185. *The Preparation of Phenyl 2-Amino-2-deoxy-β-D-gluco-pyranoside and Some 2-Acylamino-derivatives thereof.*

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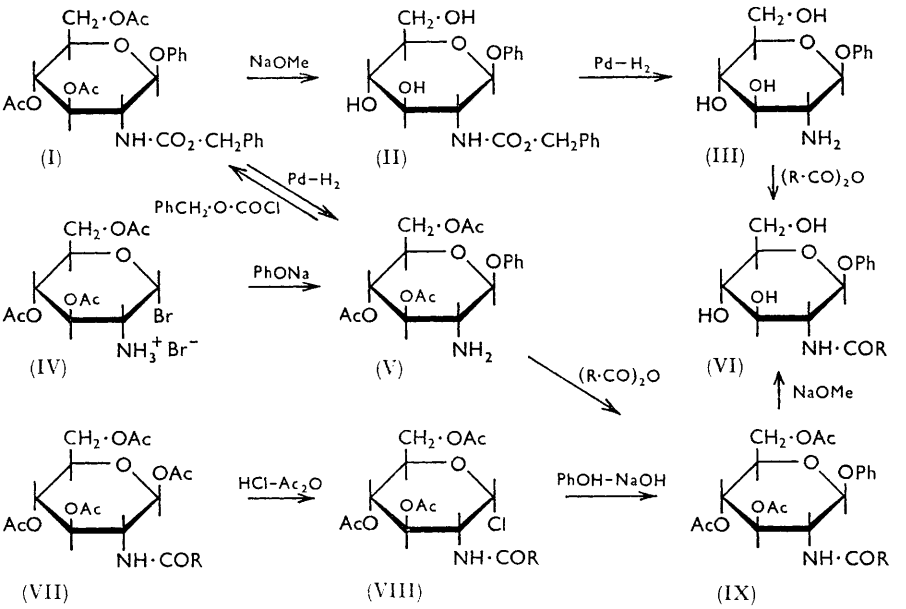
Difficulties in the preparation of phenyl 2-amino-2-deoxy-β-D-glucoside have been overcome, and syntheses of some 2-acylamino-derivatives of this compound are described.

Phenyl 2-amino-2-deoxy-β-D-glucoside (III) and some 2-acylamino-derivatives (VI) were required for studies on enzyme specificity: a preliminary account of the preparation of these compounds has appeared.[1] The preparation of phenyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucoside (V) by the condensation of 3,4,6-tri-*O*-acetyl-2-amino-1-bromo-2-deoxy-α-D-glucose hydrobromide [2] (IV) with sodium phenoxide has been described [3] but difficulties with the method have been reported.[4] In our hands, the published method [3]



gave extremely low yields of a product of poor quality; a modification [5] gave better yields of the glycoside (V) but difficulties were encountered in its purification and deacetylation. These difficulties were overcome by condensing the crude product with benzyl chloroformate, to give a highly crystalline derivative (I) which, on deacetylation and hydrogenolysis, gave the required amino-compound (III) with a higher melting point than that reported.[3] Overall yields were low but reproducible. The amino-compound (III) was converted into the known acetamido-derivative (VI; R = Me) by the method of Roseman and Ludowieg.[6] Preliminary experiments on the preparation of the amino-compound (V) through *N*-phthaloyl [7] or *N*-dinitrophenyl [8] derivatives of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucose [9] were unpromising. Acylamino-compounds of the type (IX) can be

[1] Greig and Leaback, *Chem. and Ind.*, 1960, 376.
[2] Irvine, McNicoll, and Hynd, *J.*, 1911, **99**, 250.
[3] Helferich, Iloff, and Streech, *Z. physiol. Chem.*, 1934, **226**, 258.
[4] Roseman and Dorfman, *J. Biol. Chem.*, 1951, **191**, 607.
[5] Cf. May and Mossetig, *J. Org. Chem.*, 1950, **15**, 890.
[6] Roseman and Ludowieg, *J. Amer. Chem. Soc.*, 1954, **76**, 301.
[7] Baker, Joseph, Schaub, and Willams, *J. Org. Chem.*, 1954, **19**, 1786.
[8] Lloyd and Stacey, *Chem. and Ind.*, 1956, 917.
[9] Bergman and Zervas, *Ber.*, 1931, **64**, 979.

