732. *The Preparation and Properties of Some Alkyl β-D-Glucopyranoside Tetranitrates.*

By D. M. SHEPHERD.

Ethyl, *n*-propyl, and *n*-butyl β-D-glucopyranoside tetranitrate have been prepared. Their solubilities in water have been determined and their mode of hydrolysis with dilute alkali has been studied.

DURING a study of the pharmacology of certain organic nitrates it has been necessary to prepare a series of alkyl β-D-glucopyranoside tetranitrates some of which have not previously been described. Since the pharmacological behaviour of these compounds is related to their mode of hydrolysis and to their solubility in water, particular attention has been paid to these properties in the present work. The results, which are summarized in the Table, include comparative studies carried out at the same time on the already known compounds methyl α-D-glucopyranoside tetranitrate (Will and Lenze, *Ber.*, 1898, **31**, 68) and the β-anomer (Bell and Synge, *J.*, 1937, 1711).

Baker and Easty (*J.*, 1952, 1193) showed that the hydrolysis of organic nitrates may involve three distinct but simultaneous mechanisms, *viz.*, (*a*) nucleophilic substitution with formation of the parent alcohol together with nitrate ions, (*b*) β-hydrogen elimination with formation of an olefin and nitrate ions, and (*c*) α-hydrogen elimination with formation of a carbonyl compound (aldehyde or ketone) and nitrite ions. Nef (*Annalen*, 1899, **309**, 126) observed the formation of ethers during the alkaline hydrolysis of methyl, ethyl, and higher alkyl nitrates, while the formation of cyclic ethers (anhydro-sugars) has been demonstrated in the alkaline hydrolysis of certain sugar nitrates (Gladding and Purves, *J. Amer. Chem. Soc.*, 1944, **66**, 76; Ansell, Honeyman, and Williams, *Chem. and Ind.*, 1952, 149; Ansell and Honeyman, *J.*, 1952, 2778). In studies of a series of methyl α- and β-D-glucopyranoside mononitrates from which all free hydroxyl groups were excluded by methylation or acetylation, Gladding and Purves (*loc. cit.*) found that, while the acetate groups were hydrolysed almost instantaneously by alkali, the single nitrate group (except when attached to $C_{(1)}$) was removed quite slowly. In some cases the hydrolysis was not complete even after 100 hours.

Alkyl group	Conditions *	NaOH used (equivs. per mole of tetranitrate)	NO_2^- formed (equivs. per mole of tetranitrate)	Residual NO_3^- (equivs. per mole of tetranitrate)	Solubility at 20° (g./l.)
α-Me	R.T., 2 hr.	4·3	2·92	0·83	0·04493
,,	Reflux, 3 hr.	5·4	3·11	—	—
β-Me	R.T., 1 hr.	3·8	3·02	—	0·07586
,,	R.T., 2 hr.	4·2	2·96	0·87	—
,,	Reflux, 3 hr.	5·7	2·98	—	—
β-Et	R.T., 2 hr.	4·3	2·97	0·91	0·01328
β-Pr^n	,,	4·4	3·19	0·85	0·00387
β-Bu^n	,,	4·2	3·09	0·80	0·00211

* R.T. = room temperature.

In the present work it has been found that hydrolysis of alkyl D-glucopyranoside

tetranitrates in 0·1N-methanolic sodium hydroxide is rapid, the four equivalents of alkali theoretically required being consumed in 1—2 hours. At this stage the solution contains three equivalents of alkali nitrate per molecule. When the hydrolysis is carried out under more drastic conditions, 3 hours under reflux, the consumption of alkali increases to 5·7 equivalents while the nitrite liberated remains constant at 3 equivalents. These figures indicate that the additional alkali is used for further degradation of the primary products of hydrolysis rather than for further denitration. Similar observations have been reported for the alkaline hydrolysis of glycerol trinitrate (Berl and Delpy, *Ber.*, 1910, **43**, 1421) and of erythritol tetranitrate (Paulais, *Ann. pharm. Franç.*, 1945, **3**, 73).

The quantity of nitrate in the hydrolysates, after destruction of the accompanying nitrite by ammonium sulphamate, amounted to 0·8—0·9 g.-ion of nitrate per mole of tetranitrate used; thus all the nitrogen of the original tetranitrate has been accounted for. It appears that not all of the residual nitrate is in the ionic form since, in the case of methyl β-D-glucopyranoside tetranitrate, gravimetric determination of the nitrate in the form of the nitron salt as described by Baker and Easty (*loc. cit.*) gave the much lower value of 0·38 g.-ion of nitrate per mole of tetranitrate used; no methyl β-D-glucopyranoside could be detected in this hydrolysate.

The large amount of nitrite formed suggests that the hydrolysis of alkyl D-glucopyranoside tetranitrates proceeds largely by α-hydrogen elimination, *i.e.*, the E_{CO} reaction of Baker and Easty (*loc. cit.*). Substances containing carbonyl groups will be formed simultaneously and may then react with further alkali, thus accounting for the considerable consumption of alkali which occurs after hydrolysis of the original tetranitrate is substantially complete.

Experimental

Ethyl, *n*-propyl, *n*-butyl, and *n*-pentyl β-D-glucopyranoside were obtained by treating the appropriate alcohols with tetra-*O*-acetyl-α-D-glucopyranosyl bromide in the presence of silver carbonate (Ferguson, *J. Amer. Chem. Soc.*, 1932, **54**, 4086) and hydrolysing the resulting alkyl β-D-glucopyranoside tetra-acetates by the Zemplen method. *n*-Propyl β-D-glucopyranoside was obtained crystalline; the others, being relatively difficult to crystallize, were isolated as syrups which were sufficiently pure for nitration.

