890. *Cyanohydrins of Ethyl γγγ-Trifluoroacetoacetate and 5,5,5-Trifluoro-4-oxopentanoic Acid.*

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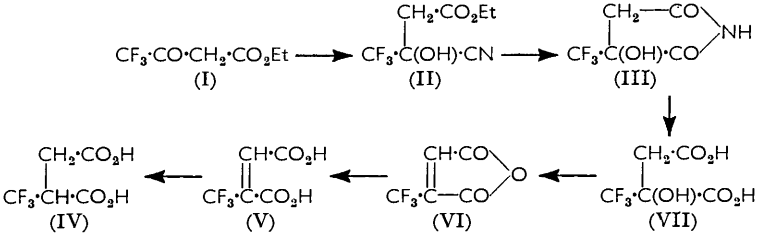
The cyanohydrins of ethyl γγγ-trifluoroacetoacetate (I) and 5,5,5-trifluoro-4-oxopentanoic acid (VIII) have been prepared by the usual method. That from the former has been hydrolysed to α-hydroxy-α-trifluoromethylsuccinic acid (VII), which was converted into α-trifluoromethylsuccinic acid (IV) by way of α-trifluoromethylmaleic acid (V). The pentanoic cyanohydrin (IX) has been hydrolysed to the corresponding acid lactone (XIII).

Ethyl acetoacetate has been converted into the corresponding cyanohydrin by a number of methods,[1,2] including treatment with aqueous potassium cyanide.[2] In an analogous manner we have prepared ethyl β-cyano-γγγ-trifluoro-β-hydroxybutyrate (II) in 56% yield from ethyl γγγ-trifluoroacetoacetate (I) by treatment with aqueous potassium cyanide at 0°, followed by sulphuric acid. The main reactions we have carried out, starting from this cyanohydrin (II), are summarised in the reaction scheme.



Mild acidic hydrolysis of the cyanohydrin (II) gave α-hydroxy-α-trifluoromethylsuccinimide (III) and not the corresponding ester-amide which was, however, almost certainly an intermediate in the hydrolysis and not unexpectedly cyclised during the reaction. More drastic hydrolysis gave the hydroxy-acid (VII), which was dehydrated fairly readily with phosphoric oxide to α-trifluoromethylmaleic anhydride (VI). Hydrolysis of this anhydride with cold dilute sulphuric acid gave the maleic acid (V): treatment with boiling water for only a few minutes liberated a small amount of fluoride ion, and use of 2N-alkali led to a much more extensive hydrolysis of the trifluoromethyl group. This is in line with the observation by Buxton, Stacey, and Tatlow,[3] that α-trifluoromethylacrylic acid and its derivatives lost fluoride ion very easily, even on treatment with boiling water. The ultraviolet spectrum of the maleic acid (V) [$\lambda_{max.}$ 207 mμ, ε 11,500] was very similar to that of maleic acid itself [$\lambda_{max.}$ 209 mμ, ε 12,000 [4]]. That this acid (V) was the *cis*- and not the *trans*-isomer is indicated by the very mild conditions under which it was obtained from the anhydride (VI), and by its relative ease of cyclisation back into the anhydride: even at 140°, approximately 10% of the anhydride (VI) had been formed after 1 hr. Maleic acid and its homologues are known [5] to be dehydrated easily at 160° and below, whereas fumaric acids are stable up to 200° at least.

Attempts have been made to convert the maleic acid (V) into its fumaric isomer. Treatment with a small amount of bromine in chloroform [5] and with sulphuric acid were both ineffective. Owing to the size of the trifluoromethyl group it is, of course, possible that the maleic acid (V) is the favoured form and not the fumaric isomer, as is usually the case [5] with these types of compound.

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[1] Demarçay, *Compt. rend.*, 1876, **82**, 1337; Mowry and Rossow, *J. Amer. Chem. Soc.*, 1945, **67**, 926.

[2] Bucherer and Grolee, *Ber.*, 1906, **39**, 1224.

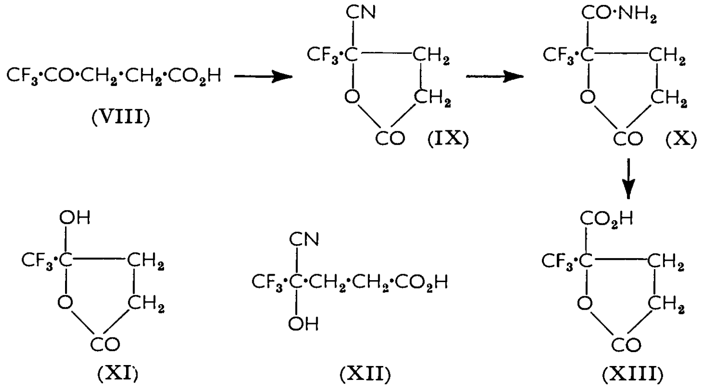
[3] Buxton, Stacey, and Tatlow, *J.*, 1954, 366.

[4] Ley and Wingchen, *Ber.*, 1934, **67**, 501.

