488. *Experiments on the Synthesis of Purine Nucleosides. Part XXV. 1 : 2 : 3 : 5-Tetra-acetyl* D-*Arabofuranose and the* D-*Arabofuranosides of Theophylline and Adenine.*

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The preparation of *5-trityl* D-*arabinose* and its conversion into 1 : 2 : 3 : 5-*tetra-acetyl* D-*arabofuranose* are described. The latter has been used to prepare acetobromo-D-arabofuranose from which D-*arabofuranosides* of *theophylline* and *adenine* have been synthesised; they belong to the α-series.

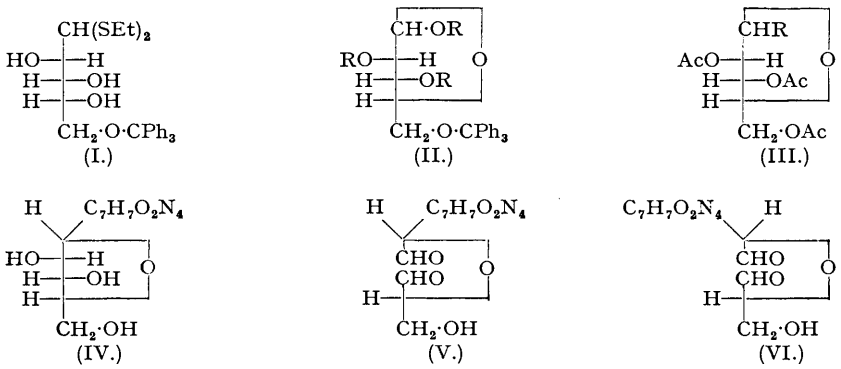
Although pyranosyl acetohalogeno-sugars have been widely used in synthetic work, only a limited use has been made of the furanosyl analogues. This is almost certainly due to the difficult accessibility of the latter; the fully acetylated *aldo*furanoses from which they can be prepared have been described only in two cases. In the hexose series, penta-acetyl D-galactofuranose has been obtained by acetylation of the parent hexose in hot pyridine solution (Schlubach and Prochownick, *Ber.*, 1929, **62**, 1502), and in the pentose series tetra-acetyl D-ribofuranose has been prepared indirectly from 5-trityl D-ribose (Howard, Lythgoe, and Todd, *J.*, 1947, 1052) and used in effecting syntheses of the natural nucleosides cytidine, adenosine, and guanosine (*loc. cit.*; Davoll, Lythgoe, and Todd, *J.*, 1948, 967, 1685). In the course of work with which we are at present engaged, including the synthesis of nucleoside analogues, the preparation of pentofuranose 1-phosphates, and investigations on the lactol ring structures of *o*-nitroaniline pentosides, we have felt the need for a general method whereby tetra-acetyl pentofuranoses could be obtained in quantity for use in the preparation of the corresponding acetohalogeno-sugars. Experiments designed to meet this need were therefore undertaken, and the present paper reports the results obtained by using D-arabinose as a representative pentose. Parallel investigations on D-xylose will be communicated later.

The method used by Howard, Lythgoe, and Todd for the preparation of tetra-acetyl D-ribofuranose cannot be applied in its entirety to pentoses such as arabinose and xylose, the stage lacking generality being that in which the pentose is converted into its 5-trityl derivative. In the case of ribose, this can be accomplished by direct interaction with trityl chloride in pyridine (Bredereck, Köthnig, and Berger, *Ber.*, 1940, **73**, 956), but when xylose or arabinose is treated in this way the desired product is not obtained, possibly owing to the smaller proportion of these sugars existing in the furanose form at equilibrium in solution; for instance, Zeile and Kruckenberg (*Ber.*, 1942, **75**, 1127) were able to isolate only small yields of a homogeneous product from the tritylation of xylose, and this proved to be a ditrityl derivative. For our purpose an indirect way of preparing 5-trityl pentoses was clearly necessary.

A suitable method seemed to lie in the removal of the alkylthio-groups from 5-trityl pentose mercaptals. 5-*Trityl* D-*arabinose diethyl mercaptal* (I), obtained by tritylation of the parent mercaptal, does not appear to have been described, although the triacetate of the L-isomer was prepared by Wolfrom, Quinn, and Christman (*J. Amer. Chem. Soc.*, 1935, **57**, 713). Stirring with mercuric chloride and cadmium carbonate in aqueous acetone was not found satisfactory as a method for removing the ethylthio-groups from (I), since extensive detritylation took place simultaneously. No such difficulty was experienced when mercuric oxide was used in place of cadmium carbonate to neutralise the hydrochloric acid set free during the reaction, and 5-*trityl* D-*arabinose* (II; R = H) was then isolated in good yield.