obtained by acylation of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucose hydrochloride, followed by chlorination of the resulting tetra-acetate (VII) and condensation of the chloro-sugar (VIII) with sodium phenoxide;[10] the propionamido- (IX; R = Et) and the monofluoroacetamido-derivative (IX; R = CH_2F) were prepared by this route as well as by way of the amino-compound (V).

Attempts to prepare a chloro-sugar from 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-formamido-β-D-glucose (VII; R = H) led to syrups; the failure was probably due to the acid lability of the formamido-group[11] and suggests that compounds of the type (IX) with acid-labile acylamino-groups can only be prepared by acylation of the amino-compound (V). The formamido-derivative (IX; R = H) was prepared from the amino-compound (V) by using acetic anhydride in formic acid[11] and was deacetylated to phenyl 2-deoxy-2-formamido-β-D-glucoside (VI; R = H).

Dicyclohexylcarbodi-imide has been used in the synthesis of peptide bonds[12] and we have examined its use for synthesis of compounds of the type (IX); we thus prepared the monofluoroacetamido-derivatives of the tetra-acetate (VII) and the acetylated phenyl glycoside (V); although yields were not high, this method should find application (as in this instance) when the appropriate acid anhydride is not available.

Fodor and Ötvös[13] reported that the optical rotation of a solution of ethyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucose [an alkyl analogue of (V)] in dry acetone changed with time, and that ethyl 2-acetamido-4,6-di-O-acetyl-2-deoxy-β-D-glucose could then be isolated. In the present work, it was important to establish whether the amino-compound (V) underwent a similar transformation. The optical rotation of solutions of the amino-compound (V) in dry acetone remained unchanged for 72 hours at room temperature, and the infrared spectra of the pure amino-compound (II) and of the material recovered from acetone solution were identical and showed no signs of the presence of an acetamido-group. It was concluded that, unlike the corresponding ethyl glycoside, under these conditions the phenyl glycoside (II) was unable to assume a conformation which favoured the *O*- ⟶ *N*-acetyl migration. However, such transformations under strongly basic conditions are well established[14,15] and might account for difficulties[16] in the direct deacetylation of the amino-compound (V).

The nature and homogeneity of preparations of phenyl 2-amino-2-deoxy-β-D-glucoside (III) and the 2-acylamino-derivatives (VI) were confirmed by the behaviour of these compounds on paper chromatograms (see Table). As expected,[17] the amino-compound (III) gave an elongated spot, but the acylamino-derivatives (VI) gave single discrete spots in both the solvents used.

With one exception,[15] the reported reactions of the bromo-sugar (IV) proceeded with inversion at position 1. Since the 2-substituent is known[18] to influence the steric course of reactions of acetohalogeno-sugars at position 1, we investigated the degree with which the bromo-sugar (IV) reacted with inversion under our conditions, taking advantage of a solvent (see Table) which gave a clear separation of the anomeric phenyl 2-acetamido-2-deoxy-D-glucosides on paper chromatograms. The crude products of a condensation of the bromo-sugar (IV) with sodium phenoxide were *N*-acetylated and catalytically de-*O*-acetylated to give chromatographically pure phenyl 2-acetamido-2-deoxy-β-D-glucoside (III; R = Me): control experiments indicate that the procedure would have detected the presence of 5% of the α-anomer in the preparation. It was concluded that this reaction

