897. *The Preparation of the Isomeric* 4,4,4-*Trifluorobutane-*1,2,3-*triols and* γγγ-*Trifluoro-*αβ-*dihydroxybutyric Acids.**

By J. Burdon, V. C. R. McLoughlin, and J. C. Tatlow.

Catalytic reduction of ethyl α-ethoxy-γγγ-trifluoro-β-oxobutyrate (V), prepared by the Claisen condensation of ethyl ethoxyacetate and ethyl trifluoroacetate, gave both isomers of ethyl α-ethoxy-γγγ-trifluoro-β-hydroxybutyrate (II and VIII). Drastic acidic hydrolysis of each gave the corresponding γγγ-trifluoro-αβ-dihydroxybutyric acid (IV and X); reduction of the esters by lithium aluminium hydride, followed by de-ethylation gave the isomeric 4,4,4-trifluorobutane-1,2,3-triols (VI and XI). Neither triol showed any antibacterial activity.

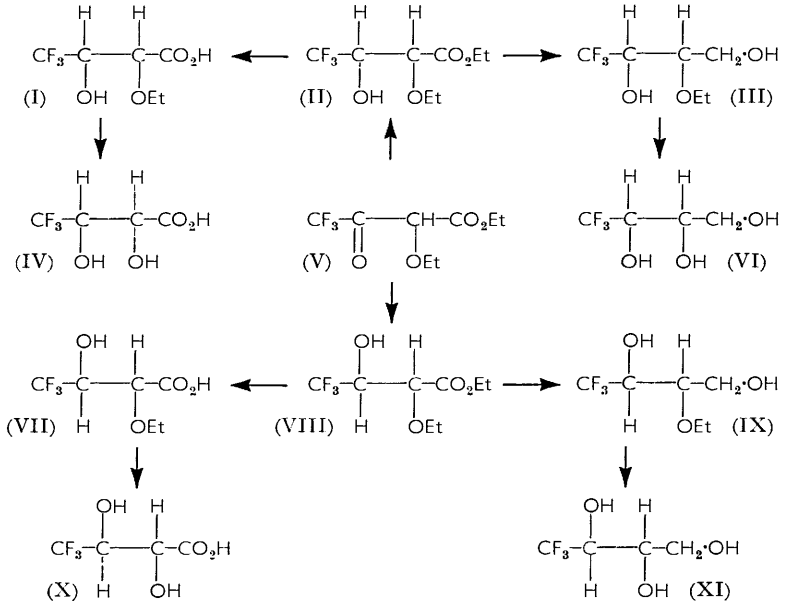
In a previous paper [1] we described the preparation of 2-trifluoromethylglycerol and 2-trifluoromethylglyceric acid. We have now prepared the related 4,4,4-trifluorobutane-1,2,3-triols and γγγ-trifluoro-αβ-dihydroxybutyric acids by the methods outlined below. Ethyl α-ethoxy-γγγ-trifluoro-β-oxobutyrate (V) was the starting material for all the syntheses. It was prepared in 42% yield by the Claisen condensation of ethyl ethoxyacetate and ethyl trifluoroacetate with sodium ethoxide as catalyst. It decomposed slightly on being heated and this appeared to affect the yield of the two isomeric ethyl α-ethoxy-γγγ-trifluoro-β-hydroxybutyrates (II and VIII),† which were obtained from it by catalytic

* Presented at the Fluorine Symposium, Birmingham, July, 1959.

† All formulæ are to be understood as referring to racemic forms.

