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The Preparation of Formate Esters of Polyols

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Treatment of polyols with formic acid and phosphorus pentoxide has been found to yield the fully formylated esters in a good yield. These formates show a strong tendency to crystallise, and should be suitable as derivatives. The formylation of D-glucose by the same method has been investigated by chromatographic methods.

A previous communication [1] on the paper chromatography of sugar acetates and related compounds, also described the separation of some fully formylated polyols. These compounds have not been reported earlier in the literature and as they crystallised with great ease and should be of potential value as derivatives, their synthesis was investigated more thoroughly. Their preparation is complicated by the fact that formic acid does not form a stable anhydride or stable halides except the fluoride.

The method first used for the formylation of polyols was simply a repeated treatment of the alcohols with anhydrous formic acid, and ethylene glycol diformate [2], glycerol triformate [3] and erythritol tetraformate [4] have been prepared in this way. Formic acid forms a fairly stable mixed anhydride with acetic acid [5] and from the reaction of this anhydride with erythritol Freudenberg and Jacob [6] obtained the corresponding tetraformate in 60 % yield. However, no definite products could be isolated when D-mannitol and D-glucitol were subjected to the same treatment.

Wolf *et al.*[7] found that a mean maximum of 2.3 hydroxyl groups per glucose unit were esterified when starch was treated with formic acid at room temperature. Attempts to remove water from the reaction mixture by distilling with benzene or by adding anhydrous calcium sulphate had almost no effect.

The reaction between D-glucose and formic acid has been investigated by Tarkow and Stamm [8] who found that formylation took place preferentially at the primary hydroxyl group, though the hydroxyl group in the 4-position would react also. Richtzenhain and Lidman [9] have shown that β- but not α-acetates of pyranosidic D-sugars react with formic acid at room temperature. The reaction products were not investigated further.

Experiments with some pentitols and hexitols showed that fully formylated products could be isolated in 20-30 % yield if the alcohols were repeatedly treated with anhydrous formic acid at 100°. Formyl fluoride [10] and the mixed anhydride from formic and acetic acid were tried as formylating agents but unfortunately both compounds decomposed in the presence of catalysts like sulphuric acid or pyridine. Preliminary attempts to formylate D-glucitol or D-glucose with formyl fluoride in dimethyl formamide solution failed and when D-glucose was allowed to react with the mixed anhydride, paper chromatograms indicated that the formates formed initially (17 h reaction time) reacted further, probably with the introduction of acetyl groups. As some experiments with transesterification reactions also were unsuccessful, the possibility of continuously removing the water formed in the reaction between formic acid and the alcohol component was considered.

Aqueous formic acid may be concentrated by azeotropic distillation with propyl formate [11] or various amines, [12,13] but attempts to use propyl formate in an esterification reaction gave negative results. According to Jones [14] a 99.5 % formic acid is obtained from dilute acid by adding phosphorus pentoxide with efficient cooling and subsequently distilling the mixture. A similar procedure is described by Schlesinger and Martin [15] who use boron trioxide as drying agent. Because of complex formation between boric acid and polyols, boron trioxide is probably less suitable for the preparation of formates; this was confirmed by experiments with D-mannitol. On the other hand addition of phosphorus pentoxide to a mixture of 99 % formic acid and D-mannitol was found to raise the yield of mannitol hexaformate considerably, and experiments were now made with D-mannitol, D-glucitol and galactitol to find the best conditions for the reaction (see Table 1). The formates of the pentitols and of *myo*-inositol were prepared under the conditions giving the highest yields of the hexitol derivatives.

All the polyol formates crystallised with unusual ease, even the xylitol derivative. Both xylitol and most of its previously known derivatives are notoriously difficult to obtain in a crystalline state. At room temperature the D-mannitol and galactitol derivatives were almost insoluble in common solvents and only slightly soluble (0.1-0.2 %) in dimethyl formamide or dimethyl sulphoxide. They were recrystallised from large volumes of boiling pyridine or acetonitrile. The low-melting formates are unfortunately rather unstable and after exposure for a few days to atmospheric moisture at room temperature they often gave a smell of formic acid. The analytical values for carbon and hydrogen were not entirely satisfactory and a more suitable method of analysis was found to be alkaline hydrolysis and titration. Paper chromatographic data for the compounds are given in a previous paper [1].