[10] Leaback and Walker, *J.*, 1957, 4754.
[11] Sheehan and Jang, *J. Amer. Chem. Soc.*, 1958, **80**, 1154.
[12] Sheehan and Hess, *J. Amer. Chem. Soc.*, 1955, **77**, 1076.
[13] Fodor and Ötvös, *Chem. Ber.*, 1956, **89**, 701.
[14] White, *J.*, 1938, 1498.
[15] Maley, Maley, and Lardy, *J. Amer. Chem. Soc.*, 1956, **78**, 5303.
[16] Greig and Leaback, unpublished work.
[17] Cf. Leaback and Walker, *Biochem. J.*, 1957, **67**, 22P.
[18] Lemieux, *Adv. Carbohydrate Chem.*, 1954, **9**, 1.

proceeded with a high degree of inversion: this result is similar to that found with the anomeric 3,4,6-tri-*O*-acetyl-1-chloro-D-glucose compounds.[19]

Experimental

Paper chromatography was carried out on Whatman No. 1 paper by the descending method with the non-polar phase of (*a*) butan-1-ol–ethanol–water (4 : 1 : 5; v/v) or (*b*) isopropyl ether–ethanol–water (2 : 1 : 1; v/v), and the separate substances were detected by a modification [20] of Rydon and Smith's method.[21] R_F values were as tabulated.

Except for compound (II), materials were dried for 16 hr. at 100° (over P_2O_5) before analysis. Solutions were evaporated under reduced pressure.

Phenyl 3,4,6-*Tri*-O-*acetyl*-2-*amino*-2-*deoxy*-β-D-*glucoside* (V).—Sodium (1·1 g.) was dissolved in a solution of phenol (11 g.) in dry acetone (50 ml.), and the mixture was added to crystalline 3,4,6-tri-*O*-acetyl-2-amino-1-bromo-2-deoxy-α-D-glucose hydrobromide (I) (11 g.) in dry acetone (100 ml.). The mixture was left for 16 hr. at room temperature, and the precipitated sodium bromide filtered off. The filtrate was evaporated to a brown oil, which was mixed with water (200 ml.) and left for 16 hr. at 5°. The brown solid was filtered off and dried *in vacuo* to give the crude phenyl glycoside (V) (9 g.). No solvent suitable for recrystallisation was found.

Compound	R_F (solvent *a*)	R_F (solvent *b*; relative to compound VI; R = Me)
III	0·46—0·58	0·62
VI; R = H	0·62	0·91
VI; R = Me	0·67	1·00
VI; R = CH_2F ...	0·69	1·28
VI; R = Et	0·78	1·40
α-Anomer of (VI; R = Me)	0·69	1·36

The crude glycoside (V) (2 g.) was treated for 16 hr. at room temperature with acetic anhydride (5 ml.) and pyridine (20 ml.). Chloroform (100 ml.) was added and the solution extracted successively with water, dilute hydrochloric acid, water, saturated sodium hydrogen carbonate, and water, before it was dried and evaporated to leave a brown residue. Dry methanol (10 ml.) and N-sodium methoxide (1 ml.) were added and the solution left for 24 hr. at 5° before evaporation to dryness: on paper chromatograms (solvent *b*), the crude residue showed the presence of only phenyl 2-acetamido-2-deoxy-β-D-glucoside.

The pure phenyl glycoside (V) was obtained by hydrogenation of phenyl 3,4,6-tri-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-β-D-glucoside (I) (1 g.) in methanol (270 ml.) in the presence of 5% palladium–charcoal (0·5 g.). After the hydrogen uptake was complete (2½ hr.), the catalyst was filtered off and the filtrate evaporated to give phenyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucoside (II) (0·6 g., 81%) which was recrystallised from ethyl acetate–light petroleum to give a product, m. p. 158—160° (decomp.), $[\alpha]_D^{21}$ −45° (*c* 1 in acetone) (Found: C, 56·7; H, 6·2; N, 3·8. $C_{18}H_{23}NO_8$ requires C, 56·7; H, 6·0; N, 3·7%). The infrared spectrum (KCl pellet) showed large bands at 3100 (NH) and 1740 cm.$^{-1}$ (O·CO) but no absorption (in the 1650—1550 cm.$^{-1}$ region) attributable to a secondary amide. The infrared spectrum and optical rotation of this compound were unchanged after its dissolution for 72 hr. in dry acetone.