[1] Burdon, McLoughlin, and Tatlow, *J.*, 1960, 3184.

hydrogenation, because high temperatures were necessary to effect this reaction. Gas-chromatographic analysis of the product of a reduction at 160—180° showed that some of the β-keto-ester (V) remained, and at 250° the total yield of mixed products was only 9%. At 190° very little starting material was unreduced, but the total yield of mixed products



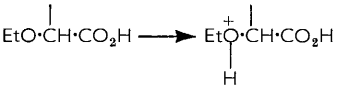
was still low, only 26%. The two esters (II and VIII) were separated by fractional distillation under reduced pressure to give the pure *threo-* (VIII) and *erythro-* (II) isomers, each in about 7% yield (see below for allocation of configuration). Reduction of each of these isomers by lithium aluminium hydride gave the corresponding 2-ethoxy-4,4,4-trifluorobutane-1,3-diols (IX and III) in good yield. The *threo*-isomer (IX) was crystalline and the *erythro*-isomer (III) a high-boiling liquid. An attempt was made to circumvent the low yield in the hydrogenation by directly reducing the β-keto-ester (V) with lithium aluminium hydride. However, gas-chromatographic analysis showed that the product was a complex mixture—analogous reductions of other β-keto-esters have given similar results.[2]

Treatment of each of the *O*-ethyl-triols (IX and III), under mild conditions, with 48% hydrobromic acid cleaved the ether linkages and gave almost quantitative yields of the corresponding 4,4,4-trifluorobutane-1,2,3-triols (XI and VI). The *threo*-isomer (XI) is crystalline and the *erythro*-isomer (VI) a high-boiling liquid. Both triols (VI and XI) were soluble in ether, as was 2-trifluoromethylglycerol,[1] in marked contrast to glycerol itself.

Treatment of the ethyl α-ethoxy-γγγ-trifluoro-β-hydroxybutyrates (VIII and II) with 48% hydrobromic acid under the conditions used to prepare the triols (VI and XI) from their ethyl ethers, did not give the parent dihydroxybutyric acids (X and IV), but instead a simple ester hydrolysis took place and the α-ethoxy-γγγ-trifluoro-β-hydroxybutyric acids (VII and I) were formed. Once again the *threo*-isomer (VII) was crystalline and the *erythro*-isomer (I) a liquid. In fact, much more drastic conditions were necessary to cleave the ether linkages and yield the free dihydroxy-acids. It is probable [3] that the

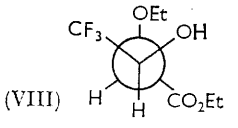
[2] Gaylord, " Reduction with Complex Metal Hydrides," Interscience Publ. Ltd., London, 1956, p. 164.
[3] Burwell, *Chem. Rev.*, 1954, **54**, 615.

initial step in the acidic cleavage of the ether links was protonation of the ether-oxygen atom:

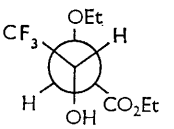


The rate of this step depends on the basicity of the oxygen atom and, because of the electronegativity of the carboxyl group, this basicity would be lower in the dihydroxy-acids than in the triols. Both γγγ-trifluoro-αβ-dihydroxybutyric acids (X and IV) were crystalline and both were soluble in ether.

The geometrical configurations of the triols (VI and XI) and the acids (IV and X) were allocated on three considerations, the first being the boiling points of the ethyl α-ethoxy-γγγ-trifluoro-β-hydroxybutyrates (VIII and II). Viewed down the line joining $C_{(2)}$ and $C_{(3)}$, in their planar zig-zag forms, which should be the most stable,[4] these molecules can be represented [5] as annexed:



(VIII)



(II)

From models, it does appear that these would be the most favoured conformations. The hydroxyl group in the *threo*-isomer (VIII) can form intramolecular hydrogen bonds with both ethoxycarbonyl and ethoxy-groups, whereas in the *erythro*-isomer (II) it can only do this with the ethoxycarbonyl group. The *erythro*-isomer (II) should therefore have the higher boiling-point since it can form intermolecular hydrogen bonds more easily.

Secondly, it has been demonstrated,[6] by paper ionophoresis, that at pH 10 the ease of formation by borate ion of complexes with adjacent pairs of hydroxyl groups is in the order αT > α > αC (these terms having the usual [7] meaning). The *threo*-triol (XI), which has αT and α pairs of hydroxyl groups, should form complexes more readily than the *erythro*-triol (VI), which has α and αC hydroxyl groups. Paper ionophoresis should therefore show that the *threo*-triol (XI) has a greater mobility in 0·05M-borate buffer than the *erythro*-isomer (VI). This was so, the M_G values [8] being 0·83 and 0·68, respectively. Thirdly, the same arguments [6] apply to paper ionophoresis in 0·2M-arsenite, and here the M_G values were 6·0 and 2·5 for the *threo*- and the *erythro*-triol respectively, although these were difficult to measure accurately.

