892. *The Transformation of* 1-*Deoxy*-1-*nitro*-D-glycero-L-manno-*heptitol into Cyclic Derivatives.*

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When 1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol was heated in aqueous solution, the elements of water were eliminated and cyclisation occurred, giving mainly β-D-galactopyranosylnitromethane.* After fractionation of the other reaction products on a column of anion-exchange resin, evidence was obtained for the presence of α-D-galactopyranosylnitromethane, α- and β-D-galactofuranosylnitromethanes, and D-galactose. The nitro-derivatives were observed to behave as very weak acids.

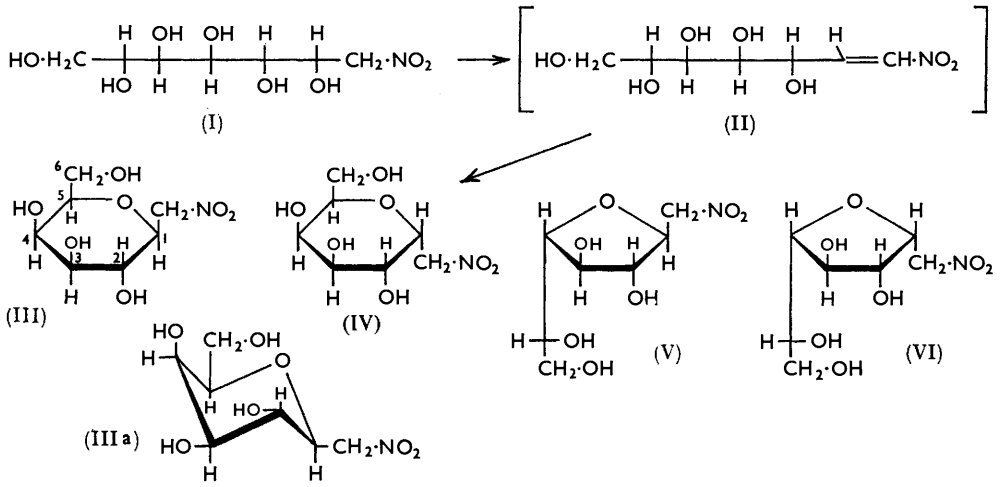
1-Deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol (I) and its D-*glycero*-L-*gluco*-isomer were prepared,[2] by condensing nitromethane with D-galactose in dimethyl sulphoxide, for subsequent conversion by the Nef reaction into aldoheptoses in order to study their sulphone derivatives.[2a] Potentiometric titration revealed that, like other nitroalkanes,[3] the nitroheptitols were slightly acidic with pK_a 9·2 and 8·8, respectively. During the preparation of the nitroheptitols, other faster-moving products were detected on paper chromatograms, suggesting an analogy with the cyclisation of 1-deoxy-1,1-diethylsulphonylhexitols *via* 1,1-diethylsulphonylhex-1-enetetraols.[4] Further investigation revealed that boiling the nitroheptitol (I) in aqueous solution for 24 hr. afforded at least five products. One of the products was readily recognised as galactose and in a related study Sowden and Oftedahl [5] have suggested that the formation of reducing sugar is due to a reversal of the nitromethane–aldose condensation. One of the nitromethane derivatives crystallised when the aqueous solution was evaporated and analysis revealed that it was an " anhydronitroheptitol," $C_7H_{13}NO_7$, with pK_a 9·0 corresponding to a molecular weight of 215. Acetylation of the product gave a crystalline tetra-acetate, suggesting that one of the hydroxyl groups of the " anhydronitroheptitol " was engaged in intramolecular ring formation. Reaction of the cyclic nitroheptitol with sodium metaperiodate at room temperature gave 1 mol. of formic acid but no formaldehyde, with the consumption of 2 mol. of oxidant, revealing the presence of a pyranosyl ring as would be predicted on conformational analysis if the hept-1-ene (II) were the precursor of the cyclic compound. The product is therefore a D-galactopyranosylnitromethane and in its preferred chair conformation the nitromethyl substituent would be predicted as occupying the equatorial β-position (IIIa). Applying Hudson's isorotation rules to the D-galactopyranosylnitromethane ($[M]_D$ +8140° in H_2O) and its tetra-acetate ($[M]_D$ +7120° in $CHCl_3$) and using methyl α- and β-D-galactopyranosides [6, 7] and their tetra-acetates [6] to determine the ring contribution (B = +19,090° and +21,670°, respectively), gave negative values for the anomeric carbon atom (−10,950° and −14,550°, respectively), in agreement with a β-configuration. It follows that the compound is β-D-galactopyranosylnitromethane (III) (2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol).

