Synthesis of 3′-Deoxynucleosides II

Synthesis of 9-(3-Deoxyaldofuranosyl) Adenines Derived from 3-Deoxy-D-glucose

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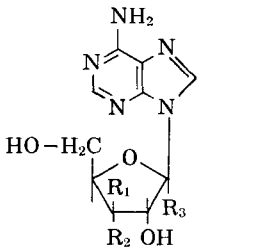
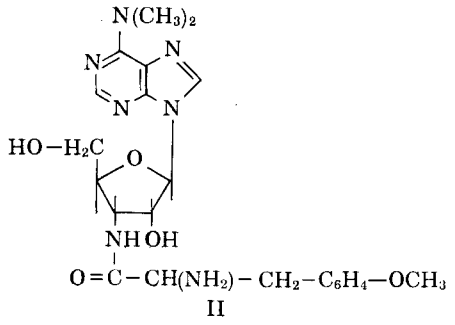
The diisopropylidene derivative of 3-deoxy-D-glucose was selectively hydrolyzed to 1,2-*O*-isopropylidene-3-deoxy-D-glucofuranose. In one series of reactions, this compound was converted *via* benzoylation, acetolysis, and halogenation to a suitably blocked halogeno sugar which, on condensation with chloromercuri-6-benzamidopurine followed by alkaline deblocking, yielded 9-(3-deoxy-β-D-glucofuranosyl)adenine. Alternatively, the acylated sugar could be condensed directly with chloromercuri-6-benzamidopurine in the presence of titanium tetrachloride to give, after deblocking, the same nucleoside in considerably higher yield. In a second series of reactions, 1,2-*O*-isopropylidene-3-deoxy-D-glucofuranose was converted through periodate oxidation and borohydride reduction to the corresponding derivative of 3-deoxy-D-ribose, convertible by the above sequence of reactions to 9-(3-deoxy-β-D-ribofuranosyl)adenine (cordycepin).

A NUMBER of nucleosidic substances with modified sugar moieties have antitumor and/or antibiotic properties. Among these are cordycepin (I) and pyromycin (II). It is of interest that of the approximately 3 doz. adenine nucleosides which have been tested for biological activity, most of the eight or nine which have shown significant activity are compounds in which the 3′-carbon does not have a hydroxyl group α. This is, of course, an imperfect generalization, since it is clear that other modifications of the sugar moiety of a nucleoside likewise lead to activity. Psicofuranine (III) and decoyinine (IV) are examples of other such modification, in which the natural analog, adenosine (V), is modified at the equivalent of 1′ and/or 4′ position. Nevertheless, the activity shown by such compounds as puromycin, cordycepin, and xylofuranosyladenine (VI) suggest a limited likelihood that modification at the 3′-position may also give rise to biological activity of possible therapeutic value. From this rationale, the authors have undertaken the synthesis of the two nucleosides reported here—9-(3-deoxy-β-D-glucofuranosyl)adenine (XIII) and 9-(3-deoxy-β-D-ribofuranosyl)adenine (I). Just as this work was completed, it was of obvious interest to learn that the latter compound (1) was, in fact, the known antibiotic, cordycepin.

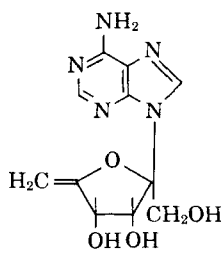
The required key starting material in the projected synthesis was 3-deoxy-D-glucose. Of the reported routes to this compound, that proceeding through reduction of a 2,3-anhydro allose derivative (2) was relatively lengthy and gave low over-all yield. Another route (3) through the dithiocarbonate derivative of diacetone glucose was similarly tedious and proceeded in low yields. The ready availability of 2-deoxy-D-ribose in recent years suggested the potential accessability of 3-deoxy-D-glucose *via* a cyanhydrin synthesis, and this route has been developed by Wood and Fletcher (4). For the purpose reported here, the authors have found it con-



I, $R_1 = R_2 = R_3 = H$
III, $R_1 = H, R_2 = OH, R_3 = CH_2OH$
V, $R_1 = R_3 = H, R_2 = OH$
VI, $R_1 = OH, R_2 = R_3 = H$



