erties of the natural and the synthetic nucleoside were also similar[21]:

| | $[\alpha]_{5890}$ Å. | $[\alpha]_{5460}$ Å. |
|---|---|---|
| Spongothymidine | +94°[22] | +111° |
| 1-β-D-Arabinofuranosylthymine | +93° | +110° |

(21) As in Part I of this series, optical rotations were determined with a polarimetric unit model D attachment to a Beckman model DU spectrophotometer. Concentrations were 0.5 g./100 ml. of aqueous solution, temperature 24°.

(22) Bergmann and Feeney[14] give $[\alpha]_D$ +80° (in 8% sodium hydroxide) and $[\alpha]_D$ +92° (in pyridine).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF VIRGINIA]

# Analogs of Nucleotides. II. Phosphonate Esters of Ribose and Glucopyranosyl Purine Derivatives[1]

BY JEKISHAN R. PARIKH, MANFRED E. WOLFF AND ALFRED BURGER

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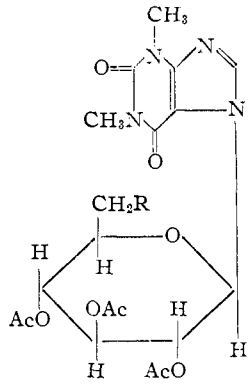
Syntheses of 1,2,3-tri-*O*-acetyl-D-ribofuranose-5-deoxy-5-(diethyl phosphonate), 7-[2,3,4-tri-*O*-acetyl-6-deoxy-6-(diethyl phosphonate)-β-D-glucopyranosyl]-theophylline, 6-benzamido-9-[2,3,4-tri-*O*-acetyl-6-deoxy-6-(diethyl phosphonate)-β-D-glucopyranosyl]-purine and related compounds are described.

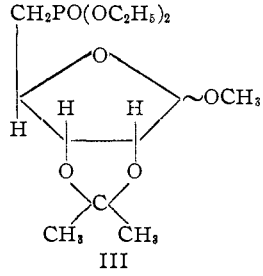
In continuation of studies of phosphonate analogs of nucleotides[2] and of carbohydrate phosphonates[3] as antimetabolites for biological screening against neoplasms and enzyme systems requiring the corresponding metabolites, the synthesis of phosphonate esters of substituted glycosidyl purines has been investigated.

7-(2,3,4-Tri-*O*-acetyl-6-deoxy-6-bromo-D-glucopyranosyl)-theophylline (I) had already been synthesized by Emil Fischer from silver theophylline and 2,3,4-tri-*O*-acetyl-6-deoxy-6-bromo-D-glucopyranosyl bromide.[4] It has now been found to undergo a Michaelis–Arbuzov reaction with triethyl phosphite, 7-[2,3,4-tri-*O*-acetyl-6-deoxy-6-(diethyl phosphonate)-β-D-glucopyranosyl]-theophylline (II) being formed in 40% yield. In attempts to introduce a 2,3-di-*O*-acetyl-5-deoxy-5-(diethyl phosphonate)-D-ribofuranosyl group into the 7-position of theophylline

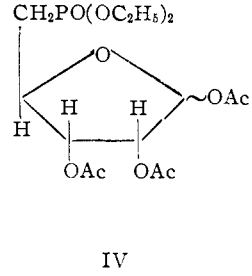


I, R = Br
II, R = $PO(OC_2H_5)_2$

methyl 2,3-isopropylidene-5-deoxy-5-iodo-D-ribofuranoside[5] was heated with triethyl phosphite, and the resulting methyl 2,3-isopropylidene-5-deoxy-5-(diethyl phosphonate)-D-ribofuranoside (III) was hydrolyzed and acetylated to 1,2,3-tri-*O*-acetyl-D-ribofuranose-5-deoxy-5-(diethyl phosphonate) (IV).

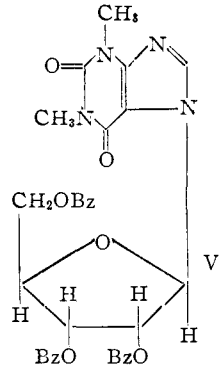


III



IV

The amorphous 1-chloro derivative obtained by treating IV with ethereal hydrogen chloride at 0° could not be condensed with either silver theophylline, or with 6-chloropurine mercuri chloride, although the reactivity of the 1-chlorine atom in a highly substituted ribose derivative was demonstrated by condensing 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride[6] with silver theophylline to yield 7-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-theophylline (V).



