Cyano-sugars. Part 4.[1] Hypochlorite Oxidation of Branched-chain Nitro-sugars and Conversion of the Products into Branched-chain Cyano-sugars

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Carbohydrate derivatives containing a primary nitro-group react with hypochlorite to give αα-dichloronitro-compounds which afford branched-chain cyano-sugars on treatment with triphenylphosphine. The preparation of 3,3-*C*-bis(nitromethyl) doubly-branched carbohydrate derivatives is also described.

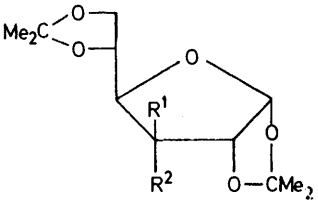
In a previous publication [1] we catalogued some of the methods that have been used for the syntheses of sugar derivatives bearing a cyano-group. Among the methods listed was that for converting [2,3] 2-deoxy-2-*C*-nitromethyl and 3-deoxy-3-*C*-nitromethyl sugar derivatives into their respective *C*-cyano-analogues *via* αα-dibromination of the methylene groups, followed by treatment with triphenylphosphine. A possible mechanism for the reaction has been discussed.[4]

We now report that cyano-sugars can be obtained in much higher yield by an analogous route. The αα-dichloro-products (2) and (8) were prepared by treating a solution of, respectively, compounds (1) or (7) in ethyl acetate with an excess of aqueous sodium hypochlorite in the presence of the phase transfer catalyst tetrabutylammonium chloride (TBAC) and were then converted into the respective cyano-compounds (3) (overall yield 40%) and (9) (overall yield 76%) by reaction with an ethereal solution containing three equivalents of triphenylphosphine.

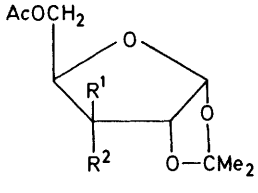
In order to investigate the possibility of obtaining 3,3-*C*-dicyano-compounds, the bis(nitromethyl) compounds (4) and (10) were prepared by Michael addition of nitromethane in the presence of triethylamine to the unsaturated sugars (6) and (11), respectively. This method is essentially that of Baer.[5] Hypochlorite oxidation of (4) gave an unstable product that, on chromatography, gave two mixed fractions which could not be further separated. The less polar mixture was shown by mass spectrometry to contain the 3,3-*C*-bis(dichloronitromethyl) derivative (5) and traces of other related, partially chlorinated products, while the more polar fractions were shown (n.m.r. and mass spectra) to contain a 1 : 7 mixture of the epoxides (13) and (14) respectively. As an unstable mixture of products was obtained from the hypochlorite oxidation of (4), oxidation of compound (10) was not attempted.

The isolation of products such as (13) and (14) from the hypochlorite oxidation of (4) can be explained by assuming that the alkaline aqueous phase induces a retro-Michael addition to give unsaturated compounds such as (6) or its C-3'-chloro-analogue which are then further oxidised to epoxides. Indeed, hypochlorite oxidation of the unsaturated sugars (6) and (11) gave mixtures of isomers of the epoxides (13) and (15), respectively, in good yields. The n.m.r. spectra of (13) and (15) indicated that they were 9 : 1 and 2 : 3 mixtures of isomers, respectively. These isomeric mixtures could not be separated. However, attempted reduction of the mixture of epoxides (15) gave only the deacetylated products (16) and (17) which were separated chromatographically.

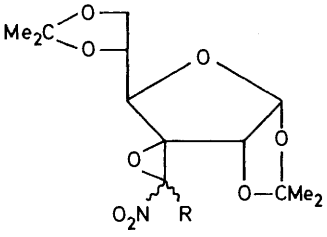
The epoxidation of nitro-alkenes with hypochlorite [6] and with alkaline peroxide [7] has been well documented and mechanisms for the reaction have been suggested.[8-10] It has been shown [7] that alkaline epoxidation of a number of 4,6-*O*-benzylidene-2,3-dideoxy-3-nitrohex-2-enopyranosides with sodium peroxide stereospecifically gives rise to products having the epoxy- and methoxy-groups in the *trans* configuration, *i.e.* that nucleophilic attack by the oxidising agent on the carbon