II



IV

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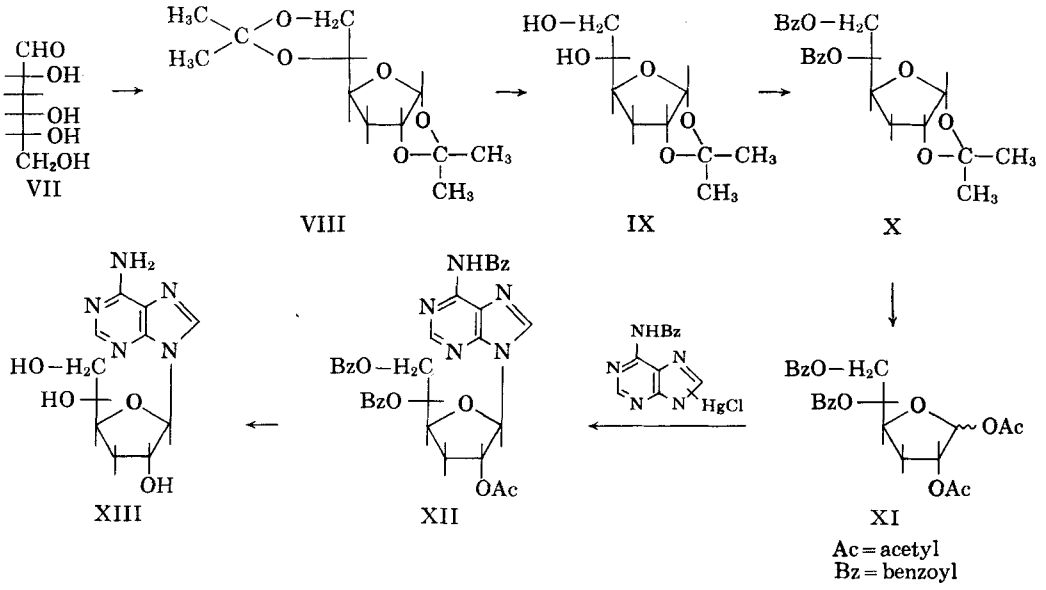
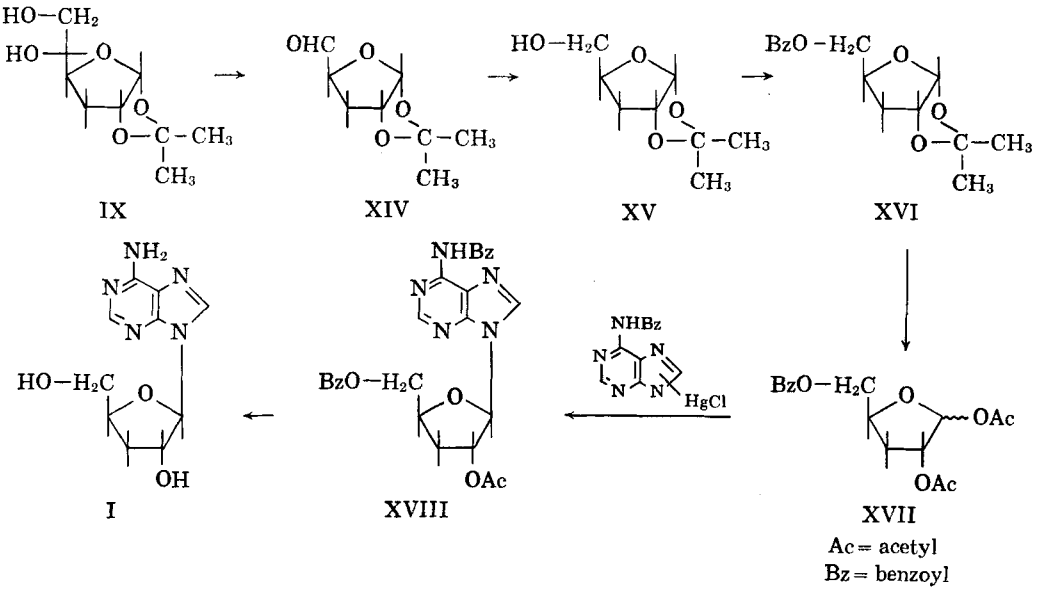


Scheme I

venient to employ a Sowden-Fischer method. Condensation of nitromethane with 2-deoxy-D-ribose, followed by a Nef reaction gives rise to a 64% yield of mixed 3-deoxy-D-glucose and 3-deoxy-D-mannose, readily separable by fractional crystallization. The development of this route is described elsewhere (5).

The routes to the two desired nucleosides I and XIII are similar to those employed in previous syntheses (6). The diacetone derivative (VIII) of 3-deoxy-D-glucose, prepared in near quantitative yield from the sugar (VII), was hydrolyzed selectively to yield the 1,2-monoacetone derivative (IX) in high yield. Conversion of IX to the 5,6-dibenzoate (X) and then *via* acetolysis to the 1,2-diacetate (XI) proceeded in an over-all yield of 98%. The 5,6-di-*O*-*p*-nitrobenzoyl and 5,6-carbonate esters of IX were also prepared crystalline but were not used in this study. Condensation of XI with chloromercuri-6-benzamidopurine (6) in the presence of titanium tetrachloride, followed by removal of the acyl groups with methanolic sodium methoxide, gave crystalline 9-(3-deoxy-β-D-glucofuranosyl)adenine (XIII) in a yield (based on the diacetate XI) of 52%. This corresponds to an over-all yield of the nucleoside



Scheme II

from the starting material, 3-deoxy-D-glucose, of approximately 40%. This nucleoside was obtained in substantially poorer yield when the halosugar derivative of XI was condensed with chloromercuri-6-benzamidopurine in the usual manner. (Scheme I.)