Similar considerations should apply to oxidation by periodate. It is known [9] that the rate of cleavage of the carbon chain of a polyol depends on the configuration of the reacting hydroxyl groups in the order αT > α > αC. Since each of the triols requires two mol. of periodate for complete cleavage, it might be expected that one mol. of periodate would preferentially cleave the carbon chain between the αT-hydroxyl groups in the *threo*-triol (XI) and between the α-hydroxyl groups in the *erythro*-isomer (VI). The *erythro*-isomer (VI) should, therefore, with one mol. of periodate, give more formaldehyde than the *threo*-isomer (XI). Experimentally, by the usual technique,[10] both isomers gave virtually the same amount of formaldehyde (determined as its dimedone derivative); the *erythro*-isomer gave 53% and the *threo*-isomer 54% of the maximum amounts possible. This

[4] Barker, Bourne, and Whiffen, *J.*, 1952, 3865; McCoubrey, and Ubbelohde, *Quart. Rev.*, 1951, **5**, 364.
[5] Newman, *J. Chem. Educ.*, 1955, **32**, 344.
[6] Frahn and Mills, *Austral. J. Chem.*, 1959, **12**, 65.
[7] Barker and Bourne, *Adv. Carbohydrate Chem.*, 1952, **7**, 137.
[8] Foster, *J.*, 1953, 982.
[9] Schwartz, *J.*, 1957, 276.
[10] Reeves, *J. Amer. Chem. Soc.*, 1941, **63**, 1476.

equality must have been due to some modification of the properties of the hydroxyl groups by the trifluoromethyl group; it is known [11] that in many compounds the latter group can exercise profound effects on the reactivities of neighbouring hydroxyl groups.

In spite of this inconclusive result we have assigned the configurations of the isomers, as indicated, on the basis of the three other self-consistent observations.

Both trifluoro-triols (XI and VI) have been tested against two Gram-positive and two Gram-negative organisms. Neither compound showed any significant activity.

Experimental

Preparation of Ethyl α-*Ethoxy-*γγγ-*trifluoro-*β-*oxobutyrate* (V).—Ethyl trifluoroacetate (200 g.) was added slowly to a stirred suspension of sodium ethoxide (104 g.) in dry ether (300 ml.). After the reaction had subsided, ethyl ethoxyacetate (186 g.) was added and the mixture was refluxed for 86 hr. Volatile products were removed at 150°/14 mm. to leave a solid cake of sodio-derivative, which was decomposed by treatment with 4N-sulphuric acid (1 l.). A water-immiscible liquid separated and was extracted with ether. Distillation of the dried ($MgSO_4$) ethereal extracts gave the crude product (213 g.), b. p. 73—87°/15 mm., which was redistilled from phosphoric oxide to give *ethyl* α-*ethoxy-*γγγ-*trifluoro-*β-*oxobutyrate* (V) (134 g.), b. p. 80—87° (mainly 83—85°)/15 mm. (slight decomp.) (Found: C, 41·6; H, 5·1. $C_8H_{11}F_3O_4$ requires C, 42·1; H, 4·9%).

On treatment with 2,4-dinitrophenylhydrazine and concentrated sulphuric acid in methanol, this ester gave the light yellow 2,4-*dinitrophenylhydrazone*, m. p. 106—106·5° (from ethanol) (Found: C, 41·3; H, 3·8. $C_{14}H_{15}F_3N_4O_7$ requires C, 41·2; H, 3·7%).

