279. *Studies of Trifluoroacetic Acid. Part II. Preparation and Properties of Some Trifluoroacetyl Esters.*

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The trifluoroacetyl esters of certain hydroxy- and polyhydroxy-compounds have been prepared under anhydrous conditions. Their properties are described; they are very susceptible to hydrolysis and to methanolysis.

Since the pioneering researches of Swarts (*Bull. Acad. roy. Belg., Classe Sci.*, 1922, **8**, 343) on the preparation and properties of trifluoroacetic acid and of its ethyl ester, comparatively little attention has been paid to trifluoroacetyl esters. As far as we are aware, the only other trifluoroacetates which have been reported are methyl (Gryszkiewicz-Trochimowski *et al.*, *Rec. Trav. chim.*, 1947, **66**, 419), vinyl (B.P. 589,197), 2 : 2 : 2-trifluoroethyl (Swarts, *Bull. Soc. chim. Belg.*, 1934, **43**, 471), butyl (Henne, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, 1944, 89), *iso*amyl (Swarts, *Bull. Soc. chim. Belg.*, 1927, **36**, 191), and 2-methylbutadien-1-yl ("isoprene 1-yl") (U.S.P. 2,432,394). The only preparative methods so far employed which appear to be at all widely applicable entail (*a*) treatment of an alcohol with trifluoroacetic acid (or its sodium salt) in the presence of concentrated sulphuric acid (Swarts, *loc. cit.*, 1922) and (*b*) condensation of trifluoroacetyl chloride with the appropriate sodium alkoxide (Henne, *loc. cit.*). Method (*a*) was too drastic for use in the carbohydrate series. Method (*b*) presented practical difficulties because of the gaseous nature of both the acid chloride and the acid bromide, for which Simons and Ramler (*J. Amer. Chem. Soc.*, 1943, **65**, 389) quote b. p.s $-27°$ and $-5°$, respectively.

Accordingly, in this work, trifluoroacetic anhydride (b. p. 39°) was chosen as the acylating agent and esterification was effected by warming the appropriate alcohol with the anhydride in the presence of dry sodium trifluoroacetate. Early attempts to isolate mannitol hexakis-trifluoroacetate by pouring such a reaction mixture into aqueous sodium hydrogen carbonate solution indicated that the product was unstable under these conditions, so a standard method was devised by which the esters could be isolated under anhydrous conditions. The reaction mixture was distilled several times with dry carbon tetrachloride to remove excess of trifluoroacetic anhydride and trifluoroacetic acid, and the ester was extracted from the residual sodium trifluoroacetate with dry carbon tetrachloride or dry petroleum. By this means p-*nitrobenzyl trifluoroacetate*, β-*naphthyl trifluoroacetate*, D-*mannitol hexakistrifluoroacetate*, *dulcitol hexakis-trifluoroacetate*, and 2 : 3-*bistrifluoroacetyl* 4 : 6-*benzylidene* α-*methylglucoside* were obtained crystalline, whilst 2 : 3 : 4 : 6-*tetrakistrifluoroacetyl* α-*methylglucoside* and 3 : 5 : 6-*tristrifluoro-acetyl* 1 : 2-iso*propylidene* D-*glucofuranose* were isolated in the form of liquids.

Pyridine did not appear to be a suitable solvent in which to conduct esterifications using trifluoroacetic anhydride, since a mixture of the two rapidly darkened and left a brown solid when distilled.

The above trifluoroacetates were reasonably stable when pure and dry. They could be stored unchanged for several days in a vacuum over phosphoric oxide and, in certain cases, could be purified by distillation under diminished pressure. In the presence of water, however, they were readily hydrolysed, apparently by an autocatalytic reaction, to give the parent alcohol and trifluoroacetic acid. This property was very marked with the esters of polyhydroxy-compounds. Whereas we were unable to recover mannitol hexakistrifluoroacetate from any reaction mixture which was poured into water, most previous workers have employed this method for the isolation of trifluoroacetates which, however, have been derived hitherto from simple monohydric alcohols only. Thus it appears that two or more adjacent trifluoroacetoxy-groups are hydrolysed more readily than is an isolated substituent of this type.