The route to the antibiotic cordycepin (I) employed as starting material the monoacetone derivative (IX). Oxidation with periodate to give the pentose (XIV), followed by borohydride reduction to 1,2-monoacetone-3-deoxyribofuranose (XV), proceeded in over-all crude yield of 92%. Similarly, the conversion of XV to the benzoate (XVI), acetolysis of XVI to the diacetate XVII, and condensation of XVII with chloromercuri-6-benzamidopurine in the presence of titanium tetrachloride, followed by deacylation with methanolic sodium methoxide, all proceeded in high yield, to give crystalline 9-(3-deoxy-β-D-ribofuranosyl)adenine in an over-all crude yield (from the diacetate) of 39%. The pure nucleoside compared favorably with that reported by Baker and co-workers (7) prepared by an alternate route. The over-all yield of cordycepin based on the starting material 3-deoxy-D-glucose is thus approximately 30% and, therefore, is a feasible practical route to the chemical synthesis of this antibiotic, provided the 3-deoxy-D-glucose itself can be made more readily accessible. Work on this is continuing. (Scheme II.)

EXPERIMENTAL[1]

1,2:5,6 - Di - O - isopropylidene - 3 - deoxy - D-glucofuranose (VIII).—A mixture of 8.00 Gm. (4.88 mmoles) of finely powdered 3-deoxy-D-gluocse (VII), 20 Gm. of anhydrous copper sulfate, and 200 ml. of reagent acetone containing 160 mg. of concentrated sulfuric acid was stirred continuously in a stoppered flask at room temperature for 24 hr. The mixture was filtered and the solid was washed with acetone (3 × 25 ml.). The combined filtrate and washings were stirred for 1 hr. with 8 Gm. of powdered barium carbonate and filtered through Celite. After washing the cake with 50 ml. of acetone, the filtrate and washings were combined and evaporated to dryness *in vacuo* at 40° giving a pale yellow, moderately viscous liquid; yield, 11.5 Gm. (96.7%). Distillation at 0.05 mm. pressure gave a clear, colorless liquid, b.p. 56–57°; yield, 10.5 Gm. (88.4%); $[\alpha]_D^{20}$ −4°[c 4.7, (Mc_2CO)]; $\nu_{max.}^{film}$ (cm.$^{-1}$) 1380 (*gem*-dimethyl), and no absorption at 3500 (OH).

Anal.—Calcd. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.10; H, 8.36.

Literature (3) $[\alpha]_D^{18}$ − 8.6°.

1,2 - O - Isopropylidene - 3 - deoxy - D - glucofuranose (IX).—To 495 ml. of 50% aqueous methanol at 40°, 0.01 *N* with respect to hydrochloric acid, was added 9.92 Gm. (40.6 mmoles) of 1,2:5,6-di-*O*-isopropylidene-3-deoxy-D-glucofuranose (VIII). The solution was held at 40° for 90 min. with continuous stirring, neutralized with 1 *N* aqueous sodium hydroxide to the phenolphthalein end point and evaporated *in vacuo* at 40° to a syrup. This was diluted with 200 ml. of water and extracted with 50 ml. of chloroform. The chloroform extract was dried over magnesium sulfate, filtered, and evaporated to dryness *in vacuo* (40°) to give 2.10 Gm. (21.2%) of a clear, colorless liquid whose infrared spectrum was identical to that of the starting material (VIII).

The aqueous phase was evaporated to dryness *in vacuo* at 40°, and the partially crystalline residue further dried by the addition of 100 ml. of absolute ethanol followed by its removal *in vacuo*. A mixture of the residue with 10 Gm. of anhydrous magnesium sulfate was extracted with 100 ml. of hot chloroform. The extract was filtered, evaporated to dryness *in vacuo* (50°), and gave a viscous syrup which solidified on cooling. Further drying *in vacuo* over phosphorus pentoxide yielded 5.67 Gm. (86.8% based on unrecovered starting material) of crude product which was sufficiently pure for the next step, m.p. 83–84°. For analysis a sample was recrystallized twice from ethyl acetate–hexane, m.p. 84.5–85.5°; $[\alpha]_D^{20}$ −15°[c 1.3, ($CH_2Cl)_2$]; $\nu_{max.}^{KBr}$ (cm.$^{-1}$) 3400 (OH), 1380 (*gem*-dimethyl).

Anal.—Calcd. for $C_9H_{16}O_5$: C, 52.93; H, 7.90. Found: C, 52.91: H, 7.69.

Literature (3) m.p. 84°; $[\alpha]_D^{18}$ −37.8°.