Hydrogenation of the nitromethane (III) in the presence of Raney nickel gave β-D-galactopyranosylmethylamine, isolated as the crystalline salt of toluene-*p*-sulphonic acid. *N*-Acetylation gave the amide, which consumed 2 mol. of periodate, giving 1 mol. of formic

* The nomenclature of the related diethylsulphonylpyranosylmethanes [1] has been adopted.

[1] Hough and Richardson, *Proc. Chem. Soc.*, 1959, 193.
[2] (*a*) T. J. Taylor, Ph.D. Thesis, Bristol, March 1956; (*b*) Sowden and Strobach, *J. Amer. Chem. Soc.*, 1960, **82**, 954.
[3] Pearson and Dillon, *J. Amer. Chem. Soc.*, 1953, **75**, 2439.
[4] Hough and Taylor, *J.*, 1956, 970.
[5] Sowden and Oftedahl, *J. Org. Chem.*, 1961, **26**, 1974.
[6] Dale and Hudson, *J. Amer. Chem. Soc.*, 1930, **52**, 2534.
[7] Augestad and Berner, *Acta Chem. Scand.*, 1954, **8**, 251.

acid, in agreement with the pyranosyl ring structure. Analysis of the proton magnetic resonance spectrum of 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosylnitromethane, kindly carried out by Dr. L. D. Hall, revealed two equatorial and one axial secondary acetoxy-group, and one equatorial primary acetoxy-group, in agreement with the predicted chair conformation (IIIa). Professor J. C. Sowden of Washington University, St. Louis, has recently informed us that, in collaboration with Mrs. Caroline H. Bowers, he has also isolated the 2,6-anhydro-derivative (III), m. p. 199—200°, $[\alpha]_D$ +33·6°, from a similar reaction mixture and detected other products with R_F values similar to those quoted here.



During the reaction of nitromethane with 4,6-*O*-benzylidene-D-glucose, Sowden and Fischer [8] noted the formation of a little 4,6-*O*-benzylidene-D-glucopyranosylnitromethane. Sowden and Oftedahl [5] have recently shown that, when heated under various conditions, 1-deoxy-1-nitro-D-mannitol and its isomer, 1-deoxy-1-nitro-D-glucitol, lose a mol. of water and cyclise to give mainly α-D-arabinopyranosylnitromethane and, in all probability, a little of the β-isomer. D-Arabinose was also found in about 5% yield from a reaction in water, presumably as a result of partial reversal of the condensation.

The other products from the nitroheptitol (I) were fractionated on a column of anion-exchange resin [9] (Cl^- form; <200 mesh), with water as eluent. The first two fractions contained D-galactose and β-D-galactopyranosylnitromethane (III), respectively. The fourth fraction yielded a crystalline product, $C_7H_{13}NO_7$, which showed two components (R_F 0·30 and 0·37) on paper chromatograms, the faster being indistinguishable from the β-pyranoside (III). Periodate oxidation of the mixed crystals gave results identical with those obtained for the β-pyranoside (III) and are therefore consistent with the other component's being α-D-galactopyranosylnitromethane (IV). The mixture had $[\alpha]_D$ +88·5°, suggesting that equal parts of α- and β-isomers were present since calculation from the isorotation rules suggested that the α-isomer (IV) would have $[\alpha]_D$ +135°.

