole) was treated under nitrogen with a 50% excess of sodium hydroxide (2N), hydroquinone (0·04 g.) added, and 1-trifluoromethylethanol distilled out as a water-azeotrope. Alcohol recovered as the lower layer was estimated at 5·16 g. (88%). The boiler contents were analysed for acrylic acid by bromine absorption from acidified bromide–bromate (0·1N). Because of the incompleteness of the bromine addition, a control absorption

---

[3] N. B. Lorette and J. H. Brown, jun., *J. Org. Chem.*, 1959, **24**, 261.

was carried out with pure sodium acrylate of approximately equal concentration, and a blank run and bromine-absorption measurements were made with hydroquinone and alkali only. The analytical results indicated 88% conversion of alkoxy-acid into acrylic acid; the identity with the estimated yield of 1-trifluoromethylethanol is doubtless fortuitous.

n-Octyl Ether of (±)-1-*Trifluoromethylethanol.*—(±)-1-Trifluoromethylethanol (11·4 g., 0·1 mole) was added to a stirred mixture of sodium hydroxide flake (4·0 g., 0·1 mole) and dioxan (55 g.), at about 45°. The alkali went into solution–dispersion. n-Octyl iodide (24 g., 0·1 mole) was added, and the mixture heated under reflux for 7·5 hr. To the cooled product, pyridine (8 ml., 0·1 mole) was added and, after being warmed, the mixture was neutralised (phenolphthalein) with sulphuric acid (2N). The whole was heated under reflux for 3 hr. to quaternise the pyridine with the unchanged octyl iodide, cooled, treated with sulphuric acid (2N; 125 ml.) and light petroleum (b. p. 40—60°; 50 ml.). The light petroleum extract was separated, washed (2N-H_2SO_4, water), and dried (Na_2SO_4); the solvent was removed, and the residue fractionated. The fraction, b. p. 77—82°/12 mm., was refractionated. The (±)-1-*trifluoromethylethanol n-octyl ether*, b. p. 78·9—80·4°/11·5 mm. (9·3 g., 41%), had n_D^{25} 1·3865, d_4^{25} 0·9651 (Found: F, 24·6. $C_{11}H_{21}F_3O$ requires F, 25·2%).

The author is indebted to Mr. F. T. Riley, University College, for gas-chromatography measurements, and for proton magnetic resonance measurements to Dr. D. T. Thompson, Imperial Chemical Industries Limited, Petrochemical and Polymer Laboratory, Runcorn.

DEPARTMENT OF CHEMISTRY, UNIVERSITY COLLEGE, DUBLIN. [*Received, January* 4*th*, 1965.]