

516. Organic Fluorides. Part IX.* The Formation and Resolution of α -Hydroxy- α -trifluoromethylpropionic Acid.

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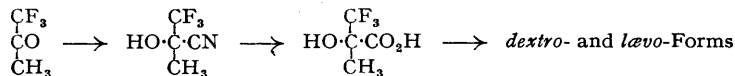
The action of sodium cyanide on 1:1:1-trifluoroacetone afforded the corresponding racemic cyanohydrin which was converted into the racemic α -hydroxy- α -trifluoromethylpropionic acid. Certain derivatives of the latter product were made, and fractional crystallisation of its brucine salt enabled the *dextro*- and the *laevo*-acid to be isolated.

TRIFLUOROACETONE was first prepared by Swarts (*Bull. Acad. roy. Belg.*, 1927, **13**, 175) by the acid hydrolysis of trifluoroacetoacetic ester, which was obtained (*idem, ibid.*, 1926, **12**, 692) by condensation of ethyl trifluoroacetate with ethyl acetate in the presence of sodium ethoxide (cf. Henne, Newman, Quill, and Staniforth, *J. Amer. Chem. Soc.*, 1947, **69**, 1819; Haszeldine, Musgrave, Smith, and Turton, *J.*, 1951, 609). When this work was initiated little was known of the chemical properties of trifluoroacetone except that it formed a relatively stable hydrate and gave an oxime, a semicarbazone, and a bisulphite compound (Swarts, *loc. cit.*, 1927). Our interest in organic fluorides led us to a further study of the chemistry of trifluoroacetone and related fluoro-ketones.

This paper deals with the application of the cyanohydrin reaction to trifluoroacetone (Smith, *Ann. Reports*, 1947, **44**, 117). Other reactions of fluoro-ketones will form the subject of later communications. Treatment of trifluoroacetone with sodium cyanide according to the method of Welch and Clemo (*J.*, 1928, 2629) readily afforded the corresponding cyanohydrin, which was hygroscopic. Although this compound was more stable than acetone cyanohydrin, small amounts being distillable at atmospheric pressure with little or no decomposition, yet prolonged heating caused dissociation into trifluoroacetone and hydrogen cyanide. Treatment of the cyanohydrin with alcoholic ammonium sulphide gave α -hydroxy- α -trifluoromethyl(thio-propionamide) and this, on hydrolysis with dilute acid, readily gave the crystalline α -hydroxy- α -

* Part VIII, *J.*, 1951, 1701.

trifluoromethylpropionic acid. The latter was also obtained directly from the cyanohydrin by graded hydrolysis, in which reaction the amide was isolated as an intermediate.



The α -hydroxy- α -trifluoromethylpropionic acid was hygroscopic; its aqueous solutions were strongly acidic ($K = 1.3 \times 10^{-3}$) and gave a yellow colour with ferric chloride. Potentiometric titrations of this acid and of the nitrile with sodium hydrogen carbonate and with methanolic sodium methoxide showed that the hydroxy-group had no acidic properties. It is of interest that 1 : 1 : 1-trifluoropropan-2-ol has acidic properties (Swarts, *Bull. Soc. chim. Belg.*, 1929, **38**, 99) and that, although dimethyltrifluoromethylcarbinol is not titratable with dilute alkalis, yet it does form an alcoholate with anhydrous potassium carbonate (*idem, ibid.*, 1927, **36**, 191). It would thus appear that in the case of α -hydroxy- α -trifluoromethylpropionic acid the trifluoromethyl group exerts its influence on the carboxyl group and not on the hydroxyl group.

Esterification of α -hydroxy- α -trifluoromethylpropionic acid with methyl alcohol proceeded normally in the presence of a sulphuric acid catalyst to give the methyl ester, which afforded α -hydroxy- α -trifluoromethylpropionamide when treated with methanolic ammonia. There was no evidence that hemilactides or lactides were formed at all readily by heating the acid, which could be sublimed and distilled (b. p. 189°) unchanged. α -Hydroxyisobutyric acid when heated to 190° gives the corresponding lactide, together with methacrylic acid and acetone (Blaise and Bagard, *Ann. Chim. Phys.*, 1907, **11**, 111).

