

**628.** *Studies on Trifluoroacetic Acid. Part I. Trifluoroacetic Anhydride as a Promoter of Ester Formation between Hydroxy-compounds and Carboxylic Acids.*

By E. J. BOURNE, M. STACEY, J. C. TATLOW, and J. M. TEDDER.

The production of esters from alcohols and phenols by treatment with carboxylic acids in the presence of trifluoroacetic anhydride is described. The method can be used to esterify carboxylic acids in both the aliphatic and the aromatic series. In many cases the reaction proceeds spontaneously and is essentially complete within a few minutes. The general conditions of the reaction are relatively mild and enable, for example, acyl derivatives to be prepared in good yield from acid-labile glycosides. The method is particularly convenient for the acetylation and benzylation of polysaccharides and also for the production of poly-esters.

DURING the course of a study of the preparation and properties of trifluoroacetates of carbohydrates, details of which will be given in subsequent communications, an attempt was made to prepare trifluoroacetyl derivatives of cellulose. Whereas there was no apparent reaction between untreated cellulose and trifluoroacetic anhydride, a sample of cellulose which had been swollen in glacial acetic acid dissolved slowly in trifluoroacetic anhydride. However, the product, which was readily soluble in chloroform, contained no fluorine and consisted of cellulose acetate. This observation prompted a comprehensive examination of the action of trifluoroacetic anhydride in the presence of carboxylic acids on various hydroxy-compounds, and some preliminary results are herein reported.

We have shown that trifluoroacetic anhydride promotes the esterification of a wide range of alcohols and phenols by carboxylic acids in both the aromatic and aliphatic series. This new method seems to be generally applicable and convenient for the preparation of esters, which can be isolated rapidly and in good yield.

Briefly, the technique consists in treating the alcohol or phenol with a slight excess of the requisite carboxylic acid in the presence of trifluoroacetic anhydride, following which the reaction mixture is poured into aqueous sodium hydrogen carbonate and the ester is isolated by one of the usual methods. Esterification frequently proceeds spontaneously and exothermally when the reagents are mixed and, in certain cases, is virtually complete by the time the temperature has returned to normal. This is true for the acetylation of  $\beta$ -naphthol and mannitol and for the propionylation of  $\alpha$ -methylglucoside. Benzylation does not usually occur spontaneously and the best results are obtained when the reaction mixture is warmed. As a general method it is probably better to warm the carboxylic acid with trifluoroacetic anhydride for a short time before adding the hydroxy-compound.

An important advantage of the new esterification process is that it can be applied, without modification, to cases in which the alcohol (or phenol) and carboxylic acid are both solids. Thus we have employed it successfully for the preparation of such esters as  $\beta$ -naphthyl palmitate,

*p*-nitrobenzyl phenylacetate, phenyl adipate, and the benzoates of phenol,  $\beta$ -naphthol, *p*-nitrobenzyl alcohol and mannitol. An attempt to prepare  $\beta$ -naphthyl toluene-*p*-sulphonate was only moderately successful.

The conditions of the reaction are less drastic than those normally employed for the direct esterification of a hydroxy-compound with a carboxylic acid, as is shown by the fact that derivatives of acid-labile glycosides can be prepared in good yield. The acetates of  $\alpha$ -methylglucoside and  $\alpha\alpha$ -trehalose and the tetrapropionate of  $\alpha$ -methylglucoside have been obtained in 55–80% yield. Sucrose, which is extremely sensitive to acid, has been converted into its octa-acetate in 67% yield. The moderate yield (28%) of crystalline product which resulted from the propionylation of maltose was probably due to the formation of a mixture of  $\alpha$ - and  $\beta$ -octapropionates, from which only the  $\alpha$ -form was isolated in crystalline state.

Cellulose and amylose (prepared from Steadfast wrinkled peas), which are somewhat difficult to acetylate by the usual methods, dissolved within 60 minutes when warmed at 50–60° with a mixture of acetic acid and trifluoroacetic anhydride. From both polysaccharides the fibrous acetylated products were soluble in chloroform and had acetyl contents greater than 40%. In a similar fashion, cellulose was converted into fibrous cellulose benzoate, having a benzoyl content of 60%. Although we have as yet no direct measure of the degree of degradation of the polysaccharide chains during this treatment, we believe that it is not extensive.

