97. *The Interaction of* aldehydo-*Sugars and Primary Aromatic Amines.*

By J. L. BARCLAY, A. B. FOSTER, and W. G. OVEREND.

The reaction of 2 : 3 : 4 : 5 : 6-penta-*O*-acetyl*aldehydo*-D-galactose (I) and 3 : 4 : 5 : 6-tetra-*O*-acetyl-2-deoxy*aldehydo*-D-glucose (IV) with certain primary aromatic amines has been studied. In each case the product was not a Schiff's base but had a structure of the type $R{\cdot}CH(NHR')_2$. An attempt has been made to correlate these results with previous observations, in terms of an equilibrium reaction.

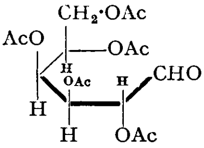
THE synthesis of nucleotides in which condensation of suitable sugar derivatives with nitrogenous bases is followed by phosphorylation is well established.[1] An alternative pathway aimed at the condensation of a phosphorylated sugar derivative with a nitrogenous base is being explored in these laboratories [2] since the total synthesis of 2-deoxy-D-ribose nucleotides has not yet been achieved. We describe now some preliminary results concerning the condensation of *aldehydo*-sugar derivatives with primary aromatic amines.

The sugars studied were 2 : 3 : 4 : 5 : 6-penta-*O*-acetyl*aldehydo*-D-galactose (I) and 3 : 4 : 5 : 6-tetra-*O*-acetyl-2-deoxy*aldehydo*-D-glucose (IV). Reaction of the former with *o*-nitroaniline in dry benzene gave only amorphous products which rapidly decomposed on exposure to air. Immediate deacetylation (sodium methoxide in methanol) of this amorphous material, followed by chromatography on alumina, afforded *N*-*o*-nitrophenyl-D-galactosylamine (characterised as the crystalline monohydrate); this was obtained in the highest yield (11·2%) by the use of ethanol as solvent and ammonium chloride as catalyst. The possibility that the galactosylamine may have originated by the condensation of D-galactose with *o*-nitroaniline following the deacetylation of unchanged *aldehydo*-sugar (I) cannot be ruled out. Under similar conditions the 2-deoxy-D-glucose derivative

[1] Baddiley, Lythgoe, McNeil, and Todd, *J.*, 1943, 383, and later papers in the same series.
[2] Cf. Barclay, Foster, and Overend, *J.*, 1955, 1541.

(IV) and *p*-toluidine did not yield a crystalline product. Clearly these experimental conditions are not satisfactory since they do not facilitate the isolation of the intermediates.

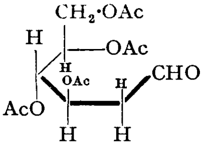
Condensation also occurred between the *aldehydo*-sugars (I or IV) and the amine hydrochloride in aqueous methanol in the presence of sodium acetate. In this manner 3 : 4 : 5 : 6-tetra-*O*-acetyl-2-deoxy*aldehydo*-D-glucose (IV) and *p*-toluidine hydrochloride (2 mol.) yielded amorphous D-*arabo*-3 : 4 : 5 : 6-tetra-acetoxy-1 : 1-di-*p*-toluidinohexane (V) (use of 1 mol. of the salt gave a lower yield); the 2-naphthylamine derivative (VI) was similarly obtained, the larger basic residue not impeding the reaction. However, no solid product could be isolated when *cyclo*hexylamine hydrochloride reacted with the *aldehydo*-sugar (IV) under the same conditions. 2 : 3 : 4 : 5 : 6-Penta-*O*-acetyl*aldehydo*-D-galactose (I) reacted slowly with 4 : 6-diamino-2-methylthiopyrimidine hydrochloride. However, a solution of the ethyl hemiacetal[2,3] (II) of the *aldehydo*-sugar (I) in water containing an excess of sodium acetate reacted readily with excess of this salt, to give D-*galacto*-2 : 3 : 4 : 5 : 6-penta-acetoxy-1 : 1-di-(6-amino-2-methylthio-4-pyrimidyl)hexane (III) (the use of 1 mol. of the base gave the same product in lower yield). It is apparent that the methylene group at $C_{(2)}$ in the *aldehydo*-sugar (IV) does not alter the type of reaction.