To convert (II; R = H) into tetra-acetyl D-arabofuranose the methods of Howard, Lythgoe, and Todd were used. The *triacetyl* derivative (II; R = Ac) could not be obtained crystalline, no doubt because both α- and β-forms were present. It was detritylated by hydrogenolysis in the presence of palladium, and after removal of triphenylmethane the product was acetylated to give 1 : 2 : 3 : 5-*tetra-acetyl* D-*arabinose* (III; R = OAc). Purified by vacuum distillation, the latter formed a clear, colourless syrup, from which no crystalline material could be obtained, even after chromatography on neutral aluminium oxide. Samples of the syrupy tetra-acetate obtained in different runs have been found to differ somewhat in optical rotation, and it seems clear that the product is a mixture of α- and β-forms in varying proportions, and that it is to this that its failure to crystallise is attributable. The high yields obtained when this material is used for the synthesis of the purine arabofuranosides described below, and the freedom of the products from contamination with the corresponding pyranosides, compounds which are much more readily isolable and much less readily soluble than the isomeric furanosides, provide evidence that the syrupy tetra-acetate is essentially homogeneous with respect to its lactol ring structure. Attention is directed to the high overall yield in which the tetra-acetate can be obtained (45% based on D-arabinose), which should make it a convenient starting material for the preparation of furanose derivatives.

When the crude acetobromo-compound (III; R = Br), obtained by treatment of (III; R = OAc) with liquid hydrogen bromide, was brought into reaction with theophylline silver in the usual manner, and the product deacetylated, a crystalline *theophylline*-7-α-D-*arabofuranoside* (IV) was obtained in good yield. The furanose structure of this compound was shown by oxidation with sodium metaperiodate, 1 mol. of which was consumed without



liberation of formic acid. The fission product formed in the oxidation must have the structure (V), since it differs markedly in solubility and molecular rotation from the dialdehyde (VI), which can be obtained as a crystalline substance by periodate oxidation of either theophylline-

7-β-D-glucopyranoside or theophylline-7-β-D-ribofuranoside (Lythgoe and Todd, *J.*, 1944, 595; Howard, Lythgoe, and Todd, *loc. cit.*). It follows that (IV) is an α-glycoside. The formation of an α-glycoside in this case is interesting, since it suggests that the acetobromo-compound from which it was formed may, like ordinary acetobromoarabopyranose, but unlike most acetobromo-sugars, be a β-form.

In order to obtain the arabofuranose isomer of adenosine, (III; R = Br) was condensed with 2 : 8-dichloroadenine silver, removal of the acetyl groups from the product then giving 2 : 8-*dichloro*-9-α-D-*arabofuranosidoadenine*. By reductive dehalogenation in the presence of a palladium catalyst this was transformed into 9-α-D-*arabofuranosidoadenine*, the furanose structure and configuration of which were established by periodate oxidation.

Unlike adenosine, the purine arabofuranosides described above contain a *trans*-α-glycol system as a feature of their sugar residues, and should therefore be capable of giving rise to 2′ : 3′-anhydro-compounds. The formation of such epoxides, and the possibilities of using them for the synthesis of deoxyglycosides and of other nucleoside derivatives, is now being studied and the results will be communicated later.

Experimental.

5-Trityl D-*Arabinose Diethyl Mercaptal* (I).—D-Arabinose diethyl mercaptal required for this experiment was prepared according to Fischer (*Ber.*, 1894, **27**, 677), but the reaction mixture was set aside overnight, then diluted with ice-water and set aside for a further 2 hours before the product was collected. In this way a 85% yield of material, m. p. 126°, was obtained. The solution obtained by allowing this material (58 g.) and trityl chloride (66·5 g.) to react in dry pyridine (350 c.c.) overnight was poured slowly into a well-stirred slurry of ice (800 g.) and water (600 c.c.). The precipitated syrup was dissolved in chloroform, the chloroform solution washed at 0° with sodium hydrogen sulphate solution, sodium hydrogen carbonate solution, and water, and finally dried and evaporated under reduced pressure. Crystallisation from benzene–light petroleum (b. p. 80—100°) gave *5-trityl* D-*arbinose diethyl mercaptal* as rosettes of prisms (103 g., 91%), m. p. 107°, $[\alpha]_D^{15}$ −37·5° (*c*, 3·1 in chloroform) (Found : C, 67·5; H, 6·8. $C_{28}H_{34}O_4S_2$ requires C, 67·5; H, 6·8%).

