531. *Deoxyribonucleosides and Related Compounds. Part I. Synthetic Applications of Some 1-Halogeno 2-Deoxy-sugar Derivatives.*

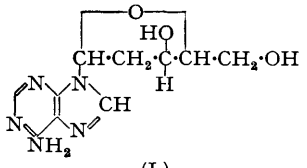
By J. Davoll and B. Lythgoe.

Possible methods for the synthesis of adenine deoxyriboside (I) are reviewed; one of these, in which the use of 1-halogeno 2-deoxy-sugar derivatives is envisaged, has been explored in model experiments.

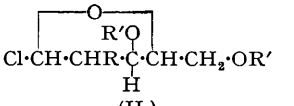
A new method for the preparation of acetylated 1-halogeno 2-deoxypyranoses has been found in the addition of halogen acids to acetylated glycals, and by its application isomeric (α, β) forms of *2′-deoxy-D-ribopyranosidotheophylline* have been synthesised. These isomers can also be obtained by an alternative method, in which theophylline silver is condensed with the product of addition of chlorine and diacetyl D-arabinal to give, after deacetylation, a *2′-chloro D-ribopyranosidotheophylline* and a *2′-chloro D-arabopyranosidotheophylline*, the halogen atoms of which can be replaced by hydrogen catalytically.

Work already reported from this laboratory had as its object the development of methods for the total synthesis of purine and pyrimidine glycosides. These studies have now been extended to the investigation of purine and pyrimidine 2′-deoxyglycosides and the results are communicated in the present series of papers; if successful, such investigations might lead to a clarification of the structures of the four naturally occurring 2′-deoxyribosides which form the building units of deoxyribose nucleic acids.

As the initial objective of these synthetic studies, adenine 2′-deoxyriboside was selected. This compound is usually considered to have the structure (I); the location of the sugar residue at $N_{(9)}$ of the purine skeleton seems probable from the spectroscopic work of Gulland and Story (*J.*, 1938, 259, 262), but the lactol ring structure is based solely on analogy (see Lythgoe, *Ann. Reports*, 1944, **41**, 200), and a rigorous confirmation seems desirable. No evidence bearing on the stereochemistry of the glycosidic centre in (I) has so far been obtained.



(I.)



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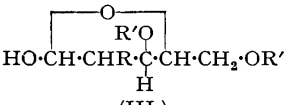

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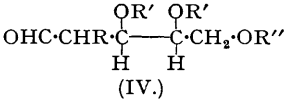

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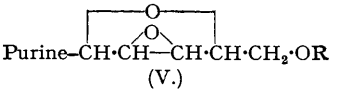


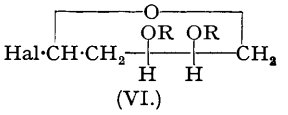
(V.)

For the synthesis of (I) three principal routes seemed possible at the outset: (*a*) Davoll, Lythgoe, and Todd (*J.*, 1948, 967) have shown that adenosine can be synthesised from the product of interaction of 2 : 8-dichloroadenine silver and 1-chloro 2 : 3 : 5-triacetyl D-ribofuranose. In order to apply this method, a compound of structure (II), where R is either H or an atom or group readily replaced by H, such as Cl, Br, SAlk, etc., would be necessary. (*b*) Kenner, Lythgoe, and Todd (*J.*, 1948, 957) and Kenner, Taylor, and Todd (this vol., p. 1620) have shown that 9-glycofuranosidoadenine derivatives can be obtained from 4 : 6-diaminopyrimidine derivatives. The extension of this method to the synthesis of (I) would require either a suitably protected 2-deoxyribofuranose derivative such as (III; R = H, Cl, Br, SAlk, etc.), or a suitably protected *aldehydo*-2-deoxyribose derivative (IV; R = H, Cl, Br, SAlk, etc.). (*c*) Reichstein, Prins, and their co-workers have shown that it is sometimes possible to obtain 2-deoxyglycosides from 2 : 3-anhydroglycosides (*Helv. Chim. Acta*, 1946, **29**, 371; 1947, **30**, 496; 1949, **32**, 22; *J. Amer. Chem. Soc.*, 1948, **70**, 3955). Intermediates of the type (V) would be necessary in order to test whether similar methods are applicable to the synthesis of 2′-deoxyglycofuranosidopurine derivatives. All three routes are under examination in this laboratory; in the present paper, model experiments are recorded which have a bearing on method (*a*) above, in which 1-halogeno 2-deoxy-sugar derivatives are envisaged as intermediates.

