161. *The Structure of Theophylline* l-*Arabinoside.*

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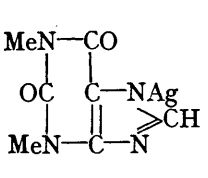
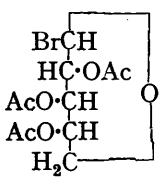
INVESTIGATIONS in progress in this laboratory on nucleic acids and naturally occurring nucleosides necessitated the synthesis of a purine pentoside. Theophylline arabinoside was selected on account of the stability of its purine residue. It was synthesised by the general method used for the synthesis of nucleosides, following the method of Helferich and Kühlewein (*Ber.*, 1920, **53**, 17).

The nucleoside was methylated with silver oxide and methyl iodide to give *trimethyl theophylline* l-*arabinoside*, which was isolated without difficulty in a crystalline state. The fully methylated arabinoside (III) was oxidised with nitric acid. The purine residue was isolated as *mononitrotheophylline*, $(C_7H_7O_2N_4{\cdot}NO_2)_2,H_2O$. No previous reference has been found in the literature to nitrotheophylline, although a nitrotheobromine has been prepared by Brunner and Leins (*Ber.*, 1897, **30**, 2584) as a bright yellow, microcrystalline powder, m. p. 270°. The new compound is probably 8-mononitrotheophylline, m. p. 275°. The

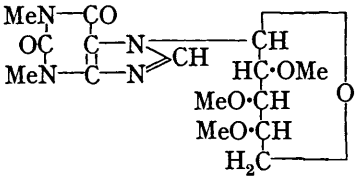
sugar residue was isolated as *d*-arabotrimethoxyglutaric acid (IV) and converted into the dimethyl ester for purposes of purification, and finally into the crystalline *d*-arabotrimethoxyglutardiamide (Hirst and Avery, J., 1929, 2466). Thus the presence of a pyranose sugar residue is established. This result obviously implies that the triacetyl arabinosidyl bromide (II) used in the initial synthesis is also a pyranoid compound. There remains to



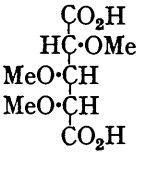
(I.)



(II.)



(III.)



(IV.)

be considered the position of attachment of the sugar residue to the theophylline molecule. In silver theophylline (I) the silver is attached to position 7, since Kossel (*Z. physiol. Chem.*, 1889, **13**, 304) has shown that silver theophylline reacts with methyl iodide to give caffeine, and caffeine is shown by synthesis to be 2 : 6-dioxy-1 : 3 : 7-trimethylpurine (Fischer, *Ber.*, 1897, **30**, 559). In the same way, it may be argued that the arabinose residue is attached to position 7, since triacetyl arabinosidyl bromide reacts with silver theophylline with elimination of silver bromide, giving triacetyl theophylline 7-arabinoside. Further, since acetyl glycosidyl bromides yield β-condensation products under the conditions employed, theophylline arabinoside may be described as 2 : 6-dioxy-1 : 3-dimethylpurine-(7)-β-l-arabopyranoside.

Experimental.

Triacetyl arabinosidyl bromide was prepared according to the method of Meisenheimer and Jung (*Ber.*, 1927, **60**, 1463), m. p. 126°; silver theophylline, according to Kossel (*loc. cit.*) (Found : Ag, 37·4. Calc. for $C_7H_7O_2N_4Ag$: Ag, 37·6%); triacetyl theophylline arabinoside, according to Helferich and Kühlewein (*loc. cit.*) (m. p. 214—216°, and $[\alpha]_{5461}^{21°}$ + 42·1°, c = 0·605, in $CHCl_3$); and theophylline arabinoside, according to Helferich and Kühlewein (*loc. cit.*). The last workers quote m. p. 276—277°, but in this investigation 282—284° was recorded; $[\alpha]_{5461}^{17°}$ +39·9°, c = 0·74, in H_2O.

Methylation of Theophylline Arabinoside. Isolation of Trimethyl Theophylline l-*Arabinoside.*—Theophylline arabinoside (1·15 g.) was dissolved in 20 c.c. of MeOH and 15 c.c. of MeI and methylated in the usual way with Ag_2O. Three methylations with fresh Ag_2O and MeI were necessary to bring the methoxyl content to the theoretical value. Extraction of the AgI residues was made in each case with MeOH. The crude crystals obtained from the third methylation were recrystallised from Et_2O and long, colourless, prismatic needles were obtained (1 g.), m. p. 125°, $[\alpha]_{5461}^{19°}$ + 61·97°, c = 0·355, in H_2O (Found: OMe, 26·2; N, 15·5. $C_{15}H_{22}O_6N_4$ requires OMe, 26·3; N, 15·8%). *Trimethyl theophylline arabinoside* is easily sol. in EtOH, MeOH and MeI, less sol. in H_2O and cold Et_2O. It is non-reducing and gives a positive reaction with Bial's reagent for pentose.

