Studies on the Oxidation of "Reversed Nucleosides" in Oxygen. II. Synthesis of Homoeritadenine and *threo*-Eritadenine[1]

NORIO TAKAMURA, NAOMASA TAGA, TAKESHI KANNO, AND MITSUTAKA KAWAZU*

Organic Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd., Toda, Saitama, Japan

Received September 11, 1972

Condensation of 6-*O*-tosyl-1,2-*O*-isopropylidene-3,5-*O*-benzylidene-D-glucofuranose (I) and 1,6-*O*-ditosyl-2,3-*O*-isopropylidene-D-fructofuranose (V) with the sodium salt of adenine in DMF afforded the corresponding reversed nucleosides (II and VI) in good yields. After removal of the protective groups on the respective compounds by hydrolysis, oxidation of the demasked compounds (III and VII) by oxygen in a dilute alkali solution gave the identical acid which was revealed as 5-(6-aminopurin-9*H*-9-yl)-2(*S*),3(*R*),4(*R*)-trihydroxyvaleric acid (IV). Reaction of 5-*O*-tosyl-1,2-isopropylidene-D-xylofuranose (XIV) or 5-*O*-tosyl-3-acetoxy-1,2-isopropylidene-D-xylofuranose (XV) with the sodium salt of adenine gave corresponding reversed nucleosides (XVIa and XVIb) in rather poor yield. D-*threo*-Eritadenine was obtained in good yield by the similar oxidation of 5-(6-aminopurin-9*H*-9-yl)-D-xylofuranose (XVII). The syntheses of some esters of these acids were also performed.

The success of the synthesis of eritadenine by oxidation of 5-(adenine-9-yl)pentoses in oxygen prompted us to proceed to further work on some reversed nucleosides of the hexose series. From the chemical as well as the pharmacological point of view, synthesis of homoeritadenine was of interest (Scheme I).

The reaction of 6-*O*-tosyl-1,2-*O*-isopropylidene-3,5-*O*-benzylidene-D-glucofuranose[2] and 6-*O*-tosyl-1,2,3,5-*O*-dibenzylidene-D-glucofuranose (I)[3] with the sodium salt of adenine in DMF afforded in good yield the corresponding reversed nucleosides (IIa and IIb), whose uv characteristics (λ_{max} 262 nm at pH 7 and 12, 259 nm at pH 2) proved them to be 6-aminopurin-9*H*-9-yl derivatives. None of the other position isomers could be isolated from the reaction mixture.

Hydrolysis to remove the protective groups of IIa or IIb with dilute hydrochloric acid was satisfactorily carried out by the usual methods. Although III was shown assumingly to be a furanose type, no evidence for this structure could be obtained because the nmr spectra of III, both in DMSO-d_6 and in D_2O, were equivocal. III was oxidized under conditions similar to those of the pentose derivatives.[4] Tlc of the reaction mixture showed several spots, including a trace spot of R_f 0.35 which was identical with that of eritadenine [developer: *n*-C_4H_9OH–HOAc–H_2O (4:1:5)]. Attempts to increase the amount of this minor product under a variety of oxidation conditions were unsuccessful; hence its structure remains unknown.

The major product was isolated as colorless plates by adding EtOH to the concentrated reaction mixture. Treatment of this product with HCOOH afforded the free acid, which was established as homoeritadenine (IV) on the basis of the spectral data and the analysis.