5-Trityl D-*Arabinose* (II; R = H).—The mercaptal (I) (99·5 g.), dissolved in aqueous acetone (900 c.c., containing 100 c.c. of water) in which yellow mercuric oxide (200 g.) was suspended, was stirred vigorously whilst a solution of mercuric chloride (225 g.) in acetone (700 c.c.) was allowed to run in slowly (2 hours). Stirring was continued for a further 15 hours, the solution filtered, evaporated under reduced pressure, and the residue extracted with chloroform (4 × 75 c.c.), a large quantity of mercuric chloride remaining undissolved. The chloroform extracts were washed with water, dried, and evaporated under reduced pressure. The residue was freed from chloroform by distillation with alcohol, and crystallised from a small volume of alcohol, giving *5-trityl* D-*arabinose* as fine needles (60 g., 76%), m. p. 68°, $[\alpha]_D^{15}$ +26·5° (6 minutes), +16·5° (25 hours (*c*, 2·0 in alcohol) (Found : C, 72·9; H, 6·8. $C_{24}H_{24}O_5$ requires C, 73·5; H, 6·1%). A crystalline form, m. p. 98°, was obtained by recrystallisation from mixtures of ethyl acetate, ether, and light petroleum (b. p. 40—60°); it had the same initial and final rotations as the form of m. p. 68°. The trityl compound is clearly of the α-series.

1 : 2 : 3-*Triacetyl 5-Trityl* D-*Arabinose* (II; R = Ac).—The above trityl compound (86 g.) in pyridine (150 c.c.) was added slowly to a well-stirred mixture of pyridine (150 c.c.) and acetic anhydride (250 c.c.) kept at −5°. After 3 days at room temperature, the solution was poured into ice and water (1 kg. each) with stirring, and the syrup separating was taken up in chloroform and washed and dried as usual. Removal of the solvent under reduced pressure gave the *triacetyl* compound as a gum, $[\alpha]_D^{16}$ 28·5° (*c*, 2·0 in chloroform) (Found : C, 69·7; H, 6·0. $C_{30}H_{30}O_8$ requires C, 69·5; H, 5·8%) (111 g., 98%). Variation of the acetylation conditions gave material whose optical rotation diverged by as much as 5° from that recorded above, which appears to reflect a difference in the proportions of α- and β-forms present in the syrup.

1 : 2 : 3 : 5-*Tetra-acetyl* D-*Arabinose* (III; R = OAc).—The preceding compound (111 g.), dissolved in anhydrous acetic acid (300 c.c.), was shaken at 40° in the presence of Adams's palladium oxide catalyst (1·8 g.) with hydrogen at atmospheric pressure. Absorption of 5·04 l. of hydrogen (theoretical = 5·18 l.) required 14 hours; the filtered solution was then evaporated under reduced pressure, and the majority of the triphenylmethane separated by crystallisation of the residue from the minimum quantity of alcohol. The mother-liquors were evaporated under reduced pressure, and extracted with light petroleum (3 × 200 c.c.; b. p. 40—60°) to remove any remaining triphenylmethane. The residue was dissolved in pyridine (200 c.c.), cooled to 0°, and treated with acetic anhydride (40 c.c.). After 24 hours the excess of acetic anhydride was destroyed by addition of alcohol, and the solution was concentrated under reduced pressure and, after dilution with chloroform, washed and dried as usual. Evaporation of the chloroform gave a syrup which was distilled at 130° (bath temp.)/10^{-3} mm. The colourless syrupy 1 : 2 : 3 : 5-*tetra-acetyl* D-*arabinose* had $[\alpha]_D^{15}$ in the range +16° to +29° (*c*, 2·5 in chloroform); the variation is probably due to varying proportions of α- and β-forms in the product (Found : C, 49·1; H, 5·8. $C_{13}H_{18}O_9$ requires C, 49·0; H, 5·7%); yield, 54 g. (79%).

