542. *Trifluoroisopropylidene Derivatives of Mannitol.**

By E. J. Bourne, A. J. Huggard, M. Stacey, and J. C. Tatlow.

Condensation of D-mannitol with 1,1,1-trifluoroacetone in the presence of concentrated sulphuric acid gives a mixture of bis- and tris-*O*-trifluoroisopropylidenemannitol.† Two crystalline compounds isolated from the diketal fraction have been shown to be isomeric forms of 1,2:5,6-bis-*O*-trifluoroisopropylidene-D-mannitol, differing in the configurations of the carbon atoms carrying the trifluoromethyl groups. The syrupy triketal fraction is probably a complex mixture of similar isomeric forms of 1,2:3,4:5,6-tris-*O*-trifluoroisopropylidene-D-mannitol. The 1,3-dioxolan rings in these compounds are exceptionally stable to acids and to other reagents.

After review [1] of published data on cyclic acetals and ketals of polyhydroxy-compounds, it was possible [2] to extend Hann and Hudson's empirical rules,[3] governing the order in which any aldehyde reacts with the hydroxyl groups in an acyclic polyol. These rules were interpreted subsequently in terms of the spatial arrangement of the atoms in the parent polyols [4] and in the cyclic products.[5] Less experimental evidence was available about syntheses of cyclic ketals of polyols, but it was apparent that there was a marked preference here for the formation of five-membered rings, which could be of either α- or αT-type.[1,2] As regards the effect of substituents, it had been reported [6,7] only that electrophilic and electrophobic substituents favoured the production of, respectively, five-membered and six-membered rings from glycerol. We now record studies of the condensation of D-mannitol with 1,1,1-trifluoroacetone.

Commercial D-mannitol and an excess of 1,1,1-trifluoroacetone in the presence of concentrated sulphuric acid yielded a fluorine-containing oil; this was separated by distillation into two fractions, which gave analyses correct for tris- and bis-*O*-trifluoroisopropylidenehexitols, the former predominating. With 2·2 mols. of ketone the diketal fraction was the main product.

It was not possible to characterise the triketal fraction by the customary technique of partial hydrolysis with dilute acid, owing to the remarkable stability of the ketal groups. Thus it was recovered unchanged after treatment with 9N-sulphuric acid at 100° for 3 hr., with 47% hydriodic acid at 160° for 3 hr., and with the acetolysing mixture described by Hann, Maclay, and Hudson [8] at 100° for 2 hr. In addition, the triketal was resistant to oxidation (permanganate), reduction (Raney nickel, lithium aluminium hydride), and aqueous alkali.

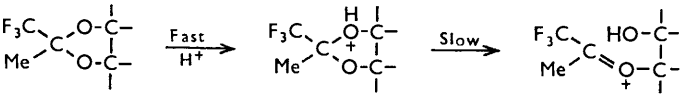
This resistance of the triketal towards acid is to be expected if the rate-determining step is the rupture of a carbon–oxygen bond in the protonated species, as in the case of acyclic acetals.[9,10] This step (and indeed the initial protonation) would be opposed by the strongly electrophilic trifluoromethyl group. Similarly, reaction with the acetylium

* Presented at XIVth Internat. Congr. Pure Appl. Chem., Zurich, 1955.

† By formal nomenclature [" Nomenclature of Organic Chemistry " (I.U.P.A.C. 1957 Rules), Butterworths, London, 1958] the name isopropylidene is restricted to the unsubstituted group (rule A–4·1), and the group CF_3·CMe= should be termed 2,2,2-trifluoro-1-methylethylidene. However, the name trifluoroisopropylidene is used in this paper to preserve the analogy with CMe_2=. Ed.

[1] Barker and Bourne, *Adv. Carbohydrate Chem.*, 1952, **7**, 137.
[2] Barker and Bourne, *J.*, 1952, 905.
[3] Hann and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 1909; Ness, Hann, and Hudson, *ibid.*, 1948, **70**, 765.
[4] Barker, Bourne, and Whiffen, *J.*, 1952, 3865.
[5] Mills, *Adv. Carbohydrate Chem.*, 1955, **10**, 2.
[6] Hibbert, Morazain, and Paquet, *Canad. J. Res.*, 1930, **2**, 131.
[7] Trister and Hibbert, *Canad. J. Res.*, 1936, **14**, *B*, 415.
[8] Hann, Maclay, and Hudson, *J. Amer. Chem. Soc.*, 1939, **61**, 2432.
[9] Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell and Sons Ltd., London, 1953, p. 334.
[10] Newman and Harper, *J. Amer. Chem. Soc.*, 1958, **80**, 6350.