(I)
(≡ R^2·CHO)

R^1·CH(OH)·OEt
(II)

R^1·CH(NHR^2)$_2$
(III) : R^2 = 6-amino-2-methylthio-4-pyrimidyl
(V) : R^3 replaces R^1; R^2 = C_6H_4Me
(VI) : R^3 replaces R^1; R^2 = $C_{10}H_7$



(IV)
(≡ R^3·CHO)

Aliphatic aldehydes (including *aldehydo*-sugars) may formally react with primary aromatic amines in four ways :

$$\text{(1)}\quad R\cdot CHO + Ar\cdot NH_2 \longrightarrow R\cdot CH(OH)\cdot NHAr \quad \text{(VII)}$$

e.g., the reaction of chloral with aniline;[4]

$$\text{(2)}\quad R\cdot CHO + 2Ar\cdot NH_2 \longrightarrow H_2O + R\cdot CH(NHAr)_2 \quad \text{(VIII)}$$

e.g., the reactions described in this communication; the reaction of aniline with acetaldehyde[5] and with 2 : 4-3 : 5-di-*O*-ethylidene*aldehydo*-L-xylose;[6] related compounds of the type R·CH(NHAcyl)$_2$ have been obtained by the treatment of acylated *aldehydo*-sugars and *O*-acyl sugars with ammonia;[7]

$$\text{(3)}\quad R\cdot CHO + Ar\cdot NH_2 + R'OH\ \text{(solvent)} \longrightarrow H_2O + R\cdot CH(OR')\cdot NHAr \quad \text{(IX)}$$

e.g., the reaction of 2 : 3 : 4 : 5-tetra-*O*-acetyl*aldehydo*-D-ribose with aniline in methanol or ethanol;[8]

$$\text{(4)}\quad R\cdot CHO + Ar\cdot NH_2 \longrightarrow H_2O + R\cdot CH{:}NAr \quad \text{(X)}$$

There is no substantiated example of the formation of a Schiff's base from an aliphatic aldehyde or *aldehydo*-sugar and a primary aromatic amine. The reaction of various *aldehydo*-sugars with 4 : 6-diamino-2-methylthiopyrimidine (which was a stage in nucleoside synthesis) was assumed to yield Schiff's bases[9] but no supporting experimental evidence was provided. Chromatographic examination (by Mr. E. B. Hancock) of the product obtained on reaction of 2 : 3 : 4-tri-*O*-acetyl-5-*O*-benzoyl*aldehydo*-D-arabinose with 4 : 6-diamino-2-methylthiopyrimidine[9a] revealed the presence of at least six components.

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[3] Wolfrom, *J. Amer. Chem. Soc.*, 1930, **52**, 2464.
[4] Eibner, *Annalen*, 1898, **302**, 361.
[5] Miller and Wagner, *J. Amer. Chem. Soc.*, 1932, **54**, 3698.
[6] Bourne, Corbett, and Stacey, *J.*, 1952, 2810.
[7] Brigl, Mühlschlegel, and Schinle, *Ber.*, 1931, **64**, 2921; cf. Deulofeu and Defarrari, *J. Org. Chem.*, 1952, **17**, 1087, 1093, 1097.
[8] Overend and Parker, unpublished work.
[9] (*a*) Kenner, Lythgoe, and Todd, *J.*, 1948, 957; (*b*) Kenner, Rodda, and Todd, *J.*, 1949, 1613; Kenner, Taylor, and Todd, *J.*, 1949, 1620.

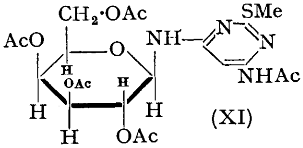
Brigl *et al.*[7] considered the product obtained from 3 : 4 : 5 : 6-tetra-*O*-benzoyl*aldehydo*-D-glucose and excess of aniline in methanol to be a true Schiff's base but the evidence they presented is not conclusive. Only syrupy products resulted on reaction of 2 : 3 : 4 : 5 : 6-penta-*O*-acetyl*aldehydo*-D-glucose with *p*-toluidine,[10] but with excess of aniline in benzene the corresponding D-galactose derivative gave a solid product which was thought to be a Schiff's base;[11] identification was complicated by the fact that, in addition to being unstable, the compound tended to crystalline with solvent. It is not improbable that this latter product and also that described by Brigl *et al.*[7] have structures of the type (VII); this is being examined further.