5,6 - Di - O - benzyl - 1,2 - O - isopropylidene - 3 - deoxy - D-glucofuranose (X).—To a well-stirred solution of 4.45 Gm. (21.8 mmoles) of crude 1,2-*O*-isopropylidene-3-deoxy-D-glucofuranose (IX) in 45 ml. of reagent pyridine at 0° was added dropwise, over a period of 10 min., 6.55 ml. (56.7 mmoles) of benzoyl chloride. The mixture was stirred for 1 hr. at 0° and stored at room temperature for 24 hr. After cooling to 0°, the reaction was quenched by the dropwise addition of 0.5 ml. of water. This mixture was then added dropwise to 500 ml. of rapidly stirred cold aqueous saturated sodium bicarbonate. A pale yellow solid soon separated. After being stirred for an additional 2 hr., the mixture was filtered and the solid was washed with cold water (3 × 50 ml.). The crude product was dried *in vacuo* over phosphorus pentoxide; yield, 8.95 Gm. (99.6%) of pale yellow solid which was sufficiently pure for the next step, m.p. 82–84°. For analysis a sample was recrystallized twice from cyclohexane, m.p. 86.5–87°; $[\alpha]_D^{20}$ 8.7° [c 1.11, ($CH_2Cl)_2$]; $\nu_{max.}^{KBr}$ (cm.$^{-1}$), 1720 (benzoate C=O), 1380 (*gem*-dimethyl), 1280 benzoate (C—O—C), 705 (monosubstituted phenyl).

Anal.—Calcd. for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87. Found: C, 66.69; H, 5.83.

1,2 - O - Isopropylidene - 5,6 - di - O - (p - nitrobenzoyl)-3-deoxy-D-glucofuranose.—To a solution of 204 mg. (1.00 mmole) of recrystallized 1,2-*O*-isopropylidene-3-deoxy-D-glucofuranose (IX) in 2 ml. of reagent pyridine was added 465 mg. (2.50 mmoles) of *p*-nitrobenzoyl chloride. The mixture was stirred in a stoppered flask at room temperature for 24 hr. and then added to 40 ml. of cold water and extracted with chloroform (3 × 10 ml.). The combined organic extracts were washed with aqueous saturated sodium bicarbonate (40 ml.) and water (40 ml.), dried over magnesium sulfate, filtered, and evaporated to dryness *in vacuo* at 40°. The last traces of pyridine were removed by the addition of toluene (3

[1] All melting points were taken in an oil bath and are uncorrected.

× 10 ml.), followed by its removal *in vacuo* at 50° to give a partially crystalline residue. Trituration with 5 ml. of ethanol containing 5% chloroform gave a crystalline product which was collected on a filter and dried; yield, 442 mg. (88%), m.p. 124–128°. For analysis a sample was recrystallized twice from chloroform–ethanol, m.p. 124.5°; $[\alpha]_D^{20}$ 28°[c 1.18, $(CH_2Cl)_2$]; $\nu_{max.}^{KBr}$ (cm.$^{-1}$) 1725 (ester C=O), 1600 (aromatic nucleus), 1525 (aromatic NO_2), 1380 (*gem*-dimethyl).

Anal.—Calcd. for $C_{23}H_{22}N_2O_{11}$: C, 54.98; H, 4.41; N, 5.58. Found: C, 54.99; H, 4.59; N, 5.63.

1,2 - O - Isopropylidene - 3 - deoxy - D - glucofuranose-5,6-carbonate.—To a rapidly stirred solution of 204 mg. (1.00 mmole) of recrystallized 1,2-*O*-isopropylidene-3-deoxy-D-glucofuranose (IX) in 1.5 ml. of reagent pyridine and 0.5 ml. of chloroform at 0° was added dropwise, over a period of 5 min., 180 mg. (1.90 mmoles) of methyl chloroformate. The mixture was stirred for 1 hr. at 0° and stored at 5° for 3 days. The mixture was then added to 50 ml. of cold water and extracted with chloroform (3 × 10 ml.). The combined extracts were washed with aqueous saturated sodium bicarbonate (20 ml.) and water (20 ml.), dried over magnesium sulfate, filtered, and evaporated to dryness *in vacuo* at 45° to give a syrup. The last traces of pyridine were removed by the addition of toluene (2 × 10 ml.), followed by its removal *in vacuo* (50°). Trituration of the residual syrup with 5 ml. of hexane containing 10% of ethanol gave a crystalline mass of small needles which were collected on a filter, washed with 2 ml. of hexane containing 5% of ethanol and hexane, and dried *in vacuo* over phosphorus pentoxide; yield, 92 mg. (40%), m.p. 116–117°. For analysis a sample was recrystallized from water–ethanol (3:1), m.p. 117–117.5°; $[\alpha]_D^{20}$ −34° [c 0.76, $(CH_2Cl)_2$]; $\nu_{max.}^{KBr}$ (cm.$^{-1}$) 1800 (carbonate C=O), 1380 (*gem*-dimethyl).