V

Following the model experiment leading to II,

(1) This work was supported by a grant-in-aid from the American Cancer Society upon recommendation of the Committee on Growth of the National Research Council.

(2) J. R. Parikh and A. Burger, THIS JOURNAL, **77**, 2386 (1955).

(3) B. S. Griffin and A. Burger, *ibid.*, **78**, 2336 (1956).

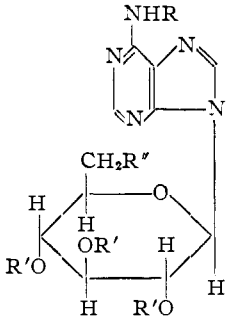
(4) E. Fischer, B. Helferich and P. Ostmann, *Ber.*, **53**, 873 (1920). The body of evidence in the literature suggests that the products from the condensation of purine metal adducts with 1-halogenoglucose and -ribose derivatives assume the β-configuration. It is likely, therefore, that I as well as other glycosidyl purines so designated in this article are β.

(5) P. A. Levene and E. T. Stiller, *J. Biol. Chem.*, **104**, 299 (1934).

(6) H. M. Kissman, C. Pidaks and B. R. Baker, THIS JOURNAL, **77**, 18 (1955).

the mercuri chloride salt of 6-benzamidopurine[7] was condensed with 2,3,4-tri-*O*-acetyl-6-deoxy-6-bromo-α-D-glucopyranosyl bromide in xylene medium, and 24% of 6-benzamido-9-(2,3,4-tri-*O*-acetyl-6-deoxy-6-bromo-β-D-glucopyranosyl)-purine (VI) was obtained as the main reaction product. The assignment of position 9 to the glucosidic moiety in the adenine system is based on observations about glycosidation of the chloromercuri salt of 6-benzamidopurine[7,8]; in addition, 6-benzamidopurine exhibits characteristic absorption bands at 287 and 230 mμ, and VI at 281 and 235 mμ, respectively, while substitution in the 7-position of the purine system is known to cause a change in this pattern.

Two other compounds were also elaborated in appreciable quantities from the 6-bromoglucosidation of 6-benzamidopurine. One of them was recognized as 2,3,4-tri-*O*-acetyl-6-deoxy-6-bromo-β-D-glucopyranosyl chloride presumably formed by exchange of the 1-bromine atom by chlorine from the mercuri chloride salt, and probably accompanied by inversion at C-1.[9] Although its physical appearance, solubility and melting point were extremely similar to those of the isomeric 2,3,4-tri-*O*-acetyl-6-deoxy-6-chloro-α-D-glucopyranosyl bromide[10] the two isomers differ in their optical rotation. The structure of the 1-chloro-6-bromo derivative was confirmed by conversion to 1,2,3,4-tetra-*O*-acetyl-6-deoxy-6-bromo-β-D-glucopyranose.[4]

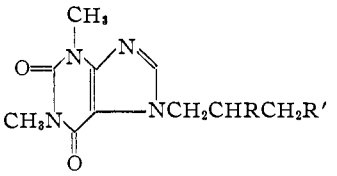


VI, R = $C_6H_5CO$, R′ = Ac, R″ = Br
VII, R = H, R′ = Ac, R″ = Br
VIII, R = R′ = H, R″ = Br
IX, R = $C_6H_5CO$, R′ = Ac, R″ = $PO(OC_2H_5)_2$

The benzamido group of VI was unusually labile. When the compound was heated with ethanolic picric acid solution, 6-amino-9-(2,3,4-tri-*O*-acetyl-6-deoxy-6-bromo-β-D-glucopyranosyl)-purine (VII) picrate was formed. Treatment of this salt with Dowex No. 1 anion-exchange resin[7] followed by alkalinization removed both the picrate ion and the acetyl groups and led to crystalline 6-amino-9-(6-deoxy-6-bromo-β-D-glucopyranosyl)-purine (VIII).

Heating of VI with triethyl phosphite furnished 6-benzamido-9-[2,3,4-tri-*O*-acetyl-6-deoxy-6-(diethyl phosphonate)-β-D-glucopyranosyl]-purine (IX). Experiments to hydrolyze its amide and ester groups with dilute ammonium hydroxide or methanolic sodium methoxide did not give the expected product. When VI was heated with ethyl diphenyl phosphite,[3,11] a material which contained neither phosphorus nor halogen was obtained.