Trifluoroacetic anhydride appears also to be a useful reagent for the synthesis of long-chain poly-esters from dihydric alcohols and dibasic acids, and from hydroxy-carboxylic acids. A poly-ester of the latter type, having m. p. >360°, was formed when *p*-hydroxybenzoic acid was treated with the anhydride alone for 15 minutes at 75°.

The mechanism of the esterification has not yet been studied, but it does not appear that the role of trifluoroacetic anhydride is catalytic. In all successful experiments the molecular ratio anhydride : hydroxy-group has been more than unity, whereas when this ratio has fallen appreciably below unity very poor yields of esters have resulted. Tentatively, we suggest that the active acylating agent is a mixed anhydride of trifluoroacetic acid and the carboxylic acid concerned. We have found that trifluoroacetates are, in general, much less stable than normal carboxylic esters, which may explain their virtual absence from the reaction products.

In conclusion, therefore, we recommend the general use of trifluoroacetic anhydride as a promoter in esterification reactions, since it enables an alcohol (or phenol) and a free carboxylic acid to react directly under mild conditions and obviates any necessity for preliminary conversion into the acid chloride or anhydride in cases where direct esterification is normally impossible. An esterification method of this type has been described for the preparation of cellulose esters (B.P. 285,858; B.P. 313,408); in this case the "impeller" is monochloroacetic anhydride, but a catalyst, namely, magnesium perchlorate or sulphuric acid, is also apparently necessary with this reagent.

#### EXPERIMENTAL.

(All yields quoted are for pure materials.)

*Preparation of the Anhydride of Trifluoroacetic Acid.*—Trifluoroacetic acid was distilled over phosphoric oxide, as recommended by Swarts (*Bull. Acad. roy. Belg., Classe Sci.*, 1922, **8**, 343). An improved yield (74%) was obtained with a smaller proportion of pentoxide (0.87 g. per g. of trifluoroacetic acid); the product had b. p. 39° (Swarts recorded b. p. 39.5–40.1°) and  $d_{20}^{25}$  1.52.

*p-Nitrobenzyl Acetate.*—A solution of *p*-nitrobenzyl alcohol (0.19 g.) in glacial acetic acid (0.70 c.c.) and trifluoroacetic anhydride (1.00 c.c.) was kept at 60° for 15 minutes, cooled, poured into aqueous sodium hydrogen carbonate, and exhaustively extracted with chloroform. The extract was dried ( $MgSO_4$ ) and evaporated to a syrup, which crystallised. When recrystallised from aqueous alcohol, the ester had m. p. 77–78° alone or in admixture with an authentic specimen. Yield, 0.20 g. (83%).

*$\beta$ -Naphthyl Acetate.*—Heat was generated when trifluoroacetic anhydride (0.80 c.c.) was added to a mixture of  $\beta$ -naphthol (0.50 g.) and glacial acetic acid (3.50 c.c.). The reaction mixture was allowed to cool slowly and then was poured into sodium hydrogen carbonate solution and extracted as above. The product, after crystallisation from aqueous alcohol, had m. p. 70° alone or in admixture with an authentic specimen of  $\beta$ -naphthyl acetate. Yield, 0.55 g. (85%).

*Mannitol Hexa-acetate.*—When trifluoroacetic anhydride (4.94 c.c.) was introduced into a mixture of D-mannitol (0.50 g.) and glacial acetic acid (2.04 c.c.), considerable heat developed and the mannitol dissolved. The ester, isolated as above and crystallised from aqueous alcohol, had m. p. and mixed  $[\alpha]_D^{20}$  +26.0° (c, 1.0 in chloroform). Yield, 0.98 g. (80%).

*2 : 3 : 4 : 6-Tetra-acetyl  $\alpha$ -Methyl-D-glucopyranoside.*— $\alpha$ -Methyl-D-glucopyranoside (0.48 g.) was heated at 60° for 15 minutes with glacial acetic acid (2.83 c.c.) and trifluoroacetic anhydride (1.80 c.c.). The tetra-acetate, isolated in the usual way and crystallised from aqueous alcohol, had m. p. 102° alone and in admixture with an authentic specimen,  $[\alpha]_D^{20}$  +129.5° (c, 1.0 in chloroform). Yield, 0.51 g. (56%).