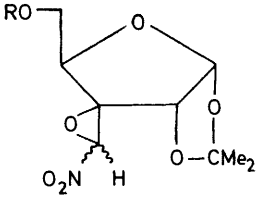
(1) R^1 = H, R^2 = CH_2NO_2
(2) R^1 = H, R^2 = CCl_2NO_2
(3) R^1 = H, R^2 = CN
(4) R^1 = R^2 = CH_2NO_2
(5) R^1 = R^2 = CCl_2NO_2
(6) R^1, R^2 = $CHNO_2$



(7) R^1 = H, R^2 = CH_2NO_2
(8) R^1 = H, R^2 = CCl_2NO_2
(9) R^1 = H, R^2 = CN
(10) R^1 = R^2 = CH_2NO_2
(11) R^1, R^2 = $CHNO_2$
(12) R^1 = CH_2NO_2, R^2 = OAc



(13) R = H
(14) R = Cl



(15) R = Ac
(16) R = H, C-3' (*R* or *S*)
(17) R = H, C-3' (*S* or *R*)

atom β to the nitro-group takes place from the less hindered side of the molecule.

With these findings in mind, and also because numerous examples have been described [11] where compounds analogous to compounds (6) and (11) have been attacked from the β-side of the molecule, we have reasoned that compounds (13)—(17) must contain β-epoxy-groups.

EXPERIMENTAL

All solvent extracts were dried (Na_2SO_4), filtered, and evaporated at <50 °C *in vacuo*. T.l.c. and column chromatography were performed on silica gel (Merck GF_{254}) [100 g of silica per g of residue for column separation]. M.p.s were determined with a hot-stage apparatus. Unless otherwise stated, i.r. spectra were measured for solutions in chloroform with a Perkin-Elmer 237 spectrophotometer. N.m.r. spectra were measured with a Varian HA-100 or a Varian EM-390 instrument as indicated (tetramethylsilane as internal standard; solutions in $CDCl_3$). Optical rotations were measured for solutions in chloroform with a Perkin-Elmer 241 automatic polarimeter (*c* 1.0 ± 0.3) and mass spectra with an A.E.I. MS9 spectrometer by direct insertion. Samples of oils were dried under high vacuum for microanalysis. In the cases where acceptable analytical values were not obtained, the oils, shown to be chromatographically homogeneous in several solvent systems, were submitted for accurate mass determination.

3-*Deoxy*-3-C-*dichloronitromethyl*-1,2:5,6-*di*-O-*isopropylidene*-α-D-*allofuranose* (2).—A solution of 3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-nitromethyl-α-D-allofuranose [12] (1) (760 mg, 2 mmol) and TBAC (100 mg) in ethyl acetate (40 ml) was vigorously stirred at 0 °C for 4 h with aqueous sodium hypochlorite (21 ml; *ca.* 5% commercial household bleach). The ethyl acetate layer was separated and the solvent removed to give an oil which was chromatographed [ethyl acetate–hexane (1 : 1)] to give compound (2) (670 mg, 72%). Recrystallisation from ethyl acetate–hexane afforded colourless *plates*, m.p. 78—79°; $[\alpha]_D^{20}$ +74°; $\nu_{max.}$ 1 600 cm^{-1} (NO_2); *m/e* 356 and 358 (M^+ − Me); τ(100 MHz) 4.18 (1 H, d, $J_{1,2}$ 4 Hz, H-1), 5.00 (1 H, t, $J_{2,1}$, $J_{2,3}$ 4 Hz, H-2), 5.66—6.15 (4 H, m, H-4, -5, -6a, and -6b), 6.32 (1 H, dd, $J_{3,4}$ 8.5, $J_{3,2}$ 4.5 Hz, H-3), and 8.43, 8.66, and 8.76 (12 H, 3 s, 4 Me) (Found: C, 41.9; H, 5.3; N, 3.9; Cl, 19.1. $C_{13}H_{19}Cl_2NO_7$ requires C, 42.0; H, 5.1; N, 3.8; Cl, 19.1%).