An attempt to synthesize eritadenine by air oxidation of the fructose derivative VI was also unsuccessful. Although it was conceivable that the reaction of 1,6-di-*O*-tosyl-2,3-*O*-isopropylidene-D-fructofuranoside (V)[5] with adenine would result in a mixture of 1-(adenin-9*H*-9-yl)fructose and 6-(adenin-9*H*-9-yl)fructose, eritadenine might be obtained if the latter compound was formed preferentially and the oxidative cleavage would occur between the inside carbon and the ketone. The main product, however, was also homoeritadenine. Thus the adduct was shown to be the 6-(adenine-9*H*-9-yl)fructose derivative VI. Synthesis of VI and oxidation of VII were carried out in the usual manner, as shown in the Experimental Section. Since each signal in the nmr of VIIb was dual whereas VIIb gave a single spot on tlc and the analysis agreed completely with the theoretical value, it appeared that VIIb might be a mixture of the α and β anomers. In the hope that evidence concerning the structure might be obtained, VIIb was treated with dilute NaOH solution to give VIIa. Unfortunately, the conformation of the sugar moiety of VIIa could not be established in detail because the nmr signals overlapped. Since no epimerization had been observed in the synthesis of eritadenine *via* 5-(6-aminopurin-9*H*-9-yl)-D-ribofuranose,[4] it appeared probable that the configuration of the three hydroxy groups of (IV) was 2(*S*), 3(*R*), and 4(*R*). Homoeritadenine possessing three hydroxy groups of *R* configuration was thus synthesized for comparison with IV physicochemically and pharmacologically.

The reaction of 5-*O*-tosyl-2,3-*O*-isopropylidene-D-ribonolactone[6] (VIII) with the sodium salt of adenine using rather milder conditions than those of the glucosides led to the formation of IX in good yield. Hydrolysis of IX with dilute hydrochloric acid afforded X accompanied by a slight amount of the lactone XI. Since neither IV nor X exhibited good nmr spectra, the synthesis of some lipid-soluble esters of these was attempted in the hope that clear-cut spectra might be obtained. Esterification of X by the usual methods, however, failed to yield the desired esters.

Humphlett[7] was successful in synthesizing higher alkyl esters unobtainable by the usual methods, such as treatment with a carbinol and hydrogen chloride, by heating D-arabino-1,4-lactone with a higher alcohol in the presence of sulfuric acid.

On the other hand, little is known about the preparation of ribonic acid esters. The difference in the ease of esterification between ribonic acid and arabinonic acid is similar to our case. Treatment of X, which

---

[1] Preliminary communication: M. Kawazu, T. Kanno, N. Takamura, T. Mizoguchi, S. Saito, and K. Okumura, *Chem. Commun.*, 1047 (1970).

[2] E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Amer. Chem. Soc.*, **82**, 2025 (1960).

[3] H. B. Wood, Jr., H. W. Diehl, and H. G. Fletcher, Jr., *ibid.*, **79**, 3862 (1957).

