A New Synthesis of D-Galactosamine from D-Glucosamine

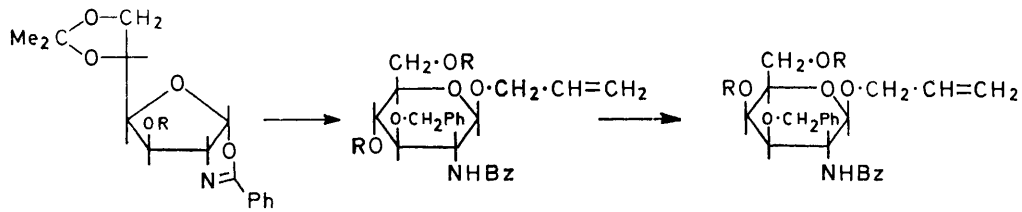
By **Patricia A. Gent, Roy Gigg,* and R. Conant,** National Institute for Medical Research, Mill Hill, London NW7 1AA

2-Amino-2-deoxy-D-galactose was prepared from allyl 2-benzamido-3-*O*-benzyl-2-deoxy-4,6-di-*O*-methylsulphonyl-β-D-glucopyranoside *via* allyl 2-benzamido-3-*O*-benzyl-2-deoxy-β-D-galactopyranoside. The latter compound should prove a suitable intermediate for the preparation of various derivatives of 2-amino-2-deoxy-D-galactose.

SUITABLY protected derivatives of 2-amino-2-deoxy-D-galactose were required for synthetic studies in connection with the glycolipids. For this purpose a new route to 2-amino-2-deoxy-D-galactose from a derivative of 2-amino-2-deoxy-D-glucose was investigated.

The limited accessibility of 2-amino-2-deoxy-D-galactose from natural sources has stimulated the investigation of several synthetic routes to this compound.[1-6] Most of these[3-6] have started from derivatives of 2-amino-2-deoxy-D-glucose containing a 4-*O*-methylsulphonyl group which was replaced, with inversion of configuration, to give a derivative of 2-amino-2-deoxy-D-galactose.

We have adopted a similar approach in the present method, making use of the readily accessible 1,2-dideoxy-5,6-*O*-isopropylidene-2′-phenyl-β-D-glucofuranoso[2,1-*d*]-$\Delta^{2'}$-oxazoline (I)[7] as starting material. The benzyl ether (II)[8b] was converted into the β-allyl pyranoside (III) on treatment with acid in allyl alcohol under the conditions described previously[7a] for the methanolysis of compound (I).



(I) R = H
(II) R = CH_2Ph

(III) R = H
(IV) R = Ac
(V) R = SO_2Me

(VI) R = Bz
(VII) R = Ac

Compound (III) was conveniently purified *via* the diacetate (IV); alternatively the crude product was converted directly into the crystalline bismethanesulphonate (V), which was treated with sodium benzoate in dimethylformamide[5,6] to give the crude dibenzoate (VI) of the corresponding 2-amino-2-deoxy-D-galactose derivative. Saponification of the crude dibenzoate and acetylation of the product gave the pure diacetate (VII). Hydrogenation of compound (VII) and subsequent acid hydrolysis gave 2-amino-2-deoxy-D-galactose, free from 2-amino-2-deoxy-D-glucose (as observed by chromatography on Dowex 50 in an amino-acid analyser[9]) and identical with the 2-amino-2-deoxy-D-galactose obtained from natural sources.

The route *via* the allyl glycoside was chosen since this will allow subsequent conversion of derivatives of compound (VII) into the corresponding prop-1-enyl glycosides,[8] which are readily hydrolysed under neutral conditions[8b] with the preservation of other protecting groups in the molecule. Similar routes to galactosamine derivatives starting from the but-2-enyl and allyl ethers of compound (I) are also being investigated.

EXPERIMENTAL

Solvents were evaporated off under reduced pressure. Optical rotations were measured at 22—24° with a Bendix Automatic Polarimeter. T.l.c. was carried out with microscope slides coated with silica gel G.

Allyl 4,6-*Di*-O-*acetyl*-3-O-*benzyl*-2-*deoxy*-β-D-*glucopyranoside* (IV).—A solution of 3-benzyl-1,2-dideoxy-5,6-*O*-isopropylidene-2′-phenyl-β-D-glucofuranoso[2,1-*d*]-$\Delta^{2'}$-oxazoline (II)[8b] (7 g) in allyl alcohol (200 ml) containing toluene-*p*-sulphonic acid (3·8 g) was kept for 16 h at 20 °C. T.l.c. (acetone–toluene, 1 : 1) then showed the presence of a major product (R_F 0·6). An excess of sodium hydrogen carbonate was added and the allyl alcohol was distilled off. Water was added to the residue and the crude product (III) (6·7g) was filtered off and dried. A portion was acetylated with acetic anhydride–pyridine to give the *diacetate* (IV), m.p. 182—184° (from ethanol), $[\alpha]_D$ +22·2° (*c* 0·9 in $CHCl_3$) (Found: C, 65·0; H, 6·1; N, 2·8. $C_{27}H_{31}NO_8$ requires C, 65·2; H, 6·3; N, 2·8%).