By treatment with acetic anhydride and fused sodium acetate, both trifluoroacetone cyanohydrin and methyl α -hydroxy- α -trifluoromethylpropionate afforded acetates, there being no evidence of the formation of any unsaturated products. Under similar conditions $\gamma\gamma\gamma$ -trichloro- β -hydroxybutyric acid undergoes dehydration and yields $\gamma\gamma\gamma$ -trichlorocrotonic acid (Auwers and Schmidt, *Ber.*, 1913, **46**, 487). Concentrated sulphuric acid reacted with the cyanohydrin to give α -hydroxy- α -trifluoromethylpropionamide; by the addition of water or of methyl alcohol to the reaction mixture followed by heating, the amide could be converted *in situ* into the acid or the methyl ester, respectively. By reactions similar to these, acetone cyanohydrin may be converted into derivatives of methacrylic acid (Crawford, B.P. 405,699, 427,810). Unsaturated products could not be isolated after reaction of trifluoroacetone cyanohydrin or of methyl α -hydroxy- α -trifluoromethylpropionate with phosphoric oxide.

Thus, as a result of the electronegative effect of the CF_3 group, the hydroxy-group of α -hydroxy- α -trifluoromethylpropionic acid and of its derivatives is more resistant to replacement than are orthodox tertiary alcoholic groups. The hydroxy-group of dimethyltrifluoromethylcarbinol behaves similarly, but Swarts (*loc. cit.*) succeeded in dehydrating this alcohol with phosphorus pentabromide, a reagent which might well convert derivatives of α -hydroxy- α -trifluoromethylpropionic acid into trifluoromethylacrylic acid derivatives.

Since this work was done Dickey (U.S.P. 2,472,812; *Chem. Abs.*, 1949, **43**, 8398) has reported the preparation of α -trifluoromethylacrylamide by treatment of trifluoroacetone cyanohydrin with concentrated sulphuric acid, and of alkyl α -trifluoromethylacrylates from the cyanohydrin and alkyl hydrogen sulphates.

The reaction between trifluoroacetone and sodium cyanide introduces asymmetry into the molecule. In order to determine the effect of a CF_3 group on optical activity, the racemic α -hydroxy- α -trifluoromethylpropionic acid was resolved into its enantiomorphs by fractional crystallisation of the diastereoisomeric brucine salts. Decomposition of the latter afforded the corresponding optically active acids which showed $[\alpha]_D +11.5^\circ$ and -11.5° . It is evident that the CF_3 group does not greatly affect the optical activity. As far as we are aware this is the first optically active acid to be isolated having a perfluoro-substituent on an asymmetric carbon atom.

EXPERIMENTAL.

Preparation of 1 : 1 : 1-Trifluoroacetone Cyanohydrin.—(a) 1 : 1 : 1-Trifluoroacetone (Swarts, *Bull. Acad. roy. Belg.*, 1927, **13**, 175). Ethyl trifluoroacetate (227.0 g., 15% excess) was treated with sodium ethoxide (94.7 g.) in dry ether (800 c.c.); ethyl acetate (148.7 g., 20% excess) was then added, and the solution was refluxed for 60 hours. The ether and excess of esters were removed by distillation *in vacuo*. To the sodio-derivative of trifluoroacetoacetic ester thus obtained, ice (220 g.) was added, followed by an ice-cold mixture of concentrated sulphuric acid (170 c.c.) and water (780 c.c.). The mixture was heated at 80–100° for 4 hours, and the trifluoroacetone (b. p. 22°) evolved was used directly for the next stage.

A portion of the trifluoroacetone gave in the usual way a semicarbazone, m. p. 127° (Found : C,

28.4; H, 3.3; F, 33.3. Calc. for $C_4H_6ON_3F_3$: C, 28.4; H, 3.6; F, 33.7%. Swarts (*loc. cit.*) recorded m. p. 127° for this compound.