Catalytic Reduction of Ethyl α-*Ethoxy-*γγγ-*trifluoro-*β-*oxobutyrate* (V).—The keto-ester (112·5 g.) was sealed in an autoclave with Raney nickel (*ca.* 6 g.) and ethanol (100 ml.). Hydrogen was introduced into the autoclave to a pressure of about 1500 lb./sq. in. The autoclave was then rocked and heated at 190° for 20 hr. The Raney nickel was filtered off, and the filtrate was fractionally distilled *in vacuo* through a 1 ft. vacuum-jacketed column packed with glass helices to give (i) a mixture of starting material and fraction (ii) (3·60 g.), b. p. 89—101·5°/14 mm., (ii) *ethyl* (±)-threo-α-*ethoxy-*γγγ-*trifluoro-*β-*hydroxybutyrate* (VIII) (8·45 g.), b. p. 101·5—105°/14 mm. (Found: C, 42·2; H, 5·7. $C_8H_{13}F_3O_4$ requires C, 41·7; H, 5·7%), (iii) a mixture of fractions (ii) and (iv) (9·1 g.), b. p. 105—110·5°/14 mm., and (iv) *ethyl* (±)-erythro-α-*ethoxy-*γγγ-*trifluoro-*β-*hydroxybutyrate* (II) (8·05 g.), b. p. 110·5—115°/14 mm. (Found: C, 41·9; H, 5·9%). Gas–liquid chromatographic analysis (didecyl phthalate–kieselguhr, N_2 carrier-gas) showed that fractions (ii) and (iv) were virtually free from each other and from the starting material.

A reduction carried out at 250° gave only a 9% yield of mixed products.

Reduction of the Isomeric Ethyl α-*Ethoxy-*γγγ-*trifluoro-*β-*hydroxybutyrates with Lithium Aluminium Hydride.*—(a) threo-*Isomer* (VIII). The ester (3·17 g.) in dry ether (20 ml.) was added to a stirred supension of lithium aluminium hydride (0·65 g.) in dry ether (20 ml.) at such a rate that the ether refluxed gently. The mixture was refluxed for 1½ hr., then water (1 ml.) was added cautiously, followed by 4N-sulphuric acid (10 ml.). The aqueous layer was continuously extracted with ether, and the ether layer and ether extracts were combined, dried ($MgSO_4$), and evaporated to leave (±)-threo-2-*ethoxy*-4,4,4-*trifluorobutane*-1,3-*diol* (IX), which was recrystallised from benzene to give the pure compound (1·78 g.), m. p. 68—68·5° (Found: C, 38·3; H, 6·0. $C_6H_{11}F_3O_3$ requires C, 38·3; H, 5·9%).

This ether (0·11 g.) and phenyl isocyanate (*ca.* 1 ml.) were refluxed together in light petroleum (10 ml.), containing two drops of pyridine, for 30 min. The solution was cooled and the solid which separated was filtered off and recrystallised from benzene–light petroleum (b. p. 80—100°) to give the 1,3-*di*-O-(*phenylcarbamoyl*) *derivative* (0·31 g.), m. p. 150—150·5° (Found: C, 56·1; H, 4·9. $C_{20}H_{21}F_3N_2O_5$ requires C, 56·3; H, 5·0%).

(b) erythro-*Isomer* (II). The ester (3·56 g.) was reduced with lithium aluminium hydride as in (a) to give (±)-erythro-2-*ethoxy*-4,4,4-*trifluorobutane*-1,3-*diol* (III) (1·85 g.), b. p. 125—128°/14 mm. (Found: C, 38·6; H, 6·1%).

This ether, treated with phenyl isocyanate as in (a), gave the 1,3-*di*-O-(*phenylcarbamoyl*)

[11] Bourne, Stacey, Tatlow, and Worrall, *J.*, 1958, 3268.

derivative, m. p. 168—169° [from benzene–light petroleum (b. p. 80—100°)] (Found: C, 56·6; H, 4·8%).