Another phase of this problem concerned the preparation of starting materials for the synthesis of purinylalkanolphosphonate esters. In one series of experiments, 1-(7-theophyllinyl)-2,3-propanediol[12] was tosylated selectively to give 1-(7-theophyllinyl)-2-hydroxypropyl-3-(*p*-toluenesulfonate) (X). The 3-iodide derivative XI prepared from X failed to enter a Michaelis–Arbuzov reaction which confirms the findings of Preis, *et al.*,[13] who could not prepare alkyl β-hydroxyphosphonates by analogous routes. Protection of the alcoholic hydroxyl group in XI did not alter this picture. Attempts to secure 1-(7-theophyllinyl)-2-acetoxypropanol-3 by tritylating the diol, acetylating the resulting 1-(7-theophyllinyl)-2-hydroxy-3-propyl triphenylmethyl ether (XII), and hydrogenolyzing off the trityl group failed because the protecting acetyl group of XIII was lost under the conditions required for the removal of the trityl group.



X, R = OH, R′ = $OSO_2C_6H_4CH_3$
XI, R = OH, R′ = I
XII, R = OH, R′ = $OC(C_6H_5)_3$
XIII, R = OAc, R′ = $OC(C_6H_5)_3$

Condensation of adenine with 1-chloro-2,3-propanediol in alkaline solution furnished an amorphous product which was identified as 1-(6-amino-*x*-purinyl)-2,3-propanediol by analysis of its dipicrate. Since the compound did not yield a satisfactory product on tosylation it was not investigated further.

## Experimental[14]

**7-[2,3,4-Tri-*O*-acetyl-6-deoxy-6-(diethyl phosphonate)-β-D-glucopyranosyl]-theophylline** (II).—A mixture of 5.31 g. (0.01 mole) of 7-(2,3,4-tri-*O*-acetyl-6-deoxy-6-bromo-D-glucopyranosyl)-theophylline (I)[4] and 6.64 g. (0.04 mole) of triethyl phosphite was heated at 165° for 4.5 hours, the yellow product was freed of excess triethyl phosphite under reduced pressure at 95°, and the oily residue washed with petroleum ether. It was triturated with 30 ml. of ether, and 2.35 g. (40%) of long colorless needles was filtered. After recrystallization from benzene–isoöctane, they exhibited m.p. 167–168°, $[\alpha]^{27}D$ −10.40° (chloroform, *c* 1.942).

*Anal.* Calcd. for $C_{23}H_{33}N_4O_{12}P$: C, 46.93; H, 5.65. Found: C, 47.30; H, 5.66.

**7-(2,3,4-Tri-*O*-acetyl-6-deoxy-6-iodo-β-D-glucopyranosyl)-theophylline.**—A solution of 1.35 g. (2.5 mmoles) of I, 0.75 g. (5 mmoles) of sodium iodide and 0.2 g. of cuprous iodide in 30 ml. of anhydrous acetone was refluxed for 24 hours, and the solvent was removed under reduced pressure. The resinous residue was dissolved in 25 ml. of chloroform, filtered and washed with 5-ml. portions of water, 5% sodium thiosulfate solution and water. The solution was dried over sodium sulfate and the solvent evaporated under reduced

(7) J. Davoll and B. A. Lowy, THIS JOURNAL, **73**, 1650 (1951).

(8) B. R. Baker R. E. Schaub and H. M. Kissman, *ibid.*, **77**, 5911 (1955).

(9) H. H. Schlubach, *Ber.*, **59**, 840 (1926), observed that α-bromoacetoglucose reacts with silver chloride to give β-chloroacetoglucose.

(10) B. Helferich and H. Bredereck, *ibid.*, **60**, 2000 (1927).

(11) A. E. Arbuzov and L. V. Nesterov, *Doklady Akad. Nauk. S.S.S.R.*, **92**, 57 (1953).

(12) P. V. Maney, J. W. Jones, E. G. Gross and H. M. Korns, *J. Am. Pharm. Assoc.*, **35**, 266 (1946).

(13) S. Preis, T. C. Myers and E. V. Jensen, THIS JOURNAL, **77**, 6225 (1955).

(14) All melting points are corrected. Microanalyses by the Misses Mai Lay and Barbara J. Williamson.

pressure. The colorless crude residue weighed 1.5 g. and crystallized from 20 ml. of absolute ethanol, m.p. 197° after softening at 125° and partially melting at 135–137°.