*Sucrose Octa-acetate.*—Dry powdered sucrose (0.50 g.) was added to a cooled mixture of glacial acetic acid (1.20 c.c.) and trifluoroacetic anhydride (4.14 c.c.). After several hours at 0° and 64 hours at

room temperature, the reaction mixture was poured into sodium hydrogen carbonate solution and extracted as above. Recrystallised from aqueous alcohol, the product had m. p. and mixed m. p. 86—87°,  $[\alpha]_D^{25} + 58.6^\circ$  (c, 1.0 in chloroform). Yield, 0.67 g. (67%).

*α-Trehalose Octa-acetate*.—Trehalose hydrate (0.21 g.) dissolved slowly in a mixture of glacial acetic acid (0.48 c.c.) and trifluoroacetic anhydride (1.05 c.c.). After 2 hours at room temperature, the solution was worked up in the usual way. Two crystallisations from alcohol gave white needles, whose m. p. varied according to the method of drying (see Brederick, *Ber.*, 1930, **63**, B, 959). Dried between filter papers, the product had m. p. 68—75°; dried for 15 hours in a vacuum-desiccator, it had m. p. 101—103° after shrinking at 70—75°; dried for 2 hours at 60°/12 mm., it had m. p. 102—103° and  $[\alpha]_D^{25} + 161.9^\circ$  (c, 1.0 in chloroform). Yield, 0.25 g. (68%) (Found: C, 49.4; H, 5.5. Calc. for  $C_{28}H_{38}O_{19}$ : C, 49.5; H, 5.7%).

*Cellulose Acetate*.—Dry cotton wool (0.30 g.) was heated at 60° with glacial acetic acid (4.0 c.c.) and trifluoroacetic anhydride (6.6 c.c.) until it had dissolved (ca. 60 minutes). The solution was poured into aqueous sodium hydrogen carbonate, and the fibrous ester was thoroughly washed with water, before being dried at 60° in a vacuum ( $P_2O_5$ ). Yield, 0.53 g. (98%) [Found: F, nil; Ac, 40—42 (in several experiments). Calc. for  $C_{12}H_{16}O_8$ : Ac, 44.8%].

*Amylose Acetate*.—The amylose sample had been isolated from Steadfast wrinkled peas by extraction with 30% chloral hydrate solution (Peat, Bourne, and Mary Nicholls, *Nature*, 1948, **161**, 206). The dry polysaccharide (0.32 g.), glacial acetic acid (3.0 c.c.), trifluoroacetic anhydride (6.0 c.c.) and chloroform (6.0 c.c.) were heated at 50° for 1 hour. A small residue of undissolved material was removed by filtration through sintered glass. The polysaccharide ester was precipitated with light petroleum (3 volumes; b. p. 80—100°) and purified by re-precipitation from chloroform with light petroleum. The gelatinous product was hardened with light petroleum to a fibrous solid, which was dried at 60° in a vacuum. Yield, 0.46 g. (82%) (Found: Ac, 41.6. Calc. for  $C_{13}H_{16}O_8$ : Ac, 44.8%).

*p-Nitrobenzyl Benzoate*.—Benzoic acid (0.96 g.) and trifluoroacetic anhydride (1.0 c.c.) were heated together at 50° for 20 minutes before *p*-nitrobenzyl alcohol (0.25 g.) was introduced. The heating was continued at 65° for 40 minutes before isolation of the ester by extraction with chloroform from aqueous sodium hydrogen carbonate. The product, crystallised from aqueous alcohol, had m. p. and mixed m. p. 89°. Yield, 0.29 g. (69%).

*Ethylene Dibenzoate*.—Benzoic acid (1.50 g.) was dissolved in warm trifluoroacetic anhydride (1.80 c.c.) and ethylene glycol (0.28 c.c.) was added. After 30 minutes at 80°, the solution was poured into aqueous sodium carbonate and extracted with chloroform in the usual manner. The dibenzoate, after crystallisation from alcohol-light petroleum (b. p. 60—80°), had m. p. 73° alone and in admixture with an authentic specimen. Yield, 0.65 g. (48%).

*Phenyl Benzoate*.—Phenol (0.50 g.), benzoic acid (1.30 g.), and trifluoroacetic anhydride (1.80 c.c.) were warmed at 60° for 25 minutes, cooled, and poured into aqueous sodium carbonate. Extraction with chloroform and crystallisation from aqueous alcohol gave phenyl benzoate, m. p. and mixed m. p. 69.5°. Yield, 0.87 g. (82%).