Anal.—Calcd. for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13. Found: C, 52.38; H, 5.85.

1,2 - Di - O - acetyl - 5,6 - di - O - benzoyl - 3 - deoxy - D-glucofuranose (XI).—To a rapidly stirred solution of 1.65 Gm. (4.00 mmoles) of recrystallized 1,2 - *O* - isopropylidene - 5,6 - di - *O* - benzoyl - 3-deoxy-D-glucofuranose (X) in 16 ml. of glacial acetic acid and 1.6 ml. of acetic anhydride was added dropwise 0.90 ml. of concentrated sulfuric acid while maintaining the temperature between 15° and 20° (about 5 min.). After the mixture was stirred for 1 hr. at this temperature, it was stored at room temperature for 23 hr. The clear solution was then poured into 100 ml. of rapidly stirred ice water. After 30 min., the mixture was extracted with chloroform (3 × 50 ml.). The extracts were combined, washed with aqueous saturated sodium bicarbonate (2 × 50 ml.), and water (50 ml.), dried over magnesium sulfate, filtered, and evaporated to dryness *in vacuo* at 60° to give a colorless, slightly turbid syrup which was sufficiently pure for the next step; yield, 1.79 Gm. (97.8%). For analysis a sample was dissolved in absolute ethanol, filtered free of a small amount of insolubles, and evaporated to dryness *in vacuo* at 60° to give a clear, colorless syrup which slowly hardened to a glass; $[\alpha]_D^{20}$ −46° [c 1.06, $(CH_2Cl)_2$]; $\nu_{max.}^{film}$ (cm.$^{-1}$) 1740 (acetate C=O), 1725 (benzoate C=O), 1275 (benzoate C—O—C), 1235 sh (acetate C—O—C).

Anal.—Calcd. for $C_{24}H_{24}O_9$: C, 63.15; H, 5.30. Found: C, 63.44; H, 5.27.

9-(3-Deoxy-β-D-glucofuranosyl)adenine (XIII).—*Method A.*—To a solution of 0.83 Gm. (1.9 mmoles) of crude 1,2-di-*O*-acetyl-5,6-di-*O*-benzoyl-3-deoxy-D-glucofuranose (XI) in 2 ml. of acetyl chloride was added 25 ml. of anhydrous ether, previously saturated with dry hydrogen chloride at 2°, and the tightly stoppered solution was stored at 5° for 3.5 days. The solvent was then removed *in vacuo* at 30° while protecting the reaction mixture from moisture. The last traces of acetic acid were removed by the addition of benzene (2 × 5 ml.) followed by its removal *in vacuo* at 40°, to give the halosugar as a pale yellow syrup. A solution of this syrup in 15 ml. of reagent xylene was added to a mixture of 0.91 Gm. (1.9 mmoles) of chloromercuri-6-benzamidopurine (6) and 0.45 Gm. of Celite (Johns-Manville), and the mixture was heated under reflux with stirring for 2 hr. The mixture was filtered while still warm and the cake washed with warm chloroform (3 × 20 ml.). The filtrate and washings were combined and evaporated to dryness *in vacuo* at 50°. A solution of the residue in 50 ml. of chloroform, filtered free of insolubles, was washed with 30% aqueous potassium iodide (2 × 20 ml.) and water (20 ml.), dried over magnesium sulfate, filtered, and evaporated to dryness *in vacuo* (40°) to give the crude blocked nucleoside (XII) as a pale yellow syrup; yield, 0.95 Gm. (78%); $\nu_{max.}^{film}$ (cm. $^{-1}$) 1750 sh (acetate C=O), 1725 (benzoate C=O), 1605, 1580 (purine ring and phenyl), 1280 (benzoate C—O—C), 1100, 1070, 1025 (sugar C—O—C), 710 (monosubstituted phenyl).

A solution of 0.93 Gm. of the crude blocked nucleoside (XII) in 10 ml. of 0.1 *N* methanolic sodium methoxide was heated under reflux for 2 hr., during which time the crude product separated from solution. The cooled mixture was neutralized with glacial acetic acid, and the solid was collected on a filter, washed with 1 ml. of cold methanol, and dried; yield, 0.088 Gm. [16% from the 1,2-diacetate (XI)], m.p. 247–249°. A second crop separated when the filtrate was cooled in an ice bath, 0.021 Gm., m.p. 247–248°. The combined yield of crude nucleoside was 0.109 Gm. (20%). Recrystallization from water gave m.p. 249–250°.

