640. *2-Trifluoromethylglycerol and Some Related Compounds.**

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2-Trifluoromethylglycerol has been synthesised by two routes, both starting from 3-bromo-1,1,1-trifluoropropan-2-one (I). One proceeded *via* the cyanohydrin (II) of this ketone and thence 2-trifluoromethylglyceric acid (IX). The other involved reaction of the ketone with diazomethane to give 1-bromomethyl-1-trifluoromethylethylene oxide (XIII), followed by hydrolysis. Neither the glycerol nor the glyceric acid had antibacterial activity.

The only recorded fluorine-containing derivatives of glycerol are monofluoro-monodeoxy-compounds [1] in which the fluorine atom has replaced a primary or secondary hydroxyl group. We have now synthesised 2-trifluoromethyl-glycerol (XI) and -glyceric acid (IX) by the methods outlined in the scheme below. 3-Bromo-1,1,1-trifluoropropan-2-one [2] (I) was the starting material for both routes.

In the first series of reactions the ketone (I) was converted into its cyanohydrin (II), by treatment with aqueous potassium cyanide followed by sulphuric acid. A small amount of a second product was also isolated; this is believed to be α-trifluoromethyl-glyceronitrile (III), though a completely pure sample was not obtained. On acidic hydrolysis this compound (III) gave a low yield of α-trifluoromethylglyceric acid (IX); this was isolated as its anilinium salt which was identical with a sample of the salt made from the acid prepared as outlined in the reaction scheme. The bromo-cyanohydrin (II) was not an intermediate in the formation of the hydroxy-cyanohydrin (III) since treatment of it with aqueous potassium cyanide did not give any of the hydroxy-compound (III). The hydrolysis of the bromine in the formation of the hydroxy-cyanohydrin (III) must therefore have taken place from the ketone (I).

Mild acidic hydrolysis of the bromo-cyanohydrin (II) gave β-bromo-α-hydroxy-α-trifluoromethylpropionamide (V), and more drastic treatment led to the corresponding bromo-hydroxy-acid (VII). The carbon–bromine bond in these two compounds (V and VII) is very labile towards alkali. The bromo-amide (V) with aqueous potassium hydroxide gave α-trifluoromethylglyceramide (VI) in almost quantitative yield. The bromo-acid (VII) lost its bromine quantitatively in a few minutes even in 0·05N-alkali; and on being heated with silver oxide and water the same acid gave silver α-trifluoromethyl-glycerate (VIII). The bromo-acid (VII) also reacted with aqueous ammonia to give β-amino-α-hydroxy-α-trifluoromethylpropionic acid (XII). This amino-acid (XII) has been prepared by another route.[3]

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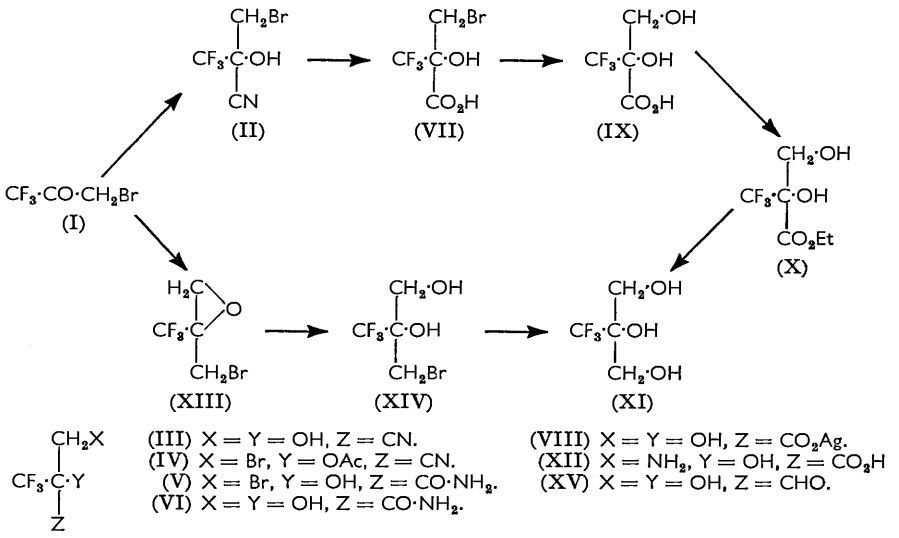
[1] Gryskiewicz-Trochimowski, *Rec. Trav. chim.*, 1949, **66**, 427; Taylor and Kent, *J.*, 1956, 2150; *Research*, 1955, **8**, S66.