*β-Naphthyl Benzoate*.—When trifluoroacetic anhydride (1.00 c.c.) was added to a mixture of *β*-naphthol (0.50 g.) and benzoic acid (1.42 g.) heat was evolved and the solid reactants dissolved. After 30 minutes, the ester was extracted in the usual manner. Recrystallised from aqueous alcohol, it had m. p. 106°, not depressed by an authentic sample. Yield, 0.69 g. (80%).

*Mannitol Hexabenzate*.—To a solution of benzoic acid (0.79 g.) in warm trifluoroacetic anhydride (1.40 c.c.), *D*-mannitol (0.09 g.) was added. The hexitol dissolved spontaneously and exothermally. After 30 minutes at room temperature the solution was worked up. The syrup recovered from the chloroform extracts crystallised when treated with alcohol-ether and had m. p. and mixed m. p. 149° (Found: C, 71.2; H, 5.1. Calc. for  $C_{48}H_{38}O_{12}$ : C, 71.4; H, 4.8%). Yield, 0.17 g. (41%). Müller (*Ber.*, 1932, **65**, B, 1051) recorded m. p. 149—150°.

*Cellulose Benzoate*.—Dry cotton wool (0.30 g.) was heated at 60° with benzoic acid (6.80 g.) and trifluoroacetic anhydride (7.80 c.c.) until dissolution was achieved (75 minutes). The cellulose ester was precipitated in fibrous form with alcohol, washed, and dried at 60° in a vacuum ( $P_2O_5$ ). Yield, 0.85 g. (97%) (Found:  $C_6H_5 \cdot CO$ , 60. Calc. for  $C_{27}H_{22}O_8$ :  $C_6H_5 \cdot CO$ , 66.4%).

*β-Naphthyl Propionate*.—*β*-Naphthol (0.50 g.) was added to a pre-heated solution of propionic acid (0.45 c.c.) in trifluoroacetic anhydride (0.65 c.c.), and the reaction was completed by heating at 60° for 30 minutes. The usual method of extraction, followed by crystallisation from aqueous alcohol, gave *β*-naphthyl propionate, m. p. and mixed m. p. 47.5°. Einhorn and Hollandt (*Annalen*, 1898, **301**, 95) give m. p. 51°. Yield, 0.47 g. (68%).

*α-Maltose Octapropionate*.—Maltose hydrate (0.50 g.) was introduced at 0° into a mixture of trifluoroacetic anhydride (3.10 c.c.) and propionic acid (1.70 c.c.). After 15 hours at 10°, the solution was poured into iced aqueous sodium hydrogen carbonate. The syrup isolated from the chloroform extract was crystallised, first from alcohol and then from isopropyl alcohol. The ester had m. p. and mixed m. p. 144° and  $[\alpha]_D^{25} + 53^\circ$  (c, 1.0 in chloroform). Hurd and Gordon (*J. Amer. Chem. Soc.*, 1941, **63**, 2657) give m. p. 144° and  $[\alpha]_D^{20} + 55^\circ$  (c, 8.0 in chloroform) for *α*-maltose octapropionate. Yield, 0.32 g. (28%).

2 : 3 : 4 : 6-*Tetra-propionyl α-Methyl-D-glucopyranoside*.—*α*-Methylglucoside (0.48 g.) dissolved exothermally in a mixture of trifluoroacetic anhydride (1.90 c.c.) and propionic acid (1.55 c.c.). After 20 minutes at room temperature, the ester was isolated in the usual manner. Evaporation of the chloroform extract yielded a syrup which distilled at 170°/0.001 mm. and had  $[\alpha]_D^{20} + 110.7^\circ$  (c, 1.0 in chloroform). Yield, 0.78 g. (77%) (Found: C, 54.7; H, 7.5; OMe, 7.31. Calc. for  $C_{18}H_{26}O_{10}$ : C, 54.5; H, 7.2; OMe, 7.42%). Wolff (*J. Amer. Chem. Soc.*, 1945, **67**, 1623) reported *α*-methylglucoside tetrapropionate to be a syrup with  $[\alpha]_D^{25} + 114.5^\circ$  in chloroform.

