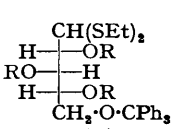
407. *Experiments on the Synthesis of Purine Nucleosides. Part XXVII. 1 : 2 : 3 : 5-Tetra-acetyl* D-*Xylofuranose and the* D-*Xylofuranosides of Theophylline and Adenine.*

By P. Chang and B. Lythgoe.

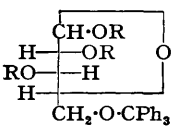
1 : 2 : 3 : 5-Tetra-acetyl D-xylofuranose has been synthesised from 5-trityl D-xylose and used for the preparation of the β-D-xylofuranosides of theophylline and adenine.

Methods for the preparation of tetra-acetyl pentofuranoses have been investigated in this laboratory because of the potential value of these compounds in the synthesis of furanose derivatives in general and of nucleoside analogues in particular; the preparation and the uses of tetra-acetyl D-ribofuranose have been reported in earlier papers of this series and recently (Bristow and Lythgoe, *J.*, 1949, 2306) we described the preparation of tetra-acetyl D-arabofuranose and its conversion into α-D-arabofuranosides of theophylline and adenine. These glycosides, and the corresponding xylofuranose analogues, are of particular interest in that they have a *trans*-1 : 2-glycol system, and should be able to form epoxides which might be of value in in the related field of deoxyribonucleoside synthesis (cf. Davoll and Lythgoe, *J.*, 1949, 2526). With this in mind we undertook the preparation of the D-xylofuranosides of theophylline and adenine.

The methods used in this work follow those found effective for the corresponding arabinose analogues, with modifications in detail. A necessary intermediate, 2 : 3 : 4-triacetyl 5-trityl D-xylose diethyl mercaptal (I; R = Ac), was prepared by Wolfrom, Quinn, and Christman



(I.)



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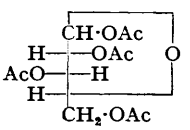

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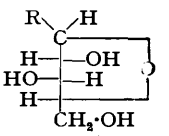

(IV.)

(*J. Amer. Chem. Soc.*, 1935, **57**, 713); in the Experimental section a modification of their procedure is described which gives this compound in an overall yield of 55% from D-xylose. The syrupy compound (I; R = H) obtained by deacetylation was converted by treatment with mercuric chloride and mercuric oxide in aqueous acetone into crystalline 5-trityl D-xylofuranose (II; R = H).

The amorphous triacetate (II; R = Ac) gave, on treatment with acetyl bromide by Bredereck and Hoepfner's method (*Ber.*, 1948, **81**, 50), 1 : 2 : 3 : 5-tetra-acetyl D-xylofuranose (III) which failed to crystallise, probably owing to the presence of both α- and β-forms. It was converted by ethereal hydrogen chloride into 2 : 3 : 5-triacetyl D-xylosyl chloride which, without being isolated pure, was used directly for the synthesis by standard methods of 7-β-D-xylofuranosyltheophylline (IV; R = $C_7H_7O_2N_4$) and 9-β-D-xylofuranosyladenine (IV; R = $C_5H_4N_5$). The configuration and ring-structure of these compounds was established by periodate oxidation; thus the theophylline compound consumed one molar proportion of the oxidant, gave no formic acid, and was converted into a crystalline dialdehyde, identical with that isolated after similar oxidation of 7-β-D-glucopyranosyltheophylline (Lythgoe and Todd, *J.*, 1944, 584).

Experimental.

2 : 3 : 4-*Triacetyl* 5-*Trityl* D-*Xylose Diethyl Mercaptal.*—Crude syrupy D-xylose diethyl mercaptal, prepared from D-xylose (47·5 g.) by the method of Wolfrom, Newlin, and Stahly (*J. Amer. Chem. Soc.*, 1931, **53**, 4379), was dissolved in pyridine (150 c.c.), and the ice-cold solution treated with acetic anhydride (200 c.c.), kept at room temperature for 24 hours, and poured into ice-water (3 l.). The product was extracted with chloroform, and the extract, after being washed and dried in the usual way, was evaporated under reduced pressure to a thick syrup which was then distilled at 10^{-3} mm. The distillate collected between 150° and 165° (bath-temp.) crystallised completely to a solid (89 g., 76%), m. p. 40—42°. Wolfrom, Newlin, and Stahly give for tetra-acetyl D-xylose diethyl mercaptal, recrystallised from aqueous methanol, m. p. 46—48°. The tetra-acetate (19·6 g.) was kept for 12 hours at room temperature with 6% methanolic ammonia (140 c.c.), solvents were removed under reduced pressure, and the residual syrup was dried by 2 evaporations with dry benzene. It was then dissolved in dry pyridine (50 c.c.), triphenylmethyl chloride (12·5 g.) added, and the solution kept at 20° for 24 hours and finally at 40° for 8 hours. Acetic anhydride (40 c.c.) was added to the cooled solution, which was then kept at 40° for 24 hours, cooled, and poured into ice-water. The product, isolated by extraction with chloroform in the usual way, was a syrup which crystallised from methanol in plates (22·7 g., 79%), m. p. 149—150°. Wolfrom, Quinn, and Christman (*loc. cit.*) record for this compound m. p. 150°.