Furanose 1-halogeno 2-deoxy-sugar derivatives of type (II) are unknown, and since they would almost certainly be difficult to prepare and very unstable it seemed desirable to undertake model experiments in which the preparation and use of suitable pyranose analogues could be

tested. One such experiment has already been recorded by Levene and Cortese (*J. Biol. Chem.*, 1931, **92**, 53), who prepared 1-bromo 3 : 4 : 6-tribenzoyl 2-deoxy-D-glucose by the method of Bergmann, Schotte, and Leschinsky (*Ber.*, 1923, **56**, 1052), and allowed it to react with theophylline silver, obtaining after removal of benzoyl groups a 2′-deoxy-D-glucopyranosidotheophylline. (This and the other theophylline deoxyglycosides mentioned in this paper almost certainly carry the sugar residue at $N_{(7)}$, but since no evidence on this point has been obtained it seems preferable at present to omit the figure 7 in naming them.) We repeated and confirmed Levene and Cortese's work, but were less successful in extending it to the deoxypentose field. Extensive decomposition took place when syrupy tribenzoyl 2-deoxy-D-ribose was treated with hydrogen bromide in acetic acid; treatment of syrupy *triacetyl 2-deoxy-D-ribose* with ethereal hydrogen chloride also resulted in decomposition, although in this case condensation of the crude product with theophylline silver gave a small quantity of 3′ : 4′-*diacetyl 2′-deoxy-D-ribopyranosidotheophylline*-II (the significance of the suffix II given to this compound will be made clear below). These relatively unsatisfactory results led to a search for a more suitable preparation of 1-halogeno 2-deoxy-sugar derivatives.

It appears at first sight that the desired derivative (VI) might be obtained by the addition of a halogen acid to diacetyl D-arabinal (VII); Fischer, Bergmann, and Schotte (*Ber.*, 1920, **53**, 517), however, recorded that triacetyl D-glucal and hydrogen bromide in acetic acid gave a crystalline "diacetyl D-glucal hydrobromide," which on reacetylation yielded a "triacetyl D-glucal hydrobromide", the bromine atom of which was inert towards silver nitrate, a behaviour which had led to the view that Fischer's compounds were 2-bromo sugar derivatives (cf. Raymond, Gilman's "Organic Chemistry," 1943, p. 1630). This view seemed difficult to accept, since in the addition of water to glycals in the presence of dilute sulphuric acid to give 2-deoxy-sugars, the opposite type of orientation is observed, the anion becoming attached to C_1. Thinking that a peroxide effect might have been involved in Fischer's experiment, we repeated his work, but were unable to isolate the compound he described; the syrupy addition product which we obtained decomposed in a way suggesting the presence of a 1-bromo 1 : 2-dideoxyglucose derivative. When the addition of hydrogen bromide to triacetyl D-glucal was carried out in benzene, clear syrupy products were obtained which from their behaviour obviously contained a large proportion of 1-bromo 3 : 4 : 6-triacetyl 2-deoxy-D-glucose; when condensed with theophylline silver they gave in moderately good yield a crystalline 3′ : 4′ : 6′-*triacetyl 2′-deoxy-D-glucopyranosidotheophylline* which on removal of acetyl groups yielded a compound identical with that prepared by Levene and Cortese's method (*loc. cit.*). Similar results were obtained whether the addition of hydrogen bromide to the triacetyl D-glucal was carried out in the presence of added benzoyl peroxide or of quinol added as an antioxidant. The yield of theophylline deoxyglucoside obtained in the latter case was indeed somewhat lower than when peroxide was used in the addition of hydrogen bromide, but it seems very doubtful whether this was due to any reversal of orientation, since we have found that hydrogen chloride can be added to acetylated glycals to give syrupy acetylated 1-halogeno 2-deoxy-sugars, and it is known that, in the addition of hydrogen chloride to ethylenic compounds, peroxide effects are not concerned.