ion ($CH_3 \cdot CO^+$), the active species in acetolysis, would be inhibited. Nevertheless, the magnitude of the difference in the stabilities to acids of isopropylidene and trifluoroisopropylidene ketals is surprising, though cyclic acetals containing trichloromethyl groups also have enhanced stability towards acids [6,11] and trifluoroacetone forms a solid hydrate.[12]



The powerful effects of neighbouring trifluoromethyl groups on the properties of the oxygen atoms in alcohols are now well established.[13,14]

The diketal fraction contained at least two isomers. A portion solidified, and on repeated recrystallisation gave a bis-*O*-trifluoroisopropylidenehexitol (isomer A, m. p. 128—129°). This gave a diacetate (m. p. 91—93°) and a dimethyl ether (m. p. 46—47°), which confirm the presence of two free hydroxyl groups. No isomeric diketal was isolated directly from the syrupy residues from the original crystallisation, but a second diacetate (m. p. 131—132°) was obtained which was deacetylated catalytically to give the parent diketal (isomer B, m. p. 82—83°); methylation of this yielded a new dimethyl ether (m. p. 67—68°). Each diketal was converted into the corresponding diacetate and then regenerated, showing that no interconversions of the ketals had occurred during their isolation.

Since the purified diketal isomers could be isolated only in relatively small yield, we established that neither was derived from D-sorbitol present as an impurity in the commercial D-mannitol first used, by preparing both from D-mannitol which had been crystallised until infrared analysis revealed no impurity.[15] Thus unless inversion occurred during their synthesis, which is unlikely, both diketals were D-mannitol derivatives.

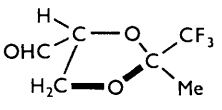
Each diketal consumed one mol. of lead tetra-acetate, without yielding formaldehyde, so that each diketal contained a non-terminal α-glycol group. This was proved in each case to involve the 3,4-positions by the isolation, from the oxidation products, of 2,3-*O*-trifluoroisopropylidene-D-glyceraldehyde (I), as crystalline derivatives with dimedone and 2,4-dinitrophenylhydrazine. Molecular-weight determinations and elemental analyses on the former derivatives showed that two dimedone residues were involved for each glyceraldehyde unit. Thus each diketal is a 1,2:5,6-bis-*O*-trifluoroisopropylidene-D-mannitol (II). This was confirmed for isomer A when its dimethyl ether (III) was synthesised from the known [16] 3,4-di-*O*-methyl-D-mannitol (IV) and 1,1,1-trifluoroacetone.

Evidently the isomeric diketals differed, not in the position of the ketal groups on the mannitol moiety, but in the stereochemical arrangements at the carbon atoms carrying the trifluoromethyl groups. This was proved when the 2,3-*O*-trifluoroisopropylidene-D-glyceraldehydes (I) derived from the two diketals gave different dimedone and 2,4-dinitrophenylhydrazine derivatives. The isomeric 2,3-*O*-trifluoroisopropylidene-D-glyceraldehydes have severally structures (Ia and b) but it is not yet possible to say which is which. It follows that the two D-mannitol diketals A and B have two of the structures (IIa—c).

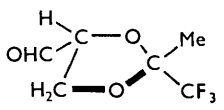
Although we cannot fix absolutely the stereochemistry of the trifluoroisopropylidene groups the following observations are significant. The diketal A, after oxidation with lead tetra-acetate, yielded 1·73 mol. of a pure crystalline dimedone derivative of 2,3-*O*-trifluoroisopropylidene-D-glyceraldehyde (isomer A); thus the two ketal rings had the same stereochemistry (IIa or IIc). On the other hand, the diketal B gave 1·72 mol. of a mixture of dimedone derivatives, from which only 0·65 mol. of pure material (isomer B) could be

[11] Goodhue, White, and Hixon, *J. Amer. Chem. Soc.*, 1930, **52**, 3191.
[12] Swarts, *Bull. Sci. Acad. Roy. Belg.*, 1927, **13**, 175.
[13] Swarts, *Bull. Soc. chim. belges*, 1929, **38**, 99.
[14] Bourne, Stacey, Tatlow, and Worrall, *J.*, 1958, 3268.
[15] Whiffen, *Chem. and Ind.*, 1957, 129.
[16] Bourne, Huggard, and Tatlow, unpublished results.