Simultaneous Hydrolysis and Oxidation of Trimethyl Theophylline Arabinoside. Isolation of Methyl d-*Arabotrimethoxyglutarate.*—The arabinoside (0·8 g.) was heated for 9½ hr. with 30 c.c. of HNO_3 (*d* 1·2) at 80°. Slight evolution of gas was observed during the oxidation, and the resulting solution had a bright greenish-yellow colour. After the addition of an equal vol. of H_2O, a small amount of a yellow cryst. ppt. was formed on cooling; this was filtered off and examined (*vide infra*). HNO_3 was removed from the filtrate by continuous distillation with H_2O under diminished press. at 40° according to the method of Hirst and Purves (J., 1923, **123**, 1356). After about 2 l. of H_2O had distilled, the aq. solution was concentrated in vac. at 40° to a pale yellow syrup strongly acid in reaction. This was taken up in MeOH, and the solution again concentrated under reduced press. to remove the last traces of H_2O. The resulting pale yellow viscous syrup was refluxed for 6 hr. with 30 c.c. of MeOH containing 3% HCl. The solution was then made neutral with Ag_2CO_3 and dehydrated by standing overnight over anhydrous Na_2SO_4. After filtration and further extraction of the residues with MeOH, the solvent was removed at 40° under reduced press. The resulting syrup, however, still contained silver salts and these were precipitated by addition of Et_2O and separated by filtration. Finally the Et_2O was evaporated, and the syrup concentrated and dried in vac. The final syrup (0·4 g.)

was then distilled in a high vac. and a water-clear mobile product distilled at a bath temperature of 131°/4 mm. The main fraction consisted of pure methyl *d*-arabotrimethoxyglutarate and had constants in agreement with those given by Hirst and Avery (*loc. cit.*), $n_D^{15°}$ 1·4398, $n_D^{21°}$ 1·4374; $[\alpha]_{5461}^{18°}$ + 47·2° (c = 0·74°) in MeOH. $[\alpha]_D$ + 40° (calc. from $[\alpha]_{5461}$) (Hirst and Avery quote $n_D^{17·5°}$ 1·4363, $[\alpha]_D$ = + 40° in MeOH) (Found: OMe, 58·1. Calc. for $C_{10}H_{18}O_7$: OMe, 62·0%).

Isolation and Identification of d-*Arabotrimethoxyglutardiamide.*—The ester (0·25 g.) was dissolved in 5 c.c. of MeOH, and the solution saturated with NH_3 at 0°. The solution turned light brown and very small prismatic needles were deposited over a period of 3 weeks and a further quantity was obtained on evaporation of the solution. The crystals were recrystallised from MeOH and identified as *d*-arabotrimethoxyglutardiamide (cf. Hirst and Avery, *loc. cit.*), m. p. 232°; $[\alpha]_{5461}^{20°}$ + 60°, c = 0·45, in H_2O; $[\alpha]_D$ + 50·8° (calc.) (Hirst and Avery quote m. p. 232—233° and $[\alpha]_D$ + 50° in H_2O) (Found: N, 12·9; OMe, 42·3. Calc. for $C_8H_{16}O_5N_2$: N, 12·7; OMe, 42·3%).

Isolation of the Purine Residue: Mononitrotheophylline.—The yellow ppt. which separated immediately after completion of the oxidation was twice recrystallised from hot H_2O and obtained as very long, fine, dark yellow needles, m. p. 275° to a dark red liquid. It gave a positive murexide test and analysis showed it to be a *mononitrotheophylline* with half a mol. of water of crystn. [Found: C, 36·3; H, 3·4; N, 29·9. $(C_7H_7O_2N_4{\cdot}NO_2)_2{,}H_2O$ requires C, 35·9; H, 3·4; N, 29·9%].

The cost of this work was in part defrayed by a grant from the Medical Research Council. One of us (R. T. W.) is indebted to the Council for a maintenance grant.

PHYSIOLOGY INSTITUTE, CARDIFF. [*Received, May 11th,* 1933.]