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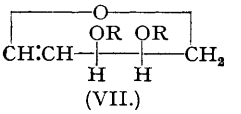

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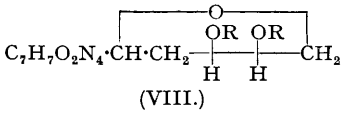

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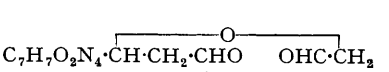


(IX.)

This procedure could now be applied to the preparation of 2′-deoxy-D-ribopyranosidotheophylline. The product (VI; Hal = Cl; R = Ac), obtained by adding hydrogen chloride to diacetyl D-arabinal in benzene, was condensed with theophylline silver to give a mixture of two isomeric compounds (VIII; R = Ac); that more soluble in benzene is referred to as 3′ : 4′-*diacetyl 2′-deoxy-D-ribopyranosidotheophylline*-I; the less soluble component was identical with the form II mentioned above. Deacetylation gave respectively the isomeric 2′-*deoxy-D-ribopyranosidotheophyllines*-I and -II; both isomers gave a strong Dische reaction for 2-deoxypentoses (*Mikrochemie*, 1930, **8**, 4), and reacted with *ca.* 1 mole. of sodium metaperiodate without liberating formic acid. Both were readily hydrolysed by hot

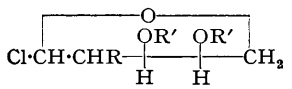
0·01N-sulphuric acid, giving solutions whose optical rotations indicated the presence of 2-deoxy-D-ribose.

In the following table are listed the optical rotations of derivatives of the Series I and Series II compounds.

Compound.	Solvent.	$[\alpha]_D$. Series I.	$[\alpha]_D$. Series II.
Diacetate (VIII; R = Ac)	$CHCl_3$	−63°	+51°
Glycoside (VIII; R = H).....	H_2O	− 9	−21·5
Dialdehyde (IX) *	H_2O	−42·5	+43

* Calculated from the rotation of a solution of the glycoside after oxidation with sodium metaperiodate.

Since the dialdehydes (IX) formed by oxidation of the two glycosides (VIII; R = H) are enantiomorphs, the two series of compounds (VIII; R = H) and (VIII; R = Ac) must represent α, β-pairs. It is noteworthy that of the two glycosides (VIII; R = H), that of Series I has the less negative rotation, whilst of the diacetates (VIII; R = Ac), that of Series II has the more positive rotation; evidently iso-rotation rules have only a limited validity in compounds of this type. Fischer, Bergmann, and Schotte (*loc. cit.*) and Bergmann, Schotte, and Leschinsky (*loc. cit.*), who obtained isomeric methyl-2-deoxy-D-glucopyranosides of $[\alpha]_D$ −48·8° and +137·9° (water), respectively, described the latter as an α-form, presumably because of its large positive rotation, and the former as a β-form. These assignments would be quite unwarranted if they rested on the above rotational data alone, since it is not certain that the contribution of the asymmetric centre $C_{(1)}$ will be of the same sign in methyl-2-deoxyglycosides as in the related methylglycosides; but that this is, in fact, true, and that the above configurational allotments are sound, is established by the circumstance that the methyl-2-deoxy-β-D-glucopyranoside has been connected configurationally with Brigl's 3 : 4 : 6-triacetyl β-methyl-D-glucoside (Bodycote, Haworth, and Hirst, *J.*, 1934, 151). In view of this, it seems likely that the 2′-deoxy-D-glucopyranosidotheophylline, $[\alpha]_D$ −26·9° (water), described by Levene and Cortese is a β-form, and that the corresponding α-form would be more dextrorotatory, but at present no definite allotment of configuration can be made on this basis in the case of the isomeric compounds (VIII; R = H), on account of the reversal in the relative values of the optical rotations of the two series which occurs when these glycosides are converted into their diacetates (VIII; R = Ac).