[2] McBee and Burton, *J. Amer. Chem. Soc.*, 1952, **74**, 3022.

[3] Bourne, Burdon, McLoughlin, and Tatlow, unpublished work.

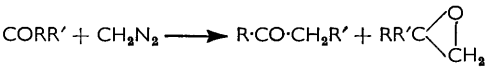
Isolation of the glyceric acid (IX) from its salt (VIII) was facilitated by the high solubility of the free acid in ether; the glycerol (XI) has a similar high solubility. These solubilities are quite surprising since ordinary glyceric acid and glycerol are almost completely insoluble in ether. Esterification of the glyceric acid (IX) with ethanol and sulphuric acid was unsatisfactory and the ethyl ester (X) was best obtained by treatment of the silver salt (VIII) with ethyl iodide. Reduction of ethyl α-trifluoromethylglycerate



(X) with lithium aluminium hydride gave 2-trifluoromethylglycerol as a hygroscopic solid having quite a high solubility in benzene, again in marked contrast to glycerol itself. With phenyl isocyanate and benzoyl chloride 2-trifluoromethylglycerol gave a diurethane and a dibenzoate only. The 2-hydroxy-group is probably the unreactive one since it is both tertiary and in an α-relation to a trifluoromethyl group; both factors are known [4] to lead to low reactivity towards acylating agents.

Reduction of the glyceric acid (IX) and the glyceramide (VI) with lithium aluminium hydride was complicated by the hydroxyl groups—many polyhydroxy-compounds form insoluble complexes with lithium aluminium hydride, preventing the reduction of other functional groups. This seemed to be the case with the glyceramide (VI) since no reduction at all took place. However, the glyceric acid (IX) was reduced but gave only about 2% of the glycerol (XI). Another, non-crystalline product was obtained in a total weight conversion of about 75%. This other product was neutral and did not sublime and hence could not have been either the glyceric acid or the glycerol. Since the product reduced Fehling's solution and the infrared spectrum indicated a carbonyl group, it is thought to be mainly a polymeric form of 2-trifluoromethylglyceraldehyde (XV); it is well-known that glyceraldehyde itself forms a dimer.

The second and simpler synthetic route to the glycerol (XI) started from the reaction of diazomethane with the ketone (I). Diazomethane can react [5] with ketones to give two products:

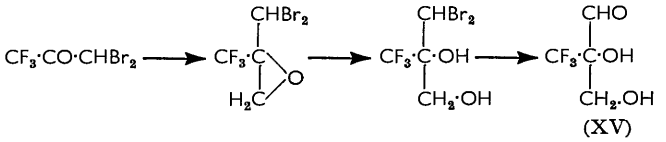


Usually, one product predominates, the proportions depending upon the nature of R and R′. If either is electron-attracting, epoxide formation is favoured. It is not, therefore, surprising that the epoxide (XIII) was the sole product when the ketone (I) was treated

[4] Bourne, Stacey, Tatlow, and Worrall, *J.*, 1958, 3268.
[5] Gutsche, " Organic Reactions," Vol. VIII, p. 364, John Wiley and Sons, Inc., New York, 1954.

with diazomethane, since both the trifluoromethyl and the bromomethyl group are powerfully electron-attracting. The epoxide (XIII) is, however, labile to heat: an attempt to fractionate it led to the formation of large amounts of high-boiling tar and even simple distillation caused slight decomposition. Hydrolysis of the epoxide with acid gave a good yield of the bromohydrin (XIV), which was hydrolysed by aqueous silver oxide to 2-trifluoromethylglycerol (XI) in excellent yield.

This success led us to attempt a similar synthesis of 2-trifluoromethylglyceraldehyde (XV):



(XV)

The dibromo-ketone [2] readily condensed with diazomethane, and acid hydrolysed the resulting epoxide to 3,3-dibromo-2-trifluoromethylpropane-1,2-diol in good yield. This compound lost bromine on being treated with dilute alkali and the product reduced Fehling's solution and had an infrared spectrum similar to, but not identical with, that of the compound obtained by reduction of the glyceric acid (IX). We have not, however, been able to purify this supposed aldehyde. Also, attempts to oxidise or reduce it have not led to recognisable products.

The glycerol (XI) and the glyceric acid (IX) have been tested for antibacterial activity against two Gram-positive and two Gram-negative organisms. Neither compound showed significant activity.