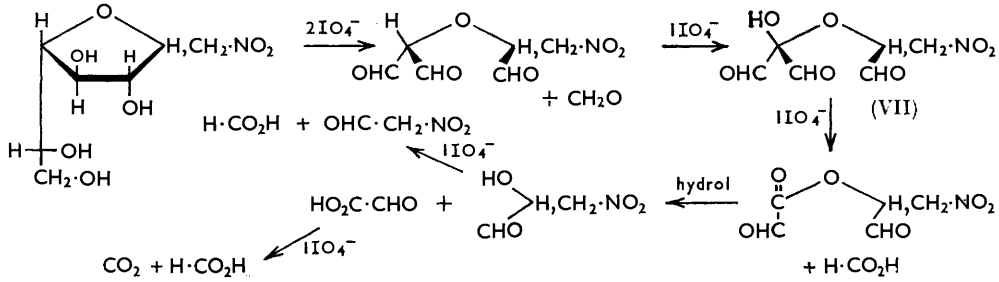
The fifth fraction ($[\alpha]_D$ −47°) contained mainly a component with R_F 0·45, also present as the major component in the sixth fraction, and gave on periodate oxidation results which are typical of a furanoside and were identical with those of yet another crystalline nitromethane derivative, $C_7H_{13}NO_7$, with R_F 0·53, also obtained from the sixth fraction. In unbuffered solution they reacted rapidly with 2 mol. of sodium metaperiodate, giving 1 mol. of formaldehyde, but only a little formic acid, but in further oxidation, the uptake

[8] Sowden and Fischer, *J. Amer. Chem. Soc.*, 1946, **68**, 1511.
[9] Priddle, Hough, and Theobald, *Chem. and Ind.*, 1960, 900; Jones, Wall, and Pittet, *Canad. J. Chem.*, 1960, **38**, 2285, 2290.

rose slowly to >5 mol. In the presence of sodium hydrogen carbonate, 6 mol. of periodate were quickly used, owing to the rapid hydrolysis at this pH of the intermediary ester (VIII) that would be expected [10] to arise from the hydroxymalonaldehyde (VII) in the main pathway shown.

The furanosyl structures (V and VI) are therefore assigned to the two components of higher R_F than the pyranosides, and it is noteworthy that this paper-chromatographic behaviour is typical of alkyl furanosides and pyranosides, the former isomers always moving the faster.

Application of the rules of isorotation to the crystalline D-galactofuranosylnitromethane ($[M]_D$ −111° in H_2O) and its crystalline tetra-acetate ($[M]_D$ +7860° in $CHCl_3$), with methyl α- and β-D-galactofuranosides [7] and penta-*O*-acetyl-α- and -β-D-galactofuranoses [11] as reference compounds (B = −770° and 3700°, respectively) gave positive values for the anomeric carbon atoms (+660° and +4160°, respectively), suggesting the α-configuration for the nitromethyl group (VI). The syrupy isomer has $[M]_D$ −10,480°, in agreement with the β-D-galactofuranosylnitromethane structure (V).



Whilst the dehydration of the 1-deoxy-1-nitroheptitols and subsequent cyclisation resemble the behaviour of the related 1,1-diethylsulphonyl derivatives,[4] and likewise probably proceed [5] through the 1-nitrohept-1-ene pentaol (II), owing to the strong, electron-withdrawing power of the nitro- and sulphone groups, the cyclic nitro-compounds were not similarly degraded in the presence of aqueous ammonia.

Experimental

M. p.s were determined on a Kofler micro-heating stage. Evaporations were under reduced pressure. Paper chromatography was carried out by the descending method at 21° on Whatman No. 1 filter paper with the mobile phases: (i) butan-1-ol–ethanol–water (40 : 11 : 19 v/v); (ii) butan-1-ol–pyridine–water (10 : 3 : 3 v/v); (iii) ethyl methyl ketone–acetic acid–boric acid (9 : 1 : 1 v/v); (iv) ethyl acetate–acetic acid–water (9 : 2 : 2 v/v). The compounds were detected with 4% w/v ammoniacal silver nitrate and rates of movement are quoted relative to the solvent front (R_F). Optical rotations were determined at 24° ± 1° and, unless otherwise stated, in water.