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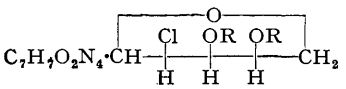

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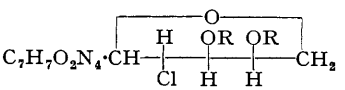

(XII.)

Whilst the work described above was in progress it was decided to examine whether 1-halogeno compounds such as (II; R = Cl, SAlk, etc.) could be used for 2′-deoxy-D-ribosidopurine synthesis; if such compounds could be obtained, they might be more stable than the corresponding derivatives (II; R = H) and the substituent R could be replaced by hydrogen at some later stage in the synthesis. It was, in fact, by a method of this kind that Fischer, Bergmann, and Schotte (*loc. cit.*) prepared methyl-2-deoxy-β-D-glucopyranoside. They allowed the mixture of dibromo-compounds resulting from the addition of bromine to triacetyl D-glucal to react with methanol and silver carbonate, and obtained after deacetylation two compounds, 2-bromo β-methyl-D-glucopyranoside and 2-bromo β-methyl-D-mannopyranoside, both of which were converted on reduction with sodium amalgam into methyl-2-deoxy-β-D-glucopyranoside.

In attempting to test the applicability of similar methods to the synthesis of 2′-deoxy-D-ribosidopurines, an accessible pyranose analogue of (II) was sought; the crystalline dichloride (X; R = Cl, R′ = Ac) which Gakhokidze (*J. Gen. Chem. Russia*, 1945, **15**, 539) described as resulting in high yield from the addition of chlorine to diacetyl D-arabinal seemed a suitable model substance. In our hands, however, this addition reaction gave a syrupy product, which must be a mixture of at least two isomers. When this was condensed with theophylline silver in the usual manner, a mixture of two compounds was obtained which was separated by crystallisation into *2′-chloro 3′ : 4′-diacetyl* D-*ribopyranosidotheophylline*-I (XI; R = Ac) and *2′-chloro 3′ : 4′-diacetyl 2′-deoxy*-D-*arabopyranosidotheophylline*-II (XII; R = Ac). The structures of these compounds were determined as follows. Deacetylation of (XI; R = Ac) with either methanolic ammonia or methanolic sodium methoxide gave *2′-chloro* D-*ribopyrano-*

sidotheophylline-I (XI; R = H), which when shaken in alkaline solution with hydrogen and a palladium–barium sulphate catalyst, gave 2′-deoxy-D-ribopyranosidotheophylline-I, identical with the material previously described. The isomeric diacetate (XII; R = Ac) likewise gave with methanolic ammonia 2′-*chloro* D-*arabopyranosidotheophylline*-II (XII; R = H), but when methanolic sodium methoxide was used for the deacetylation loss of hydrogen chloride took place simultaneously, and 2′ : 3′-*anhydro*-D-*ribopyranosidotheophylline*-II was isolated. The formation of the anhydro-compound shows that (XII; R = Ac) must have the arabinose configuration; the failure of (XI; R = Ac) to yield an anhydro-compound when treated with methanolic sodium methoxide shows that it possesses the ribose configuration.

Reductive dehalogenation of (XII; R = H) in alkaline solution led unexpectedly to two products. The major product was 2′-deoxy-D-ribopyranosidotheophylline-II, identical with material already described. Accompanying it was a small quantity of an isomeric compound which did not respond to the Dische test, and which is almost certainly 3′-*deoxy*-D-*ribopyranosidotheophylline*-II. At first sight, formation of the latter might be attributed to the initial production of an anhydro-riboside under the influence of the alkaline medium, followed by reductive opening of the epoxide ring, which, as shown by Mukherjee and Todd (*J.*, 1947, 969), might be expected to give a 3′-deoxyriboside. Although such an explanation cannot be ruled out, it must be remarked that in our experience the conditions required to effect both the formation and the opening of such epoxide rings are much more vigorous that those of the actual experiment. It is noteworthy that the formation of (XI; R = Ac) and (XII; R = Ac) in our experiments contrasts with the results of Fischer, Bergmann, and Schotte with triacetyl D-glucal in that the two isomers formed in the present work have different configurations at $C_{(1')}$ as well as at $C_{(2')}$.