The formylation of D-glucose by the same method was investigated qualitatively by a chromatographic technique. To obtain mild reaction conditions a pyrophosphoric acid mixture with the average composition $H_3PO_4.2P_2O_5$ was substituted for the phosphorus pentoxide. On chromatograms run in a benzene - dimethyl sulphoxide system, the reaction product gave mainly 3 fairly fast spots. In addition to these there were also a few weak and very slow spots. When a sample was deformylated with ethanol containing catalytic amounts of sodium ethoxide, the product gave a spot only for glucose on paper

Table 1 *. Esterification of some hexitols with formic acid in the presence of phosphorus pentoxide.

Hexitol	HCOOH ml	P_2O_5 g	Time h	Yield of hexaformate %
D-Mannitol	5.0	1.0	20	68
»	5.0	1.5	20	79
»	5.0	1.75	20	85
»	5.0	2.0	20	87
»	5.0	2.2	20	85
»	10.0	2.0	20	90
»	10.0	2.5	20	89
»	10.0	2.2	2	67
»	10.0	2.2	4	81
»	10.0	2.2	6	85
Galactitol	5.0	2.0	20	80
»	10.0	2.2	20	90
»	10.0	2.5	20	91
D-Glucitol	10.0	2.2	1	17
»	10.0	2.2	2	37
»	10.0	2.2	3.5	51
»	10.0	2.2	20	71

* All yields refer to crude crystalline products. The phosphorus pentoxide was added over a period of 10 min to a solution of the hexitol (1.00 g) in 99 % formic acid with cooling in ice-water. The reaction was then allowed to proceed at room temperature.

chromatograms run in an ethyl acetate - acetic acid - water system. The formate mixture was then separated on a cellulose column using a light petroleum - benzene - dimethyl sulphoxide mixture as solvent. The fastest component (Fraction 1) was obtained in a chromatographically pure state but did not crystallise. No separation was observed with the following two components (Fraction 2), but this behaviour could be expected if they were an anomeric pair with a moderately slow interconversion.

Fraction 1 was acetylated with acetic anhydride and pyridine, but the product showed the same R_F value as the starting material. This indicated that Fraction 1 was penta-*O*-formyl D-glucose, either as a single compound or as an inseparable mixture. Acetylation of Fraction 2 in the same way gave a product which gave two spots both of which were much faster than those observed before acetylation. When sodium acetate was substituted for pyridine in the acetylation of Fraction 2 only the faster of the acetate spots was observed on paper chromatograms. This result indicates that Fraction 2 was most probably an anomeric mixture of D-glucose tetraformates with a free hydroxyl group on carbon atom 1. The β-acetate, assuming that this is as usual the anomer formed preferentially with sodium acetate as a catalyst, has, contrary to earlier experience [1], a higher R_F value than the α-anomer. Attempts to obtain the acetylated formates in a crystalline state after separation on a cellulose column were unsuccessful.

EXPERIMENTAL*

Formylation of polyols. The polyol (1 g) was dissolved in commercial *ca.* 99 % formic acid (10 ml), if necessary with slight warming and phosphorus pentoxide (2.2 g) was added gradually with shaking and efficient cooling in ice-water. At the beginning, the addition of phosphorus pentoxide caused a rather vigorous evolution of gas but the reaction soon subsided. After 10 min the cooling bath was removed and the reaction was allowed to proceed at room temperature for 20 h. If the formate crystallised during the reaction (this occurred with the D-mannitol, D-glucitol, galactitol, D-arabitol and erythritol derivatives) the mixture was stirred mechanically with crushed ice and water (10 ml) and the crystals were then filtered off as quickly as possible. If the formate was more soluble the formic acid solution was diluted with ice and water (15 ml), extracted with ethyl acetate and the extract washed with cold aqueous sodium bicarbonate and water. The ethyl acetate solution was dried over ignited magnesium sulphate and concentrated under reduced pressure yielding the crude formate. Because of the low stability of the formates the last procedure was later modified by adding pyridine (20 ml) to the formic acid solution before dilution with ice-water.