[1] R. Kuhn and W. Kirshenlohr, *Annalen*, 1956, **600**, 126; R. Brossmer, *Methods Carbohydrate Chem.*, 1962, **1**, 216.
[2] S. P. James, F. Smith, M. Stacey, and L. F. Wiggins, *J. Chem. Soc.*, 1946, 625; R. W. Jeanloz and P. J. Stoffyn, *Methods Carbohydrate Chem.*, 1962, **1**, 221.
[3] K. Brendel, P. H. Gross, and H. K. Zimmerman, *Annalen*, 1965, **683**, 182.
[4] P. H. Gross, F. Du Bois, and R. W. Jeanloz, *Carbohydrate Res.*, 1967, **4**, 244.
[5] J. Hill and L. Hough, *Carbohydrate Res.*, 1968, **8**, 398.
[6] M. W. Horner, L. Hough, and A. C. Richardson, *J. Chem. Soc.* (*C*), 1970, 1336.
[7] (*a*) S. Konstas, I. Photaki, and L. Zervas, *Chem. Ber.*, 1959, **92**, 1288; (*b*) B. Lindberg and H. Agback, *Acta Chem. Scand.*, 1964, **18**, 185; R. Gigg and C. D. Warren, *J. Chem. Soc.*, 1965, 1351.
[8] (*a*) J. Gigg and R. Gigg, *J. Chem. Soc.* (*C*), 1966, 82; (*b*) R. Gigg and C. D. Warren, *J. Chem. Soc.* (*C*), 1968, 1903.
[9] M. W. Fanger and D. G. Smyth, *Analyt. Biochem.*, 1970, **34**, 494.

Allyl 2-Benzamido-3-O-benzyl-2-deoxy-4,6-di-O-methylsulphonyl-β-D-glucopyranoside (V).—Methanesulphonyl chloride (4 ml) was added to a solution of the crude diol (III) (6·5 g) in dry pyridine (150 ml) at 0°. The solution was kept at 20° for 2 h and then poured on to ice–water. The crude product was filtered off and recrystallised from 95% ethanol to give the *bismethanesulphonate* (V) (4·2 g), m.p. 186·5—187°, $[\alpha]_D$ +35·5° (*c* 0·4 in $CHCl_3$) (Found: C, 52·6; H, 5·5; N, 2·35; S, 11·1. $C_{25}H_{31}NO_{10}S_2$ requires C, 52·7; H, 5·5; N, 2·5; S, 11·3%).

Allyl 4,6-Di-O-acetyl-2-benzamido-3-O-benzyl-2-deoxy-β-D-galactopyranoside (VII).—A solution of the bismethanesulphonate (V) (4 g) in *NN*-dimethylformamide (130 ml) containing suspended sodium benzoate (4 g) was heated under reflux for 17 h. The cooled mixture was diluted with chloroform and the solid material was filtered off. The filtrate was evaporated and the residue was taken up in chloroform; the solution was washed with water, dried ($MgSO_4$), and evaporated, and the crude dibenzoate (VI) was treated with N-sodium hydroxide in methanol (20 ml) under reflux for 30 min. Glacial acetic acid was added and the solvents were evaporated off. The residue was acetylated with acetic anhydride–pyridine. The crude product gave the *diacetate* (VII) (0·7 g, 20%), m.p. 175—177° (from ethanol), $[\alpha]_D$ +56·6° (*c* 1 in $CHCl_3$) (Found: C, 65·2; H, 6·3; N, 2·9. $C_{27}H_{31}NO_8$ requires C, 65·2; H, 6·3; N, 2·8%).

2-Amino-2-deoxy-D-galactose Hydrochloride.—A solution of the diacetate (VII) (0·6 g) in glacial acetic acid was treated with hydrogen in the presence of 10% palladium–charcoal at atmospheric pressure for 17 h. T.l.c. (toluene–acetone, 2 : 1) then showed conversion of the starting material (R_F 0·5) into a product (R_F 0·3). The mixture was filtered through Celite, the catalyst was washed with methanol, and the filtrate was evaporated to give a crystalline residue of propyl 4,6-di-*O*-acetyl-2-benzamido-2-deoxy-β-D-galactopyranoside. 2N-Hydrochloric acid (30 ml) was added and the mixture was heated under reflux for 4 h, cooled, and extracted with ether to remove benzoic acid. Evaporation of the aqueous solution gave a syrup which yielded crystalline 2-amino-2-deoxy-D-galactose on trituration with methanol. The product charred at 168° in the same way as an authentic sample of D-galactosamine hydrochloride obtained from natural sources, $[\alpha]_D$ +119·3 (4 min) ⟶ +94·1° (1·5 h) (*c* 0·75 in H_2O) (Found: C, 33·3; H, 6·6; Cl, 15·9; N, 6·4. Calc. for $C_6H_{13}NO_5$,HCl: C, 33·4; H, 6·55; Cl, 16·4; N, 6·5%) {lit.,[1] $[\alpha]_D^{23}$ +124 (4 min) ⟶ +93° (final value) (*c* 0·75 in H_2O); lit.,[2] $[\alpha]_D^{23}$ +125 ⟶ +98° (1 h) (H_2O)}. On elution from a Dowex 50 × 8 column with citrate buffer (pH 5·28) (a system which separates [9] glucosamine from galactosamine) the product had the same retention time as an authentic sample of D-galactosamine.

We thank Dr. D. G. Smyth for the chromatography of the galactosamine hydrochloride on the amino-acid analyser.

[1/1745 *Received, September 23rd,* 1971]