Method B.—A mixture of 1.24 Gm. (2.72 mmoles) of crude 1,2-di-*O*-acetyl-5,6-di-*O*-benzoyl-3-deoxy-D-glucofuranose (XI), 1.61 Gm. (3.40 mmoles) of chloromercuri-6-benzamidopurine, 1.7 Gm. of Celite, and 125 ml. of ethylene dichloride was distilled until 25 ml. of distillate had been collected. To the partially cooled mixture was added dropwise a solution of 0.37 ml. (3.4 mmoles) of titanium tetrachloride in 5 ml. of ethylene dichloride, and the reaction was heated under reflux for 24 hr. The mixture was cooled to 0°, and 50 ml. of aqueous saturated sodium bicarbonate was added. After stirring vigorously for 2 hr., the mixture was filtered through Celite and the cake washed with chloroform (3 × 20 ml.). The organic phase was separated from the filtrate and evaporated to near dryness *in vacuo*. A solution of the residue in 20 ml. of chloroform was washed with 20 ml. of 30% aqueous potassium iodide and 20 ml. of water, dried over magnesium sulfate, filtered, and evaporated to dryness *in vacuo* finally at 0.05 mm., to give the crude blocked nucleoside (XII) as a yellow glass; yield, 1.46 Gm. (84%); $\nu_{max.}^{KBr}$ (cm.$^{-1}$) 1750 sh (acetate C=O), 1725 (benzoate C=O), 1605, 1580

(purine ring and phenyl), 1280 (benzoate C—O—C), 1220 sh (acetate C—O—C), 1090, 1070, 1025 (sugar C—O—C), 710 (monosubstituted phenyl).

A solution of 1.38 Gm. of the crude blocked nucleoside (XII) in 35 ml. of 0.1 *N* methanolic sodium methoxide was heated under reflux for 2.5 hr. during which time a crystalline solid separated from solution. The cooled mixture was neutralized with glacial acetic acid, stirred at 0° for 2 hr., and the nearly white, crystalline solid collected on a filter, washed with 2 ml. of cold methanol, and dried; yield, 0.379 Gm. [52.2% from the 1,2-diacetate, (XI)], m.p. 250–252°. Mixed melting point with the product obtained in *Method A* showed no depression. For analysis, a sample was recrystallized twice from water with light charcoaling, m.p. 252°; $\lambda_{max.}^{pH\ 1}$ (mμ) 257 (ε 15,500), $\lambda_{max.}^{pH\ 13}$ (mμ) 260 (ε 15,900), $\lambda_{max.}^{H_2O}$ (mμ) 259 (ε 15,900); $\nu_{max.}^{KBr}$ (cm.$^{-1}$) 3500–3200 (OH and NH), 1620, 1575 (C=C and C=N); $[\alpha]_D^{29}$ −50° [c 1.38, (*N* HCl)].

Anal.—Calcd. for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.38; N, 24.90. Found: C, 46.81; H, 5.59; N, 24.80.

1,2 - O - Isopropylidene - 3 - deoxy - D - erythro-pentodialdofuranose (XIV).—To a well-stirred solution of 1.77 Gm. (8.69 mmoles) of 1,2-*O*-isopropylidene-3-deoxy-D-glucofuranose (IX), m.p. 83–84°, in 45 ml. of water was added 1.86 Gm. (8.69 mmoles) of sodium metaperiodate and the solution adjusted to a pH of 6–6.5 (pH paper) with 0.2 *N* sodium hydroxide solution. The pH was maintained in this range for 1 hr. by the periodic addition of sodium hydroxide solution, followed by evaporation of the solution to dryness *in vacuo* at 40°. Further drying was accomplished by the addition of 50 ml. of absolute ethanol, followed by its removal *in vacuo* at 40°. To the partially crystalline residue was added 10 Gm. of anhydrous magnesium sulfate and the mixture extracted with chloroform (3 × 25 ml.). The extracts were combined and evaporated to dryness *in vacuo* at 50° giving the crude product as a clear, colorless, moderately viscous syrup; yield, 1.74 Gm. (105% based on the hydrate structure). This material was sufficiently pure for the next step. For analysis a sample was sublimed at 65°/0.05 mm. giving a moderately viscous syrup which gradually hardened on standing; $\nu_{max.}^{film}$ (cm.$^{-1}$) 3500 (OH), 1735 (aldehyde C=O), 1380 (*gem*-dimethyl).

Anal.—Calcd. for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Calcd. for $C_8H_{12}O_4 \cdot H_2O$: C, 50.52; H, 7.42. Found C, 54.27; H, 7.59.