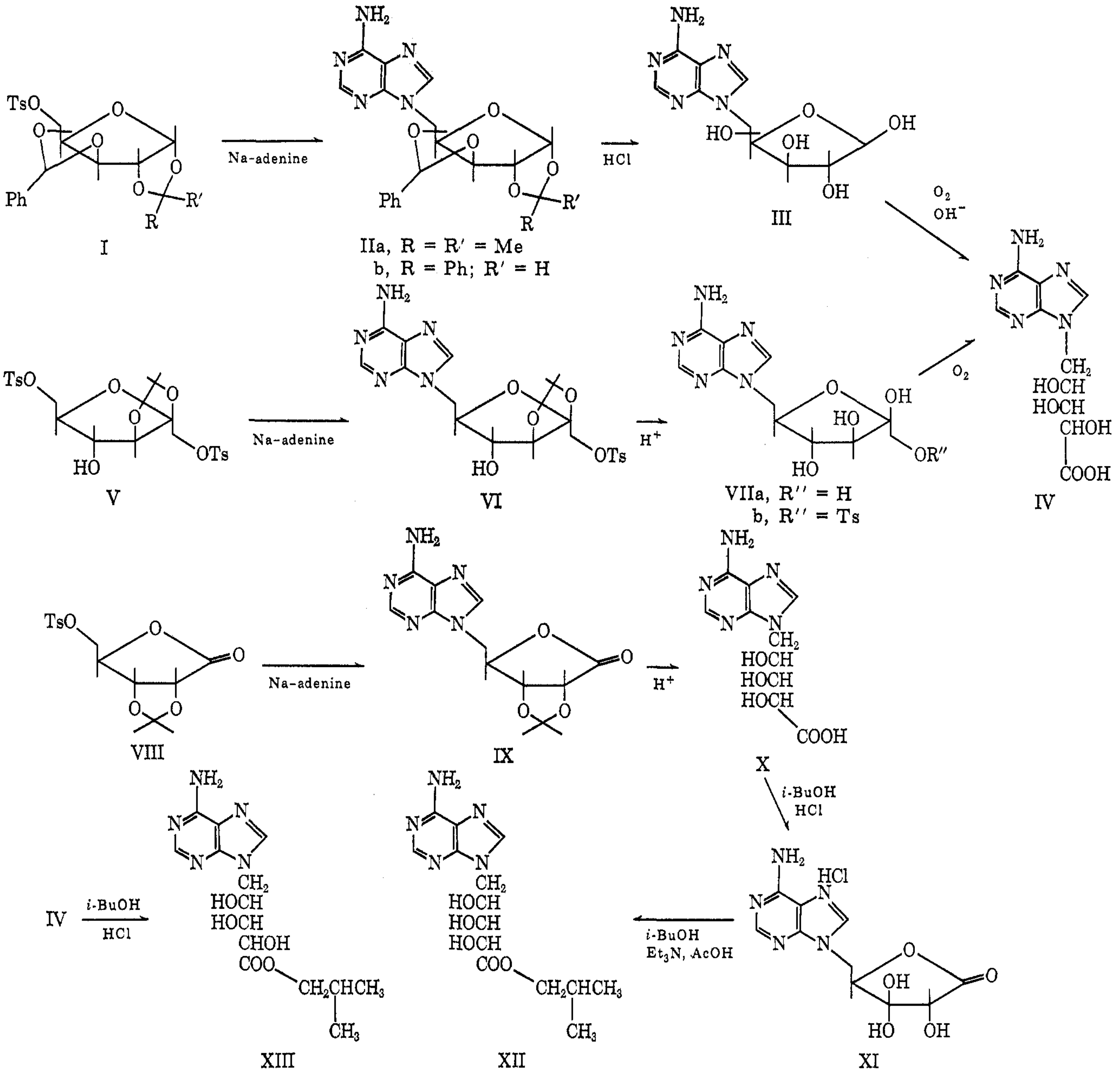
[4] Refer to part I of this series: M. Kawazu, T. Kanno, S. Yamamura, T. Mizoguchi, and S. Saito, *J. Org. Chem.*, **38**, 2887 (1973).

[5] W. T. T. Morgan and T. Reichstein, *Helv. Chim. Acta*, **21**, 1023 (1938).

[6] L. Hough, J. K. N. Jones, and D. L. Michell, *Can. J. Chem.*, **36**, 720 (1958).

[7] W. J. Humphlett, *Carbohyd. Res.*, **4(2)**, 157 (1967).

SCHEME I



should be 5-(6-aminopurin-9*H*-9-yl)-D-ribonic acid, with isobutyl alcohol and hydrogen chloride led to the formation of the lactone XI only, whereas isobutyl 5-(6-aminopurin-9*H*-9-yl)-D-arabinonate (XIII) was obtained from IV under similar conditions. Isobutyl 5-(6-aminopurin-9*H*-9-yl)-D-ribonate (XII) could be synthesized only when XI in isobutyl alcohol was warmed in the presence of triethylamine and acetic acid.

Unfortunately, neither of the esters afforded nmr spectra unequivocal enough to permit comparison of the absolute configuration of XIII with that of XII. However, the behavior of IV and X during esterification appeared to explain the structural relationship between these compounds.