Condensation of D-*Galactose with Nitromethane.*—To a solution of D-galactose (40 g.) in dimethyl sulphoxide (350 ml.) and nitromethane (105 ml.) was added anhydrous calcium sulphate (15 g.), followed by 12% w/v sodium methoxide in methanol (250 ml.). After 4 hr. at room temperature, the sodium *aci*-nitroheptitol salts were precipitated by the addition of sodium-dried ether (500 ml.) and cooling to 4°. The cream-coloured precipitate was filtered off, washed with ether, and extracted with water. After removal of the insoluble calcium sulphate the solution was de-ionised by passage down a column of Amberlite IR-120 (H^+) resin. Concentration of the eluate gave crystals of 1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol monohydrate and eventually a residual orange syrup. After two recrystallisations from 90%

[10] Cantley, Hough, and Pittet, *Chem. and Ind.*, 1959, 1126; Hough, Taylor, Thomas, and Woods, *J.*, 1958, 1212.
[11] Hudson and Johnson, *J. Amer. Chem. Soc.*, 1916, **38**, 1223.

ethanol, the monohydrate (16·5 g., 30%) had m. p. 155—157°, $[\alpha]_D$ +6·0° (*c* 2·0), and pK_a 9·2. On drying over phosphoric oxide for several days, the m. p. rose to 166—168°. Sowden and Strobach [2] found m. p. 158—159° (hydrate), m. p. 165—166° (anhydrous), and $[\alpha]_D$ +6·3°.

The orange syrup crystallised when kept in a little ethanol. Recrystallised from 95% ethanol 1-deoxy-1-nitro-D-*glycero*-L-*gluco*-heptitol (4·8 g., 9%) had m. p. 152—153°, m. p. 141—146° in admixture with the L-*manno*-isomer, pK_a 8·8, and $[\alpha]_D$ +7·7° (*c* 2·0). The two isomers could not be separated from one another by paper chromatography and had R_F 0·27 (solvent i), 0·33 (solvent ii), 0·36 (solvent iii), and 0·53 (solvent iv). Sowden and Strobach [2] reported m. p. 152—153° and $[\alpha]_D$ +7·8°.

β-D-*Galactopyranosylnitromethane* (III).—A solution of 1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol monohydrate (15 g.) in water (150 ml.) was boiled under reflux for 24 hr. Concentration of the solution gave a syrup (12·5 g.) which crystallised. A paper chromatogram (solvent i) revealed a major component (R_F 0·37) and four minor components [R_F 0·12 (galactose) 0·30, 0·45, and 0·53]. The same products were detected in a similar experiment with the D-*glycero*-L-*gluco*-isomer and on de-acetylation with sodium methoxide of 1-nitro-D-*galacto*-3,4,5,6,7-penta-*O*-acetylhept-1-ene.

The main component was isolated by washing the syrupy crystals with hot ethanol (*ca.* 200 ml.). The crude product (8 g.) was contaminated with a little galactose which was removed only after several recrystallisations from ethanol, giving β-D-*galactopyranosylnitromethane* (3 g.), m. p. 198·5—199·5°, $[\alpha]_D$ +36·5° (*c* 2·0), R_F 0·37 (solvent i) (Found: C, 37·9; H, 5·8; N, 6·25. $C_7H_{13}NO_7$ requires C, 37·7; H, 5·85; N, 6·3%).

The compound (150·7 mg.) was dissolved in water (*ca.* 100 ml.), mixed with 0·3M-sodium metaperiodate (10 ml.), and quickly made up to 250 ml. with water and kept in the dark at room temperature. A similar oxidation mixture was made up and kept at 4° in the dark. Suitable controls were also prepared. At various intervals, aliquot portions (10 ml.) were removed from each reaction mixture and control for the determination of periodate uptake [10, 12] and formic acid.[13] At room temperature 1·9 mol. of oxidant were consumed in 2 hr. with the liberation of 0·85 mol. of formic acid, slowly rising thereafter to 2·14 mol. and 1·04 mol. at 32 hr., respectively. Tests for formaldehyde by the chromotropic acid method [10] were negative, even after 48 hr.