By extending the methods described above to suitable purine and pyrimidine derivatives, such as 2 : 8-dichloroadenine and 2 : 6-diethoxypyrimidine, it should be possible to effect syntheses of 2′-deoxy-D-ribopyranosides of adenine, uracil, and cytosine. Initial experiments with these aims in view, undertaken with 2 : 8-dichloroadenine, have given only very low yields of crystalline products; it seems possible, however, that these difficulties may be overcome by modifying the reaction conditions or by the use of a more reactive purine silver derivative. Experiments to this end will be continued.

Experimental.

Triacetyl 2-Deoxy-D-ribopyranose.—2-Deoxy-D-ribose (1 g.), prepared according to Levene and Mori (*J. Biol. Chem.*, 1929, **83**, 803), was kept overnight at 0° with pyridine (12 c.c.) and acetic anhydride (5 c.c.). After addition of alcohol, solvents were removed under reduced pressure, the residue was dissolved in chloroform, washed with water, sodium hydrogen sulphate, and sodium hydrogen carbonate solutions, and dried, and the solvent again evaporated under reduced pressure. Distillation of the residue at 180° (bath temp.)/0·1 mm. gave the *triacetyl* derivative as a pale yellow syrup (1·4 g.; 72%); $[\alpha]_D^{17}$ −52·5° (*c*, 2·5 in chloroform) (Found: C, 50·0; H, 6·0. $C_{11}H_{16}O_7$ requires C, 50·7; H, 6·2%).

3′ : 4′-*Diacetyl 2′-Deoxy-D-ribopyranosidotheophylline*-II.—The above triacetyl derivative (1·4 g.) was kept at 0° with ethereal hydrogen chloride (25 c.c., saturated at 0°) for 4 days, and the solution evaporated under reduced pressure first alone and then with dry benzene. The dark residue was heated under reflux for 4 hours with xylene (50 c.c.) containing dry, finely-divided theophylline silver (3 g.), the liquid filtered, and the cooled filtrate treated with a large volume of light petroleum (b. p. 40—60°). Crystallisation of the gummy precipitate from alcohol gave theophylline and 3′ : 4′-diacetyl 2′-deoxy-D-ribopyranosidotheophylline-II (15 mg.). The latter had m. p. 207—208°, undepressed on admixture with an authentic specimen prepared as described below.

3′ : 4′ : 6′-*Triacetyl 2′-Deoxy-D-glucopyranosidotheophylline.*—A solution of triacetyl D-glucal (4 g.) in dry benzene (30 c.c.) containing benzoyl peroxide (50 mg.) was saturated with hydrogen bromide at 15°, the solvent removed under reduced pressure, and the residue evaporated under reduced pressure at 30° with benzene. The syrupy product was heated at 100° for 30 minutes with a suspension of dry theophylline silver (4·5 g.) in dry xylene (60 c.c.), the mixture filtered, and the residual silver bromide washed with warm xylene. The combined filtrate and washings, on being cooled and diluted with light petroleum, gave a gummy precipitate which when dissolved in benzene and kept overnight deposited a small quantity of theophylline. Evaporation of the benzene solution and crystallisation of the residue from alcohol gave the *triacetyl deoxyglucoside* as needles, m. p. 188°, $[\alpha]_D^{20}$ 0° (*c*, 1·15 in chloroform) (2·33 g., 34%) (Found, in material dried at 110°/1 mm.: C, 50·3; H, 5·5; N, 12·8. $C_{19}H_{24}O_9N_4$ requires C, 50·4; H, 5·3; N, 12·4%). When the experiment was repeated without adding benzoyl peroxide during the addition of hydrogen bromide, the yield of triacetyl deoxyglucoside was 23%; when quinol was added instead of benzoyl peroxide, the yield was 19%.