Theophylline-7-α-D-arabofuranoside.—1 : 2 : 3 : 5-Tetra-acetyl D-arabinose (2·07 g.), contained in a steel tube fitted with a glass liner, was covered with liquid hydrogen bromide (15 c.c.), and the tube closed, allowed to warm to room temperature, and remain for a further ½ hour before being opened. After most of the excess of hydrogen bromide had been removed under reduced pressure, the last traces were removed by evaporating the product under reduced pressure with dry benzene. The crude acetobromo-compound was dissolved immediately in xylene (100 c.c.) containing dry finely divided theophylline silver (3·0 g.), and the mixture heated under reflux for ½ hour, then filtered, cooled, and

treated with a large volume of light petroleum (b. p. 40—60°). The precipitate was collected, dissolved in hot benzene (30 c.c.), and set aside at room temperature for 48 hours. The small quantity of theophylline which separated was filtered off, the solution evaporated under reduced pressure, and the residue dissolved in 0·155N-methanolic barium methoxide (30 c.c.). After 24 hours at room temperature, barium was removed by addition of sulphuric acid and the solution filtered and evaporated. Crystallisation of the residue from alcohol gave *theophylline-7-α-D-arabofuranoside* (1·3 g., 62%), m. p. 173°, $[\alpha]_D^{15}$ +21° (*c*, 1·3 in water) (Found: C, 46·2; H, 5·3; N, 17·8. $C_{12}H_{16}O_6N_4$ requires C, 46·2; H, 5·1; N, 18·0%). The compound is very soluble in water.

Periodate oxidation. Sodium metaperiodate consumed: 1·06 mols. per mol. of glycoside. Formic acid liberated: nil. Rotation of fission product, determined from the solution on completion of the oxidation: $[M]_D^{16}$ −0·78 × 10⁴. Lythgoe and Todd (*loc. cit.*) give for the fission product from theophylline-7-β-D-glucopyranoside $[M]_D^{19}$ −1·29 × 10⁴.

2 : 8-*Dichloro*-9-α-D-*arabofuranosidoadenine*.—Crude acetobromo-D-arabofuranose (prepared as described above, from 4·5 g. of 1 : 2 : 3 : 5-tetra-acetyl D-arabinose) was dissolved in dry xylene (100 c.c.) containing dry, finely divided 2 : 8-dichloroadenine silver (4·1 g.), and the suspension heated under reflux for 3 hours and then filtered. To the cooled filtrate light petroleum (350 c.c., b. p. 60—80°) was added, and the precipitate collected, dried, and recrystallised from alcohol. The product was set aside for 12 hours at 0° with methanol (50 c.c.) and methanolic ammonia (65 c.c., saturated at 0°), the solution evaporated under reduced pressure, and the residue crystallised from hot water (charcoal). The 2 : 8-*dichloro*-9-α-D-*arabofuranosidoadenine* separated as needle tufts (1·35 g., 28%), m. p. 222° (decomp.; rapid heating) (Found: C, 35·6; H, 3·1; N, 20·1. $C_{10}H_{11}O_4N_5Cl_2$ requires C, 35·7; H, 3·3; H, 20·8%).

9-α-D-*Arabofuranosidoadenine*.—A solution of the above dichloro-compound in water (200 c.c.) to which N-sodium hydroxide (7 c.c.) and a 5% palladium–barium sulphate catalyst (1 g.) had been added was shaken with hydrogen at room temperature for 3 hours, after which no more hydrogen was absorbed. The solution was filtered, neutralised with hydrochloric acid, and concentrated to 7 c.c. under reduced pressure. The 9-α-D-*arabofuranosidoadenine* was collected and recrystallised from hot water; it formed small rosettes of needles (0·69 g., 75%), m. p. 208°, $[\alpha]_D^{17}$ +69° (*c*, 1·1 in water) (Found: C, 44·8; H, 4·6; N, 25·8. $C_{10}H_{13}O_4N_5$ requires C, 44·9; H, 4·9; N, 26·2%). A further quantity of the same material was isolated as the *picrate* by addition of picric acid to the mother-liquors; this showed no m. p. below 360° (Found: C, 38·7; H, 3·2; N, 22·9. $C_{10}H_{13}O_4N_5,C_6H_3O_7N_3$ requires C, 38·7; H, 3·2; N, 22·6%).

Periodate oxidation. 9-α-D-Arabofuranosidoadenine consumed 0·97 mol. of sodium metaperiodate per mol., and liberated no formic acid. Treatment of the solution with picric acid when the oxidation was complete gave the *picrate*, $[M]_D^{14}$ 0·4 × 10⁴ (*c*, 0·3 in 0·1N-sodium hydrogen carbonate) (Found: C, 39·3; H, 3·0; N, 22·0. $C_{10}H_{11}O_4N_5,C_6H_3O_7N_5$ requires C, 38·9; H, 2·9; N, 22·7%), of the fission product. Davoll, Lythgoe, and Todd (*J.*, 1946, 833) give for the similar picrate from adenosine $[M]_D^{14}$ −1·08 × 10⁴ (*c*, 1·2 in 0·1N-sodium hydrogen carbonate). This difference shows that 9-α-D-arabofuranosidoadenine belongs to the α-series.

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