Experimental

β-Bromo-α-hydroxy-α-trifluoromethylpropionitrile (II).—A solution of potassium cyanide (43·5 g.) in water (200 ml.), cooled to 0°, was added during 90 min. to a stirred solution of the bromo-ketone [2] (I) (128 g.) in water (30 ml.) at −15°. The mixture was stirred for a further 4 hr. at −15° before 20% sulphuric acid (120 ml.) was added slowly. The lower organic layer was separated and the aqueous layer extracted continuously with ether for 14 hr. The ethereal extracts and the organic layer were combined, dried ($MgSO_4$), filtered, and distilled to give: (i) a mixture of bromo-ketone (I) and water (37 g.), b. p. 80—100°; (ii) *β-bromo-α-hydroxy-α-trifluoromethylpropionitrile* (II) (72 g.), b. p. 82—83°/20 mm. (Found: C, 22·0; H, 1·4. $C_4H_3BrF_3NO$ requires C, 22·0; H, 1·4%); and (iii) a liquid (6·3 g.), b. p. 111—119°/20 mm., which solidified and recrystallised, with difficulty, from benzene to give *α-trifluoromethylglyceronitrile* (III), m. p. 158° (Found: C, 30·4; H, 2·6; F, 36·5. $C_4H_4F_3NO_2$ requires C, 31·0; H, 2·6; F, 36·8%).

In a reaction at higher temperatures some decomposition occurred, the yield of the by-product increased, and the yield of the bromo-cyanohydrin (II) was very poor.

When the bromo-cyanohydrin (II) was treated with acetic anhydride and a catalytic amount of 98% sulphuric acid, the *acetate* (IV) was obtained, having b. p. 83—84°/14 mm. (Found: C, 28·1; H, 2·2. $C_6H_5BrF_3NO_2$ requires C, 27·7; H, 1·9%).

Acidic Hydrolysis of the Cyanohydrins.—(*a*) The bromo-cyanohydrin (II) (3·6 g.) was heated at 110° for 1 hr. with 98% sulphuric acid (3·6 ml.), cooled, and poured into iced water (25 g.). The aqueous solution was continuously extracted with ether for 14 hr. and the extracts were dried ($MgSO_4$), filtered, and evaporated to leave *β-bromo-α-hydroxy-α-trifluoromethylpropionamide* (V) (3·25 g.), m. p. 63—63·5° (from benzene) (Found: C, 20·2; H, 2·2. $C_4H_5BrF_3NO_2$ requires C, 20·4; H, 2·1%).

(*b*) The bromo-cyanohydrin (II) (27·8 g.) was added with stirring in 30 min. to 98% sulphuric acid (25 ml.). After being heated to 110° for 45 min. the mixture was cooled and poured into iced water (60 g.). The aqueous solution was refluxed for 6 hr. before being continuously extracted with ether for 14 hr. The extracts were dried ($MgSO_4$), filtered, and evaporated to a syrup which crystallised in a vacuum-desiccator over phosphorus pentoxide. Sublimation at 50—70°/0·05 mm. gave hygroscopic *β-bromo-α-hydroxy-α-trifluoromethylpropionic acid* (VII)

(16·0 g.), m. p. 85° (sealed tube) (Found: C, 20·3; H, 1·8%; equiv., 235. $C_4H_4BrF_3O_3$ requires C, 20·3; H, 1·7%; equiv., 237).

Addition of excess of 0·066N-sodium hydroxide after the equivalent-weight determination liberated bromide ion. Determination as silver bromide showed that this hydrolysis was complete in a few minutes.

Treatment of the bromo-acid (VII) (5·3 g.) with dry ethanol (6 ml.) and 98% sulphuric acid (0·2 ml.) for 18 hr. under reflux gave *ethyl β-bromo-α-hydroxy-α-trifluoromethylpropionate* (3·7 g.), b. p. 195—200° (Found: C, 26·9; H, 3·0. $C_6H_8BrF_3O_3$ requires C, 27·2; H, 3·0%), and unchanged bromo-acid (0·55 g.), m. p. 80—84°.

(*c*) The hydroxy-cyanohydrin (III) (2·3 g.) was treated with 98% sulphuric acid (2·2 ml.) and then with water (8 ml.) as in (*b*). The product, isolated as a syrup as in (*b*), was treated with aniline in dry ether to give anilinium α-trifluoromethylglycerate (0·68 g.), m. p. 131·5—132·5° (from acetone–chloroform) alone and on admixture with a specimen obtained from authentic α-trifluoromethylglyceric acid.

Action of Alkali on the Bromo-amide (V).—The bromo-amide (V) (2·25 g.) was shaken with cold 10% aqueous potassium hydroxide (10 ml.) for 5 min. The resulting solution was acidified with dilute sulphuric acid. Continuous ether-extraction gave an oil which was dissolved in chloroform. Addition of ethanol precipitated *α-trifluoromethylglyceramide* (VI) (1·55 g.), m. p. 140—141° (Found: C, 27·5; H, 3·2. $C_4H_6F_3NO_3$ requires C, 27·8; H, 3·5%).