(b) 1 : 1 : 1-Trifluoroacetone cyanohydrin. The trifluoroacetone from the previous experiment was passed directly into a stirred solution of sodium cyanide (63.6 g.) in water (272 c.c.) cooled to 0°. When all the trifluoroacetone had been absorbed in the solution, 6N-sulphuric acid (455 g.) cooled to 0° was added slowly, with stirring, and the solution was kept overnight at room temperature. The reaction mixture was then extracted with ether. The combined ethereal extracts (1 l.) were dried (Na_2SO_4) and filtered, and the ether was removed by distillation through a short column. The residue was redried (Na_2SO_4), filtered, and distilled under diminished pressure into a receiver cooled in ice and salt. The distillate was mixed with an equal volume of dry ether and again dried (Na_2SO_4), the ether was removed by distillation, and the residue was distilled to give 1 : 1 : 1-trifluoroacetone cyanohydrin (139.0 g.), b. p. 68—69°/40 mm., 138—139°/760 mm., n_D^{20} 1.3385 (Found: C, 34.5; H, 3.1; F, 40.9. $C_4H_6ONF_3$ requires C, 34.55; H, 2.9; F, 41.0%). This cyanohydrin was hygroscopic. Potentiometric titration of it in 91% aqueous methanol with 0.54N-sodium methoxide in 91% aqueous methanol showed that it was a neutral substance.

Treatment of the cyanohydrin (5.00 g.) with a mixture of acetic anhydride (14.0 c.c.) and fused sodium acetate (1.50 g.) at 100—105° for 3 hours, followed by pouring of the reaction mixture into water, and extraction with ether, afforded the acetate (3.57 g.), b. p. 150—152°, n_D^{15} 1.355 (Found: F, 31.7. $C_4H_6O_2NF_3$ requires F, 31.5%).

Thioamide of α -Hydroxy- α -trifluoromethylpropionic Acid.—Trifluoroacetone cyanohydrin (20.0 g.) was dissolved in ethyl alcohol (44.0 c.c.) and a saturated solution of ammonia in ethyl alcohol (44.0 c.c.) was added. The mixture was cooled in ice, and dry hydrogen sulphide was passed in until a copious precipitate had appeared. After being kept for 18 hours and the precipitate had redissolved, the mixture was concentrated *in vacuo* at 100°. Distillation of the residue yielded the thioamide as a pale yellow oil (20.0 g.), b. p. 70—76°/0.9 mm., which crystallised spontaneously on cooling; it had m. p. 52° before or after crystallisation from carbon tetrachloride (Found: C, 27.8; H, 3.6. $C_4H_6ONSF_3$ requires C, 27.7; H, 3.5%).

Amide of α -Hydroxy- α -trifluoromethylpropionic Acid.—The cyanohydrin (10.0 g.) was added dropwise to concentrated sulphuric acid (5.9 c.c.), with mechanical stirring. The temperature of the reaction mixture rose spontaneously to 70—80°, and was kept there by regulation of the rate of addition of the cyanohydrin. When the addition was complete the white semi-solid mass was heated at 115—120° for 15 minutes, and was then cooled in an ice-bath whilst water (30 c.c.) was added. The clear solution was kept for 48 hours at 0°; the crystalline precipitate of amide which had formed was combined with that extracted from the aqueous solution with ether to give, after crystallisation from benzene-acetone, α -hydroxy- α -trifluoromethylpropionamide (5.3 g.), m. p. 142° (Found: C, 31.0; H, 3.7; F, 36.4. $C_4H_6O_2NF_3$ requires C, 30.6; H, 3.8; F, 36.3%).

The aqueous solution, after the ether-extraction, was heated at 100° for 7 hours and was then extracted exhaustively with ether. The ethereal extracts were dried (Na_2SO_4), filtered, and distilled; the residue was sublimed to give α -hydroxy- α -trifluoromethylpropionic acid (3.05 g.), m. p. and mixed m. p. 87.5°.

Preparation of α -Hydroxy- α -trifluoromethylpropionic Acid.—(a) The thioamide (22.15 g.) (see above) was heated at 100° with 20% hydrochloric acid (110 c.c.) for 18 hours, and the solution, after cooling, was extracted exhaustively with ether. The extract was dried (Na_2SO_4), the ether distilled, and the residue sublimed at 45—70° (bath-temp.)/0.25 mm. Resublimation of the product afforded α -hydroxy- α -trifluoromethylpropionic acid (17.85 g.), m. p. 88°, b. p. 189° (Found: C, 30.5; H, 3.2; F, 36.2%; *M* (by McCoy's method with benzene as solvent), 163; *E* (by potentiometric titration either in water or in 91% aqueous methanol), 159. $C_4H_5O_3F_3$ requires C, 30.4; H, 3.2; F, 36.1%; *M*, 158; *E*, 158]. The acid was deliquescent and gave a yellow colour with ferric chloride.