Related to the compounds (VII, VIII, and IX) are the hydrates and hemiacetals formed on reaction of *aldehydo*-sugars with water and alcohols respectively.[12]

Since the establishment of equilibria on dissolution of glycosylamines in hydroxylic solvents has been proved,[13] the above observations on the reaction of aliphatic aldehydes with primary aromatic amines may perhaps generally be explained on the assumption that equilibria exist in the reaction solutions involving structures of the type (VII, VIII, IX, and X). It is, perhaps, significant that examples are now known of the types (VII, VIII, and IX). A number of factors could influence the type of product obtained in a specific reaction, *e.g.*, preferential crystallization. It is interesting that under identical conditions 2 : 4-3 : 5-di-*O*-ethylidene*aldehydo*-L-xylose and aniline gave a product of the type (VIII),[6] whereas 2 : 3 : 4 : 5-tetra-*O*-acetyl*aldehydo*-D-ribose gave solely a product of the type (IX).[8]

It has been observed [6, 14] in certain cases that the products obtained on the interaction of *aldehydo*-sugars with aniline showed " mutarotation " in B.P. chloroform. The small percentage of alcohol added to chloroform as a stabiliser may lead to changes in optical rotation dependent on the equilibria involving compounds of the type (VII, VIII, IX, and X). The " mutarotation " of the hemiacetals of 2 : 3 : 4 : 5 : 6-penta-*O*-acetyl*aldehydo*-D-galactose under similar conditions has been well studied.[12]

At this stage it is noteworthy that, in preliminary experiments, it was found that deacetylation of D-*galacto*-2 : 3 : 4 : 5 : 6-penta-acetoxy-1 : 1-di-(6-amino-2-methylthio-4-pyrimidyl)hexane (III) with methanolic ammonia followed by acetylation with acetic anhydride and pyridine gave a product tentatively identified as *N*-(6-acetamido-2-methylthio-4-pyrimidyl)-2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-galactosylamine (XI). It is evident that in this process a molecule of base has been eliminated, and this and related reactions are being further investigated. Thus the possibility must be considered that compounds of the type (III) are true intermediates in nucleoside synthesis involving the reaction of *aldehydo*-sugars with primary aromatic amines (cf. Kenner *et al.*[9]).



(XI)

EXPERIMENTAL

Starting Materials.—2 : 3 : 4 : 5 : 6-Penta-*O*-acetyl*aldehydo*-D-galactose (I) and its ethanol hemiacetal (II) were prepared according to Wolfrom's method.[12b] 3 : 4 : 5 : 6-Tetra-*O*-acetyl-2-deoxy*aldehydo*-D-glucose (IV), obtained by the action of mercuric chloride in the presence of cadmium carbonate on 3 : 4 : 5 : 6-tetra-*O*-acetyl-2-deoxy-D-glucose diethyl thioacetal,[15] had m. p. 100°, $[\alpha]_D^{14}$ $+23°$ (*c*, 1·5 in $CHCl_3$).

Reaction of 2 : 3 : 4 : 5 : 6-*Penta*-O-*acetyl*aldehydo-D-*galactose* (I) *with* o-*Nitroaniline.*—A suspension of the acetate (I) (0·5 g.) in dry benzene (5 ml.) was treated with excess of *o*-nitroaniline (0·35 g.) at 60° for 3 hr. Removal of the solvent under diminished pressure gave only a syrup.

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[10] Kuhn and Dansi, *Ber.*, 1936, **69**, 1745.

[11] Smith, Butler, Overend, and Stacey, *Chem. and Ind.*, 1949, 551.