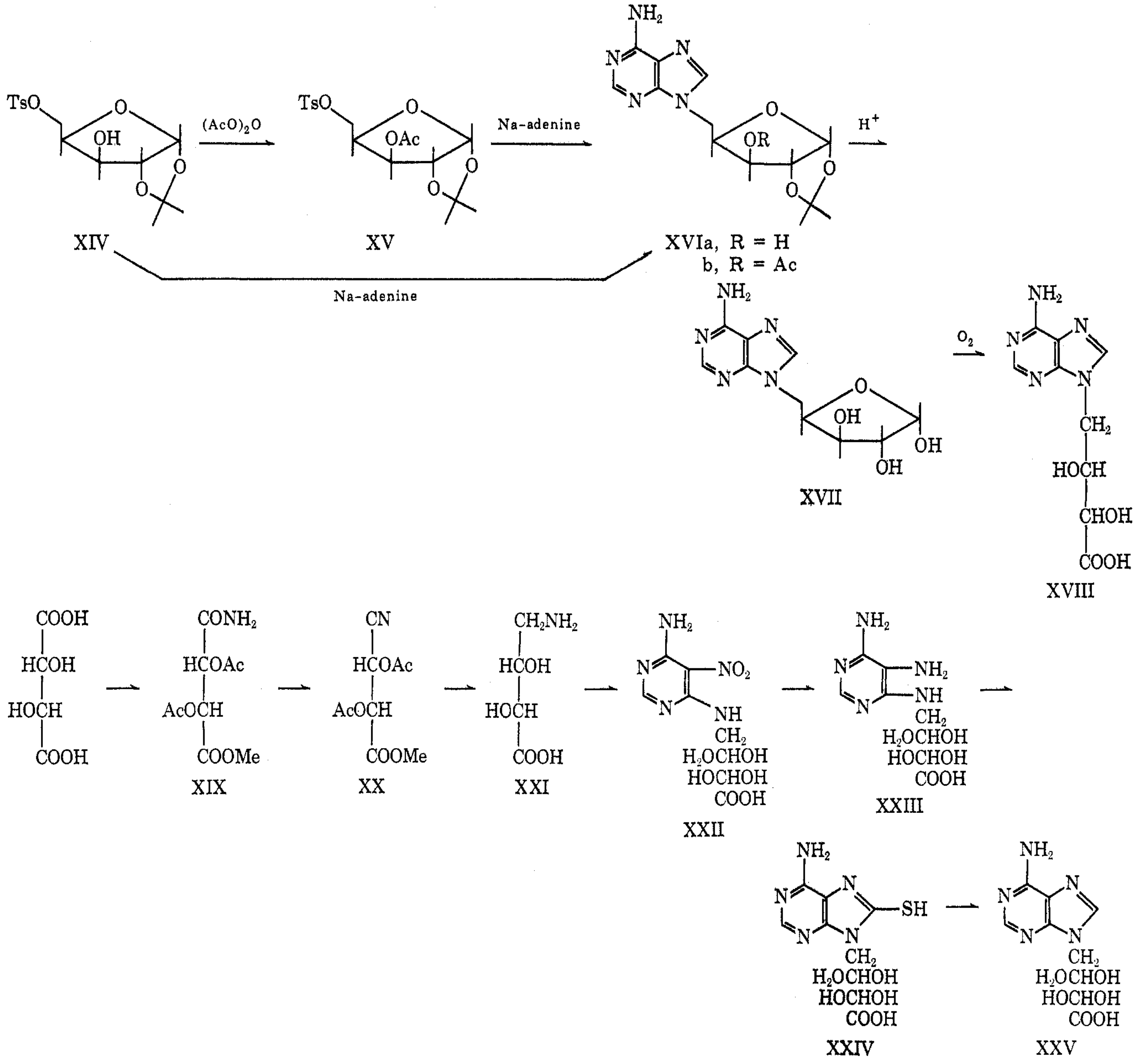
An attempted extension of our method involving the preparation of a reversed nucleoside and its oxidation by oxygen to a synthesis of *threo*-eritadenine was disappointing, since condensation of 5-*O*-tosyl-1,2-*O*-isopropylidene-D-xylofuranose (XIV)[8] with the sodium salt of adenine gave an extremely poor yield of XVIa (Scheme II). Since the yield of the condensation product was excellent when the free hydroxyl group of the sugar had been masked in the case of the arabinose series,[4] it appeared that the yield of the product might be improved if 5-*O*-tosyl-3-acetoxy-1,2-*O*-isopropylidene-D-xylofuranose (XV) was used. The yield of XVIb, however, was only 30%, probably owing not only to the steric hindrance of the 3-acetoxy group but also to decomposition of the sugar. After removal of the protecting groups, XVIa or XVII were directly oxidized without purification because of its hygroscopic properties. The structure of D-*threo*-eritadenine obtained by this oxidation was conclusively confirmed by comparison with L-*threo*-eritadenine synthesized from L-tartaric acid *via* the 4-amino-4-deoxy-L-threonic acid as shown in Scheme II.[9] Prepa-

---

[8] B. Helferich and M. Burgdorf, *Tetrahedron*, **3**, 274 (1958).