Phenyl 3,4,6-*Tri*-O-*acetyl*-2-*benzyloxycarbonylamino*-2-*deoxy*-β-D-*glucoside* (I).—The crude glycoside (V) (9 g.) was dissolved in acetone (216 ml.) and water (54 ml.); sodium hydrogen carbonate (1·95 g.) and benzyl chloroformate (3·15 ml.) were added with shaking, the mixture left for 16 hr. at room temperature, then filtered and evaporated at 37°. The brown residue was washed with ether and recrystallised from ethanol to give the *derivative* (I) (3·2 g., 27%), m. p. 186—187°, $[\alpha]_D^{19}$ +5·9° (*c* 1 in $CHCl_3$) (Found: C, 60·6; H, 6·1; N, 2·8. $C_{26}H_{29}NO_{10}$ requires C, 60·6; H, 5·6; N, 2·7%).

Phenyl 2-*Benzyloxycarbonylamino*-2-*deoxy*-β-D-*glucoside* (II).—Phenyl 3,4,6-tri-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-β-D-glucoside (3 g.) was suspended in dry methanol (15 ml.),

[19] Lemieux and Huber, *Canad. J. Chem.*, 1955, **33**, 128.
[20] Greig and Leaback, *Nature*, 1960, **188**, 310.
[21] Rydon and Smith, *Nature*, 1952, **169**, 922.

N-sodium methoxide (3 ml.) added, the suspension shaken gently for 15 min., and the solution left for 16 hr. at 5°. The solid material was filtered off and recrystallised from water, to give the de-acetylated glycoside (II) (1·7 g., 75%), m. p. 209—211°, $[\alpha]_D^{24}$ −10·7° (*c* 1 in MeOH) (Found: C, 59·1; H, 6·2; N, 3·5. $C_{20}H_{23}NO_7,H_2O$ requires C, 59·0; H, 6·2; N, 3·4%).

Phenyl 2-Amino-2-deoxy-β-D-glucoside (III).—Phenyl 2-benzyloxycarbonylamino-2-deoxy-β-D-glucoside (2·3 g.) was hydrogenated in methanol (225 ml.) in the presence of 5% palladium–charcoal (0·5 g.) (2½ hr.). The catalyst was filtered off and the filtrate evaporated. The residue recrystallised from ethanol to give the phenyl glycoside (III) (1·2 g., 80%), m. p. 174—175° (lit.,[3] 167·5—170°), $[\alpha]_D^{20}$ −77·5° (*c* 0·6 in H_2O) (Found: C, 56·1; H, 6·7; N, 5·6. Calc. for $C_{12}H_{17}NO_5$: C, 56·5; H, 6·7; N, 5·5%). The compound gave a positive ninhydrin reaction on paper chromatograms.

Phenyl 2-Acetamido-2-deoxy-β-D-glucoside (VI; R = Me).—Phenyl 2-amino-2-deoxy-β-D-glucoside (0·9 g.) in water (100 ml.) and methanol (10 ml.) was stirred in ice with the carbonate form of Deacidite FF resin (27 ml.). Acetic anhydride (0·5 ml.) was added and the mixture stirred for 90 min. before the resin was filtered off and the filtrate passed through a column (20 × 1·5 cm.) of IR-100 resin (H^+). The eluate was evaporated to a residue which recrystallised from water to give phenyl 2-acetamido-2-deoxy-β-D-glucose (0·36 g., 35%) identical in m. p., mixed m. p., and optical rotation with an authentic sample.[10]