We have found also that the above trifluoroacetates can be reconverted into their parent

alcohols by treatment with dry methyl alcohol under mild conditions. An indication of the ease with which this reaction proceeds was obtained polarimetrically in the case of mannitol hexakistrifluoroacetate. At 17°, the observed rotation of a dry methanolic solution of the ester fell to 70% of its original value in 1 hour and to zero overnight, by which time mannitol had crystallised out. The possibility of using methanolysis for the determination of trifluoroacetoxy-groups in the presence of other ester substituents is being examined.

It is noteworthy that, although the strength of trifluoroacetic acid approaches that of a mineral acid (Swarts, *loc. cit.*, 1922), a trifluoroacetyl residue, like acyl groups in general, is removed from an optically active ester without an accompanying Walden inversion or the formation of an anhydro-ring.

Experimental.

Precautions.—Unless otherwise stated, all operations involving trifluoroacetates were conducted with dry reagents under anhydrous conditions.

Preparation of Trifluoroacetic Anhydride.—The anhydride was prepared by the method of Swarts (*loc. cit.*, 1922), as modified by Bourne, Stacey, Tatlow, and Tedder (*J.*, 1949, 2976).

p-*Nitrobenzyl Trifluoroacetate.*—(a) *Preparation.* When *p*-nitrobenzyl alcohol (0·407 g.) was added to a mixture of trifluoroacetic anhydride (2·0 c.c.) and sodium trifluoroacetate (0·161 g.) a spontaneous reaction ensued. After being gently refluxed for 15 minutes, the homogeneous reaction mixture was distilled four times with carbon tetrachloride at 40—50° under slightly diminished pressure. The residue was extracted with three portions (15 c.c. each) of boiling light petroleum (b. p. 40—60°), filtered, and concentrated to a syrup, which crystallised. The product (0·502 g.), m. p. 46—48°, was decolorised with charcoal in boiling light petroleum and filtered. The filtrate deposited crystals of p-*nitrobenzyl trifluoroacetate* (0·232 g.), m. p. 47° (Found : CF_3·CO, 39·2. $C_9H_6O_4NF_3$ requires CF_3·CO, 38·95%).

(b) *Hydrolysis.* The neutral residues from the trifluoroacetyl estimation were extracted thrice with chloroform. The combined extracts were dried ($MgSO_4$), filtered, and concentrated, the solid residue being recrystallised from light petroleum (b. p. 100—120°) to give *p*-nitrobenzyl alcohol (yield, 73%), m. p. and mixed m. p. 93—95° (Found : C, 55·2; H, 4·4. Calc. for $C_7H_7O_3N$: C, 54·9; H, 4·6%).

(c) *Methanolysis.* A solution of *p*-nitrobenzyl trifluoroacetate (0·078 g.) in magnesium-dried methyl alcohol (10 c.c.) was kept at room temperature for 2 days. The solvent was removed under diminished pressure and the residue was crystallised from light petroleum (b. p. 100—120°). The product (0·030 g.) had m. p. 93—95°, alone and in admixture with authentic *p*-nitrobenzyl alcohol.

β-Naphthyl Trifluoroacetate.—(a) *Preparation.* β-Naphthol (0·800 g.), trifluoroacetic anhydride (3·50 c.c.), and sodium trifluoroacetate (0·301 g.) were gently refluxed for 15 minutes and then distilled thrice with carbon tetrachloride under slightly diminished pressure. The residue was extracted several times with boiling light petroleum (b. p. 40—60°) and filtered. The filtrate, concentrated to 5 c.c., deposited crystals of *β-naphthyl trifluoroacetate* (1·193 g.), m. p. 75—76°, unchanged by recrystallisation [Found : F, 23·4; CF_3·CO (end-point determined potentiometrically), 39·8. $C_{12}H_7O_2F_3$ requires F, 23·7; CF_3·CO, 40·4%].

(b) *Methanolysis.* A solution of β-naphthyl trifluoroacetate (0·176 g.) in magnesium-dried methyl alcohol (7 c.c.) was kept at 45° for 90 minutes before the solvent was removed under diminished pressure. The residue, recrystallised from light petroleum (b. p. 60—80°), afforded β-naphthol (0·078 g.), m. p. and mixed m. p. 122—123°.

