Synthesis of Glycosyl α-Amino Acids

By KARL BISCHOFBERGER, RICHARD H. HALL*, and AMOR JORDAAN
(*National Chemical Research Laboratory, Council for Scientific and Industrial Research, Pretoria* 0001, *Republic of South Africa*)

Summary. The major isomer, (*E*)-1,4-anhydro-1-ethoxycarbonyl(formylamino)methylene-2,3:5,6-di-*O*-isopropylidene-D-mannitol (**2**), obtained by the reaction of α-metallated ethyl isocyanoacetate with 2,3:5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone, gives, on hydrogenation and acidic hydrolysis, 2-L-(and 2-D-)(β-D-mannofuranosyl)glycines (**10**) and (**11**), and can be converted into 2-L- and 2-D-(β-D-lyxofuranosyl)glycines (**12**) and (**13**).

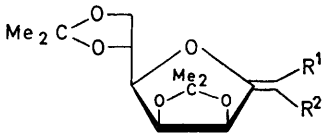
THE discovery of the polyoxins[1] has led to interest in sugars linked to amino acids *via* a carbon–carbon linkage and compounds with an amino acid group attached to C-4[2] and C-3[3] of furanosyl sugars have been prepared. We report the synthesis of derivatives linked *via* C-1 of furanosyl sugars.

The key step in the synthesis is the formylaminomethylenation[4] ($EtO_2C{\cdot}CH_2NC$, KH, THF, − 10 °C) of a lactone, 2,3:5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone to give, after chromatography on silica, an unstable compound which was not further investigated, followed by (*Z*)-1,4-anhydro-1-ethoxycarbonyl(formylamino)methylene-2,3:5,6-di-*O*-isopropylidene-D-mannitol (**1**)† (4%), a homogeneous syrup, $[\alpha]_D^{22}$ + 112°, and the *E*-isomer (**2**) (51%), m.p. 106—108 °C, $[\alpha]_D^{22}$ + 304°. The analogous reaction with γ-butyrolactone does not take place.

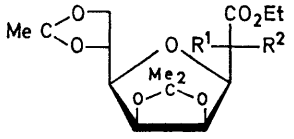
Catalytic hydrogenation of (**2**) (Raney Ni in 95% EtOH, 50 lb in^{-2}, 25 °C) gave after separation by chromatography on silica, 2-L-ethyl-(2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranosyl)-*N*-formylglycinate (**3**) (90%), a homogeneous oil, $[\alpha]_D^{22}$ − 6°, and the D-isomer (**4**) (6%), m.p. 137—138 °C, $[\alpha]_D^{22}$ + 7°. Under similar conditions (**1**) was not hydrogenated.

The 5,6-*O*-isopropylidene group of (**3**) was removed by mild hydrolysis, the resulting diol was cleaved with $NaIO_4$, and the aldehyde obtained was hydrogenated (Raney Ni in 80% aq. EtOH, 50 lb in^{-2}, 25 °C) to give 2-L-ethyl-(2,3-*O*-isopropylidene-β-D-lyxofuranosyl)-*N*-formylglycinate (**5**) [85% from (**3**)], m.p. 128—130 °C, $[\alpha]_D^{22}$ − 6°. Similar treatment of (**4**) gave the D-isomer (**6**) (84%), m.p. 153—155 °C, $[\alpha]_D^{22}$ + 13°. The reduction of the aldehydes with $NaBH_4$ was avoided because of the possible reduction of the ester with excess of the reagent[5] as shown by the reaction of (**3**) with excess of $NaBH_4$ to give the anhydrooctitol (**7**) (39%), m.p. 149—150 °C, $[\alpha]_D^{22}$ − 33°. Reduction of (**3**) with 1 equiv of $LiAlH_4$ also gave (**7**) (35%), whereas with a large excess the *N*-formyl group was reduced to give (**8**) (41%), m.p. 43—48°, $[\alpha]_D^{22}$ 0°.

