493. *Deoxyribonucleosides and Related Compounds. Part III.* Experiments with 2′ : 3′-Anhydropentofuranosyltheophyllines.*

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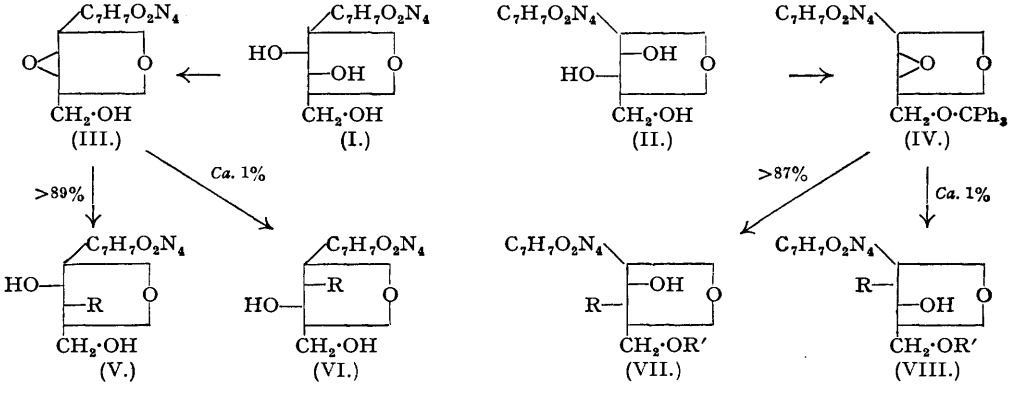
The 2′ : 3′-anhydropentofuranosides (III) and (IV) have been prepared and examined in order to test the suitability of similar compounds for the synthesis of the natural 2′-deoxyribofuranosides. An orientation unfavourable to this purpose was observed when the epoxide rings were opened with sodium thioethoxide. From the products, 3′-deoxy-7-α-D-arabofuranosyltheophylline and 3′-deoxy-7-β-D-ribofuranosyltheophylline were prepared.

Recent attempts by Mukherjee and Todd (*J.*, 1947, 969) and by Kent, Stacey, and Wiggins (*J.*, 1949, 1232) to convert 2 : 3-anhydropentopyranosides into 2-deoxypentopyranosides by Prins's method (*Helv. Chim. Acta*, 1946, **29**, 371), or one of its variants, have met with only limited success on account of the unfavourable orientation observed during the opening of the epoxide ring. The nucleophilic part of the reagent molecule entered predominantly at position 3, giving derivatives from which 3-deoxypentopyranosides were obtained; the most successful experiments, carried out by Kent *et al.* with hydrobromic acid as the reagent, gave no more than 9% of the required 2-deoxypentose derivative; the reasons for this unfavourable orientation are not known.

2 : 3-Anhydropentofuranosides have not previously been accessible and so have not been investigated from this standpoint, but it was clearly desirable that this should be done, since, even if only 25%, say, of the product of the ring-opening of such a compound were a 2-deoxypentose derivative, an attractive method would be open for the synthesis of the natural 2′-deoxyribofuranosides. Recently, D-arabofuranosyl and D-xylofuranosyl derivatives of purines have become comparatively readily available (Bristow and Lythgoe, *J.*, 1949, 2306; Chang and Lythgoe, *J.*, 1950, 1992), and these compounds, which possess the *trans*-α-glycol system necessary for epoxide formation, seemed to offer the opportunity for testing this synthetic method. This has now been done, theophylline derivatives being used for convenience, and this paper reports the preparation of the epoxides (III) and (IV) and the mode of their reaction with sodium thioethoxide.



7-α-D-Arabofuranosyltheophylline (I) was converted by the usual methods into 5′-trityl and 2′ : 3′-ditoluene-*p*-sulphonyl 5′-trityl derivatives; the latter was treated with sodium methoxide, and removal of the trityl group then gave a crystalline anhydropentofuranoside whose reactions showed it to be the lyxose derivative (III). The major product of its reaction with sodium thioethoxide was the 3′-deoxy-3′-ethylthio-derivative (V; R = SEt), isolated as its crystalline 2′ : 5′-diacetate in 89% yield. This was desulphurised with Raney nickel and the acetyl groups removed, giving 3′-deoxy-7-α-D-arabofuranosyltheophylline (V; R = H), which was shown to be a 3-deoxy-sugar derivative by its failure to give the Dische diphenylamine test.

* Part II, *J.*, 1950, 1990.