5-O-*Acetyl*-3-*deoxy*-3-C-*dichloronitromethyl*-1,2-O-*isopropylidene*-α-D-*ribofuranose* (8.)—To a solution of 5-*O*-acetyl-3-deoxy-3-*C*-nitromethyl-1,2-*O*-isopropylidene-α-D-ribofuranose [13] (7) (1.38 g, 5 mmol) and TBAC (70 mg) in ethyl acetate (100 ml), a large excess of aqueous sodium hypochlorite (25 ml; *ca.* 9%; commercial household bleach) was added and the mixture was vigorously stirred at 20 °C for 30 min. Work-up as for compound (2) gave a homogeneous oil (8) which crystallised from ethyl acetate–hexane as *needles* (1.31 g, 87%), m.p. 84°; $[\alpha]_D^{20}$ +83°; $\nu_{max.}$ 1 750 (CO) and 1 595 cm^{-1} (NO_2); *m/e* 330 and 328 (M^+ − Me); τ(100 MHz) 4.17 (1 H, d, $J_{1,2}$ 4 Hz, H-1), 5.09 (1 H, t, $J_{2,1} = J_{2,3} = 4$ Hz, H-2), 5.53 (1 H, 2 t, $J_{4,3}$ 9, $J_{4,5a} = J_{4,5b} = 3.5$ Hz, H-4), *ca.* 5.64 (2 H, m, H-5a and -5b), 6.54 (1 H, dd, $J_{3,4}$ 9, $J_{3,2}$ 4 Hz, H-3), 7.94 (3 H, s, OAc), and 8.48 and 8.68 (6 H, 2 s, 2 Me) (Found: C, 38.6; H, 4.6; N, 4.0; Cl, 20.6. $C_{11}H_{15}Cl_2NO_7$ requires C, 38.4; H, 4.4; Cl, 20.6; N, 4.1%).

It was shown that in the above method for obtaining the chloro-sugar (8) from the compound (7) the addition of TBAC to the two-phase system was essential for fast oxidation.

3-C-*Cyano*-3-*deoxy*-1,2:5,6-*di*-O-*isopropylidene*-α-D-*allofuranose* (3).—To a solution of 3-deoxy-3-*C*-dichloronitromethyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (2) (262 mg, 0.7 mmol) in dry ether (10 ml), a solution of triphenylphosphine (600 mg, 2.3 mmol) in dry ether (5 ml) was added and the mixture was stirred at 20 °C for 30 min. Evaporation left an oily mixture which was chromatographed [ethyl acetate–chloroform (1 : 2)] to give compound (3) (106 mg, 56%) as a solid which crystallised from acetone as colourless plates, m.p. 109—110°; identical (m.p., mixed m.p., and mass and i.r. spectra) with an authentic sample of 3-*C*-cyano-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose.[2]

5-O-*Acetyl*-3-C-*cyano*--3-*deoxy*-1,2-O-*isopropylidene*-α-D-*ribofuranose* (9).—To a solution of 5-*O*-acetyl-3-deoxy-3-*C*-dichloronitromethyl-1,2-*O*-isopropylidene-α-D-ribofuranose (8) (109 mg, 0.32 mmol) in dry ether (8 ml), a solution of triphenylphosphine (272 mg, 1 mmol) in dry ether (4 ml) was added and the mixture was stirred at 20 °C for 30 min. Work-up as for compound (3) afforded compound (9) (67 mg, 88%) as a solid which crystallised from acetone–hexane as colourless plates, m.p. 102—103°; identical (m.p., mixed m.p., mass and i.r. spectra) with the authentic 5-*O*-acetyl-3-*C*-cyano-3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose.[3]