5-*Trityl* D-*Xylofuranose*.—A solution of the above triacetate (42·5 g.) in chloroform (400 c.c.) was cooled to 0° and stirred mechanically whilst 0·4N-methanolic sodium methoxide (250 c.c.) was added slowly. The solution was kept at 0° for 12 hours, then shaken with several portions of ice-water until the chloroform phase was clear, the aqueous phases were extracted with a little chloroform, and the combined chloroform extracts dried and evaporated. The syrupy 5-trityl D-xylose diethyl mercaptal could not be obtained crystalline, so it was dissolved in acetone (330 c.c.) and water (33 c.c.), and the solution stirred vigorously with mercuric oxide (65 g.) whilst a solution of mercuric chloride (73·5 g.) in acetone (115 c.c.) was added during 2 hours. Stirring was continued for 24 hours, the solution filtered, and acetone removed from the filtrate under reduced pressure. The residue was diluted with water (500 c.c.) and extracted with chloroform (2 × 500 c.c.), the extract was washed once with 40% aqueous potassium iodide (200 c.c.) and twice with water (500 c.c.), dried (Na_2SO_4), and evaporated. The residual syrup crystallised slowly from ethyl acetate–light petroleum (b. p. 60—80°) giving 5-*trityl* D-*xylofuranose* (19·5 g., 73%) as clusters of needles, m. p. 124—126°, $[\alpha]_D^{19}$ −14° (7 minutes) ⟶ −19·5° (final value, 90 minutes) (*c*, 3·17 in pyridine) (Found: C, 73·0; H, 6·8. $C_{24}H_{24}O_5$ requires C, 73·4; H, 6·2%). The crystalline material is clearly an α-form.

1 : 2 : 3 : 5-*Tetra-acetyl* D-*Xylose*.—The trityl compound (14 g.), pyridine (35 c.c.), and acetic anhydride (25 c.c.) were kept together at room temperature for 12 hours and the solution was poured slowly into cold water with efficient stirring. The white amorphous solid was collected and dissolved in hot alcohol, and the solution poured slowly into water with stirring. 2 : 3 : 5-*Triacetyl* 5-*trityl* D-*xylofuranose* (17·5 g.), which could not be crystallised, had $[\alpha]_D^{19}$ +33° (*c*, 1·9 in alcohol) (Found: C, 69·1; H, 5·7. $C_{30}H_{30}O_8$ requires C, 69·5; H, 5·8%). It was dissolved in acetic anhydride (32 c.c.) and to the solution acetyl bromide (5·2 c.c.) was added. After 30 minutes the solution was filtered from triphenylmethyl bromide, and the filtrate poured into ice-water (1 l.), whereupon triphenylcarbinol separated and was filtered off. The filtrate was extracted with chloroform, and the extract washed first with sodium hydrogen carbonate solution and then with water, dried, and evaporated under reduced pressure. The residue was distilled at 125—140° (bath-temp.)/6 × 10^{-4} mm., 1 : 2 : 3 : 5-*tetra-acetyl* D-*xylose* being obtained as a colourless syrup (7·4 g., 69%), $[\alpha]_D^{19}$ +56° (*c*, 2·17 in alcohol) (Found: C, 49·1; H, 5·5. $C_{13}H_{18}O_9$ requires C, 49·0; H, 5·7%).