[12] Wolfrom, *J. Amer. Chem. Soc.*, (*a*) 1929, **51**, 2188; (*b*) 1930, **52**, 2464; (*c*) 1931, **53**, 2275; Wolfrom and Morgan, *ibid.*, 1932, **54**, 3390.

[13] Barclay, Foster, and Overend, *Chem. and Ind.*, 1953, 462; *J.*, 1955, 1541.

[14] Butler, Thesis, Birmingham.

[15] Barclay, Cleaver, Foster, and Overend, *J.*, 1956, in the press.

In a second experiment the acetate (I) (0·5 g.), *o*-nitroaniline (0·35 g.), ethanol (5 ml.), and ammonium chloride (0·05 g.) were heated under the same conditions. The syrupy residue isolated as described above was dissolved in dry methanol, and deacetylation effected by the addition of a small pellet of sodium. After 12 hr. the mixture was neutralized with solid carbon dioxide and concentrated. Material separated which decomposed on filtration. The syrupy residue remaining after evaporation of the mother-liquors was dissolved in ethanol and separated chromatographically on alumina (40 × 2 cm.). Excess of *o*-nitroaniline was eluted with ethanol and a slower-moving zone with aqueous ethanol (1 : 1; v/v). Concentration of this eluate gave a syrup which crystallized on nucleation with *N*-*o*-nitrophenyl-D-galactosylamine hydrate. After recrystallization from water the product (40 mg., 5·2%) had m. p. and mixed m. p. 182°, $[\alpha]_D^{23}$ +90° (*c*, 1·0 in pyridine) (Found : C, 45·3; H, 5·6; N, 9·0. Calc. for $C_{12}H_{16}O_7N_2,H_2O$: C, 45·3; H, 5·7; N, 8·8%).

Reaction of 3 : 4 : 5 : 6-*Tetra*-O-*acetyl*-2-*deoxy*aldehydo-D-*glucose* (IV) *with Amines.*—(a) *With* p-*toluidine and* o-*nitroaniline.* Reaction of the acetate (IV) with *p*-toluidine or *o*-nitroaniline as described yielded only tars.

(b) *With* p-*toluidine hydrochloride.* Solutions of sodium acetate trihydrate (0·45 g., 2·2 mol.) in water (2 ml.) and *p*-toluidine hydrochloride (0·43 g., 2 mol.) in water (4 ml.) were added successively to a solution of the acetate (IV) (0·5 g.) in methanol (10 ml.). After 2 hr. at 0° the yellow amorphous precipitate (0·4 g.) was collected and air-dried. Dilution of the mother-liquor with water to turbidity gave a further 0·2 g. of product. The impure solid was dissolved in the minimum volume of ethanol (containing 10% of acetic acid) at room temperature, diluted with water to turbidity, and set aside at 0°. Thereafter the solid which separated was collected and further purified by precipitation from cold ethanol by water (to turbidity). This process was repeated four times, to yield amorphous D-arabo-3 : 4 : 5 : 6-*tetra*-O-*acetoxy*-1 : 1-*di*-p-*toluidinohexane* (V) (0·39 g., 49%), sinters at 58°, m. p. 68—72°, $[\alpha]_D^{18}$ +105° (*c*, 1·43 in EtOH) (Found : C, 64·1; H, 6·8; N, 5·3. $C_{28}H_{36}O_8N_2$ requires C, 63·6; H, 6·8; N, 5·3%). The product did not reduce Fehling's solution. It was very soluble in organic solvents, and the solutions became coloured on being heated. A solution in ethanol showed ε 18,100 at 2480 Å, and 4800 at 3010 Å.

Repetition of the above experiment using equimolar quantities of reactants gave 27% of the same product.

(c) *With* 2-*naphthylamine hydrochloride.* By method (b) 2-naphthylamine hydrochloride (0·54 g., 2 mol.; m. p. 244—246°) yielded buff-coloured amorphous D-arabo-3 : 4 : 5 : 6-*tetra*-O-*acetoxy*-1 : 1-*di*-(2-*naphthylamino*)*hexane* (VI) (0·57 g., 62%), m. p. 90—94° (sinters at 88°), $[\alpha]_D^{14}$ −12·5° (*c*, 1·6 in $CHCl_3$) (Found : C, 67·8; H, 5·8; N, 4·4. $C_{34}H_{36}O_8N_2$ requires C, 68·0; H, 6·0; N, 4·7%). Its properties were similar to those of the product (V).