D-*Mannitol Hexakistrifluoroacetate.*—(a) *Preparation.* D-Mannitol (0·307 g.), sodium trifluoroacetate (0·210 g.), and trifluoroacetic anhydride (6·50 c.c.) were gently refluxed for 2 hours, before being distilled four times with carbon tetrachloride under slightly diminished pressure. The residue was extracted with three portions (20 c.c. each) of boiling carbon tetrachloride. The combined extracts were filtered and, on cooling, the filtrate afforded the *ester* (1·054 g.), m. p. 54°. Recrystallised from carbon tetrachloride, it (0·804 g.) had m. p. 55—56°, $[\alpha]_D^{21}$ +24·1° (*c*, 1·77 in chloroform) (Found : F, 45·4; CF_3·CO, 75·8. $C_{18}H_8O_{12}F_{18}$ requires F, 45·1; CF_3·CO, 76·8%).

(b) *Hydrolysis.* D-Mannitol hexakistrifluoroacetate (0·190 g.) was dissolved at 21° in aqueous alcohol (10 c.c.; water, 20% by vol.) and kept at 21° for 20 hours, by which time $[\alpha]_D^{21}$ had fallen from +14·8° (4 minutes) to ±0·0° and acidity had developed. The solution was evaporated at 70°/15 mm., and the residue crystallised from aqueous alcohol in needles (0·033 g.), m. p. 165—167°, alone and in admixture with authentic D-mannitol. Acetylation of the product afforded D-mannitol hexa-acetate in 62% yield, m. p. and mixed m. p. 122—123°, $[\alpha]_D^{19}$ +24·0° (*c*, 0·75 in chloroform).

(c) *Methanolysis.* The hexa-ester (0·299 g.) was dissolved at 17° in magnesium-dried methyl alcohol (10 c.c.) and kept at 17° for 20 hours, by which time needles had separated and $[\alpha]_D^{17}$ had fallen from +17·0° (2 minutes) to ±0·0°. The crystalline product (0·041 g.) had m. p. 165°, alone and in admixture with authentic D-mannitol, and by acetylation gave D-mannitol hexa-acetate in 68% yield, m. p. and mixed m. p. 122—123°, $[\alpha]_D^{19}$ +24·5° (*c*, 0·86 in chloroform).

Dulcitol Hexakistrifluoroacetate.—(a) *Preparation.* Dulcitol (0·298 g.), sodium trifluoroacetate (0·306 g.), and trifluoroacetic anhydride (4·50 c.c.) were gently refluxed for 75 minutes. The homogeneous reaction mixture, treated as in the case of the mannitol ester, yielded *dulcitol hexakistrifluoroacetate* in white plates (0·990 g.), m. p. 89—91°, unchanged by recrystallisation (Found : F, 44·95; CF_3·CO, 77·0. $C_{18}H_8O_{12}F_{18}$ requires F, 45·1; CF_3·CO, 76·8%).

(b) *Methanolysis.* This ester (0·286 g.) was heated for 45 minutes with boiling magnesium-dried methyl alcohol (5 c.c.). Crystals of dulcitol (0·060 g.) were deposited on cooling, m. p. and mixed m. p. 186—188° (Found : C, 39·8; H, 7·5. Calc. for $C_6H_{14}O_6$: C, 39·55; H, 7·75%).

2 : 3 : 4 : 6-*Tetrakistrifluoroacetyl* α-*Methyl*-D-*glucopyranoside.*—(a) *Preparation.* α-Methylglucoside (0·537 g.), sodium trifluoroacetate (0·202 g.), and trifluoroacetic anhydride (4·50 c.c.) were gently refluxed for 15 minutes and then treated as in the case of *p*-nitrobenzyl trifluoroacetate. The residual syrup,

which did not crystallise, was distilled at 158—160° (bath temp.)/12 mm. to give a clear colourless oil (0·945 g.), n_D^{20} 1·3641, $[\alpha]_D^{21}$ +88° (*c*, 0·88 in carbon tetrachloride) (Found : F, 39·1; CF_3·CO, 67·35. $C_{15}H_{10}O_{10}F_{12}$ requires F, 39·4; CF_3·CO, 67·1%).