*Anal.* Calcd. for $C_{19}H_{23}IN_4O_9$: C, 39.45; H, 4.00. Found: C, 39.50; H, 4.21.

**6-Benzamido-9-(2,3,4-tri-*O*-acetyl-6-deoxy-6-bromo-β-D-glucopyranosyl)-purine (VI).**—A mixture of 15.0 g. (31.6 mmoles) of chloromercuri 6-benzamidopurine,[7,15] 18.0 g. (41.7 mmoles) of I, 12 g. of Celite and 500 ml. of dry xylene was stirred and refluxed for 1 hour, filtered and the solid washed with hot xylene. The filtrate on cooling deposited 14.5 g. of colorless crystals, m.p. 100–135°. Three recrystallizations from 40 ml. of absolute ethanol yielded 4.45 g. (24%) of material, m.p. 213–214°; $[\alpha]^{27}D$ −23.64° (chloroform, *c* 1.903); $\lambda_{max}$ 0.01 *N* HCl 281 mμ (ε 22,699.6), $\lambda_{min}$ 0.01 *N* HCl 235 mμ (ε 10,303.6).

*Anal.* Calcd. for $C_{24}H_{24}BrN_5O_8 \cdot H_2O$: C, 47.37; H, 4.30. Found: C, 47.74; H, 4.34.

Water of hydration was removed by drying at 139° (1 mm.) for 24 hours. The anhydrous material melted at 214–215°.

*Anal.* Calcd. for $C_{24}H_{24}BrN_5O_8$: C, 48.82; H, 4.09; N, 11.86. Found: C, 48.85; H, 4.18; N, 12.08.

The yellow **picrate** crystallized from ice-cold ethanol, m.p. 185–186° dec.

*Anal.* Calcd. for $C_{30}H_{27}BrN_8O_{15}$: C, 43.96; H, 3.32. Found: C, 43.85; H, 3.40.

**2,3,4-Tri-*O*-acetyl-6-deoxy-6-bromo-β-D-glucopyranosyl Chloride.**—The xylene solution (*vide supra*) from which VI had been filtered was concentrated to 30 ml. and diluted with petroleum ether. It deposited 1.1 g. of colorless needles which after recrystallization from absolute ethanol melted at 165.5–166.5°, $[\alpha]^{28}D$ +170.1° (chloroform, *c* 1.19).

*Anal.* Calcd. for $C_{12}H_{16}BrClO_7$: C, 37.18; H, 4.16; halogen, 25.89. Found: C, 37.36; H, 4.20; halogen, 24.35.

Treatment of 0.3 g. of this substance with a mixture of 0.16 g. of silver acetate and 5 ml. of glacial acetic acid at 95° for 30 minutes, filtration from silver chloride, evaporation of the solvent and dilution with 30 ml. of water yielded 0.26 g. of colorless needles which after recrystallization from ethanol melted at 126–126.5°. A mixture melting point with an authentic sample[4] of 1,2,3,4-tetra-*O*-acetyl-6-deoxy-6-bromo-β-D-glucopyranose showed no depression.

The ethanolic mother liquors from the recrystallization of the 14.5 g. of crude VI described above gave on concentration and cooling 1.6 g. of buff-colored crystals which were recrystallized from absolute ethanol, m.p. 203–204°. The compound contained halogen, reacted rapidly with silver nitrate, and showed *p*H 5.

*Anal.* Found: C, 24.6; H, 3.1.

**6-Amino-9-(2,3,4-tri-*O*-acetyl-6-deoxy-6-bromo-β-D-glucopyranosyl)-purine (VII).**—When VI was treated with a hot ethanolic solution of picric acid, the picrate of VII crystallized out, m.p. 231–232° dec.

*Anal.* Calcd. for $C_{23}H_{23}BrN_8O_{14}$: C, 38.61; H, 3.24. Found: C, 38.65; H, 3.26.

**6-Amino-9-(6-deoxy-6-bromo-β-D-glucopyranosyl)-purine (VIII).**—Removal of picrate ion from the picrate of VII with Dowex No. 1 anion-exchange resin (in the chloride form) in 50% aqueous acetone followed by alkalinization with 10% ammonium hydroxide yielded colorless crystals which melted at 214–216° dec. after sintering at 200°.