7-β-D-*Xylofuranosyltheophylline*.—A solution of the above tetra-acetate (1·18 g.) in ether (20 c.c.) was saturated with dry hydrogen chloride at 10° and kept at 0° for 4 days. The ether was then removed under reduced pressure and the residue evaporated thrice under reduced pressure with dry benzene in order to free it from hydrogen chloride. To the product a suspension of dry theophylline silver (2 g.) in dry xylene (40 c.c.) was added and the mixture was boiled under reflux for 2 hours and then filtered, and the filtrate evaporated to dryness under reduced pressure. The syrup so obtained did not crystallise and was therefore deacetylated by treatment with 6% methanolic ammonia (50 c.c.) at 0° for 24 hours. Evaporation of the solvent and crystallisation of the residue from water (2 c.c.) gave 7-β-D-*xylofuranosyltheophylline* as needles (570 mg., 50%), m. p. 230—232°, $[\alpha]_D^{17}$ +38° (*c*, 0·87 in water) (Found: C, 46·3; H, 5·1; N, 18·0. $C_{12}H_{16}O_4N_4$ requires C, 46·1; H, 5·2; N, 17·9%).

Oxidation of a portion of this material (75 mg.) with sodium metaperiodate (*ca.* 0·24M.) required 3 days for completion, and 1·02 mols. of oxidant per mol. of glycoside were reduced. The reaction solution deposited crystals which were dried in a vacuum-desiccator at room temperature and then had $[\alpha]_D^{17}$ −37° (*c*, 0·45 in water) and m. p. 206° (decomp.), undepressed on admixture with a specimen of the dialdehyde obtained from theophylline glucoside by Lythgoe and Todd (*loc. cit.*).

9-β-D-*Xylofuranosyladenine*.—Crude triacetyl D-xylofuranosyl chloride, prepared from tetra-acetyl D-xylofuranose (2·5 g.) as described above, was boiled under reflux for 5 hours with a suspension of dry 2 : 8-dichloroadenine silver (2·5 g.) in xylene (50 c.c.). To the cooled and filtered solution light petroleum (250 c.c.; b. p. 60—80°) was added and the powdery precipitate collected, washed with more light petroleum, and dried in the air. It was then kept with 10% methanolic ammonia (100 c.c.) at 0° for 18 hours, solvents were removed under reduced pressure, and the residue was crystallised from water, whereby 2 : 8-*dichloro*-9-β-D-*xylofuranosyladenine* was obtained as needles (1 g., 40%) which darkened and frothed at *ca.* 140° but had no definite m. p.; it had $[\alpha]_D^{17}$ −13·8° (*c*, 0·22 in water) (Found: C, 35·3; H, 3·4; N, 20·3. $C_{10}H_{11}O_4N_5Cl_2$ requires C, 35·7; H, 3·3; N, 20·8%).

When a portion (82 mg.) was treated with sodium metaperiodate solution, 0·99 mol. of the oxidant per mol. of glycoside was reduced after 7 days, and the fission product in the solution had $[M]_D$ +11,300°. Davoll, Lythgoe, and Todd (*J.*, 1948, 967) record for the fission product from 2 : 8-dichloro-9-β-D-ribofuranosyladenine, $[M]_D$ +9,200°. In view of the length of time which the fission product in the present work was necessarily in contact with the oxidant, these values are in reasonable agreement.

Dehalogenation of the xyloside was achieved catalytically. A portion (480 mg.) in water (100 c.c.) containing N-sodium hydroxide (3·6 c.c.) together with 5% palladised barium sulphate (1 g.) was shaken with hydrogen. In 8 hours the theoretical amount (2·9 millimols.) of hydrochloric acid was liberated, and 74 c.c. of hydrogen had been absorbed; the solution was filtered and evaporated to dryness. To free the product from inorganic salts it was converted into its acetyl derivative which was dissolved in chloroform. The solution was washed with water, dried, and evaporated, and the residue deacetylated by methanolic barium methoxide. The 9-β-D-xylofuranosyladenine so obtained formed a glassy solid (220 mg., 58%), $[\alpha]_D^{18}$ −19° (*c*, 1·2 in water), which could not be obtained crystalline as such, but was converted into the *picrate*, yellow needles (from water), m. p. 210° (decomp.), $[\alpha]_D^{17}$ −43° (*c*, 0·62 in pyridine) (Found: C, 38·7; H, 3·6; N, 22·5. $C_{10}H_{13}O_4N_5,C_6H_3O_7N_3$ requires C, 38·7; H, 3·3; N, 22·6%).

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