Potentiometric titration of a solution of the β-pyranosylnitromethane (III) (0·250 g.) in water (10 ml.) against 0·1N-sodium hydroxide showed pK_a 9·0 at the half-neutralisation point, giving a mol. wt. of 215·5 (Calc. for $C_7H_{13}NO_7$: *M*, 223).

When a solution of the nitromethane (III) in aqueous ammonia at pH 11 was left for 2 weeks, no trace of galactose could be detected on paper chromatograms and the solution showed no change in $[\alpha]_D$.

2,3,4,6-*Tetra*-O-*acetyl*-β-D-*galactopyranosylnitromethane*.—A solution of β-D-galactopyranosylnitromethane (0·5 g.) in a mixture of acetic anhydride (5 ml.) and concentrated sulphuric acid (1 drop) was heated at 95—100° for 15 min., then cooled and poured into stirred ice–water, and the product was extracted with chloroform and washed with a saturated solution of sodium hydrogen carbonate and then several times with water. Concentration of the chloroform solution gave a colourless syrup which crystallised. Recrystallised from ethanol–light petroleum, the *tetra-acetate* (0·76 g., 87%) had m. p. 102—103° and $[\alpha]_D$ +18·2° (*c* 2·0 in chloroform) (Found: C, 46·25; H, 5·35; N, 3·8. $C_{15}H_{21}NO_{11}$ requires C, 46·05; H, 5·4; N, 3·6%). Deacetylation of the tetra-acetate with methanolic sodium methoxide for 4 hr. gave the starting material, m. p. and mixed m. p. 197—199°, $[\alpha]_D$ +36·4° (*c* 1·0).

β-D-*Galactopyranosylmethylamine*.—A solution of the β-D-galactopyranosylnitromethane (0·5 g.) in water (50 ml.) was treated with Raney nickel (0·2 g.) and hydrogen at atmospheric pressure for 6 hr., hydrogenation being then complete. After filtration, concentration gave pale green crystals which were difficult to decolorise. They had m. p. 175—180° and R_F 0·07 (solvent i). Concentration of a solution containing the amine (0·22 g.) and toluene-*p*-sulphonic acid (0·195 g.) gave, after washing with ethanol, the salt (0·215 g.) as the crystalline *hemihydrate* (Found: C, 45·05; H, 6·41. $C_{14}H_{23}NO_8S,\frac{1}{2}H_2O$ requires C, 44·9; H, 6·4%). At 90° under reduced pressure over phosphoric oxide the crystals lost the water of crystallisation in 4 hr. and then had m. p. 141—143°, $[\alpha]_D$ +19·7 (*c* 1·5).

[12] Neumuller and Vasseur, *Arkiv Kemi*, 1953, **5**, 235.
[13] Halsall, Hirst, and Jones, *J.*, 1947, 1427.

The amine (0·1 g.) was treated with acetic anhydride (1 ml.) in 50% aqueous methanol (5 ml.) until a negative test with ninhydrin was obtained (*ca.* 1 min.). After evaporation several times with ethanol a pale orange syrup was obtained. The acetamido-β-D-galacto-pyranosylmethane had $[\alpha]_D$ +30° (*c* 1·12) and R_F 0·24 (solvent i) (Found: C, 45·8; H, 7·2. $C_9H_{17}O_6N$ requires C, 45·95; H, 7·25%). The acetamido-derivative (56 mg.) was treated with 0·015M-sodium metaperiodate (100 ml.) at room temperature, in the dark; 1·7 mol. of oxidant were consumed in 1 hr., giving 0·75 mol. of formic acid, these amounts rising slowly to 2·09 mol. and 1·07 mol., respectively, after 33 hr.