2′-*Deoxy-D-glucopyranosidotheophylline.*—The above triacetyl deoxyglucoside (1 g.) was kept at 0° for 4 days with methanolic ammonia (70 c.c., saturated at 0°), the solution evaporated under reduced pressure, and the residue crystallised from water. The deoxyglucoside separated in plates (0·4 g., 56%), m. p. 220° (decomp.), $[\alpha]_D^{16}$ −27° (*c*, 0·95 in water) (Found, in material dried at 110°/1 mm.: C, 48·1; H, 5·7; N, 17·5. Calc. for $C_{13}H_{18}O_6N_4$: C, 47·8; H, 5·5; N, 17·2%). Material prepared by the method of Levene and Cortese (*loc. cit.*) had m. p. 238—241° (decomp.), $[\alpha]_D^{17}$ −27·4° (*c*, 0·97 in water).

The m. p. behaviour of this compound appears, as Levene and Cortese observed, to be of little value for identification purposes; acetylation of material prepared by their method gave a triacetyl derivative the m. p. of which was identical with that of material described above, and undepressed in admixture with it.

Condensation of Crude 1-*Chloro* 3 : 4-*Diacetyl* 2-*Deoxy*-D-*ribose with Theophylline Silver*.—Diacetyl D-arabinal was prepared from D-arabinose in a yield of 43% by an application of the procedure used by Iselin and Reichstein (*Helv. Chim. Acta*, 1944, **27**, 1148) for the preparation of diacetyl rhamnal. A portion (3 g.) was dissolved in benzene (20 c.c.) and saturated with hydrogen chloride at room temperature, solvents were removed, and the syrup evaporated under diminished pressure with dry benzene. The crude syrupy 1-chloro 3 : 4-diacetyl 2-deoxy-D-ribose so obtained was heated at 100° with a suspension of dry theophylline silver (5 g.) in xylene (50 c.c.) for 3 hours, and the solution filtered, cooled, and diluted with light petroleum (300 c.c., b. p. 40—60°). The gummy precipitate, when dissolved in benzene (120 c.c.) and set aside overnight, deposited a small quantity of theophylline; the residue left by evaporation of the benzene, when dissolved in alcohol and the solution set aside for some time, gave a crystalline mass. The crystals were collected (1·82 g.) and extracted with cold benzene (30 c.c.); evaporation of the extract and crystallisation from alcohol then gave 3′ : 4′-*diacetyl* 2′-*deoxy*-D-*ribopyranosidotheophylline-I* as needles (1·29 g.; 23%), m. p. 152°, $[\alpha]_D^{15}$ −63° (*c*, 1·4 in chloroform) (Found, in material dried at 110°/1 mm.: C, 50·8; H, 5·5; N, 15·1. $C_{16}H_{20}O_4N_7$ requires C, 50·5; H, 5·3; N, 14·7%). The residue from the benzene extraction gave on recrystallisation from alcohol 3′ : 4′-*diacetyl* 2′-*deoxy*-D-*ribopyranosidotheophylline*-II as long prims (0·17 g.; 3%), m. p. 208°, $[\alpha]_D^{16}$ +51° (*c*, 0·78 in chloroform) (Found, in material dried at 110°/1 mm.: C, 50·6; H, 5·0; N, 14·8%).

Exactly similar results were obtained when hydrogen bromide was added to diacetyl D-arabinal in benzene in the presence of added benzoyl peroxide, and the product condensed with theophylline silver as described above.