1,2 - O - Isopropylidene - 3 - deoxy - D - ribo-furanose (XV).—To a cold, well-stirred solution of 1.61 Gm. (8.06 mmoles) of crude 1,2-*O*-isopropylidene-3-deoxy-D-erythro-pentodialdofuranose (XIV) in 25 ml. of 50% aqueous methanol was added a cold solution of 0.61 Gm. (16 mmoles) of sodium borohydride in 25 ml. of water. The resulting solution was stirred at room temperature for 4 hr., then neutralized with 10% aqueous acetic acid and evaporated to dryness *in vacuo* at 40°. The partially crystalline residue was further dried by the addition of 50 ml. of absolute ethanol, followed by its removal *in vacuo* at 40°. To the residue was added 6 Gm. of anhydrous magnesium sulfate and the mixture was heated under reflux with 25 ml. of chloroform for 30 min., then filtered, and the cake washed with chloroform (3 × 5 ml.). The combined filtrate and washings were evaporated to dryness *in vacuo* at 50° giving the crude product as a white, crystalline solid which was sufficiently pure for conversion to the benzoate ester; yield, 1.29 Gm. (92.2% from the monoacetone-3-deoxyglucose), m.p. 76–77.5°. For analysis, a sample was recrystallized from cyclohexane, m.p. 79–80°; $\nu_{max.}^{KBr}$ (cm.$^{-1}$) 3525, 3425, 3430 sh (OH), 1375 (*gem*-dimethyl); $[\alpha]_D^{29}$ −10° [c 0.80, $(CH_2Cl)_2$].

Anal.—Calcd. for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.66; H, 8.07.

5 - O - Benzoyl - 1,2 - O - isopropylidene - 3 - deoxy - D - ribofuranose (XVI).—To a well-stirred solution of 0.087 Gm. (0.5 mmole) of crude 1,2-*O*-isopropylidene-3-deoxy-D-ribofuranose (XV) in 1 ml. of reagent pyridine was added dropwise 0.09 ml. (0.78 mmole) of benzoyl chloride. After standing at room temperature for 5 hr., the reaction was quenched with 1 drop of water, then poured into 10 ml. of vigorously stirred aqueous saturated sodium bicarbonate. After 30 min., an oil had separated. The mixture was extracted with chloroform (3 × 5 ml.) and the combined extracts washed with water (10 ml.), dried over magnesium sulfate, filtered, and evaporated to dryness *in vacuo* at 50°. The last traces of pyridine were removed by the addition of toluene (2 × 5 ml.), followed by its removal *in vacuo* at 50° to give the crude product as a slightly turbid, pale-yellow syrup; 0.123 Gm. (88.5%). An analytical sample was prepared by sublimation of a sample at 80°/0.05 mm. to give a clear, colorless syrup; $\nu_{max.}^{film}$ (cm.$^{-1}$) 1720 (benzoate C=O), 1600 (phenyl), 1380 (*gem*-dimethyl), 1270 (benzoate C—O—C), 710 (monosubstituted phenyl); $[\alpha]_D^{29}$ −7.1° [c 0.72, $(CH_2Cl)_2$].

Anal.—Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.76; H, 6.71.

1,2 - Di - O - acetyl - 5 - O - benzoyl - 3 - deoxy - D-ribofuranose (XVII).—To a well-stirred solution of 1.84 Gm. (6.64 mmoles) of crude 5-*O*-benzoyl-1,2-*O*-isopropylidene-3-deoxy-D-ribofuranose (XVI) in 32 ml. of glacial acetic acid and 3.64 ml. (38.5 mmoles) of acetic anhydride was added dropwise 1.49 ml. of concentrated sulfuric acid while maintaining the temperature between 15–20°. The solution was allowed to stand overnight at room temperature, then poured into 250 ml. of vigorously stirred 10% aqueous sodium acetate at 0°. After 30 min., the mixture was extracted with chloroform (3 × 30 ml.), and the combined extracts washed with aqueous saturated sodium bicarbonate (2 × 90 ml.) and water (90 ml.), dried over magnesium sulfate, filtered, and evaporated to dryness *in vacuo* at 60°. The last traces of acetic acid were removed by the addition of benzene (2 × 10 ml.), followed by its removal *in vacuo* at 60° giving a colorless, slightly turbid syrup which was sufficiently pure for the next step; yield, 1.64 Gm. (77.0%). For analysis a sample was dried for several hours *in vacuo* at 100°: $\nu_{max.}^{film}$ (cm.$^{-1}$) 1750 (acetate C=O), 1720 (benzoate C=O), 1600 (phenyl), 1275 (benzoate C—O—C), 1220 (acetate C—O—C), 712 (monosubstituted phenyl).

Anal.—Calcd. for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63. Found: C, 59.00, H, 5.58.