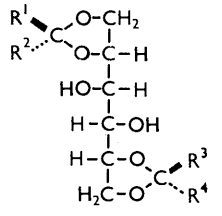
isolated. Likewise the two 2,4-dinitrophenylhydrazones were isolated in yields of 0·45 mol. (from isomer A) and 0·24 mol. (from isomer B). Probably, therefore, the diketal B has the " mixed " structure (IIb). It is likely that the crude diketal fraction contained also the third isomer but this could not be isolated. In addition, small amounts of the 1,2:3,4-diketals were probably present in the crude diketal fraction since a trace of formaldehyde



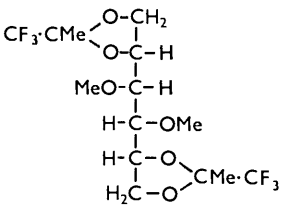
(Ia)



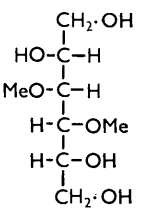
(Ib)



(II) a: $R^1 = R^3 = Me$, $R^2 = R^4 = CF_3$
b: $R^1 = R^4 = Me$, $R^2 = R^3 = CF_3$
c: $R^1 = R^3 = CF_3$, $R^2 = R^4 = Me$



(III)



(IV)

was isolated, as its dimedone derivative, from the products of oxidation with lead tetra-acetate. Undoubtedly, the syrupy triketal fraction was a mixture of the various isomeric forms of 1,2:3,4:5,6-tris-*O*-trifluoroisopropylidene-D-mannitol.

From this work it is clear that 1,1,1-trifluoroacetone parallels acetone itself [1,2] in the pattern of its condensation with D-mannitol; each gives rise to the 1,2:3,4:5,6-triketal, principally *via* the 1,2:5,6-diketal. However, the trifluoromethyl group greatly stabilises the 1,3-dioxolan ring, and this is believed to be the principal reason why it was possible to isolate isomers differing in the orientation of the trifluoroisopropylidene groups. Isolation of such isomers, long recognised as theoretically possible, is usually impossible in practice; it has been reported for 1,3:5,7-di-*O*-benzylideneperseitol [3] and 1,3-*O*-benzylideneglycerol; [17,18] but in these cases the isomers are very readily interconverted under mild conditions. Syntheses of cyclic acetals and ketals from polyols and carbonyl compounds are normally readily reversible, so that the stereochemistry of a given ring in a product is determined by thermodynamic considerations.[5] In the present case, it seems unlikely that the reaction is reversible, because of the stability of the ketal, and thus the stereochemistry of the products is determined by kinetic factors.

Experimental

Bis- and Tris-O-trifluoroisopropylidene-D-mannitol.—A mixture of D-mannitol (19·0 g.), 1,1,1-trifluoroacetone (20 ml.; 2·2 mol.) and concentrated sulphuric acid (70 ml.) was shaken at room temperature for 50 hr., then poured into ice-water and extracted exhaustively with ether. The extract was neutralised with sodium hydrogen carbonate, washed, dried ($MgSO_4$), and concentrated to a syrup (20·4 g.), which was fractionally distilled to give a mixture of tris-*O*-trifluoroisopropylidene-D-mannitols (1·94 g.), b. p. 74°/0·1 mm., n_D^{15} 1·3900, $[\alpha]_D^{17}$ +9·2° (*c* 3·15 in EtOH) (Found: C, 38·8; H, 3·7; F, 36·8. Calc. for $C_{15}H_{17}O_6F_9$: C, 38·8; H, 3·7; F, 36·8%), and a mixture of bis-*O*-trifluoroisopropylidene-D-mannitols (10·53 g.), b. p. 120—123°/0·15 mm. (Found: C, 39·2; H, 4·2; F, 31·4. Calc. for $C_{12}H_{16}O_6F_6$: C, 38·9; H, 4·4; F, 30·8%).

In the same way, D-mannitol (6·57 g.), 1,1,1-trifluoroacetone (5·4 mol.), and concentrated sulphuric acid (25 ml.), shaken together at room temperature for 96 hr., yielded the triketal

[17] Brimacombe, Foster, and Stacey, *Chem. and Ind.*, 1958, 1228.
[18] Baggett, Foster, and Stacey, *Chem. and Ind.*, 1958, 1229.

(6·01 g.) and diketal (3·32 g.) fractions. Thus an increased proportion of the ketone gave relatively more of the triketal.