D-*Mannitol hexaformate* was obtained in 90 % yield. Recrystallisation from large volumes of boiling pyridine gave a product with m. p. 208—210° (decomp.). When it was recrystallised from acetonitrile the melting point fell, even when a small quantity of pyridine was added to the solvent. $[\alpha]_D^{22}$ +60° (dimethyl sulphoxide, c = 0.1). (Found: C 40.9; H 4.37; HCO_2 76.0. Calc. for $C_{12}H_{14}O_{12}$: C 41.2; H 4.03; HCO_2 77.2.)

Galactitol hexaformate was obtained in 90 % yield. It was slightly more soluble than the mannitol derivative and after recrystallisation from boiling pyridine it had m. p. 200—202° (decomp.). (Found: C 42.2; H 4.27; HCO_2 77.7. Calc. for $C_{12}H_{14}O_{12}$: C 41.2; H 4.03; HCO_2 77.2.)

D-*Glucitol hexaformate* was obtained in 76 % yield and was recrystallised from acetone. M. p. 164—166.5°, $[\alpha]_D^{22}$ +19° (dimethyl formamide, c = 2.0). (Found: C 41.0; H 4.03; HCO_2 78.7. Calc. for $C_{12}H_{14}O_{12}$: C 41.2; H 4.03; HCO_2 77.2.)

D-*Arabitol pentaformate* was obtained in 76 % yield. It was recrystallised from aqueous acetone. M. p. 142.5—143.5°, $[\alpha]_D^{22}$ +48° (dimethyl formamide, c = 2.0). (Found: HCO_2 76.8. Calc. for $C_{10}H_{12}O_{10}$: HCO_2 77.0.)

Ribitol pentaformate was isolated by diluting the reaction mixture with pyridine (20 ml) and ice-water (15 ml) and extracting with ethyl acetate as described above. The crude product crystallised from chloroform — ethyl ether in 68 % yield. It was recrystallised from aqueous acetone, m. p. 63—64°. (Found: HCO_2 75.7. Calc. for $C_{10}H_{12}O_{10}$: HCO_2 77.0.)

Xylitol pentaformate. Part of the formate (0.48 g) crystallised when the reaction mixture was diluted with ice-water (15 ml). Immediately after filtration the mother liquors were combined with the aqueous washings and extracted with ethyl acetate. The extract phase was washed, dried and concentrated. The residue (0.47 g) was crystallised from aqueous methanol giving a further quantity of formate (0.15 g). The total yield of the crude product was thus only 35 % of theory. The m. p., after recrystallising from water, was 88—90.5°. (Found: HCO_2 76.2. Calc. for $C_{10}H_{12}O_{10}$: HCO_2 77.0.)

Erythritol tetraformate was obtained in 93 % yield and was recrystallised from acetone. M. p. 155.5—158°. (Found: HCO_2 76.7. Calc. for $C_8H_{10}O_8$: HCO_2 76.9.)

(From a solution of erythritol (1 g) in formic acid (10 ml) the tetraformate slowly crystallised in 44 % yield.)

myo-*Inositol hexaformate* was isolated as described for adonitol pentaformate. The syrup remaining after concentration of the ethyl acetate extract was dissolved in acetone and the solution was saturated with ethyl ether. The crude formate crystallised overnight. Yield 41 %. After recrystallisation from aqueous acetone it had m. p. 183—185°. (Found: HCO_2 77.5. Calc. for $C_{12}H_{12}O_{12}$: HCO_2 77.6.)

Determination of ester groups by saponification. The sample (ca 100 mg) was dissolved in 0.25 N ethanolic potassium hydroxide solution (10 ml). After 24 h an excess of 0.25 M hydrochloric acid was added, and after a few hours the acid was back-titrated with 0.1 M sodium hydroxide using phenolphthalein as indicator. A blank was run simultaneously.

* All melting points are corrected.

Formylation of D-*glucose.* The pyrophosphoric acid used in the formylation of glucose had the average composition $H_3PO_4 . 2P_2O_5$ and was prepared by dropping 85 % phosphoric acid onto phosphorus pentoxide with vigorous shaking. It formed granules 2 – 4 mm in diameter.

Pyrophosphoric acid (2.5 g) was added to a solution of D-glucose (1 g) in 99 % formic acid (10 ml) with cooling in ice-water and mechanical stirring. After all the granules had dissolved the mixture was left at room temperature overnight. A slight evolution of gas was observed. The solution was then stirred into ice-water and the mixture was extracted with ethyl acetate (3 × 25 ml). The extract was washed with aqueous sodium bicarbonate and water, dried over magnesium sulphate and concentrated at 15 mm pressure and 35 – 40° bath temperature. The yield of syrup was 0.55 g (31 % of the theoretical yield of pentaformate).