Reaction of 4 : 6-*Diamino*-2-*methylthiopyrimidine Dihydrochloride with* 2 : 3 : 4 : 5 : 6-*Penta*-O-*acetyl*aldehydo-D-*galactose.*—4 : 6-Diamino-2-methylthiopyrimidine,[16] m. p. 187—188°, gave a *dihydrochloride*, m. p. 210° (Found : C, 25·95; H, 4·75; N, 24·0; S, 14·3; Cl, 30·7. $C_5H_{10}N_4SCl_2$ requires C, 26·2; H, 4·4; N, 24·4; S, 14·0; Cl, 31·0%). Solutions of sodium acetate trihydrate (4·7 g., 5 mol.) in water (5 ml.) and pyrimidine dihydrochloride (3·15 g., 2 mol.) in water (5 ml.) were added successively to a solution of 2 : 3 : 4 : 5 : 6-penta-*O*-acetyl-*aldehydo*-D-galactose ethyl hemiacetal (3 g.) in water (20 ml.), and the mixture was set aside at 35° for 48 hr. Thereafter the solution was extracted with chloroform (4 × 25 ml.), and the combined extracts were washed with water and dried ($MgSO_4$). Evaporation of the solvent under diminished pressure gave an orange syrup. It was dissolved in the minimum quantity of ethanol, partially decolorised with charcoal and diluted with water to incipient turbidity. After 24 hr. at 0° the amorphous precipitate (3 g.) was collected and dried. Extraction of the mother-liquors with chloroform and repetition of the above procedure gave a further 1 g. of product. The combined materials were purified by precipitation from concentrated ethanolic solution by water (to turbidity; chilling for 24 hr.). Repitition of this process 5 times gave D-galacto-2 : 3 : 4 : 5 : 6-*penta*-O-*acetoxy*-1 : 1-*di*-(6-*amino*-2-*methylthio*-4-*pyrimidyl*)*hexane* (III) (2·8 g., 58%) as a buff-coloured solid, m. p. 125—130° (sinters at 118—119°), $[\alpha]_D^{18}$ *ca.* −50° (*c*, 1·43 in EtOH; an exact value for α could not be obtained because of the low transparency of the solution) (Found : C, 45·9; H, 5·6; S, 8·8. $C_{26}H_{36}O_{10}N_8S_2$ requires C, 45·6; H, 5·3; S, 9·4%). The product was soluble in the common organic solvents to give highly coloured solutions, and in acetic acid from which it was precipitated by the addition of ammonia.

Repetition of the reaction with equimolar quantities gave the same product in 25% yield.

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[16] Wheeler and Jamieson, *Amer. Chem. J.*, 1904, **32**, 349.

Attempts to Deacetylate the Product (III).—The use of sodium and methanol gave only syrupy products.

Dry ammonia gas was passed into a solution of the compound (III) (1·0 g.) in dry methanol (20 ml.) at 0° for 90 min. Thereafter the solution was set aside at 0° for 24 hr., and at room temperature for a further 24 hr. Evaporation of the solution, and sublimation of unidentified products left a syrup which was acetylated by acetic anhydride (5 ml.) in dry pyridine (10 ml.) at room temperature during 12 hours. The solution was worked up and the amorphous residue reprecipitated four times from ethanolic solution by the addition of water. The product, N-(6-*acetamido*-2-*methythio*-4-*pyrimidyl*)-2 : 3 : 4 : 6-*tetra*-O-*acetyl*-D-*galactosylamine* (0·3 g.), sintered at 140° and had $[\alpha]_D^{18}$ −76° (*c*, 1·0 in $CHCl_3$) (Found: C, 47·5; H, 5·6; N, 11·9; S, 6·5. $C_{21}H_{28}O_{10}N_4S$ requires C, 47·7; H, 5·3; N, 10·6; S, 6·1%).

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