3-*Deoxy*-1,2:5,6-*di*-O-*isopropylidene*-3,3-C-*bis*(*nitromethyl*)-α-D-ribo-*hexofuranose* (4).—3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-nitromethylene-α-D-*ribo*-hexofuranose [12] (6) (301 mg, 1 mmol) in dry nitromethane (10 ml) containing dry triethylamine (0.2 ml) was stirred for 16 h at 20 °C. The solvents were removed and the residue was co-evaporated with toluene (2 × 10 ml) to leave an oil which was chromatographed [ethyl acetate–hexane (1 : 1)] to give the *dinitro-compound* (4) as a glass (228 mg, 68%); $[\alpha]_D^{20}$ +44°; $\nu_{max.}$ 1 560 cm^{-1} (NO_2); *m/e* 347 (M^+ − Me); τ(100 MHz) 4.22 (1 H, d, $J_{1,2}$ 4 Hz, H-1), 4.86 (1 H, d, $J_{2,1}$ 4 Hz, H-2), 5.1 (2 H, q, CH_2NO_2), 5.18 (2 H, q, CH_2NO_2), 5.60—6.35 (4 H, m, H-4, -5, -6a, and -6b), and 8.47, 8.52, and 8.67 (12 H, 3 s, 4 Me) (Found: *m/e*, 247.112. $C_{13}H_{19}N_2O_9$ requires M^+ − Me, 347.109).

5-O-*Acetyl*-3-*deoxy*-1,2-O-*isopropylidene*-3,3-C-*bis*-(*nitromethyl*)-α-D-erythro-*pentofuranose* (10).—A solution of 3,5-di-*O*-acetyl-1,2-*O*-isopropylidene-3-*C*-nitromethyl-α-D-ribofuranose [3] (12) (333 mg, 1 mmol) in dry nitromethane (10 ml) containing dry triethylamine (0.2 ml) was stirred and worked up as for compound (4) to give an oil which was chromatographed [chloroform–ethyl acetate (4 : 1)] to give the *dinitro-compound* (10) (187 mg, 56%) which crystallised from ethyl acetate–hexane as white needles, m.p. 114—115°; $[\alpha]_D^{20}$ +35°; $\nu_{max.}$ 1 750 (CO) and 1 560 cm^{-1} (NO_2); *m/e* 319 (M^+ − Me); τ(100 MHz) 4.13 (1 H, d, $J_{1,2}$ 3.5 Hz, H-1), 5.11 (2 H, q, CH_2NO_2), 5.17 (1 H, d, $J_{2,1}$ 3.5 Hz, H-2), 5.42 (2 H, q, CH_2NO_2), 5.70—5.89 (3 H, m, H-4, -5a, and -5b), 7.95 (3 H, s, OAc), and 8.46 and 8.67 (6 H, 2 s, 2 Me) (Found: C, 43.1; H, 5.7; N, 8.3. $C_{12}H_{18}N_2O_9$ requires, C, 43.1; H, 5.4; N, 8.4%).

3,3′-*Anhydro*-1,2:5,6-*di*-O-*isopropylidene*-3-C-[(RS)-*hydroxynitromethyl*]-α-D-*glucofuranose* (13).—A solution of 3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-nitromethylene-α-D-*ribo*-hexofuranose [12] (6) (444 mg, 1.5 mmol) and TBAC (75 mg) in ethyl acetate (30 ml) was vigorously stirred at

20 °C for 15 min with aqueous sodium hypochlorite (8 ml; *ca.* 9%). Work-up as for compound (2) gave the inseparable (*R*)- and (*S*)-mixture (13) as a colourless oil (380 mg, 80%); $\nu_{max.}$ 1 575 cm^{-1} (NO_2); *m/e* 302 (M^+ — Me); τ(90 MHz) 3.98 (1 H, d, $J_{1,2}$ 4 Hz, H-1), 4.32 (1 H, s, H-3′), 5.17 (1 H, d, $J_{2,1}$ 4 Hz, H-2), 5.6—6.1 (4 H, m, H-4, -5, -6a, and -6b), and 8.47, 8.53, and 8.69 (12 H, 3 s, 4 Me). N.m.r. showed that the product (13) consisted of a 9 : 1 mixture of optical isomers (Found: *m/e*, 302.089. $C_{12}H_{16}NO_8$ requires M^+ — Me, 302.088).