The sugar liberated by hydrolysis of (V; R = H) gave on reduction an optically active 3-deoxypentitol; this must therefore be 3-deoxy-D-arabitol, which justifies the configurations assigned to the compounds (III) and (V).

It was of interest to determine how much, if any, of the 2′-deoxy-2′-ethylthioxylofuranosyl compound (VI; R = SEt) was formed along with (V; R = SEt) as a product of the ring-opening of (III). The mother-liquors from which the diacetate of (V; R = SEt) had separated were desulphurised with Raney nickel, and the product, after removal of the acetyl groups, was assayed for derivatives of 2-deoxy-sugars by the colorimetric method of Sevag, Smolens, and Lackmann (*J. Biol. Chem.*, 1940, **134**, 523). The results indicated that only about 0·8% of the anhydro-compound (III) had been opened in the desired direction.

In the hexopyranose series, removal of the toluene-*p*-sulphonyl residues from 4 : 6-benzylidene 2 : 3-ditoluene-*p*-sulphonyl methyl-α-D-altroside gives an anhydromannoside (Robertson and Whitehead, *J.*, 1940, 319) which with sodium thiomethoxide is converted into a 3-deoxy-3-methylthioaltrose derivative (Bolliger and Prins, *Helv. Chem. Acta*, 1946, **29**, 1061); the formation and ring-opening of (III) are exactly similar to these reactions. On the other hand, 2 : 3-ditoluene-*p*-sulphonyl D-glucoside derivatives give rise to 2 : 3-anhydro-D-alloside derivatives (Robertson and Griffiths, *J.*, 1935, 1193) from which 2-deoxy-2-methylthio-D-glucose derivatives are accessible in very good yield (Jeanloz, Prins, and Reichstein, *Helv. Chim. Acta*, 1946, **29**, 371). If the parallelism between the hexopyranose and pentofuranose series remarked above were general, then 2′-deoxyribofuranosides (VIII) should be accessible from the xylofuranoside (II) through the anhydroribofuranoside (IV).

The 2′ : 3′-ditoluene-*p*-sulphonyl 5′-trityl derivative of (II) did indeed give, when treated with sodium methoxide, an anhydro-compound, identified as having the ribose configuration (IV; R = CPh_3) by its reactions. This anhydro-compound did not, however, undergo ring-opening in the same direction as a 2 : 3-anhydroallopyranoside. With sodium thioethoxide the main product of reaction was 3′-deoxy-3′-ethylthio-7-β-D-xylofuranosyltheophylline 5′-trityl ether (VII; R = SEt, R′ = CPh_3), isolated crystalline in 87% yield. Successive detritylation, acetylation, desulphurisation, and deacetylation converted it into 3′-deoxy-7-β-D-xylofuranosyltheophylline (VII; R = R′ = H), which gave no colour with the Dische reagent. The sugar obtained by hydrolysis of (VII; R = R′ = H) gave optically inactive 3-deoxyxylitol when reduced, which justifies the configurations assigned to compounds (IV) and (VII). As before, the mother-liquor from which the 3′-deoxy-3′-ethylthio-compound had crystallised was treated separately so as to convert any ethylthio-compounds present into deoxy-compounds, and the product examined by the method of Sevag *et al.* The amount of 2-deoxy-sugar derivative found indicated that about 0·75% of the anhydro-compound (IV) had undergone ring-opening to give the desired 2′-deoxy-2′-ethylthio-derivative (VIII; R = SEt, R′ = CPh_3).

Preliminary experiments in which the anhydro-compound (III) was treated with lithium aluminium hydride indicate that the use of this reagent gives results no more favourable than those described above. It is clear that anhydrofuranosides similar to (III) and (IV) will be of little value for the synthesis of the natural deoxyribonucleosides until some means of reversing the orientation of their ring-opening is found.

In Part I (Davoll and Lythgoe, *J.*, 1949, 2526) the preparation of 2′-chloro D-arabopyranosyltheophylline-II and the reductive dehalogenation of 2′-chloro D-ribopyranosyltheophylline-I were described, but owing to an oversight experimental details were omitted. These are now given on p. 2233.

Experimental.