*Anal.* Calcd. for $C_{11}H_{14}BrN_5O_4$: C, 36.67; H, 3.91. Found: C, 36.28; H, 4.10.

The yellow **picrate** crystallized from ethanol, m.p. 204–205° dec.

*Anal.* Calcd. for $C_{17}H_{17}BrN_8O_{11}$: C, 34.64; H, 2.90. Found: C, 34.27; H, 3.00.

**6-Benzamido-9-[2,3,4-tri-*O*-acetyl-6-deoxy-6-(diethyl phosphonate)-β-D-glucopyranosyl]-purine (IX).**—A mixture of 1.9 g. (3.2 mmoles) of VI and 2.65 g. (16 mmoles) of triethyl phosphite was heated at 160–165° for five hours and excess triethyl phosphite was distilled from the orange-red solution under vacuum. The oily residue was washed with petroleum ether, dissolved in 15 ml. of absolute ethanol, cleared with Norite and allowed to crystallize after addition of ether. The mother liquor was evaporated, and the residue crystallized from water. A total of 0.8 g. (45%) of material of m.p. 200–201° was obtained. In another run, the product was isolated in comparable yield by chromatography of the oily material over activated alumina.

*Anal.* Calcd. for $C_{28}H_{34}N_5O_{11}P \cdot H_2O$: C, 50.52; H, 5.45; N, 10.52; P, 4.65. Found: C, 50.05; H, 5.58; N, 10.28; P, 5.29.

A solution of 0.8 g. of IX in 15 ml. of 1:1 aqueous acetone was treated with ammonium hydroxide to *p*H 9 and allowed to stand at 6° for 16 hours. The solvents were evaporated *in vacuo* and the resinous residue dissolved in chloroform. The chloroform solution was washed with water, dried and evaporated. The residue crystallized from water as shiny plates, m.p. 112–113°.

*Anal.* Found: C, 50.47; H, 5.31; N, 9.85; P, 5.08.

**Action of Ethyl Diphenyl Phosphite on VI.**—When VI was heated with a fourfold excess of ethyl diphenyl phosphite[3,11] at 165°, the reaction mixture turned dark within 2.5 hours and decomposed on further heating. Since warming at 100° did not furnish a homogeneous solution even after 190 hours, the reactants were heated at 155° for 3 hours, in another run. The resulting dark yellow solution was heated at 131° for another 48 hours, and now the clear brown mixture no longer contained bromine. It was taken up in isopropyl ether, and a residual insoluble gum was triturated with ether until it became an amorphous solid. This material was chromatographed over alumina in benzene–chloroform. The main oily fraction became amorphous on treatment with isopropyl ether and ether. It contained neither halogen nor phosphorus and decomposed at 70°.

*Anal.* Found: C, 52.07; H, 4.78.

**Methyl 2,3-Isopropylidene-5-deoxy-5-(diethyl phosphonate-D-ribofuranoside (III).**—A mixture of 41.1 g. (0.131 mole) of methyl 2,3-isopropylidene-5-deoxy-5-iodo-D-ribofuranoside[5] and 120 g. of triethyl phosphite was heated at 160–170° for ten hours and fractionated. After a forerun consisting essentially of diethyl ethylphosphonate, the product distilled as a pale yellow sirup, b.p. 128° (0.05 mm.), $n^{30}D$ 1.451; $[\alpha]^{30}D$ −48.6° (*c* 2.984, in acetone). The yield was 31%.

*Anal.* Calcd. for $C_{13}H_{25}O_7P$: C, 48.14; H, 7.77. Found: C, 47.42; H, 7.81.

When, instead of triethyl phosphite, ethyl diphenyl phosphite[3,11] was used and the reaction mixture was heated as above but for 120 hours, distillation furnished an oil, b.p. 159–160° (0.07 mm.), as the main product while the ribosidic material decomposed. The composition of the oily distillate corresponds to that of diphenyl ethylphosphonate.[11]

*Anal.* Calcd. for $C_{14}H_{15}O_3P$: C, 64.12; H, 5.78. Found: C, 63.88; H, 5.97.