(b) *Methanolysis.* 2 : 3 : 4 : 6-*Tetrakistrifluoroacetyl* α-*methyl*-D-*glucopyranoside* (0·037 g.) was dissolved at 15° in magnesium-dried methyl alcohol (5 c.c.) and after 16 hours the solvent was removed at 40°/12 mm. The crystalline residue, recrystallised from methyl alcohol–ether, afforded α-methylglucoside (0·009 g.), m. p. and mixed m. p. 164—167°.

2 : 3-*Bistrifluoroacetyl* 4 : 6-*Benzylidene* α-*Methyl*-D-*glucopyranoside.*—(a) *Preparation.* When 4 : 6-benzylidene α-methylglucoside (3·039 g.), sodium trifluoroacetate (0·223 g.), and trifluoroacetic anhydride (6·00 c.c.) were mixed a vigorous reaction ensued. After several minutes, the reaction mixture was distilled under slightly diminished pressure with four portions (20 c.c. each) of carbon tetrachloride, and the residue was extracted with three portions (20 c.c. each) of boiling carbon tetrachloride. The combined extracts were filtered and evaporated to a syrup, which crystallised. Recrystallised twice from light petroleum (b. p. 40—60°), the *bistrifluoroacetyl* compound (1·522 g.) had m. p. 88—89°, $[\alpha]_D^{18}$ +77·6° (*c*, 0·80 in carbon tetrachloride). Although the ester was appreciably soluble in cold light petroleum, it appeared to be far more soluble in all the other common organic solvents and hence high losses during recrystallisation were inevitable (Found : F, 24·1; CF_3·CO, 41·15. $C_{18}H_{16}O_8F_6$ requires F, 24·0; CF_3CO, 40·9%).

(b) *Hydrolysis.* The titration liquors from the trifluoroacetyl determination were made just alkaline to phenolphthalein, and the acetone removed under diminished pressure. The aqueous residue was extracted with chloroform. The extract was dried ($MgSO_4$), filtered, and evaporated, leaving a solid, which was recrystallised from water in the presence of a trace of ammonia. The product, isolated in 62% yield, had m. p. 163°, not depressed in admixture with 4 : 6-benzylidene α-methylglucoside, $[\alpha]_D^{18}$ +115° (*c*, 0·30 in chloroform) (Found : C, 59·6; H, 6·4. Calc. for $C_{14}H_{18}O_6$: C, 59·55; H, 6·4%).

(c) *Methanolysis.* A solution of the bistrifluoroacetate (0·058 g.) in magnesium-dried methyl alcohol (5 c.c.) was kept at room temperature for 18 hours. Evaporation of the solvent under diminished pressure afforded 4 : 6-benzylidene α-methylglucoside (0·034 g.).

3 : 5 : 6-*Tristrifluoroacetyl* 1 : 2-iso*Propylidene* D-*Glucofuranose.*—(a) *Preparation. iso*Propylidene glucose (0·802 g.), sodium trifluoroacetate (0·207 g.), and trifluoroacetic anhydride (3·85 c.c.) were gently refluxed for 15 minutes and treated as in the case of the above benzylidene derivative. The resulting product, which failed to crystallise, was distilled at 163—165° (bath temp.)/12 mm. to give a colourless viscous syrup (1·490 g.), $[\alpha]_D^{18}$ +15·7° (*c*, 1·20 in carbon tetrachloride) (Found : F, 33·1; CF_3·CO, 58·3. $C_{15}H_{13}O_9F_9$ requires F, 33·6; CF_3·CO, 57·25%).

(b) *Methanolysis.* The *ester* (0·134 g.) was gently refluxed with magnesium-dried methyl alcohol (20 c.c.) for 1 hour. Removal of the solvent under diminished pressure left a solid, which was recrystallised from ethyl acetate, giving mono*iso*propylidene glucose (0·041 g.), m. p. and mixed m. p. 161—163°.

Analytical Methods.—(a) *Trifluoroacetyl determination.* The trifluoroacetate (equivalent to *ca.* 8 c.c. of 0·05N-sodium hydroxide) was dissolved in acetone (5 c.c.) and 0·05N-sodium hydroxide (10·0 c.c.) was added. After 6—15 hours the excess of alkali was titrated with 0·015N-hydrochloric acid, phenolphthalein being used as the indicator.

(b) *Fluorine determination.* The method employed was that reported by Musgrave, Smith, and Tatlow (*J.*, 1949, 3021).

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