2′-*Deoxy*-D-*ribopyranosidotheophylline*-I.—3′ : 4′-Diacetyl 2′-deoxy-D-ribopyranosidotheophylline-I (200 mg.) and methanolic ammonia (5 c.c., saturated at 0°) were kept together at 0° over-night, the solvent removed under diminished pressure, and the residue recrystallised from alcohol. The *deoxyriboside* was obtained as needle clusters (105 mg.; 68%), m. p. 212°, $[\alpha]_D^{12}$ −9° (*c*, 1·54 in water) (Found, in material dried at 110°/1 mm.: C, 48·7; H, 5·4; N, 18·6. $C_{12}H_{16}O_5N_4$ requires C, 48·7; H, 5·4; N, 18·9%). The compound gave a purple-brown colour in the Keller–Kiliani test, and a vivid blue colour with the Dische diphenylamine reagent. After it had been kept for 27 hours with sodium metaperiodate solution, 1·23 mols. of oxidant per mol. of glycoside were consumed; this value was unchanged after a further 14 hours, and the rotation of the solution showed the dialdehyde produced to have $[\alpha]_D^{11}$ −42·5°. When the deoxyriboside was hydrolysed with 0·01N-hydrochloric acid at 100°, the optical rotation became constant after 80 minutes; the value then corresponded to $[\alpha]_D^{16}$ −42° for the liberated 2-deoxy-D-ribose.

2′-*Deoxy*-D-*ribopyranosidotheophylline*-II.—The corresponding diacetate (0·13 g.) and methanolic ammonia (5 c.c., saturated at 0°) were kept together for 4 days at 0°, and the *deoxyriboside* isolated by evaporation of the solvent under reduced pressure. It separated from alcohol as needles (80 mg.), m. p. 190°, $[\alpha]_D^{16}$ −21·5° (*c*, 0·93 in water) (Found, in material dried at 110°/1 mm.: C, 48·9; H, 5·3; N, 19·1. $C_{12}H_{16}O_5N_4$ requires C, 48·7; H, 5·4; N, 18·9%). In the Dische and Keller–Kiliani reactions it showed behaviour as described above for the isomeric deoxyriboside. After it had been kept for 24 hours with sodium metaperiodate, 1·05 mols. of oxidant per mol. of glycoside were consumed; the dialdehyde produced had $[\alpha]_D^{11}$ +43° (calculated from the rotation of the solution). When the deoxyriboside was heated with 0·01N-hydrochloric acid, the optical rotation of the solution became stationary after 90 minutes, corresponding then to $[\alpha]_D^{16}$ −43° for the liberated deoxyribose.

2-*Chloro* 3′ : 4′-*Diacetyl Pentosidotheophyllines*.—A solution of diacetyl D-arabinal (5·4 g.) in carbon tetrachloride (30 c.c.) was treated with a slight excess of chlorine at 10°, the solvent removed under reduced pressure, and the residue evaporated twice under reduced pressure with benzene. The syrupy product was heated under reflux for 2½ hours with xylene (80 c.c.) containing suspended theophylline silver (8·5 g.), the precipitated silver chloride collected and washed with xylene, and the combined xylene solutions diluted with light petroleum (500 c.c., b. p. 40—60°). The powdery precipitate was collected and crystallised from methanol (50 c.c.). The first crop of crystals gave on recrystallisation from methanol–ethanol 2-*chloro* 3′ : 4′-*diacetyl* D-*arabopyranosidotheophylline*-II as small prisms (1·5 g.; 13%), m. p. 233°, $[\alpha]_D^{16}$ +31° (*c*, 1·25 in chloroform) (Found, in material dried at 110°/1 mm.: C, 46·4; H, 4·9; N, 13·2. $C_{16}H_{19}O_7N_4Cl$ requires C, 46·3; H, 4·6; N, 13·5%). Evaporation of the methanolic mother-liquors to small bulk and recrystallisation from methanol–ethanol gave *form*-I as plates (0·8 g., 7%), m. p. 188°, $[\alpha]_D^{16}$ −58° (*c*, 2·69 in chloroform) (Found, in material dried at 110°/1 mm.: C, 46·9; H, 4·5; N, 13·8%).

2′-*Chloro* D-*Ribopyranosidotheophylline*-I.—The corresponding diacetate (1 g.) and methanolic ammonia (50 c.c., saturated at 0°) were kept together at 0° for 2 days, the solvent removed under reduced pressure, and the residue crystallised from water, giving the 2′-*chloro* D-*riboside* as needles (0·62 g.; 78%), m. p. 230°, $[\alpha]_D^{15}$ −71·5° (*c*, 0·78 in water) (Found, in material dried at 110°/1 mm.: C, 44·0; H, 4·4; N, 17·0. $C_{12}H_{15}O_5N_4Cl$ requires C, 43·6; H, 4·5; N, 16·9%).