Isomeric 4,4,4-*Trifluorobutane*-1,2,3-*triols*.—(a) threo-*Isomer* (XI). (±)-*threo*-2-Ethoxy-4,4,4-trifluorobutane-1,3-diol (IX) (0·49 g.) was refluxed with 48% hydrobromic acid (6 ml.) for 1·5 hr. The mixture was treated with excess of barium carbonate, and the neutralised material was extracted continuously with ether for 16 hr. Evaporation of the dried ($MgSO_4$) extracts left crude (±)-threo-4,4,4-*trifluorobutane*-1,2,3-*triol* (XI) (0·39 g.), m. p. 60—68°, which was recrystallised from benzene to give the pure compound, m. p. 69—70°, depressed below room temperature on admixture with starting material (Found: C, 29·8; H, 4·1. $C_4H_7F_3O_3$ requires C, 30·0; H, 4·4%).

Treatment of this triol with an excess of phenyl isocyanate and a few drops of pyridine in light petroleum (b. p. 80—100°) gave the 1,2,3-*tri*-O-(*phenylcarbamoyl*) *derivative*, m. p. 189—192° [from benzene–light petroleum (b. p. 80—100°)] (Found: C, 58·0; H, 4·0. $C_{25}H_{22}F_3N_3O_6$ requires C, 58·0; H, 4·3%).

(b) erythro-*Isomer* (VI). (±)-*erythro*-2-Ethoxy-4,4,4-trifluorobutane-1,3-diol (III) (1·1 g.) was treated with 48% hydrobromic acid (10 ml.) as in (a), to give a crude product which was dried over phosphoric oxide for 2 days, filtered, and distilled to give (±)-erythro-4,4,4-*trifluorobutane*-1,2,3-*triol* (VI) (0·90 g.), b. p. 150—160° (bath)/20 mm. (Found: C, 30·6; H, 4·7%).

Treatment of this triol with phenyl isocyanate as in (a) gave the 1,2,3-*tri*-O-(*phenylcarbamoyl*) *derivative*, m. p. 212—213° (from benzene) (Found: C, 58·2; H, 4·3%).

Mild Acidic Hydrolysis of the Isomeric Ethyl α-*Ethoxy-γγγ-trifluoro*-β-*hydroxybutyrates*.—(a) threo-*Isomer* (VIII). The ester (2·18 g.) was refluxed for 1 hr. with 48% hydrobromic acid (7 ml.), then water (8 ml.) was added and the solution was refluxed for a further hour. The mixture was neutralised with silver carbonate, the silver salts were filtered off, and the filtrate was acidified with sulphuric acid. The acidic solution was continuously extracted with ether for 16 hr., and the ether extracts were dried ($MgSO_4$) and evaporated to leave a syrup (1·61 g.). This syrup partially crystallised in a vacuum-desiccator, and the crystals were recrystallised from benzene to give (±)-threo-α-*ethoxy-γγγ-trifluoro*-β-*hydroxybutyric acid* (VII) (0·3 g.), m. p. 105—105·5° (Found: C, 36·1; H, 4·2. $C_6H_9F_3O_4$ requires C, 35·6; H, 4·5%).

Treatment of the acid with aniline in dry ether gave a precipitate of the *anilinium salt*, m. p. 122° (from acetone–chloroform) (Found: C, 48·8; H, 5·2. $C_{12}H_{16}F_3NO_4$ requires C, 48·8; H, 5·5%).

(b) erythro-*Isomer* (II). The ester (3·75 g.) was refluxed for 1 hr. with 48% hydrobromic acid (10 ml.), then water (14 ml.) was added and the solution refluxed for 1 hr. more. The product, an oil, was isolated as in (a) and was presumably (±)-*erythro*-α-ethoxy-γγγ-trifluoro-β-hydroxybutyric acid (I). It did not crystallise and on distillation it decomposed slightly. Treatment of it with aniline in dry ether gave the *anilinium salt*, m. p. 86—88° [from light petroleum (b. p. 80—100°)] (Found: C, 48·8; H, 5·1%).