[9] A short communication on the synthesis of this compound by similar methods has been reported: M. Hashimoto, Y. Sato, H. Seki, and T. Kamiya, *Tetrahedron Lett.*, 1359 (1970).

SCHEME II



rations of these compounds are given in the Experimental Section.

Experimental Section

Ir and nmr spectra were also recorded by the instruments described in the Experimental Section of this series part I. Melting points are uncorrected. Optical rotations were measured with a Yanagimoto polarimeter Model OR-20. All analytical samples were dried over P_2O_5 or KOH at 50–70° *in vacuo* overnight.

1,2:3,5-Di-*O*-benzylidene-6-*O*-*p*-tolylsulfonyl-D-glucofuranose (I, R = Ph; R′ = H).—To a solution of 1,2:3,5-di-*O*-benzylidene-D-glucofuranose (6.0 g, 16.8 mmol, mp 161–162°) in pyridine (20 ml) was added *p*-toluenesulfonyl chloride (3.52 g, 18.5 mmol) in $CHCl_3$ (22 ml) under ice cooling. The mixture was stirred for 17 hr at room temperature and evaporated *in vacuo* to give a syrup, which was dissolved in $CHCl_3$ (50 ml) and benzene (200 ml), washed with 1.2 *N* HCl, H_2O, saturated $NaHCO_3$, and H_2O, then dried over Na_2SO_4 and evaporated to dryness *in vacuo* to give a colorless solid (7.70 g, 90%).

Recrystallization from benzene–isopropyl ether afforded colorless needles (5.88 g, 68%): mp 162°; $[\alpha]^{20}D$ +29.8° (*c* 1.03, $CHCl_3$); nmr ($CDCl_3$) τ 2.05–2.95 (m, 4 H, $-SO_2C_6H_4CH_3$), 2.60 (s, 5 H, $>CHC_6H_5$), 2.63 (s, 5 H, $>CHC_6H_5$), 3.84 (d, 1 H), 3.97 (s, 1 H), $>CHC_6H_5$), 4.25 (s, 1 H, $>CHC_6H_5$), 5.23 (d, 1 H), 5.36 (d, 1 H), 5.60 (s, 3 H), 5.90 (broad d, 1 H), 7.60 (s, 3 H, $-C_6H_4CH_3$).

Anal. Calcd for $C_{27}H_{26}O_8S$: C, 63.52; H, 5.13; S, 6.28. Found: C, 63.76; H, 5.23; S, 6.14.

6-(6-Aminopurin-9*H*-9-yl)-1,2:3,5-di-*O*-benzylidene-6-deoxy-D-glucofuranose (IIb).—Adenine (1.64 g, 12.1 mmol) and NaH (0.46 g, 64% in mineral oil, 12.1 mmol) in DMF (50 ml) and I (5.62 g, 11.0 mmol) in DMF (30 ml) were allowed to react and treated in the manner of the general procedure described in the Experimental Section of part I of this series. The residue was washed with ether and $CHCl_3$. Recrystallization from EtOH gave IIb as colorless prisms (3.12 g, 60%): mp 228°; $[\alpha]^{20}D$ 64.1° (*c* 1.17, DMSO); nmr (DMSO-d_6) τ 1.82 (s, 1 H), 1.86 (s, 1 H, C_2 H, C_8 H of purine), 2.61 (s, 5 H, $>CHC_6H_5$), 2.77 (s, 5 H, $>CHC_6H_5$), 2.94 (s, 2 H, $-NH_2$), 3.80 (d, 1 H), 3.85 (s, 1 H, $>CHC_6H_5$), 3.88 (s, 1 H, $>CHC_6H_5$), 4.80–5.55 (m, 5 H), 5.65 (broad d, 1 H).