[5] Rodd, " Chemistry of Carbon Compounds." Elsevier, London, Vol. 1B, 1952, pp. 987—1002.

The maleic acid (V) could not be hydrogenated to α-trifluoromethylsuccinic acid (IV) over Raney nickel: fluoride ion was liberated, presumably owing to the residual alkali present in this catalyst when it is prepared in the usual way. The reduction has, however, been effected in 34% yield with hydriodic acid and red phosphorus. Like other β-fluoro-acids [3] possessing an α-hydrogen atom, the succinic acid (IV) lost fluoride ion readily with dilute alkali.

The γγγ-trifluoro-analogue [6] (VIII) of lævulic acid, on being treated with aqueous potassium cyanide and then sulphuric acid, also gave a cyanohydrin (IX) (59% yield). This compound and the amide (X) and acid (XIII) derived from it, exist as lactones, and not as free acids [cf. (XII)]. Lævulic acid cyanohydrin and the acid obtained from it by hydrolysis are also known to have lactone structures.[7] In a previous paper [6] we suggested that the fluorinated lævulic acid itself (VIII) might exist in an isomeric cyclic form (XI). The infrared absorption of the cyanohydrin (IX) in the carbonyl region at 1830 cm.$^{-1}$ is also consistent [8] only with the lactone structure.



(VIII) (IX) (X) (XI) (XII) (XIII)

Experimental

Ethyl β-Cyano-γγγ-trifluoro-β-hydroxybutyrate (II).—A solution of potassium cyanide (15·0 g., 0·231 mole) in water (30 ml.) was added, with stirring, during 30 min. to an ice-cooled solution of ethyl γγγ-trifluoroacetoacetate (I) (30 g., 0·163 mole) in ethanol (100 ml.) and water (150 ml.). The mixture was stirred for 8 hr. at 0° and then acidified with 6N-sulphuric acid (125 ml.) and extracted continuously with ether for 18 hr. Distillation of the dried ($MgSO_4$) extracts afforded unchanged ethyl γγγ-trifluoroacetoacetate (4·5 g.), b. p. 28—36°/12 mm., identified by its infrared spectrum, and the crude product (16·4 g.), b. p. 92—96°/12 mm., which was redistilled to give *ethyl β-cyano-γγγ-trifluoro-β-hydroxybutyrate* (II) (12·3 g.), b. p. 93—94°/12 mm., n_D^{16} 1·3850 (Found: C, 40·0; H, 4·0. $C_7H_8F_3NO_3$ requires C, 39·8; H, 3·8%).

The crude product from the initial distillation was used for the later conversions.

When the reaction mixture was stirred at room temperature for 14 hr. it became very dark and only a 26% yield of the cyanohydrin was obtained.

4-Cyano-5,5,5-trifluoro-4-hydroxypentanoic Acid Lactone (IX).—5,5,5-Trifluoro-4-oxopentanoic acid [6] (VIII) (17·0 g., 0·10 mole) was neutralised with aqueous sodium hydrogen carbonate, and the solution was made up to 150 ml. This was cooled to 0° and potassium cyanide (6·5 g., 0·10 mole) in water (25 ml.), pre-cooled to 0°, was added, with stirring, during 30 min. The mixture was stirred at 0° for 7 hr. and then at room temperature for a further 16 hr. Acidification with 8N-sulphuric acid (25 ml.), followed by isolation as in the previous experiment, yielded *4-cyano-5,5,5-trifluoro-4-hydroxypentanoic acid lactone* (IX) (10·5 g.), b. p. 52·5—54·5°/0·3 mm., n_D^{16} 1·3916, $\nu_{max.}$ 1830 cm.$^{-1}$ (Found: C, 40·4; H, 2·5. $C_6H_4F_3NO_2$ requires C, 40·2; H, 2·3%).

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[6] Brown, Burdon, Smith, and Tatlow, *Tetrahedron*, 1960, **10**, 164.

[7] Adams and Hauserman, *J. Amer. Chem. Soc.*, 1952, **74**, 694.

[8] Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen & Co., London, 1954, pp. 159, 160.

Hydrolysis of the Cyanohydrins to the Amides.—(a) *α-Hydroxy-α-trifluoromethylsuccinimide* (III). Ethyl β-cyano-γγγ-trifluoro-β-hydroxybutyrate (II) (2·2 g.) and sulphuric acid (2 ml.; *d* 1·84) were heated together at 110—120° for 1 hr. The solution was cooled to 0°, water (50 ml.) was added, and the crude product was isolated by ether extraction. Recrystallisation from benzene gave *α-hydroxy-α-trifluoromethylsuccinimide* (III) (1·7 g.), m. p. 118—119° (Found: C, 32·7; H, 2·2. $C_5H_4F_3NO_3$ requires C, 32·8; H, 2·2%).

(b) 4-*Carbamoyl*-5,5,5-*trifluoro*-4-*hydroxypentanoic acid lactone* (X). The cyanohydrin (IX) (2·2 g.) was treated with sulphuric acid (2 ml.; *d* 1·84) as in (a), to give the *amide* (X) (1·8 g.), m. p. 136—137° (from water), $\nu_{max.}$ 1637, 1718, and 1810 cm.$^{-1}$ (Found: C, 37·0; H, 3·3. $C_6H_6F_3NO_3$ requires C, 36·6; H, 3·1%).