9-(3-Deoxy-β-D-ribofuranosyl)adenine (I).—A mixture of 1.47 Gm. (4.71 mmoles) of crude 1,2-di-*O* - acetyl - 5 - *O* - benzoyl - 3 - deoxy - D - ribofuranose (XVII), 2.79 Gm. (5.89 mmoles) of chloromercuri-6-benzamidopurine, 2.8 Gm. of Celite, and 200 ml. of ethylene dichloride were distilled until 25 ml. of distillate had been collected. To the partially

cooled mixture was added a solution of 0.65 ml. (5.9 mmoles) of titanium tetrachloride in 10 ml. of ethylene dichloride and the mixture heated under reflux for 22 hr. While still warm, 85 ml. of aqueous saturated sodium bicarbonate was added with vigorous stirring. After 2 hr., the mixture was filtered through Celite and, after washing the cake with chloroform (3 × 20 ml.), the organic phase was separated from the filtrate and evaporated to near dryness *in vacuo* at 40°. The residue was dissolved in 40 ml. of chloroform, washed with 40 ml. of 30% aqueous potassium iodide and water (40 ml.), dried over magnesium sulfate, filtered, and evaporated to dryness *in vacuo* at 60° to give the crude, blocked nucleoside (XVIII) as a yellow foam which hardened to a glass; yield, 1.71 Gm. (74.7%); $\nu_{max.}^{KBr}$ (cm.$^{-1}$) 1750 (acetate C=O), 1720 (benzoate C=O), 1690 sh (amide C=O), 1605, 1580 (C=N and C=C), 1270 (benzoate C—O—C), 1220 sh (acetate C—O—C), 1085, 1070, 1020 (sugar C—O—C), 710 (monosubstituted phenyl).

A solution of 1.66 Gm. of the crude, blocked nucleoside (XVIII) in 35 ml. of 0.1 *N* methanolic sodium methoxide was heated under reflux for 2.5 hr. The cooled solution was neutralized with glacial acetic acid, then set aside at 5° overnight, during which the crude product separated as a nearly white, crystalline solid. The crude nucleoside was collected on a filter, washed with 5 ml. of methanol, and dried; yield, 0.437 Gm. [39% from the diacetate (XVII)], m.p. 216–219°. For analysis, a sample was recrystallized from 90% aqueous ethanol with light charcoaling and again from water, and the white, crystalline solid was dried for several hours *in vacuo* at 100°, m.p. 221–222°; $\lambda_{max.}^{pH\ 1}$ (mμ) 257 (ε 14, 600); $\lambda_{max.}^{pH\ 13}$ (mμ) 258 (ε 15,000), $\lambda_{max.}^{H_2O}$ (mμ) 259 (ε 14,900), $\nu_{max.}^{KBr}$ (cm.$^{-1}$) 3300, 3150 (OH, NH), 1610, 1570 (C=C and C=N); $[\alpha]_D^{20}$ −38° (c 1.19, supersaturated in H_2O).

Anal.—Calcd. for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.22; N, 27.88. Found C, 47.28; H, 5.17; N, 27.66.

Literature (7) m.p. 222–224°; $[\alpha]_D^{27}$ −42°.

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Steroids XXV

Synthesis of Some 4-Azapregnanes

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The reaction of 3,5-seco-4-norpregnane-5,20-dion-3-oic acid (I) with methylamine yielded 4-methyl-4-aza-5-pregnene-3,20-dione (V) and 4-methyl-20-methylimino-4-aza-5-pregnen-3-one (VII). VII was hydrolyzed by hydrochloric acid to V. The reaction of I with ethanolamine gave 4-(β-hydroxyethyl)-4-aza-5-pregnene-3,20-dione. 5ξ-Hydroxy-4-methyl-4-azapregnane-3,20-dione (VI) was formed by the reaction of 4-oxa-5-pregnene-3,20-dione and methylamine at room temperature. VI was dehydrated to V by heating above 100 or by the use of an acid catalyst. Reduction of 4-aza-5-pregnene-3,20-dione (II), V, and VII with lithium aluminum hydride yielded 4-aza-4-pregnen-20β-ol, 4-methyl-4-aza-5-pregnen-20β-ol, and 4-methyl-20β-methylamino-4-aza-5-pregnene, respectively. By the following sequence of reactions, 4-methyl-4-aza-5-pregnen-20-one was prepared from V: ketal formation, lithium aluminum hydride reduction, and acid hydrolysis.

INTEREST in azasteroids has been increasing because of their potential value as pharmacodynamic and chemotherapeutic agents. 4-Azasteroids with antimicrobial (1–4), hypotensive (5), anti-inflammatory (5, 6), and hypocholesterolemic (5, 7) activities have been prepared in this laboratory. This paper describes the synthesis of some 4-azapregnanes.

The synthesis of 4-aza-5-pregnene-3,20-dione (8) by two methods has been described (9): (*a*) the reaction of ammonia with 3,5-seco-4-norpregnene-5,20-dion-3-oic acid (I) at 150° and (*b*) the reaction of ammonia with 4-oxa-5-pregnene-3,20-dione (III) to yield 5ξ-hydroxy-4-aza-pregnan-3-one (IV) which was then dehydrated by an acid catalyst or by heating above 100°. In this investigation, 4-methyl-4-aza-5-

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