Anal. Calcd for $C_{25}H_{23}O_5N_5$: C, 63.41; H, 4.90; N, 14.79. Found: C, 63.46; H, 4.95; N, 14.50.

6-(6-Aminopurin-9*H*-9-yl)-3,5-*O*-benzylidene-6-deoxy-1,2-*O*-isopropylidene-D-glucofuranose (IIa).—Adenine (9.65 g, 71.5 mmol), NaH (2.68 g, 64% in mineral oil, 71.5 mmol) in DMF (210 ml), and I (R = R′ = Me) (30.1 g, 65.0 mmol) in DMF (160 ml) were allowed to react and treated in a manner similar to that of IIb. The residual gummy solid was washed with ether and dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried over Na_2SO_4, and evaporated *in vacuo* to give a pale yellow solid. Recrystallization from EtOH afforded colorless needles (19.2 g, 69%): mp 230°; $[\alpha]^{20}_{\mathrm{D}}$ +72.2° (*c* 1.10, DMSO); nmr (DMSO-d_6) τ 1.87 (s, 1 H), 1.90 (s, 1 H, C_2 H, C_8 H of purine), 2.78 (s, 5 H, C_6H_5–), 2.97 (s, 2 H, –NH_2), 3.94 (s, 1 H, CHC_6H_5), 4.05 (d, 1 H), 4.80–5.70 (m, 5 H), 5.88 (broad d, 1 H), 8.60 (s, 3 H, –CH_3), 8.75 (s, 3 H, –CH_3).

Anal. Calcd for $C_{21}H_{23}O_5N_5$: C, 59.28; H, 5.45; N, 16.46. Found: C, 59.24; H, 5.47; N, 16.30.

6-(6-Aminopurin-9*H*-9-yl)-6-deoxy-D-glucose (III).—A solution of IIb (2.7 g, 5.71 mmol) and concentrated HCl (1.5 ml) in H_2O (40 ml) was warmed at 70° for 3 hr. It was then cooled, washed with ether, and passed through a column of an ion-exchange resin (Amberlite IR-45, OH^- form, 50 ml). The column was eluted with H_2O (300 ml). The eluate was concentrated *in vacuo* to *ca.* 20 ml, to which was added EtOH to crystallize out III (1.12 g, 66%). The recrystallizations from H_2O–EtOH afforded colorless prisms,[10] mp 230° dec, $[\alpha]^{20}_{\mathrm{D}}$ +60.0° (*c* 0.69, DMSO). III was also obtained from IIa in 83% yield by treatment similar to that described.

Anal. Calcd for $C_{11}H_{15}O_5N_5 \cdot {}^1/_4H_2O$: C, 43.78; H, 5.18; N, 23.21. Found: C, 43.99; H, 5.24; N, 23.06.

6-(6-Aminopurin-9*H*-9-yl)-6-deoxy-2,3-*O*-isopropylidene-1-*O*-*p*-tolylsulfonyl-D-fructofuranose (VI).—A mixture of adenine (2.44 g, 18.0 mmol) and NaH (0.68 g, 64% in mineral oil, 18.0 mmol) in DMF (60 ml) was stirred at room temperature for 30 min and at 50° for 1 hr. To the suspension was added V (10.57 g, 20.0 mmol) in DMF (60 ml), and the solution was stirred at 100° for 5 hr. The dark brown mixture was evaporated *in vacuo* to give a semisolid, which was washed with ether and dissolved in $CHCl_3$. The $CHCl_3$ solution was filtered to remove insoluble material and the filtrate was washed with H_2O and dried over Na_2SO_4. Filtration and evaporation gave a solid (6.36 g, 72%). Twice, recrystallizations from AcOEt–isopropyl ether afforded colorless, silky crystals: mp 129–132°; $[\alpha]^{20}_{\mathrm{D}}$ +61.0° (*c* 0.22, $CHCl_3$); nmr ($CDCl_3$) τ 3.61 (s, 2 H, –NH_2), 7.62 (s, 3 H, –SO_2–, $C_4H_4CH_3$), 8.52 (s, 3 H, –CH_3), 8.66 (s, 3 H, –CH_3).