Action of Ammonia on the Bromo-acid (VII).—A solution of the bromo-acid (VII) (4·5 g.) in aqueous ammonia (*d* 0·88; 40 ml.) was kept at 20° for 16 hr. before being evaporated to small bulk. Ethanol (15 ml.) was then added and the precipitate recrystallised from aqueous ethanol, to give *β-amino-α-hydroxy-α-trifluoromethylpropionic acid* (XII), m. p. 310—311° (decomp.) (Found: C, 27·9; H, 3·3. $C_4H_6F_3NO_3$ requires C, 27·8; H, 3·5%), shown by infrared spectroscopy to be identical with the compound prepared by another route.[3]

Action of Silver Oxide on the Bromo-acid (VII).—(*a*) This bromo-acid (0·6 g.) was heated at 100° for 3 hr. with silver oxide (1·2 g.) in water (30 ml.). The solid remaining was filtered off and washed with dilute nitric acid to leave silver bromide (0·45 g.). The filtrate was evaporated *in vacuo* below 0° to leave *silver α-trifluoromethylglycerate* (0·46 g.) (Found: Ag, 37·8. $C_4H_4AgF_3O_3$ requires Ag, 38·4%).

(*b*) The pure bromo-acid (VII) (15·9 g.) was treated with silver oxide (22 g.) in water (250 ml.) as in (*a*). Acidification of the filtrate with 10% sulphuric acid (25 ml.) and isolation by continuous ether-extraction gave the hygroscopic *2-trifluoromethylglyceric acid* (IX) (8·6 g.), m. p. 95—97° (from benzene) (Found: C, 27·7; H, 3·1. $C_4H_5F_3O_4$ requires C, 27·6; H, 2·9%). Impure specimens of the bromo-acid give syrupy products.

On being treated with aniline in dry ether the acid (IX) gave an *anilinium salt*, m. p. 131·5—132·5° (from acetone–chloroform) (Found: C, 44·4; H, 4·5. $C_{10}H_{12}F_3NO_4$ requires C, 44·9; H, 4·5%).

Ethyl α-Trifluoromethylglycerate (X).—The powdered silver salt (VIII) (6·5 g.) was added slowly to ethyl iodide (22 g.). Reaction was immediate and was completed by refluxing for 1 hr. The precipitated silver iodide was filtered off and the filtrate distilled. After removal of solvent there was obtained the *ethyl ester* (X) (2·3 g.), b. p. 89—92°/15 mm. (Found: C, 35·3; H, 4·6. $C_6H_9F_3O_4$ requires C, 35·6; H, 4·5%). Only a 10% yield of this ester was obtained when α-trifluoromethylglyceric acid was treated with ethanol and concentrated sulphuric acid.

Reduction of Ethyl α-Trifluoromethylglycerate (X).—The ester (1·9 g.) in dry ether (20 ml.) was added to a stirred suspension of lithium aluminium hydride (1·1 g., 3 mol.) in dry ether (30 ml.). The mixture was refluxed for 3 hr., then cooled. Water (2 ml.) was added, followed by 20% sulphuric acid (20 ml.). The aqueous layer was extracted continuously with ether, the extracts were dried ($MgSO_4$), and evaporated to leave an oil which solidified in a vacuum-desiccator over phosphorus pentoxide. The solid recrystallised from dry benzene and then sublimed at 50°/0·05 mm., to give the hygroscopic *2-trifluoromethylglycerol* (XI) (1·3 g.), m. p. 50—51° (sealed tube) (Found: C, 29·9; H, 4·1. $C_4H_7F_3O_3$ requires C, 30·0; H, 4·4%).

Benzoyl chloride and aqueous alkali converted the glycerol into its *dibenzoate*, m. p. 64—69° (purified by distillation at 125°/0·1 mm.) (Found: C, 58·8; H, 4·0. $C_{18}H_{15}F_3O_5$ requires C, 58·7; H, 4·1%).

The glycerol also formed a *diurethane* when refluxed with phenyl isocyanate for 30 min. in light petroleum (b. p. 80—100°) containing a trace of pyridine. It had m. p. 124—124·5° (from benzene) (Found: C, 54·8; H, 4·3. $C_{18}H_{17}F_3N_2O_5$ requires C, 54·3; H, 4·3%).