Fractionation of the Mixed Diketals.—The mixture (10·5 g.) solidified when cold. Crystallised from carbon tetrachloride (20 ml.), it gave a solid (4·1 g.), together with a syrup (X) (6·3 g.) from the mother-liquors. Repeated recrystallisation of the solid from carbon tetrachloride and from benzene gave 1,2:5,6-*bis*-O-*trifluoroisopropylidene*-D-*mannitol* (*isomer A*) (1·56 g.), m. p. 128—129°, $[\alpha]_D^{10}$ +12·0° (*c* 2·50 in EtOH) (Found: C, 38·7; H, 4·6; F, 30·5%). Acetic anhydride (0·5 ml.) in pyridine (3 ml.) converted the diketal (A) (0·22 g.) in 72 hr. at 23° into its 3,4-*diacetate* (*isomer A*) (70%), m. p. 91—93° (from aqueous ethanol), $[\alpha]_D^{13}$ +28·0° (*c* 2·65 in $CHCl_3$) (Found: C, 42·5; H, 4·7; F, 24·7; Ac, 20·3. $C_{16}H_{20}O_8F_6$ requires C, 42·3; H, 4·4; F, 25·1; Ac, 18·9%). The m. p. of this diacetate was depressed on admixture with its isomer B. The diketal (isomer A) was regenerated (65%) by deacetylation with sodium methoxide in dry methanol.

Syrup (X) was treated with acetic anhydride (10 ml.) in pyridine (15 ml.) at 15° for 48 hr. Isolation of the product in the usual manner, followed by five crystallisations from ethanol, yielded 3,4-*di*-O-*acetyl*-1,2:5,6-*bis*-O-*trifluoroisopropylidene*-D-*mannitol* (*isomer B*) (1·34 g.), m. p. 131—132°, $[\alpha]_D^{18}$ +19·7° (*c* 6·90 in $CHCl_3$) (Found: C, 42·5; H, 4·6; F, 25·0; Ac, 19·2%). Catalytic deacetylation afforded, in 72% yield, 1,2:5,6-*bis*-O-*trifluoroisopropylidene*-D-*mannitol* (*isomer B*), m. p. 82—83°, $[\alpha]_D^{16}$ +2·2° (*c* 0·92 in $CHCl_3$) (Found: C, 39·1; H, 4·5; F, 31·0%). Reacetylation regenerated the diacetate (isomer B) (79%).

In repetitions of this experiment, the D-mannitol used had been crystallised repeatedly from aqueous ethanol until infrared analysis indicated that a small impurity (probably sorbitol) had been removed completely.[15] The diketal, m. p. 128—129°, and diacetate, m. p. 131—132°, were again isolated, in proportions similar to those above.

Oxidation of 1,2:5,6-*Bis*-O-*trifluoroisopropylidene*-D-*mannitol* (*Isomer A*).—Quantitative determination [19] of the oxidation of the diketal with lead tetra-acetate in glacial acetic acid showed that, after 50, 70, and 120 min., the consumption of the oxidant was 0·86, 0·99, and 1·04 mol., respectively.

The diketal (0·0455 g.) was oxidised with excess of a saturated solution of lead tetra-acetate in acetic acid, and the products were steam-distilled under reduced pressure. The distillate, adjusted to pH 6·0, was treated with dimedone (0·120 g.) in ethanol (1·5 ml.) at 100° for 10 min. and then at room temperature for 12 hr. The precipitate was the *bisdimedone derivative* (*isomer A*) of 2,3-*O*-trifluoroisopropylidene-D-glyceraldehyde (1·73 mol.), m. p. 133—134°, unchanged by crystallisation from aqueous alcohol, $[\alpha]_D^{10}$ −8·2° (*c* 3·16 in $CHCl_3$), fluorine test positive (Found: C, 58·9; H, 6·7%; *M*, by cryoscopy in benzene, 410. $C_{22}H_{29}O_6F_3$ requires C, 59·2; H, 6·5%; *M*, 446).

In a similar experiment, the steam-distillate from the oxidised diketal (isomer A) (0·076 g.) was mixed with 2,4-dinitrophenylhydrazine (0·081 g.) in concentrated hydrochloric acid (50 ml.). The yellow precipitate was 2,3-O-*trifluoroisopropylidene*-D-*glyceraldehyde* 2,4-*dinitrophenylhydrazone* (*isomer A*) (0·45 mol.), m. p. 128—129° (from ethanol) (Found: C, 39·7; H, 3·2; F, 15·3. $C_{12}H_{11}O_6N_4F_3$ requires C, 39·6; H, 3·1; F, 15·6%).

Oxidation of 1,2:5,6-*Bis*-O-*trifluoroisopropylidene*-D-*mannitol* (*Isomer B*).—The methods employed were as for isomer A. The consumption of lead tetra-acetate after 115, 160, and 250 min. was 0·86, 0·98, and 0·98 mol., respectively.