3,3′-*Anhydro*-5-O-*acetyl*-1,2-O-*isopropylidene*-3-C-[(RS)-*hydroxynitromethyl*]-α-D-*xylofuranose* (15).—A solution of 5-*O*-acetyl-3-deoxy-1,2-*O*-isopropylidene-3-*C*-nitromethylene-α-D-*erythro*-pentofuranose [3] (11) (412 mg, 1.5 mmol) and TBAC (75 mg) in ethyl acetate (20 ml) was stirred at 20 °C for 30 min with aqueous sodium hypochlorite (8 ml; *ca.* 9%). Work-up as described for the preparation of the compound (2) gave an oil which was chromatographed [ethyl acetate–hexane (2 : 3)] to give a pure inseparable (R)- and (S)-mixture (15) (350 mg, 80%) as a colourless oil; $\nu_{max.}$ 1 740 (CO) and 1 580 cm^{-1} (NO_2); *m/e* 274 (M^+ — Me). N.m.r. showed that the product (15) consisted of a 2 : 3 mixture of optical isomers (Found: *m/e*, 274.054. $C_{10}H_{12}NO_8$ requires M^+ — Me, 274.056).

3,3′-*Anhydro*-1,2-O-*isopropylidene*-3-C-[(R *or* S)-*hydroxynitromethyl*]-α-D-*xylofuranose* (16) *and its* (S *or* R)-*Isomer* (17).—To a solution of 3,3′-anhydro-5-*O*-acetyl-1,2-*O*-isopropylidene-3-*C*-[(*RS*)-hydroxynitromethyl]-α-D-xylofuranose (15) (430 mg, 1.5 mmol) in absolute ethanol (30 ml), sodium tetrahydroboride (200 mg, 5.3 mmol) was added slowly, and the mixture was stirred at 20 °C for 2 h and then neutralised with aqueous acetic acid (2%). Water (50 ml) was added and the solution was concentrated to half its volume before extraction with chloroform. The combined chloroform fractions were dried and the solvent was removed to give a colourless oil (330 mg). Chromatography [ethyl acetate–hexane (1 : 1)] afforded first 3,3′-anhydro-1,2-*O*-isopropylidene-3-*C*-[(*R* or *S*)-hydroxynitromethyl]-α-D-xylofuranose (16) (52 mg, 14%); $[\alpha]_D^{20}$ +27°; $\nu_{max.}$ 1 570 cm^{-1} (NO_2); *m/e* 232 (M^+ — Me); τ(90 MHz) 3.86 (1 H, d, $J_{1,2}$ 4 Hz, H-1), 4.24 (1 H, s, H-3′), 5.37 (1 H, d, $J_{2,1}$ 4 Hz, H-2), 5.83 (1 H, t, $J_{4,5a} = J_{4,5b} = 2$ Hz, H-4), 6.1 (2 H, d, $J_{5a,4} = J_{5b,4}$ 2 Hz, H-5a and -5b), *ca.* 7.8 (1 H, s, disappears on addition of D_2O, OH), and 8.45 and 8.54 (6 H, 2 s, 2 Me) (Found: *m/e*, 232.046. $C_8H_{10}NO_7$ requires M^+ — Me, 232.046).

Next eluted was 3,3′-anhydro-1,2-*O*-isopropylidene-3-*C*-[(*S* or *R*)-hydroxynitromethyl]-α-D-xylofuranose (17) (184 mg, 50%); $[\alpha]_D^{20}$ +150°; $\nu_{max.}$ 1 580 cm^{-1} (NO_2); *m/e* 232 (M^+ — Me); τ(90 MHz) 3.95 (1 H, d, $J_{1,2}$ 4 Hz, H-1), 4.36 (1 H, s, H-3′), 5.19 (1 H, d, $J_{2,1}$ 4 Hz, H-4), 5.42 (1 H, m, H-4), 6.34 (2 H, m, H_2-5), 7.57 (1 H, s, disappears on addition of D_2O, OH), and 8.50 and 8.70 (6 H, 2 s, 2 Me) (Found: *m/e*, 232.046 (M^+ — Me). $C_8H_{10}NO_7$ requires M — Me, 232.046).