Phenyl 3,4,6-Tri-O-acetyl-2-deoxy-2-formamido-β-D-glucoside (IX; R = H).—Crude phenyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucoside (12 g.) was dissolved in 90% formic acid (78 ml.), and acetic anhydride (32 ml.) was added at a rate which kept the temperature of the solution at 50—60°; the solution was maintained for 1 hr. at this temperature and then set aside for 16 hr. Chloroform (200 ml.) was added, and the solution extracted successively with water, cold saturated sodium hydrogen carbonate solution, water, dilute hydrochloric acid, and water. The chloroform layer was dried ($MgSO_4$), decolorised (charcoal), and evaporated, and the residue recrystallised from ethanol to give the *formamido-compound* (1·0 g., 8%) (IX; R = H), m. p. 187—188°, $[\alpha]_D^{24}$ −29° (*c* 0·5 in $CHCl_3$) (Found: C, 56·3; H, 5·5; N, 3·2. $C_{19}H_{23}NO_9$ requires C, 55·8; H, 5·6; N, 3·4%).

Phenyl 2-Formamido-2-deoxy-β-D-glucoside (VI; R = H).—Phenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-formamido-β-D-glucoside (0·98 g.) was suspended in dry methanol (5 ml.), and N-sodium methoxide (1 ml.) was added with swirling. After 24 hr. at 5°, the solid was filtered off and recrystallised from water, to give the deacetylated *glycoside* (VI; R = H) (0·6 g., 89%), m. p. 203—204°, $[\alpha]_D^{20}$ −13·7° (*c* 0·6 in H_2O) (Found: C, 54·3; H, 6·0; N, 4·9. $C_{13}H_{17}NO_6$ requires C, 55·1; H, 6·0; N, 4·9%).

1,3,4,6-*Tetra*-O-*acetyl*-2-*deoxy*-2-*formamido*-β-D-*glucose* (VII; R = H).—Crude 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucose [9] (2 g.) was dissolved in 90% formic acid (20 ml.), and acetic anhydride (4·9 ml.) added with stirring. The mixture was kept at 50—60° for 1 hr. and the whole left at room temperature for 16 hr. Chloroform (100 ml.) was then added. Working up as above gave the *formamido-compound* (0·7 g., 33%), m. p. 191—192°, $[\alpha]_D^{23}$ +2·5° (*c*, 1 in $CHCl_3$) (Found: C, 48·8; H, 5·9; N, 3·7. $C_{15}H_{21}NO_{10}$ requires C, 48·0; H, 5·6; N, 3·7%). Attempts to prepare the chloro-sugar (VIII; R = H) from the formamido-compound led to syrups.

1,3,4,6-*Tetra*-O-*acetyl*-2-*deoxy*-2-*propionamido*-β-D-*glucose* (VII; R = Et).—To a suspension of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucose hydrochloride [9] (30 g.) in chloroform (200 ml.) was added sodium carbonate (9·5 g.) in water (100 ml.). The mixture was stirred until dissolution was complete, propionic anhydride (40 ml.) added, and stirring continued for 30 min. The chloroform layer was extracted successively with water, cold aqueous sodium hydrogen carbonate, water, dilute hydrochloric acid, and water. The dried chloroform layer was evaporated and the residue recrystallised from ethanol to give the *propionamide* (19 g., 47%), m. p. 174—176°, $[\alpha]_D^{20}$ −4·2° (*c* 0·9 in $CHCl_3$) (Found: C, 50·6; H, 6·1; N, 3·5. $C_{17}H_{25}NO_{10}$ requires C, 50·6; H, 6·2; N, 3·4%).

The butyramide tetra-acetate (VII; R = Pr^n), prepared similarly in 55% yield, had m. p. 168—170°, $[\alpha]_D^{20}$ −4·5° (*c* 1 in $CHCl_3$).