**1,2,3-Tri-*O*-acetyl-D-ribofuranose-5-deoxy-5-(diethyl phosphonate) (IV).**—A solution of 5.0 g. (0.0154 mole) of methyl 2,3-isopropylidene-5-deoxy-5-(diethyl phosphonate)-D-ribofuranoside in 100 ml. of 0.05 *N* aqueous ethanolic (1:1) hydrochloric acid was refluxed for three hours, 3 ml. of pyridine was added, and the solvents were removed by co-distillation with benzene under reduced pressure. The residual oil strongly reduced Fehling solution and formed a sirupy diethyl mercaptal.[16] It was dissolved in 100 ml. of dry pyridine, cooled to 0°, and allowed to stand with 40 ml. of acetic anhydride for 24 hours. Excess acetic anhydride was decomposed carefully with water, the solution was diluted to 500 ml. and extracted repeatedly with chloroform. The chloroform extract was washed with 20% sulfuric acid, sodium carbonate solution and water, dried and distilled.

(15) 6-Benzamidopurine was prepared by a modification of the directions of A. Kossel, *Z. physiol. Chem.*, **12**, 241 (1888), by heating adenine with benzoic anhydride at 180° for 30 minutes. The yield was 83%, m.p. 242–244° dec.; $\lambda_{max}$ 0.01 *N* HCl 287 mμ (ε 12,429), $\lambda_{min}$ 0.01 *N* HCl 230 mμ (ε 5812).

(16) Additional evidence for the hydrolysis of the methyl ribofuranoside linkage of III may be gathered from the fact that G. W. Kenner, C. W. Taylor and A. R. Todd, *J. Chem. Soc.*, 1620 (1949), had hydrolyzed methyl 2,3-isopropylidene-5-benzyl-D-ribofuranoside under the same conditions. Again, a selective hydrolysis of the isopropylidene group in methyl 2,3-isopropylidene-5-deoxy-D-ribofuranoside could be achieved only in 70% methanolic dilute sulfuric acid [C. H. Shunk, J. B. Lavigne and K. Folkers, THIS JOURNAL, **77**, 2210 (1955)].

The product (3.8 g., 62%) was a pale yellow oil, b.p. 165–168° (0.08 mm.).

*Anal.* Calcd. for $C_{13}H_{25}O_{10}P$: C, 45.48; H, 6.36. Found: C, 44.49; H, 6.29.

Treatment of IV with ethereal hydrogen chloride at 0° for 48 hours and thorough removal of the volatile reagents yielded a colorless amorphous product which gave a strong test for halogen and readily precipitated ethanolic silver nitrate solution.

**7-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-theophylline (V).**—A solution of 0.02 mole of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride[6] in 35 ml. of anhydrous benzene was added to a stirred suspension of 6.98 g. (0.0242 mole) of silver theophylline in 50 ml. of dry xylene, the benzene was distilled off and the mixture stirred and refluxed for 3 hours. Silver chloride was filtered and the filtrate diluted with 500 ml. of low-boiling petroleum ether. The precipitated colorless soft needles (yield 25%) were recrystallized from isopropyl ether, m.p. 75° dec.; $[\alpha]^{22}D$ −22.1° (*c* 3.63, acetone).

*Anal.* Calcd. for $C_{33}H_{28}N_4O_9$: C, 63.45; H, 4.52. Found: C, 63.72; H, 4.35.

**1-(7-Theophyllinyl)-2-hydroxypropyl-3-*p*-toluenesulfonate (X).**—A solution of 85.0 g. (0.45 mole) of *p*-toluenesulfonyl chloride in 200 ml. of dry pyridine was added, over a period of 6 hours, to a stirred, ice-cold solution of 113.5 g. (0.45 mole) of 1-(7-theophyllinyl)-2,3-propanediol[12] in 300 ml. of dry pyridine and 250 ml. of dry ethylene dichloride. After stirring another 90 minutes at 0° and standing overnight, the mixture was treated carefully with 50 ml. of water, extracted with 200 ml. of water, and distilled under reduced pressure, moisture and some pyridine being removed by codistillation with toluene. The semi-solid residue was taken up in 300 ml. of ethanol, 100 ml. of water was added, and the resulting colorless crystals (83.5 g., 45%) were collected. Recrystallization from ethanol gave a sample, m.p. 134–135°.

*Anal.* Calcd. for $C_{17}H_{20}N_4O_6S$: C, 49.99; H, 4.93. Found: C, 49.95; H, 5.17.

**1-(7-Theophyllinyl)-3-iodo-2-propanol (XI).**—This compound was prepared from X by heating with sodium iodide in acetone solution at 100° for 2 hours, and working up the mixture. It crystallized from absolute ethanol, m.p. 165–166°. The yield was 73%.