Separation of Other Components from the Cyclisation of 1-*Deoxy*-1-*nitro*-D-glycero-L-manno-*heptitol.*—The combined alcoholic washings and liquors from the crystallisation of β-D-galacto-pyranosylnitromethane were evaporated to a syrup (4 g.) which was dissolved in a little water and run on a column [85 × 2·5 cm. De-Acidite FF (SRA 68) anion-exchange resin (3·5% cross-linked; <200 mesh; Cl^- form)]. Water was then percolated down the column at a flow rate of 15—20 ml./hr. After examination of samples on paper chromatograms the effluent was grouped into six fractions and each was evaporated to dryness. Fractions 1 and 2 gave D-galactose (0·2 g.) and β-D-galactopyranosylnitromethane (0·12 g.), respectively. Fraction 3 (0·4 g.) also gave the latter together with a little of another compound, R_F 0·30 (solvent i), and the same components were found in fraction 4. On evaporation the mixture crystallised, the crystals (0·14 g.) containing equal parts of each component as judged from paper chromatograms. The mixture of α- and β-D-galactopyranosylnitromethane had m. p. 171—181°, $[\alpha]_D$ +88·5° (*c* 1·97) (Found: C, 37·8; H, 5·8; N, 6·4. Calc. for $C_7H_{13}NO_7$: C, 37·7; H, 5·85; N, 6·3%).

Periodate oxidation of the mixed product as above at room temperature gave similar results to those shown by β-D-galactopyranosylnitromethane, namely, consumption of 2·01 mol. of periodate with the liberation of 0·90 mol. of formic acid after 9 hr., slowly rising to 2·15 mol. and 1·13 mol., respectively, after 50 hr. No formaldehyde was liberated.

Fraction 5 (0·3 g.) contained mainly the component with R_F 0·45 (solvent i) and had $[\alpha]_D$ −47° (*c* 4·5). Fraction 6 (0·7 g.) yielded the two components having higher R_F than the pyranosides and gave crystals on concentration. The crystals were washed with a little ethanol and recrystallised from ethanol, giving α-D-*galactofuranosylnitromethane* (0·35 g.), m. p. 155—157°, R_F 0·53 (solvent i), $[\alpha]_D$ −0·5° (*c* 2·0) (Found: C, 37·8; H, 5·85. $C_7H_{13}NO_7$ requires C, 37·7; H, 5·85%). Evaporation of the combined ethanolic washings and liquors gave a syrup (3·3 g.) (fraction 6a) with $[\alpha]_D$ −55° (*c* 1·4 in methanol), containing mainly the component with R_F 0·46.

Periodate oxidations of α-D-galactofuranosylnitromethane, the syrupy fraction 6a, and fraction 5 were carried out at room temperature as above and gave the following results:

(*a*) Unbuffered solution.

Time (hr.)	5	10·5	21·5	45·5	73
Periodate uptake (mol.)	2·1	2·55	3·2	4·3	4·9
Formic acid (mol.)	0·16	0·42	0·90	2·02	2·56
Formaldehyde (mol.)	1·0	—	—	—	1·0

(*b*) Sodium hydrogen carbonate solution.

Time (hr.)	24·6	43	52	55	68
Periodate uptake (mol.)	5·6	5·75	5·85	5·9	5·9

2,3,5,6-*Tetra*-O-*acetyl*-α-D-*galactofuranosylnitromethane.*—A solution of the α-furanoside (0·2 g.) in acetic anhydride (5 ml.) and concentrated sulphuric acid (1 drop) was heated under reflux at 95—100° for 20 min. After isolation as above and recrystallisation from ethanol–light petroleum, the *acetate* had m. p. 98·5—99·5° and $[\alpha]_D$ +20·1° (*c* 1·09 in chloroform) (Found: C, 46·05; H, 5·3. $C_{15}H_{21}NO_{11}$ requires C, 46·05; H, 5·4%). On admixture with β-D-galacto-pyranosylnitromethane tetra-acetate the m. p. fell to 75°.

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