Reductive Dehalogenation of 2′-*Chloro* D-*Arabopyranosidotheophylline*-II.—The chloro compound (0·95 g.), dissolved in 0·04N-sodium hydroxide (100 c.c.), was hydrogenated at atmospheric temperature and pressure in the presence of palladised barium sulphate (0·7 g.). After 7 hours hydrogenation was complete, and the solution was filtered, neutralised with hydrochloric acid, and evaporated to dryness under reduced pressure. Acetylation of the residue with pyridine–acetic anhydride in the usual manner gave a product which on recrystallisation from alcohol gave as the first crop 3′ : 4′-diacetyl 2′-deoxy-D-ribopyranosidotheophylline-II (0·13 g.), identical with material prepared as described above. The mother-liquors, on being concentrated, gave a second crop of crystals consisting of 2′ : 4′-*diacetyl* 3′-*deoxy*-D-*ribopyranosidotheophylline*-II (285 mg.), which formed needles, m. p. 151—152°; in admixture with a specimen of 3′ : 4′-diacetyl 2′-deoxy-D-ribopyranosidotheophylline-I of m. p. 152°, it had m. p. 128—130° (Found, in material dried at 110°/1 mm.: C, 50·6; H, 5·2; N, 14·6. $C_{16}H_{20}O_7N_4$ requires

C, 50·5; H, 5·3; N, 14·7%). In a second experiment, in which the 2′-chloro arabinoside (0·42 g.) was reduced by means of a more active catalyst, absorption of hydrogen was complete in 3 hours, and the yields of the diacetyl 2′-deoxyriboside and diacetyl 3′-deoxyriboside were respectively 0·14 g. and 0·03 g.

3′-*Deoxy*-D-*ribopyranosidotheophylline*-II.—The above diacetyl compound (0·21 g.) was deacetylated with methanolic ammonia in the usual manner, and the product crystallised from alcohol, giving the 3′-deoxyriboside in needles, m. p. 195°, $[\alpha]_D^{11}$ −25° (*c*, 1·52 in water) (Found, in material dried at 110°/1 mm.: C, 48·4; H, 5·4; N, 18·9. $C_{12}H_{16}O_5N_4$ requires C, 48·7; H, 5·4; N, 18·9%). On treatment with sodium metaperiodate it consumed 0·14 mol. of oxidant per mol. of glycoside in 24 hours.

Action of Sodium Methoxide on the Isomeric 2′-Chloro Diacetyl Pentosidotheophyllines.—(a) *On 2′-chloro 3′ : 4′-diacetyl* D-*ribopyranosidotheophylline*-I. The diacetyl compound (207 mg.) was kept overnight at room temperature with chloroform (3 c.c.) and methanolic sodium methoxide (0·55 c.c. of 10%), the solution evaporated to dryness under reduced pressure at 20°, and the residue dissolved in water and neutralised with acetic acid. Concentration of the solution gave 2′-chloro D-ribopyranosidotheophylline-I (107 mg.), m. p. 227°, undepressed in admixture with authentic material. No evidence of the presence of any anhydro-compound could be obtained.

(b) *On 2′-chloro 3′ : 4′-diacetyl* D-*arabopyranosidotheophylline*-II. The diacetyl compound (207 mg.), treated exactly as described above for the isomeric compound, gave 2′ : 3′-*anhydro*-D-*ribopyranosidotheophylline*-II (58 mg.), which separated from 80% alcohol as needles, m. p. 212°, $[\alpha]_D^{15}$ +40° (*c*, 1·11 in water) (Found, in material dried at 100°/1 mm.: C, 49·2; H, 4·4; N, 19·2. $C_{12}H_{14}O_5N_4$ requires C, 49·0; H, 4·8; N, 19·1%).

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