5′-Trityl 7-α-D-Arabofuranosyltheophylline.—Dry 7-α-D-arabofuranosyltheophylline (12·35 g.) and triphenylmethyl chloride (12·1 g.) were dissolved in pyridine (50 c.c.), the solution kept at 50° for 3 days and then poured into stirred ice-water (400 c.c.), and the product extracted with chloroform. The extract was washed with aqueous sodium hydrogen sulphate and with water, dried, and evaporated under reduced pressure, and the residue crystallised from a mixture of alcohol (160 c.c.) and acetone (70 c.c.). The *trityl* derivative so obtained had m. p. 215—217°, $[\alpha]_D^{18}$ −12·6° (*c*, 1·1 in chloroform) (Found: N, 9·9. $C_{31}H_{30}O_6N_4$ requires N, 10·1%).

2′ : 3′-Ditoluene-p-sulphonyl 5′-Trityl 7-α-D-Arabofuranosyltheophylline.—A solution of the above trityl compound (16 g.) and toluene-*p*-sulphonyl chloride (16·8 g.) in pyridine (75 c.c.) was kept at 50° for 4 days, then cooled to 0° and treated with water (2 c.c.). After being kept for 1 hour it was poured into ice-water (400 c.c.) and extracted with chloroform, and the chloroform extract washed, dried, and evaporated. Addition of hot alcohol (250 c.c.) to a solution of the residue in benzene (50 c.c.) caused crystallisation of the *ditoluene-p-sulphonyl trityl ether* (22·2 g.), m. p. 218°, $[\alpha]_D^{16}$ +26° (*c*, 1·3 in chloroform) (Found: C, 62·6; H, 4·9; N, 6·5. $C_{45}H_{42}O_{10}N_4S_2$ requires C, 62·6; H, 4·9; N, 6·5%).

2′ : 3′-Anhydro-7-α-D-lyxofuranosyltheophylline.—The above compound (22·2 g.), dissolved in chloroform (120 c.c.), was treated at 0° with a solution of sodium methoxide (3 g. of sodium) in methanol

(75 c.c.), and the mixture kept at 0° for 3 days and then at room temperature for a further 3 days. It was then filtered, washed with sodium hydrogen sulphate solution, dried, and evaporated under reduced pressure. The syrupy residue could not be made to crystallise, so it was hydrolysed by heating it with 80% acetic acid at 100° for 20 minutes. The filtered solution was poured into water (500 c.c.) and filtered, and the filtrate evaporated under reduced pressure; crystallisation of the residue from alcohol gave the *anhydro*-compound (2·8 g.), m. p. 204—205°, $[\alpha]_D^{18}$ −53·5° (*c*, 1·3 in pyridine) (Found: C, 49·2; H, 4·4; N, 19·2. $C_{12}H_{14}O_5N_4$ requires C, 49·1; H, 4·7; N, 19·1%).

*3′-Deoxy-3′-ethylthio-7-α-*D*-arabofuranosyltheophylline 2′ : 5′-Diacetate.*—A solution of the above anhydro-compound (1·5 g.) in methanol (150 c.c.) containing ethanethiol (2·1 c.c.) and sodium methoxide (0·6 g. of sodium) was heated under reflux for 2·5 hours, then cooled and neutralised with carbon dioxide. The residue left by removal of solvent under reduced pressure was extracted with hot alcohol, the filtered extract evaporated, and the residue kept overnight at 0° with pyridine (15 c.c.) and acetic anhydride (5 c.c.). The product, isolated in the usual manner, was crystallised from alcohol, giving the *diacetyl* derivative (2·02 g.), m. p. 158—160°, $[\alpha]_D^{18}$ +38·8° (*c*, 2·3 in chloroform) (Found: C, 49·5; H, 5·5 N, 13·1. $C_{18}H_{24}O_7N_4S$ requires C, 49·2; H, 5·5; N, 12·8%). The mother-liquor from which the above compound separated was evaporated and gave a resin (0·1 g.) which was desulphurised and deacetylated in the manner described below. The product, subjected to a quantitative determination by the method described by Sevag *et al.* (*loc. cit.*), was found to contain 12·2 mg. of a 2-deoxypentose, equivalent to a yield of 0·8% from the parent anhydro-compound.