Isomeric γγγ-Trifluoro-αβ-*dihydroxybutyric Acids*.—(a) threo-*Isomer* (X). The (±)-*threo*-α-ethoxy-acid (VII) (0·36 g.) and 48% hydrobromic acid (15 ml.) were refluxed together for 24 hr. The reaction mixture was treated as in (a) of the previous experiment to give (±)-threo-*γγγ-trifluoro*-αβ-*dihydroxybutyric acid* (X) (0·21 g.) (from benzene), m. p. 114—116°, depressed to 80—90° on admixture with the starting material (Found: C, 27·9; H, 3·1. $C_4H_5F_3O_4$ requires C, 27·6; H, 2·9%).

(b) erythro-*Isomer* (IV). The (±)-*erythro*-ethoxy-acid (I) (1·2 g.) was refluxed with 48% hydrobromic acid (5 ml.) for 6 hr. Isolation as in (a) gave (±)-erythro-*γγγ-trifluoro*-αβ-*dihydroxybutyric acid* (IV) (0·95 g.), m. p. 135—136·5° (softens *ca.* 100°) (from benzene) (Found: C, 27·4; H, 2·7%).

Paper Ionophoresis of the Isomeric 4,4,4-*Trifluorobutane*-1,2,3-*triols*.—The separations were effected on Whatman No. 3 filter paper by the enclosed-strip technique previously described.[12] In 0·05M-sodium borate (pH 10), a voltage gradient of *ca.* 20 v/cm. and a current of *ca.* 8 milliamp. were used; and in 0·2M-sodium arsenite (pH 9·6) the voltage gradient was *ca.* 20 v/cm. and the current *ca.* 18 milliamp. The 0·05M-borate experiment was run for 2 hr., and the 0·2M-arsenite one for 3 hr. The ionophoretograms were developed [13] with alkaline silver nitrate. M_G values were (*trans*-cyclohexane-1,2-diol marker): (*a*) in 0·05M-borate; (±)-*threo*-4,4,4-trifluorobutane-1,2,3-triol (XI) 0·83, the (±)-*erythro* isomer (VI) 0·68: (*b*) in

[12] Foster, *Chem. and Ind.*, 1952, 1050.
[13] Trevelyan, Proctor, and Harrison, *Nature*, 1950, **166**, 444.

0·2M-arsenite; the (±)-*threo*-triol 6·0, the (±)-*erythro*-isomer 2·5. The values for the arsenite buffer are very approximate, owing to the difficulty in accurately measuring the (small) movement of glucose from the marker. Nevertheless, the ratio of M_G values of the two triols for this buffer lies between two and three.

Periodate Oxidation of the Isomeric Trifluoro-triols.—The triols (0·096 g.) were each dissolved in 0·012M-potassium periodate (50 ml., 1 mol.), and the solutions were left at room temperature for 45 hr. A spot test with potassium iodide showed that, in both cases, less than 10% of the periodate then remained. Each solution was poured into a saturated solution (in water containing 0·5% of ethanol) of dimedone (150 ml.), and the resulting solutions were left at room temperature for 24 hr. before the formaldehyde dimedone derivatives were filtered off and dried at 90°. The (±)-*threo*-triol (XI) gave 0·096 g. of the derivative, and the *erythro*-isomer (VI) 0·094 g. Both derivatives had m. p. 185—187°, raised to 188—189° on admixture with an authentic specimen (cited [10] value, 189—190°).

Bacteriological Tests.—Neither triol affected the growth, on a nutrient broth, of *Staphylococcus aureus*, *Streptococcus pyogenes*, *Klebsiella aerogenes*, or *Escherichia coli* to any significant extent. The minimum inhibitory concentrations of these substances were in excess of 1000 μg./ml., observed over a period of 24 hr. at 37°.

The authors thank Professor M. Stacey, F.R.S., for his interest, the University of Birmingham for the award of a Research Scholarship (to V. C. R. M.), Dr. A. S. Jones and Mr. E. T. J. Chelton for carrying out the bacteriological tests, and Dr. A. B. Foster for help with the ionophoresis experiments.

CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

[*Received, May 18th*, 1960.]