Hypochlorite Oxidation of 3-*Deoxy*-1,2:5,6-di-O-*isopropylidene*-3,3-C-*bis*(*nitromethyl*)-α-D-ribo-*hexofuranose* (4).—A solution of the bis(nitromethyl)-compound (4) (540 mg, 1.5 mmol) and TBAC (75 mg) in ethyl acetate (30 ml) was stirred with aqueous sodium hypochlorite (16 ml; 9%) at 20 °C for 2 h. Work-up as for compound (2) gave a mixture of products that, on chromatography [ethyl acetate–hexane (1 : 1)], gave two mixed fractions which could not be separated further. The less polar mixture (100 mg) was shown by mass spectrometry to contain 3-deoxy-1,2:5,6-di-*O*-isopropylidene-3,3-*C*-bis(dichloronitromethyl) α-D-*ribo*-hexofuranose (5), $\nu_{max.}$ 1 600 cm^{-1} (NO_2); *m/e* 485, 487, and 489 (M^+ — Me), and traces of other related, partially chlorinated, products. The more polar fraction (200 mg) was shown (n.m.r. and mass spectra) to contain a 7 : 3 mixture of the epoxides 3,3′-anhydro-1,2:5,6-di-*O*-isopropylidene-3-*C*-[(*RS*)-chlorohydroxynitromethyl]-α-D-glucofuranose (14) (*ca.* 26%), $\nu_{max.}$ 1 590 cm^{-1} (NO_2); *m/e* 338 and 336 (M^+ — Me) (Found: *m/e*, 336.051. $C_{12}H_{15}ClNO_8$ requires M^+ — Me, 336.049); and 3,3′-anhydro-1,2:5,6-di-*O*-isopropylidene-3-*C*-[(*RS*)-hydroxynitromethyl]-α-D-glucofuranose (13) (*ca.* 14%), $\nu_{max.}$ 1 575 cm^{-1} (NO_2). Complete separation and characterisation of the mixtures were impossible because of the instability of the compounds formed during the reaction.

[9/556 *Received*, 9*th April*, 1979]

REFERENCES

[1] Part 3, R. H. Hall, K. Bischofberger, A. J. Brink, O. G. de Villiers, and A. Jordaan, *J.C.S. Perkin I*, 1979, 781.
[2] A. J. Brink, O. G. de Villiers, and A. Jordaan, *S. African J. Chem.*, 1978, **31**, 59.
[3] O. G. de Villiers, A. Jordaan, and G. J. Lourens, *J. S. African Chem. Inst.*, 1975, **28**, 27.
[4] S. Trippett and D. M. Walker, *J. Chem. Soc.*, 1960, 2976.
[5] H. H. Baer and K. S. Ong, *Canad. J. Chem.*, 1968, **46**, 2511.
[6] T. Sakakibara, S. Kumazawa, and T. Nakagawa, *Bull. Chem. Soc. Japan*, 1970, **43**, 2655.
[7] H. Newman and R. B. Angier, *Chem. Comm.*, 1963, 369; *Tetrahedron*, 1970, **26**, 825; H. H. Baer and W. Rank, *Canad. J. Chem.*, 1971, **49**, 3192.
[8] D. D. Keane, W. I. O'Sullivan, E. M. Philburn, R. M. Simons, and P. C. Teague, *Tetrahedron*, 1971, **27**, 3535.
[9] A. Robert and A. Foucaud, *Bull. Soc. chim. France*, 1969, **7**, 2531.
[10] D. H. Rosenblatt and G. H. Broome, *J. Org. Chem.*, 1963, **28**, 1290.
[11] A. Jordaan, M. Malherbe, and G. R. Woolard, *J. Chem. Research*, 1979, (*M*) 701, (*S*) 60, and references cited therein.
[12] H. P. Albrecht and J. G. Moffatt, *Tetrahedron Letters*, 1970, 1063.
[13] G. J. Lourens, *Carbohydrate Res.*, 1971, **17**, 35.