*Anal.* Calcd. for $C_{10}H_{13}IN_4O_3$: C, 32.98; H, 3.60. Found: C, 33.13; H, 3.67.

**1-(7-Theophyllinyl)-2-acetoxypropyl-3-*p*-toluenesulfonate.**—Acetylation of XI with acetic anhydride in excess dry pyridine at 0°, standing at 30° for 24 hours and decomposition with water, yielded 75% of a colorless product which was recrystallized from ethanol, m.p. 173–175°.

*Anal.* Calcd. for $C_{19}H_{22}N_4O_7S$: C, 50.63; H, 4.92. Found: C, 50.32; H, 5.11.

**1-(7-Theophyllinyl)-2-acetoxy-3-iodopropane.**—This compound was prepared in 54% yield from 1-(7-theophyllinyl)-2-acetoxypropyl-3-*p*-toluenesulfonate as described for XI above. The colorless plates (from ethanol) melted at 177–179° dec.

*Anal.* Calcd. for $C_{12}H_{15}IN_4O_4$: C, 35.48; H, 3.72. Found: C, 35.30; H, 3.68.

**1-(7-Theophyllinyl)-2-hydroxy-3-propyl Triphenylmethyl Ether (XII).**—A solution of 2.09 g. (0.01 mole) of 1-(7-theophyllinyl)-2,3-propanediol[12] and 2.79 g. (0.01 mole) of triphenylchloromethane in 20 ml. of dry pyridine was refluxed for 30 minutes, cooled and diluted with water. The gummy precipitate was washed with water, dried azeotropically with benzene, and crystallized from ethanol–pentane. The shiny plates melted at 174–176°.

*Anal.* Calcd. for $C_{29}H_{28}N_4O_4$: C, 70.14; H, 5.68. Found: C, 70.30; H, 5.86.

Acetylation with acetic anhydride in hot pyridine solution for 30 minutes gave **1-(7-theophyllinyl)-2-acetoxy-3-propyl triphenylmethyl ether** (XIII) which crystallized from ethanol, m.p. 169–171°.

*Anal.* Calcd. for $C_{31}H_{30}N_4O_5$: C, 69.13; H, 5.97. Found: C, 69.19; H, 5.85.

**1-(6-Amino-x-purinyl)-2,3-propanediol Dipicrate.**—A solution of 5.40 g. (0.04 mole) of adenine in 200 ml. of 0.2 *N* sodium hydroxide was treated with 4.42 g. (0.04 mole) of 1-chloro-2,3-propanediol, and the mixture was refluxed for five hours. The solvent was removed *in vacuo*, the residue was taken up in boiling methanol and filtered from sodium chloride. An amorphous precipitate was obtained by adding ether to the filtrate. It was converted to the yellow dipicrate which was recrystallized from a large volume of ethanol and did not melt below 300°.

*Anal.* Calcd. for $C_{20}H_{17}N_{11}O_{16}$: C, 35.99; H, 2.57. Found: C, 35.96; H, 2.42.

**1,3-Bis-(7-theophyllinyl)-propanol-2.**—To a suspension of 14.35 g. (0.05 mole) of dry silver theophylline in 350 ml. of dry dimethylformamide was added 6.85 g. (0.05 mole) of epibromohydrin. The mixture was stirred and heated at 130° but stirring had to be interrupted when a thick yellow precipitate separated. After standing for one hour, stirring and heating were resumed and continued for 4 hours. The granular precipitate was filtered, the solvent removed under reduced pressure, and the tan solid residue washed with cold acetone and ethanol. It was dissolved in dilute acid, reprecipitated with ammonium hydroxide, and weighed 4.5 g. (42%). Recrystallization from water with the aid of Norite gave colorless needles, m.p. 273–274°.

*Anal.* Calcd. for $C_{17}H_{20}N_8O_5$: C, 49.03; H, 4.84. Found: C, 49.09; H, 5.04.

**(7-Theophyllinylmethyl)-oxirane.**—When the reaction between silver theophylline and epibromohydrin described above was conducted in boiling xylene for 24 hours and the solvent was evaporated, a small amount of a solid could be extracted from the residue with boiling ligroin. The colorless product from the ligroin extract was recrystallized from ligroin–ethanol, m.p. 160–162°.

*Anal.* Calcd. for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12. Found: C, 50.33; H, 5.00.

CHARLOTTESVILLE, VIRGINIA