Anal. Calcd for $C_{21}H_{25}O_7N_5S$: C, 51.30; H, 5.13; N, 14.25; S, 6.53. Found: C, 50.77; H, 5.07; N, 14.22; S, 6.54.

6-(6-Aminopurin-9*H*-9-yl)-6-deoxy-1-*O*-*p*-tolylsulfonyl-D-fructose (VIIb).—A mixture of VI (1.9 g, 3.87 mmol) and concentrated HCl (1 ml) in H_2O (30 ml) was warmed at 70° for 3.5 hr. It was then cooled and adjusted to pH 7 with $NaHCO_3$ to crystallize out VIIb, which was triturated with a small amount of MeOH to give pure VIIb (1.05 g, 60%), mp 155–158° dec. Twice, recrystallizations from EtOH–H_2O afforded colorless prisms, mp 161–163° dec, $[\alpha]^{26}_{\mathrm{D}}$ +36.0° (*c* 1.12, DMSO).

Anal. Calcd for $C_{18}H_{21}O_7N_5S \cdot {}^1/_2H_2O$: C, 46.94; H, 15.26; S, 6.96. Found: C, 46.92; H, 4.82; N, 15.33; S, 6.81.

6-(6-Aminopurin-9*H*-9-yl)-6-deoxy-D-fructose (VIIa).—A mixture of VIIb (1.10 g, 2.44 mmol) and 1 *N* NaOH (6 ml) in H_2O (60 ml) was stirred for 15 min at room temperature. The clear solution was passed through a column (Amberlite IR-120, H^+ form, 20 ml). The column was washed with H_2O and then eluted with dilute NH_4OH (120 ml). The eluate was evaporated to dryness *in vacuo* to give a solid (0.50 g, 69%). Recrystallization from EtOH gave a colorless, crystal powder: mp 179° dec; $[\alpha]^{26}_{\mathrm{D}}$ +48.7° (*c* 0.83, DMSO); nmr (D_2O) τ 1.75 (s, 1 H), 1.78 (s, 1 H, C_2 H, C_8 H of purine), 4.50–6.70 (m).

Anal. Calcd for $C_{11}H_{15}O_5N_5 \cdot {}^1/_2C_2H_5OH$: C, 45.00; H, 5.66; N, 21.85. Found: C, 44.82; H, 5.62; N, 21.47.

5-(6-Aminopurin-9*H*-9-yl)-2(*S*),3(*R*),4(*R*)-trihydroxyvaleric Acid (IV). A. From 6-(6-Aminopurin-9-yl)-6-deoxy-D-glucose (III).—III (2.0 g, 6.75 mmol) was dissolved in warm H_2O (180 ml), and the clear solution was cooled. To the solution was added 1 *N* NaOH (20 ml, 20 mmol) and this was stirred for 48 hr at room temperature under O_2 atmosphere and concentrated *in vacuo* to *ca.* 40 ml. To the residue was added EtOH to crystallize out the Na salt of IV as colorless crystals (1.59 g, 78%), mp 230° dec. The Na salt (1.0 g) was dissolved in H_2O. The solution was acidified with formic acid to pH 3–4 to give IV (0.78 g, 84%) as a colorless, crystal powder: mp 224° dec; $[\alpha]^{26}_{\mathrm{D}}$ +26.5° (*c* 1.21, 1 *N* NaOH); ir (Nujol) 3340 (–OH), 3210, 3050 (–NH), 1695 cm^{-1} (–CO).

Anal. Calcd for $C_{10}H_{13}O_5N_5$: C, 42.40; H, 4.63; N, 24.73. Found: C, 42.29; H, 4.78; N, 24.33.