*3′-Deoxy-7-α-*D*-arabofuranosyltheophylline.*—The crystalline diacetate described above (1·5 g.) was heated under reflux in alcohol (60 c.c.) with Raney nickel (8 g.) containing adsorbed hydrogen for 3·5 hours, the suspension filtered hot, and the nickel washed well with hot alcohol. Evaporation of filtrate and washings gave a resin which was kept overnight at 0° with 0·17N-methanolic barium methoxide (30 c.c.). After dilution with water (30 c.c.) most of the barium was removed as the carbonate by passage of carbon dioxide and the last traces were removed from the filtered solution with N-sulphuric acid. The solution was filtered again and evaporated under reduced pressure; crystallisation of the residue from alcohol then gave *3′-deoxy-7-α-*D*-arabofuranosyltheophylline*, (0·37 g.), m. p. 206—207°, $[\alpha]_D^{18}$ −1·7° (*c*, 0·6 in water) (Found: C, 48·7; H, 5·4; N, 18·8. $C_{12}H_{16}O_5N_4$ requires C, 48·7; H, 5·4; N, 18·9%). It gave no colour with the Dische reagent. A sample was hydrolysed at 100° with 0·5N-sulphuric acid, and the reaction followed polarimetrically. It was complete after 75 minutes, and a rotation of $[\alpha]_D^{18}$ −7·8° was found for the liberated 3-deoxyarabinose.

*3-Deoxy-*D*-arabitol.*—A solution of the 3′-deoxy-D-arabofuranoside (0·25 g.) in 0·5N-sulphuric acid (4 c.c.) was kept at 100° for 75 minutes and then at 0° overnight. The theophylline was filtered off, sulphuric acid removed by addition of barium hydroxide, and the filtered solution hydrogenated at 100°/100 atm. during 10 hours in the presence of Raney nickel (1 g.). After the catalyst had been removed, the solution was evaporated, and the residue crystallised from ether–alcohol, giving *3-deoxy-*D*-arabitol*, m. p. 102°, $[\alpha]_D^{18}$ +31° (*c*, 0·4 in water) (Found: C, 44·2; H, 8·6. $C_5H_{12}O_4$ requires C, 44·1; H, 8·8%). This compound formed a second crystalline modification, m. p. 73—75°; either form could be obtained at will by seeding a solution with the appropriate crystal.

*2′ : 3′-Ditoluene-*p*-sulphonyl 5′-Trityl 7-β-*D*-Xylofuranosyltheophylline.*—A solution of 7-β-D-xylofuranosyltheophylline (2·85 g.) and triphenylmethyl chloride (3·0 g.) in pyridine (15 c.c.) was kept at 50° for 3 days and then poured into ice-water (200 c.c.). The syrup was extracted with chloroform, the extract washed with sodium hydrogen sulphate solution and with water, and dried, and the solvent removed under reduced pressure. As the residue could not be caused to crystallise, it was dissolved in pyridine (30 c.c.), toluene-*p*-sulphonyl chloride (5·4 g.) added, and the solution kept at 50° for 4 days. It was then cooled to 0°, water (2 c.c.) added, and the whole poured into ice-water (200 c.c.). The syrup was extracted with chloroform, the extract washed, dried, and evaporated as usual, and the residue crystallised from benzene–alcohol, giving the *ditoluene-*p*-sulphonyl* derivative (5 g.), m. p. 195—197°, $[\alpha]_D^{18}$ +9° (*c*, 0·8 in chloroform) (Found: N, 6·7. $C_{45}H_{42}O_{10}N_4S_2$ requires N, 6·5%).

*5′-Trityl 2′ : 3′-Anhydro-7-β-*D*-ribofuranosyltheophylline.*—A solution of the above compound (5 g.) in chloroform (30 c.c.) was treated at 0° with methanolic sodium methoxide (20 c.c.; 0·68 g. of sodium), and the solution kept at 0° for 3 days, then at room temperature for 3 days. After the separated solid had been filtered off, the solution was washed, dried, and evaporated as usual; crystallisation of the residue from benzene–alcohol then gave the *anhydro*-compound (3·3 g.), m. p. 202—203°, $[\alpha]_D^{17}$ +23·6° (*c*, 1·6 in chloroform) (Found: C, 72·2; H, 5·8; N, 9·2. $C_{31}H_{28}O_5N_4,C_6H_6$ requires C, 72·4; H, 5·6; N, 9·1%).

*5′-Trityl 3′-Deoxy-3′-ethylthio-7-β-*D*-xylofuranosyltheophylline.*—The above anhydro-compound (3 g.) was heated under reflux with methanol in which sodium (0·65 g.) and ethanethiol (2·3 c.c.) had been dissolved. After 2·5 hours acetic acid (5 c.c.) was added to the cooled solution, which was then evaporated under reduced pressure. Crystallisation of the residue from methanol (180 c.c.) gave *5′-trityl 3′-deoxy-3′-ethylthio-7-β-*D*-xylofuranosyltheophylline* (2·53 g.), m. p. 186—188°, $[\alpha]_D^{17}$ +2·8° (*c*, 1·0 in chloroform) (Found: C, 66·0; H, 5·4; N, 9·4. $C_{33}H_{34}O_5N_4S$ requires C, 66·1; H, 5·7; N, 9·4%).