(b) The reaction described above for the preparation of α -hydroxy- α -trifluoromethylpropionamide was repeated with the same quantities; after the addition of water (31.5 c.c.), the mixture was heated at 100° for 6½ hours. Exhaustive extraction of the clear solution with ether, followed by removal of solvent as above, gave, after purification by sublimation, α -hydroxy- α -trifluoromethylpropionic acid (10.4 g.), m. p. and mixed m. p. 88°.

Methyl α -Hydroxy- α -trifluoromethylpropionate.— α -Hydroxy- α -trifluoromethylpropionic acid (33.2 g.) was boiled under reflux for 15 hours with magnesium-dried methyl alcohol (16.0 c.c.) and concentrated sulphuric acid (0.5 c.c.). The alcohol was then removed by distillation through a short column, and the residue was poured into ice-water. The aqueous phase was extracted three times with ether, and the extracts were washed with water, dried ($MgSO_4$), and freed from ether. Distillation of the residue gave methyl α -hydroxy- α -trifluoromethylpropionate (27.3 g.), b. p. 127—129°, n_D^{14} 1.358 (Found: C, 34.9; H, 4.2; F, 33.3. $C_5H_7O_3F_3$ requires C, 34.9; H, 4.1; F, 33.1%). From the aqueous layers there was obtained unchanged α -hydroxy- α -trifluoromethylpropionic acid (5.2 g.), m. p. and mixed m. p. 88°. The methyl ester could be distilled unchanged over sulphuric acid and over phosphoric oxide.

Methyl α -hydroxy- α -trifluoromethylpropionate (5.00 g.) was heated for 2 hours at 100° with a mixture of acetic anhydride (5.0 c.c.) and fused sodium acetate (0.48 g.). The mixture, after being poured into water and extracted with ether in the usual way, gave the acetate (3.07 g.), b. p. 155—156°, n_D^{15} 1.368 (Found: F, 26.5. $C_7H_9O_4F_3$ requires F, 26.6%).

When a solution of the methyl ester (0.950 g.) in methyl alcohol (10.0 c.c.), saturated at 0° with ammonia, was kept for 18 hours at room temperature, distillation of the solution left a residue which, on recrystallisation from benzene-acetone, afforded α -hydroxy- α -trifluoromethylpropionamide (0.715 g.), m. p. 142° alone or on admixture with a specimen prepared from the cyanohydrin (see above).

Optical Resolution of α -Hydroxy- α -trifluoromethylpropionic Acid.—A solution of the racemic fluoro-acid (5.28 g.) in methyl alcohol was mixed with a solution of brucine (15.59 g.) in methyl alcohol (total volume 350 c.c.), and the mixture was heated to boiling, filtered, and set aside until crystallisation appeared to be complete (3 days). This brucine salt was recrystallised (five times) from methanol until the rotation was constant. The product obtained (1.17 g.) consisted of large needles which showed $[\alpha]_D^{20} - 30.3^\circ$ (c , 1.0 in water). A portion of this salt (0.583 g.) was treated with sodium hydroxide solution, the precipitated brucine was removed by filtration, the solution was acidified, and the product was extracted with ether and purified as already described. The *laevo*-acid thus obtained (0.124 g.) had $[\alpha]_D^{16} - 11.3^\circ$ (c , 5.0 in water).

The mother-liquors from which the original precipitate was obtained were concentrated, and the more soluble isomer of the brucine salt was purified by systematic fractional crystallisation until it showed a constant negative rotation. The pure diastereoisomer (0.434 g.) thus produced had $[\alpha]_D^{20} - 17.4^\circ$ (c , 1.0 in water). Treatment of this brucine salt as above gave the *dextro*-form of the acid (0.092 g.), which showed $[\alpha]_D^{20} + 11.4^\circ$ (c , 3.7 in water).

The authors acknowledge their gratitude to the late Professor Sir Norman Haworth, F.R.S., for his interest in this work, and to Dr. L. M. Turton for carrying out the molecular-weight determination. The work was carried out with support from the Ministry of Supply and thanks are due to the Chief Scientific Officer for permission to publish it.

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[Received, May 4th, 1951.]