*Glyceryl Tripalmitate*.—Palmitic acid (0.97 g.) slowly dissolved when warmed at 40° with trifluoroacetic anhydride (2.30 c.c.). The solution was added to dry glycerol (0.077 g.), and the reaction mixture was kept at room temperature for 1 hour and then at 50° for 30 minutes before being poured into aqueous potassium carbonate. The bulk of the ester was extracted with chloroform, but efficient separation of

the chloroform layer was hindered by the formation of an emulsion. A second fraction of the ester was recovered from the aqueous phase by precipitating the excess of palmitic acid as its calcium salt and extracting the filtrate with chloroform. The chloroform extracts were combined, washed with water, dried, and evaporated. The residue, after 2 crystallisations from ether, had m. p. 61—62°, depressed to 52° by palmitic acid. Yield, 0.48 g. (70%). Stephenson (*Biochem. J.*, 1913, 7, 429) recorded m. p. 62° for glyceryl tripalmitate. The molecular weight of the product, determined cryoscopically in camphor, was ca. 780 (theoretical values of 806 and 256 for the tri-ester and the parent acid, respectively).

*β-Naphthyl Palmitate*.—Palmitic acid (0.93 g.) and trifluoroacetic anhydride (2.90 c.c.) were mixed and kept at room temperature for 30 minutes before β-naphthol (0.49 g.) was added. After 45 minutes at room temperature and 5 minutes at 50°, the reaction mixture was neutralised and extracted in the customary fashion. Crystallised twice from alcohol, the *palmitate* had m. p. 67.5° and showed a marked depression with palmitic acid. Yield, 1.11 g. (85%) (Found: C, 81.6; H, 9.9. C<sub>26</sub>H<sub>38</sub>O<sub>2</sub> requires C, 81.6; H, 10.0%).

*p-Nitrobenzyl Phenylacetate*.—*p*-Nitrobenzyl alcohol (0.29 g.) dissolved spontaneously when added to a solution of phenylacetic acid (0.35 g.) in trifluoroacetic anhydride (0.95 c.c.). After 20 minutes at room temperature, the product was isolated as above and crystallised twice from alcohol in colourless needles, having m. p. 65.5° alone or in admixture with an authentic specimen prepared by the method of Lyman and Reid (*J. Amer. Chem. Soc.*, 1917, 39, 701). Yield, 0.33 g. (64%).

*Phenyl Adipate*.—Adipic acid (0.40 g.) dissolved in 30 minutes at room temperature in trifluoroacetic anhydride (0.75 c.c.). The solution was heated at 50° for 40 minutes with phenol (0.49 g.), then diluted with chloroform, and washed with aqueous sodium carbonate. The chloroform layer was dried (MgSO<sub>4</sub>) and evaporated to a syrup, which crystallised from aqueous alcohol. The adipate had m. p. 105—106° (Found: C, 72.8; H, 6.0. Calc. for C<sub>18</sub>H<sub>18</sub>O<sub>4</sub>: C, 72.5; H, 6.1%). Yield, 0.45 g. (57%). Hill (*J. Amer. Chem. Soc.*, 1930, 52, 4110) recorded m. p. 105.5—106°.

*β-Naphthyl Toluene-p-sulphonate*.—Toluene-*p*-sulphonic acid (0.79 g.) was dissolved in warm trifluoroacetic anhydride (1.55 c.c.) and β-naphthol (0.48 g.) was added. After 3 hours at room temperature, the solution was poured into aqueous sodium carbonate and extracted with chloroform. The chloroform solution was evaporated and the residue dissolved in ether, washed twice with 0.5*N*-sodium hydroxide and then with water, and dried (MgSO<sub>4</sub>). The ether-soluble material was crystallised from alcohol and had m. p. and mixed m. p. 124°. Yield, 0.12 g. (13%).

*Polymerisation of p-Hydroxybenzoic Acid*.—Trifluoroacetic anhydride (1.50 c.c.) was heated at 75° for 15 minutes with *p*-hydroxybenzoic acid (0.75 g.). The solid mass was ground with aqueous sodium hydrogen carbonate and then with chloroform. The insoluble fraction was dried to a white powder, which was practically insoluble in the common organic solvents. The powder showed a tendency to darken at 360°, but did not melt (*p*-hydroxybenzoic acid has m. p. 213°).

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THE A.E. HILLS LABORATORIES,  
THE UNIVERSITY, EDGBASTON, BIRMINGHAM, 15.

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