Reduction of α-Trifluoromethylglyceric Acid (IX).—The acid (6·2 g.) in dry ether (200 ml.) was slowly added to a stirred suspension of lithium aluminium hydride (3·5 g., 2·6 mol.) in dry ether (150 ml.). The mixture was refluxed for 3 hr. with stirring before being hydrolysed and acidified. Ether-extraction gave a pale syrup (4·7 g.) from which some 2-trifluoromethylglycerol (0·1 g.), m. p. 50—51°, was sublimed at 70°/0·05 mm. The remaining material was not volatile under these conditions. It was a neutral syrup which reduced Fehling's solution and had a strong absorption at 1630—1710 cm.$^{-1}$, indicative of either a carbonyl or a hydrated carbonyl group. The other infrared bands were broad, suggestive of a mixture or a polymer. The spectra of the materials obtained from different experiments were not identical, although they were very similar.

3-Bromo-2-trifluoromethylpropylene Oxide (XIII).—A dried solution of diazomethane (*ca.* 5·5 g.) in ether (300 ml.) was added during 30 min. with stirring to the ice-cooled bromo-ketone (I) (15·4 g.) under a low-temperature reflux condenser. After the solution had been kept for 16 hr. at 15°, it was refluxed for 1 hr. to remove excess of diazomethane and then distilled, to give the *epoxide* (6·4 g.), b. p. 115—118° (slight decomp.) (Found: C, 23·7; H, 2·0. $C_4H_4BrF_3O$ requires C, 23·4; H, 2·0%). Considerable decomposition occurred in an attempt to distil this compound, and much tar was produced.

3,3-Dibromo-2-trifluoromethylpropylene Oxide.—By the procedure used in the previous experiment, diazomethane (*ca.* 5·5 g.) in ether (300 ml.) reacted with the dibromo-ketone (31·5 g.), to give the corresponding *epoxide* (24 g.), b. p. 155—163° (Found: C, 17·1; H, 1·0. $C_4H_3Br_2F_3O$ requires C, 16·9; H, 1·1%).

Acidic Hydrolysis of the Epoxides.—(*a*) The monobromo-epoxide (XIII) (4·9 g.) and 2N-sulphuric acid (15 ml.) were heated together at 100° for 12 hr. The homogeneous aqueous solution obtained was continuously extracted with ether for 16 hr., and the extracts were dried ($MgSO_4$) and distilled, to give *3-bromo-2-trifluoromethylpropane-1,2-diol* (XIV) (4·0 g.), b. p. 92—95°/14 mm., n_D^{19} 1·4378 (Found: C, 21·5; H, 2·8. $C_4H_6BrF_3O_2$ requires C, 21·5; H, 2·7%).

(*b*) The dibromo-epoxide (17·75 g.) was treated with 2N-sulphuric acid (50 ml.) as in (*a*) for 6 hr., to give *3,3-dibromo-2-trifluoromethylpropane-1,2-diol* (14·5 g.), b. p. 117—120°/14 mm. (Found: C, 15·6; H, 1·6. $C_4H_5Br_2F_3O_2$ requires C, 15·9; H, 1·7%).

Alkaline Hydrolysis of the Bromo- and Dibromo-diols.—(*a*) The bromo-diol (XIV) (1·7 g.) was treated with a suspension of silver oxide (*ca.* 2·0 g.) in water (15 ml.) at 100° for 12 hr. The silver salts were removed and the filtrate was acidified and continuously extracted with ether for 16 hr. The extracts were dried ($MgSO_4$) and evaporated to leave a syrup which crystallised in a vacuum-desiccator over phosphorus pentoxide. The solid was sublimed at 50°/0·05 mm., to give 2-trifluoromethylglycerol (1·1 g.), m. p. 50—51°, shown by infrared spectroscopy to be identical with the material obtained by reduction of ethyl α-trifluoromethylglycerate.

(*b*) The dibromo-diol (5·12 g.) was treated with N-sodium hydroxide (50 ml.) for 5 min. at room temperature. Isolation as in (*a*) left a syrup (2·34 g.) which decomposed on attempted distillation. This syrup had the properties recorded on p. 3186. With sodium borohydride it did not give 2-trifluoromethylglycerol, and treatment with bromine water gave no α-trifluoromethylglyceric acid.

Bacteriological Tests.—The glyceric acid (IX) and the glycerol (XI) did not affect the growth, on a nutrient broth, of *Staphylococcus aureus*, *Streptococcus pyogenes*, *Klebsiella aerogenes*, or *Escherichia coli* to a significant extent. The minimum inhibitory concentrations of these substances were in excess of 500 μg./ml., observed for 24 hr. at 37°.

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