The product was chromatographed on paper using the technique previously described[1]. Before adding the sample the chromatogram was impregnated with a 25 % v/v solution of dimethyl sulphoxide in toluene, blotted and dried for 2 min at 60°. After a second impregnation the toluene was allowed to evaporate at room temperature and the sample was put on the paper as a 3 % solution in chloroform. Benzene containing 4 % v/v of dimethyl sulphoxide and 1 % v/v of water (Solvent 1) or benzene – light petroleum (3:1, v/v) with 4 % v/v of dimethyl sulphoxide and 1 % v/v of water added (Solvent 2) were used as developing solutions. The spots were detected by spraying the chromatograms with aqueous silver nitrate and ethanolic sodium hydroxide. The main spots had R_F 0.45, 0.25 and 0.16 (Solvent 1) and R_F 0.13, 0.05 and 0.00 (Solvent 2).

The main part of the syrup (500 mg) was dissolved in a 4:1, v/v benzene – light petroleum mixture (25 ml) by adding the minimum quantity of dimethyl sulphoxide. The solution was added to the top of a cellulose column (36 × 2.2 cm) which had been prewashed with benzene – light petroleum (4:1, v/v) containing 5 % v/v of dimethyl sulphoxide. The column was then irrigated with the same solvent. The first part of the eluate gave a spot for the fastest component only. It was concentrated and the residue was dissolved in ethyl acetate. The solution was washed repeatedly with water, dried and concentrated yielding Fraction 1 as a syrup (110 mg). After a small empty fraction the next two compounds appeared simultaneously in the eluate. The mixture was isolated as before yielding Fraction 2 (140 mg).

Samples of Fraction 1 and 2 were acetylated by heating to 100° for 5 min with acetic anhydride and pyridine, and the products were run on paper chromatograms. According to these Fraction 1 had been recovered unchanged, but Fraction 2 had been acetylated to give two spots with R_F 0.77 and 0.65 in Solvent 1 and R_F 0.47 and 0.28 in Solvent 2. Fraction 2 when heated with acetic anhydride and sodium acetate at 100° for 1 h gave a product which showed mainly a single spot with R_F 0.77 in Solvent 1 and R_F 0.47 in Solvent 2.

A second lot of D-glucose (1.5 g) was formylated as before using formic acid (15 ml) and pyrophosphoric acid (3.8 g). After standing overnight the reaction mixture was stirred into pyridine (50 ml), ethyl acetate was added and the upper phase was washed repeatedly with water and aqueous sodium bicarbonate. It was dried and concentrated under reduced pressure to give a syrup (2.6 g) which still contained traces of pyridine. The product was shown by paper chromatography to be similar to that obtained in the first formylation, but the fastest spot was a little fainter. Treatment with acetic anhydride and sodium acetate (1 h at 100°) yielded a syrup which gave spots with R_F 0.77, 0.65 and 0.45 (Solvent 1) and R_F 0.47, 0.28 and 0.13 (Solvent 2).

Part of the acetylated formate mixture (480 mg) was separated on a cellulose column as before, using Solvent 2 as eluant. The two fastest components were obtained in separate fractions which were worked up in the usual way. However, these preparations did not crystallise. As only a part (160 mg) of the material added to the column was recovered in this way, the column was afterwards stripped with ethyl acetate. The washings were extracted with water to remove dimethyl sulphoxide, dried and concentrated. The residue (270 mg), which gave rather faint spots with R_F 0.65 and 0.45 on chromatograms run in Solvent 1, was deformylated in cold absolute ethanol containing catalytic amounts of sodium ethoxide. To prevent the hydrolysis of any orthoesters, the mixture was afterwards diluted with a small quantity of water and neutralised by saturation with carbon dioxide. On chromatograms run in ethyl acetate – acetic acid – water (3:1:1) the deformylated product gave a single spot, indistinguishable from that of D-glucose. This was also the only product detected on paper chromatograms after deformylation in the same way of a freshly prepared D-glucose formate mixture.

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