Phenyl 2-Deoxy-2-propionamido-β-D-glucoside (VI; R = Et).—1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-propionamido-β-D-glucose (21 g.) was dissolved in acetic anhydride (60 ml.), saturated at 0° with dry hydrogen chloride, and left for 16 hr. Chloroform (200 ml.) was added, and the solution extracted with cold water, aqueous $NaHCO_3$, and water. The chloroform layer was dried ($MgSO_4$) and evaporated to dryness to yield the chloro-sugar (VIII; R = Et)

(13·1 g.), m. p. 122—124°, $[\alpha]_D^{20}$ +132·5° (*c* 1 in acetone). This was left with phenol (4·1 g.) in acetone (90 ml.) and N-sodium hydroxide (35 ml.) for 16 hr. at room temperature, the acetone then evaporated at room temperature, and chloroform (300 ml.) added to the residue. The chloroform layer was extracted successively with water, aqueous sodium hydroxide, and water, dried ($MgSO_4$), and evaporated, to give the glycoside (IX; R = Et) (3·6 g.), m. p. 194—195°, $[\alpha]_D^{20}$ −22·4° (*c* 0·6 in acetone).

This glycoside (2·5 g.) was suspended in dry methanol (25 ml.), and N-sodium methoxide (2·5 ml.) added with shaking. After 16 hr. at 5° the solid was filtered off and recrystallised from water to give *phenyl 2-deoxy-2-propionamido-β-D-glucoside* (1·4 g.), m. p. 237—238°, $[\alpha]_D^{18}$ −8·3° (*c* 0·6 in H_2O) (Found: C, 57·5; H, 6·6; N, 4·3. $C_{15}H_{21}NO_6$ requires C, 57·9; H, 6·8; N, 4·5%).

Phenyl 2-Deoxy-2-fluoroacetamido-β-D-glucoside (VI; R = CH_2F).—(i) The pure amino-compound (V) (1·7 g.) and dicyclohexylcarbodi-imide (0·8 g.) were dissolved in a cooled mixture of dry chloroform (40 ml.) and pyridine (3·2 ml.). Monofluoroacetic acid (0·7 ml.) was added with shaking and the mixture left for 16 hr. at 5°. The solid was filtered off and the filtrate washed with water, dilute hydrochloric acid, and water. The chloroform layer was dried and evaporated, to leave a solid which recrystallised from ethanol to give phenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoroacetamido-β-D-glucoside (0·52 g., 27%), m. p. 186—188°, $[\alpha]_D^{19}$ −18·5° (*c* 1 in MeOH).

The fluoroacetamide (0·5 g.) was dissolved in dry methanol (5 ml.) containing N-sodium methoxide (0·5 ml.) and left for 16 hr. at room temperature. The solid was filtered off and recrystallised from water to give phenyl 2-deoxy-2-fluoroacetamido-β-D-glucoside (0·3 g., 84%), m. p. 242—245°, $[\alpha]_D^{20}$ −14·0° (*c* 0·5 in H_2O) (Found: C, 54·0; H, 5·9; N, 4·3. $C_{14}H_{18}FNO_6$ requires C, 53·3; H, 5·7; N, 4·4%).

(ii) 1,3,4,6-Tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucose [9] (8 g.) and dicyclohexylcarbodi-imide (3·9 g.) were left in chloroform (100 ml.), pyridine (15·8 ml.), and monofluoroacetic acid (3·4 ml.) at 5° for 16 hr. before the solid was filtered off and the chloroform layer washed as above and evaporated to a residue which recrystallised from ethanol to yield 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoroacetamido-β-D-glucose (VII; R = CH_2F) (4·2 g., 50%), m. p. 176—179°, $[\alpha]_D^{20}$ −5·4° (*c* 1 in $CHCl_3$). This was converted (cf. the propionamide) into the chloro-sugar (VIII; R = CH_2F) and condensed with phenol, and the resultant glycoside was deacetylated; this gave material (VI; R = CH_2F) (0·3 g., overall yield 9%) identical in optical rotation, m. p., and mixed m. p. with that prepared as under (i).

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