The mother-liquor from which this compound separated was hydrolysed and desulphurised as described below for the crystalline material, and the product, which gave a positive Dische reaction, was assayed for 2-deoxy-sugar derivatives by the method of Sevag *et al.* (*loc. cit.*). The results indicated the presence of 11 mg. of 2′-deoxyribofuranosyltheophylline, which corresponds to a yield of 0·75% on the parent anhydro-compound.

*3′-Deoxy-7-β-*D*-ribofuranosyltheophylline.*—The above crystalline ethylthio-compound (2 g.) was heated for 20 minutes at 100° with 80% acetic acid (40 c.c.), and the solution cooled, and poured into water (300 c.c.). Triphenylcarbinol was filtered off, the filtrate evaporated to dryness, and the residue dried by repeated evaporation with alcohol. It was then acetylated in the usual manner with acetic

anhydride (3 c.c.) and pyridine (10 c.c.), and the product, isolated as usual, was boiled under reflux in methanol (60 c.c.) with Raney nickel (10 g.) containing adsorbed hydrogen. After 3·5 hours the nickel was removed, and the solution evaporated to give a syrup which was deacetylated by treatment overnight at 0° with 0·167N-methanolic barium methoxide (30 c.c.). Crystallisation of the product from methanol gave the 3′-*deoxyribofuranoside* (0·6 g.), m. p. 195—196°, $[\alpha]_D^{17}$ +37·8° (*c*, 0·9 in water) (Found: C, 48·4; H, 5·2; N, 18·9. $C_{12}H_{16}O_5N_4$ requires C, 48·7; H, 5·4; N, 18·9%). This material gave no colour with the Dische diphenylamine reagent. It was hydrolysed with 0·5N-sulphuric acid at 100°, and the reaction followed polarimetrically. After 75 minutes the rotation of the solution was constant, and corresponded to a value $[\alpha]_D^{18}$ −2° for the liberated 3-deoxypentose.

3-*Deoxyxylitol.*—A hydrolysate prepared as just described from the 3′-deoxyribofuranoside (0·4 g.) was freed from theophylline by refrigeration and filtration, and from sulphuric acid by treatment with barium hydroxide, the filtered solution was evaporated, and the residue dissolved in methanol (50 c.c.) and hydrogenated for 10 hours at 100°/100 atm. in the presence of Raney nickel catalyst (1 g.). The nickel was removed, the solution evaporated, and the residue crystallised from ether–alcohol, giving 3-deoxyxylitol, m. p. 66—67°, $[\alpha]_D^{18}$ ±0° (cf. Kent *et al.*, *loc. cit.*) (Found: C, 43·9; H, 9·0. Calc. for $C_5H_{12}O_4$: C, 44·1; H, 8·8%).

2′-*Chloro* D-*Arabopyranosyltheophylline*-II.—The corresponding 3′ : 4′-diacetate (0·36 g.) (Davoll and Lythgoe, *loc. cit.*) was kept at 0° for 3 days with methanolic ammonia (50 c.c., saturated at 0°), solvents removed under reduced pressure, and the residue crystallised from water, giving the 2′-*chloro* D-*arabinoside* (0·2 g.) as needles which sintered at 140°, m. p. 200°, $[\alpha]_D^{14}$ +68° (*c*, 0·69 in water) (Found: C, 43·4; H, 4·5; 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-*Ribopyranosyltheophylline*-I.—The 2′-chloro D-riboside (0·46 g.), dissolved in 0·04N-sodium hydroxide (52 c.c.), was hydrogenated at room temperature and pressure in the presence of palladised barium sulphate (5%; 1 g.). The calculated volume of hydrogen was absorbed in 5 hours, and the filtered solution was neutralised with hydrochloric acid and evaporated under reduced pressure. The residue was treated with pyridine and acetic anhydride, and the product isolated in the usual manner. Crystallisation from alcohol gave 3′ : 4′-diacetyl 2′-deoxy-D-ribopyranosyltheophylline-I (0·3 g.), identical in m. p. with material prepared as previously described.

We thank Professor A. R. Todd, F.R.S., for his interest in this work, and the Department of Scientific and Industrial Research for a Senior Assistant's Grant (to J. D.).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, April 30th*, 1951.]