The diketal (isomer B) (0·192 g.), after oxidation, gave a precipitate (1·72 mol.) of fluorine-containing dimedone derivatives, m. p. 139—144°. Several crystallisations from aqueous ethanol were necessary to obtain the *bisdimedone derivative* (*isomer B*) of 2,3-*O*-trifluoroisopropylidene-D-glyceraldehyde (0·65 mol.), m. p. 161—162°, $[\alpha]_D^{11}$ −22·1° (*c* 1·72 in $CHCl_3$) (Found: C, 59·3; H, 6·2%; *M*, by cryoscopy in benzene, 413). This compound depressed the m. p. of its isomer A. No more pure material could be isolated from the mother-liquors.

From the diketal (isomer B) there was isolated, after oxidation, 2,3-*O*-*trifluoroisopropylidene*-D-*glyceraldehyde* 2,4-*dinitrophenylhydrazone* (*isomer B*) (0·24 mol.), m. p. 101—102° (from ethanol), depressed by its isomer A (Found: C, 39·8; H, 2·9; F, 15·2%). Again no more pure material could be isolated from the mother-liquors.

3,4-*Di*-O-*methyl*-1,2:5,6-*bis*-O-*trifluoroisopropylidene*-D-*mannitol.*—(a) *From the diketals by methylation.* Sodium (0·40 g.) was added in small portions to a solution of the diketal (isomer A; m. p. 128—129°; 1·26 g.) in liquid ammonia. The solution was cooled to −70° and methyl

[19] Hockett and McClenahan, *J. Amer. Chem. Soc.*, 1939, **61**, 1667.

iodide (4·0 ml.) added slowly. Volatile material was removed and the residue was extracted exhaustively with chloroform; the extracts were washed, dried ($MgSO_4$), and concentrated to a syrup (0·89 g.) which crystallised. Recrystallisation from ethanol gave plates of the **3,4-*dimethyl ether* (*isomer A*)** (0·40 g.), m. p. 46—47°, $[\alpha]_D^{18}$ +13·4° (*c* 3·12 in $CHCl_3$) (Found: C, 42·5; H, 5·2; F, 28·5; OMe, 15·3. $C_{14}H_{20}O_6F_6$ requires C, 42·2; H, 5·1; F, 28·6; OMe, 15·6%).

Likewise, the diketal (isomer B, m. p. 82—83°) gave a 67% yield of the **3,4-*dimethyl ether* (*isomer B*)**, m. p. 67—68°, $[\alpha]_D^{16}$ +8·6° (*c* 0·84 in $CHCl_3$) (Found: C, 42·6; H, 5·0; F, 28·1; OMe, 15·8%).

Although several mixtures of the two isomeric dimethyl ethers were examined none had m. p. below 46°; the two ethers gave markedly different infrared spectrographs in the region 700—1500 cm.$^{-1}$.

(b) *From* **3,4-*di*-O-*methyl*-D-*mannitol*.** Concentrated sulphuric acid (20 ml.) was added slowly to a mixture of 1,1,1-trifluoroacetone (15·0 ml.) and 3,4-di-*O*-methyl-D-mannitol (5·33 g., prepared [16] from 1,2:5,6-di-*O*-isopropylidene-D-mannitol). The mixture was shaken at room temperature for 2 days, poured into ice-water, and extracted with chloroform. The extract was washed with sodium hydrogen carbonate, dried ($MgSO_4$), and concentrated to a syrup (5·99 g.), which on distillation afforded a fraction (1·75 g.), b. p. 90°/0·1 mm., which crystallised. Crystallisation thrice from ethanol gave 3,4-di-*O*-methyl-1,2:5,6-bis-*O*-trifluoroisopropylidene-D-mannitol (isomer A) (0·72 g.), m. p. 46—47°, $[\alpha]_D^{15}$ +12·7° (*c* 2·37 in $CHCl_3$) (Found: C, 42·5; H, 5·2; F, 28·9; OMe, 15·1%). The m. p. of this compound was not depressed by either of the isomers described above, but its infrared spectrum was identical with that of isomer A.

The authors thank Dr. C. E. M. Tatlow who carried out preliminary experiments, and the Department of Scientific and Industrial Research for the award of a scholarship (to A. J. H.).

CHEMISTRY DEPARTMENT, THE UNIVERSITY, BIRMINGHAM 15.
CHEMISTRY DEPARTMENT, ROYAL HOLLOWAY COLLEGE,
ENGLEFIELD GREEN, SURREY.

[*Received, January 8th*, 1960.]