Hydrolysis of the Amides to the Acids.—(a) *α-Hydroxy-α-trifluoromethylsuccinic acid* (VII). The imide (III) (4·15 g.) was refluxed with 6N-sulphuric acid (50 ml.) for 17 hr. Extraction with ether, followed by evaporation of the dried ($MgSO_4$) extracts, left a gum (4·5 g.), which was distilled [130—150° (bath)/15 mm.]. The distillate solidified in a vacuum-desiccator over phosphoric oxide to give the hygroscopic *acid* (VII), m. p. 122—124° (Found: C, 29·7; H, 2·7%; equiv., 102. $C_5H_5F_3O_5$ requires C, 29·7; H, 2·5%; equiv., 101).

A neutralised aqueous solution of the acid, on treatment with aqueous *S*-benzylthiouronium chloride, gave the *bis*-S-*benzylthiouronium salt*, m. p. 168° (decomp.) (from aqueous ethanol) (Found: C, 46·9; H, 5·0. $C_{21}H_{25}F_3N_4O_5S_2$ requires C, 47·2; H, 4·7%).

(b) 4-*Carboxy*-5,5,5-*trifluoro*-4-*hydroxypentanoic acid lactone* (XIII). The amide (X) (0·30 g.) and 6N-sulphuric acid (10 ml.) were refluxed together for 8 hr. The crude product was isolated by continuous extraction with ether for 24 hr. and recrystallised from benzene, to give the *lactone* (XIII) (0·29 g.), m. p. 111—112° (Found: C, 36·7; H, 2·4%; equiv., 196. $C_6H_5F_3O_4$ requires C, 36·4; H, 2·5%; equiv., 198).

α-Trifluoromethylmaleic Anhydride (VI).—α-Hydroxy-α-trifluoromethylsuccinic acid (VII) (1·70 g.) was heated at 160—180° with an equal bulk of phosphoric oxide for 1 hr. The product was distilled *in vacuo* and then redistilled at atmospheric pressure, to give *α-trifluoromethylmaleic anhydride* (VI) (1·10 g.), b. p. 170—175° (Found: equiv., 85. $C_5HF_3O_3$ requires equiv., 83).

α-Trifluoromethylmaleic Acid (V).—A mixture of α-trifluoromethylmaleic anhydride (VI) (1·10 g.) and 4N-sulphuric acid (100 ml.) was left at room temperature until the anhydride had all dissolved (*ca.* 4 hr.). The solution was then extracted continuously with ether and the dried ($MgSO_4$) extracts were evaporated, to leave the slightly hygroscopic *α-trifluoromethylmaleic acid* (V) (1·12 g.), m. p. 99—104°, unchanged by recrystallisation from benzene, $\lambda_{max.}$ 207 mμ (ε 11,500 in water) (Found: C, 32·3; H, 2·0%; equiv., 95. $C_5H_3F_3O_4$ requires C, 32·6; H, 1·6%; equiv., 92).

Treatment of the acid with 2N-sodium hydroxide for 1 hr. at room temperature liberated fluoride ion. Infrared spectroscopy indicated that about 10% of the anhydride was formed when the acid was heated at 140° for 1 hr. The acid was recovered after being treated with concentrated sulphuric acid at room temperature for 3 days, or with boiling 2N-sulphuric acid for 3 hr., or with bromine (0·1 mol.) in chloroform in ultraviolet light for 8 hr.

The acid formed a *bis*-S-*benzylthiouronium salt*, m. p. 135—136° (decomp.) (from aqueous ethanol) (Found: C, 48·8; H, 4·5. $C_{21}H_{23}F_3N_4O_4S_2$ requires C, 48·8; H, 4·5%).

α-Trifluoromethylsuccinic Acid (IV).—α-Trifluoromethylmaleic acid (V) (0·81 g.), red phosphorus (*ca.* 0·4 g.), hydriodic acid (1·25 ml., *d* 1·70), and glacial acetic acid (12 ml.) were refluxed together for 3 hr., then diluted with water, acidified with sulphuric acid, filtered, and extracted continuously with ether. Evaporation of the dried ($MgSO_4$) extracts and recrystallisation of the residue from benzene gave *α-trifluoromethylsuccinic acid* (IV) (0·28 g.), m. p. 99°, depressed to 65—75° on admixture with the maleic acid (Found: C, 32·2; H, 2·9. $C_5H_5F_3O_4$ requires C, 32·3; H, 2·7%). Treatment of the acid with 2N-sodium hydroxide for 1 hr. at room temperature liberated fluoride ion.

The acid formed a *bis*-S-*benzylthiouronium salt*, m. p. 155—156° (from water) (Found: C, 48·5; H, 4·9. $C_{21}H_{25}F_3N_4O_4S_2$ requires C, 48·6; H, 4·9%).

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