Ethyl β-D-Glucopyranoside Tetranitrate.—Ethyl β-D-glucopyranoside (5 g.) was suspended in acetic anhydride (12·5 ml.) at 0° and a mixture of fuming nitric acid (10 ml.) and acetic anhydride (25 ml.), also at 0°, added fairly rapidly (Honeyman and Morgan, *Chem. and Ind.*, 1953, 1035). The nitration mixture was stirred for 1 hr. at 0° by which time all the glucoside had dissolved. The tetranitrate quickly solidified when the reaction mass was poured into a large volume of ice-water and was washed several times with cold water. The crude solid, after recrystallization from absolute ethanol (15 ml.), gave *ethyl β-D-glucopyranoside tetranitrate* as colourless needles (5·3 g.), m. p. 99—100°, $[\alpha]_D^{22}$ +6·9° (*c*, 4·4816 in $CHCl_3$) (Found: C, 25·1; H, 3·5. $C_8H_{12}O_{14}N_4$ requires C, 24·8; H, 3·1%).

n-*Propyl β-D-Glucopyranoside Tetranitrate.*—*n*-Propyl β-D-glucopyranoside (5 g.) gave n-*propyl β-D-glucopyranoside tetranitrate* (5·6 g.) which separated from absolute ethanol as colourless needles, m. p. 81—82°, $[\alpha]_D^{21}$ +6·7° (*c*, 4·0400 in $CHCl_3$) (Found: C, 26·6; H, 3·8. $C_9H_{14}O_{14}N_4$ requires C, 26·9; H, 3·5%).

n-*Butyl β-D-Glucopyranoside Tetranitrate.*—*n*-Butyl β-D-glucopyranoside (5 g.) gave the tetranitrate as a syrup (5 g.) which crystallized after several days at 0°. Recrystallization from absolute ethanol gave n-*butyl β-D-glucopyranoside tetranitrate* as colourless, slender needles (2·1 g.), m. p. 39—40°, $[\alpha]_D^{20}$ +5·4° (*c*, 3·9336 in $CHCl_3$) (Found: C, 28·5; H, 3·5. $C_{10}H_{16}O_{14}N_4$ requires C, 28·9; H, 3·8%).

n-*Pentyl β-D-Glucopyranoside Tetranitrate.*—*n*-Pentyl β-D-glucopyranoside (5 g.) gave on nitration a syrup which did not crystallize. As such a product would be unsuitable for pharmacological study it was not examined further.

The solid nitrates were not sensitive to friction, but they exploded violently when a few mg. were suddenly heated in a sealed m. p. tube.

Determination of Alkali Consumed.—To the tetranitrate (0·1—0·15 g.) dissolved in absolute methanol (20 ml.) was added 0·5N-aqueous sodium hydroxide (5 ml.). After a suitable period an aliquot portion (10 ml.) of the hydrolysate was withdrawn and the excess of alkali titrated with 0·1N-hydrochloric acid (phenolphthalein).

Determination of Nitrite.—An aliquot (1 ml.) of the hydrolysate was diluted with distilled water to 100 ml. 0·25 Ml. of the diluted material was then taken for estimation by the Griess–Ilosvay method with an " Eel " photoelectric colorimeter. 0·25 Ml. of a solution containing 0·0202 g./l. of " AnalaR " sodium nitrite was used as the standard.

Determination of Nitrate.—Nitrate was similarly determined colorimetrically by conversion into 5-nitro-2 : 4-xylenol as described by Yagoda (*Ind. Eng. Chem. Anal.*, 1943, **15**, 27). 1 Ml. of a solution containing 0·3608 g./l. of " AnalaR " potassium nitrate was used as the standard in all determinations. The validity of the method was checked with a solution containing 0·000534 g./ml. of methyl β-D-glucopyranoside tetranitrate (Found: 0·0005169, 0·0005281 g./ml.).

Determination of Nitrate in Presence of Nitrite.—To 5 ml. of a 1 : 10 dilution of the hydrolysate were added ammonium sulphamate (0·1 g.) and 2N-sulphuric acid (1 ml.). The solution was then left for 10 min. at room temperature and the nitrate in the resulting nitrite-free solution was determined colorimetrically as already described. The validity of this procedure was shown by the use of a solution containing 0·0001804 g./ml. of potassium nitrate and 0·000505 g./ml. of potassium nitrite (Found 0·0001744 g./ml. of potassium nitrate).

Solubility Determinations.—Each finely powdered tetranitrate (0·5 g.) was shaken at room temperature with distilled water (150 ml.) for 24 hr. and the resulting suspensions were equilibrated in a thermostat at 20° for a further 24 hr. Immediately before the colorimetric estimation, each suspension was filtered at 20° and a suitable volume of filtrate withdrawn. Aliquot portions (5 ml.) of methyl α- and β-D-glucopyranoside tetranitrate were used, but with the ethyl, *n*-propyl, and *n*-butyl compounds it was necessary to concentrate 100-ml. portions nearly to dryness to obtain sufficient material for colorimetric estimation.

Paper Chromatography.—The hydrolysate from methyl β-D-glucopyranoside tetranitrate was neutralized with 2N-sulphuric acid, filtered, and evaporated under reduced pressure. The resulting semi-solid mass, when dissolved in water and subjected to paper chromatography as described by Hough (*Nature*, 1950, **165**, 400), showed no trace of methyl β-D-glucopyranoside, and acid hydrolysis of the residue with boiling dilute hydrochloric acid did not give glucose.

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DEPARTMENT OF PHARMACOLOGY AND THERAPEUTICS,
UNIVERSITY OF ST. ANDREWS MEDICAL SCHOOL, DUNDEE. [*Received, August 5th*, 1953.]