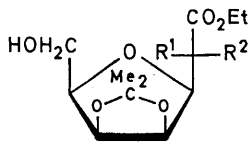
Signals at τ 6·01 (1H, dd, $J_{1,1'}$ 6, $J_{1,2}$ 3·5 Hz, H-1) and 6·00 (1H, dd, $J_{1,1'}$ 6, $J_{1,2}$ 3 Hz, H-1) in the n.m.r. spectra in $CDCl_3$ of (**5**) and (**6**), respectively, showed[6] that they are the β-compounds. Furthermore, removal of the 5,6-*O*-isopropylidene group of (**8**), cleavage with $NaIO_4$, reduction with $NaBH_4$, and finally acetylation gave 1,6-di-*O*-acetyl-2,5-anhydro-3,4-*O*-isopropylidene-D-galacitol (**9**) [42% from (**8**)], m.p. 114—115 °C, $[\alpha]_D^{22}$ 0° which because of its plane of symmetry gave simple n.m.r. spectra (^1H and ^{13}C) and is optically inactive. These results are incompatible with a D-talitol configuration and consequently with the α-configuration for compounds (**3**)—(**8**).



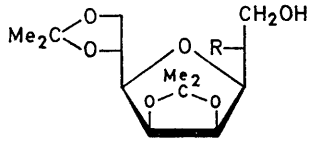
(1) R^1 = NHCHO, R^2 = CO_2Et
(2) R^1 = CO_2Et, R^2 = NHCHO



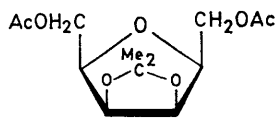
(3) R^1 = NHCHO, R = H
(4) R^1 = H, R^2 = NHCHO



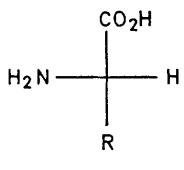
(5) R^1 = NHCHO, R^2 = H
(6) R^1 = H, R^2 = NHCHO

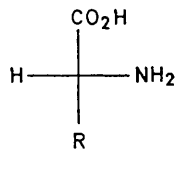


(7) R = NHCHO
(8) R = NHMe



(9)





(10) R = β-Mannofuranosyl (11)
(12) R = β-Lyxofuranosyl (13)

Compound (**3**) was hydrolysed (aq. 0·5M HCl, 5 h, 96 °C) and, after removal of the acid *in vacuo*, an aqueous solution of the salt obtained was passed through a column of basic resin [Amberlite IR-45(OH)] and the solvent was removed to give the free amino acid, L-2-(β-D-mannofuranosyl)-glycine (**10**) (58%), decomp. *ca.* 205 °C (H_2O–EtOH), $[\alpha]_D^{20}$ − 60° (*c ca.* 1, H_2O), $[\alpha]_D^{20}$ − 52° (*c ca.* 1, aq. 0·5M HCl), o.r.d., $[\phi]_{224}$ + 290 (peak). Similar treatment of (**4**) gave

† All new compounds had satisfactory microanalytical and spectral properties. Optical rotations were measured for solution in chloroform (*c* 1·0 ± 0·3%) unless otherwise stated. O.r.d. spectra were recorded for solutions in aqueous 0·5M HCl (*c* 1·3—1·7 × 10^{-3}).

the D-amino acid (**11**) (41%), decomp. *ca.* 140 °C (amorphous), $[\alpha]_D^{20}$ + 12° (*c ca.* 1, H_2O), $[\alpha]_D^{20}$ − 6° (*c ca.* 1, aq. 0·5M HCl); o.r.d., $[\phi]_{220}$ − 800 (trough). Hydrolysis of (**5**) gave L-2-(β-D-lyxofuranosyl)glycine (**12**) (54%), decomp. *ca.* 217 °C (H_2O–EtOH), $[\alpha]_D^{20}$ − 48° (*c ca.* 1, H_2O), $[\alpha]_D^{20}$ − 29° (*c ca.* 1, aq. 0·5M HCl); o.r.d., $[\phi]_{223}$ + 2040 (peak) and hydrolysis of (**6**) gave the D-amino acid (**13**) (54%), decomp. *ca.* 100 °C (amorphous), $[\alpha]_D^{20}$ + 41° (*c ca.* 1, H_2O), $[\alpha]_D^{20}$ + 18° (*c ca.* 1, aq. 0·5M HCl); o.r.d. $[\phi]_{219}$ − 890 (trough).

The configurations of the amino acids (**10**)—(**13**) were assigned from their o.r.d. spectra.[7] These assignments are supported by the specific rotational shifts induced by acidification.[8]

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