B. From 6-(6-Aminopurin-9*H*-9-yl)-6-deoxy-1-*O*-*p*-tolylsulfonyl-D-fructose (VIIb).—A clear solution of VIIb (0.68 g, 1.5 mmol) and 1 *N* NaOH (6 ml) in H_2O (62 ml) was stirred for 47 hr at room temperature under an O_2 atmosphere. The reaction mixture was filtered, concentrated to *ca.* 20 ml, and adjusted to pH 3 with formic acid to give a colorless, crystal powder (0.18 g, 42%), mp 216–219° dec. After recrystallization from 1 *N* NaOH–formic acid, this product showed mp 221–223° dec. The ir of these crystals was identical with that of an authentic sample of IV.

5-(6-Aminopurin-9*H*-9-yl)-5-deoxy-2,3-*O*-isopropylidene-D-ribono-1,4-lactone (IX).—A mixture of adenine (3.38 g, 25 mmol) and NaOH (0.94 g, 64% in mineral oil, 25 mmol) in DMF (100 ml) was stirred at room temperature for 30 min and at 50° for 1 hr. To the suspension was added VIII (8.55 g, 25 mmol) in DMF (80 ml), and the solution was stirred at 50° for 6 hr. The reaction mixture was evaporated to dryness to give a semisolid, which was washed with ether, $CHCl_3$, and H_2O to give a colorless solid (4.29 g, 56%), mp 187–190°. Recrystallization from acetone afforded colorless, small needles: mp 192°; $[\alpha]^{26}_{\mathrm{D}}$ +31.7° (*c* 0.98, DMSO); ir (Nujol) 3320, 3110 (–NH), 1774 cm^{-1} (–CO); nmr (DMSO-d_6) τ 1.58 (s, 1 H), 1.66 (s, 1 H, C_2 H, C_8 H of purine), 2.45 (s, 2 H, –NH_2), 4.4–5.4 (m, 5 H), 8.48 (s, 3 H, –CH_3), 8.50 (s, 3 H, –CH_3).

Anal. Calcd for $C_{13}H_{15}O_4N_5$: C, 51.14; H, 4.95; N, 22.94. Found: C, 50.79; H, 4.88; N, 22.77.

5-(6-Aminopurin-9*H*-9-yl)-2(*R*),3(*R*),4(*R*)-trihydroxyvaleric Acid (X).—A mixture of IX (1.50 g, 4.91 mmol) and concentrated HCl (1.2 ml) in H_2O was warmed at 70° for 2.5 hr. This was cooled, adjusted to pH 8.5 with solid $NaHCO_3$, and heated on a steam bath for 5 min. The clear solution was cooled and acidified to pH 3 with formic acid to give colorless crystals (1.31 g, 94%), mp 218° dec. The crystals were reprecipitated from 1 *N* NaOH–formic acid to afford pure X: mp 225° dec; $[\alpha]^{26}_{\mathrm{D}}$ +40.6° (*c* 1.04, 1 *N* NaOH); ir (Nujol) 1695 cm^{-1} (–CO).

Anal. Calcd for $C_{10}H_{13}O_5N_5 \cdot {}^1/_4H_2O$: C, 41.74; H, 4.74; N, 24.34. Found: C, 41.64; H, 4.84; N, 24.07.

5-(6-Aminopurin-9*H*-9-yl)-D-ribono-1,4-lactone Hydrochloride (XI).—Through the suspension of X (0.80 g, 2.83 mmol) in isobutyl alcohol (50 ml), HCl gas was bubbled for 15 min under ice cooling. The mixture was stirred at 100–110° for 3 hr and cooled to afford colorless crystals (0.72 g, 85%), mp 253° dec. Recrystallization from H_2O–DMSO–acetone afforded small, colorless needles: mp 255° dec; $[\alpha]^{26}_{\mathrm{D}}$ +61.0° (*c* 1.29, H_2O); ir (Nujol) 1769 cm^{-1} (–CO).

Anal. Calcd for $C_{10}H_{11}O_4N_5 \cdot HCl$: C, 39.81; H, 4.01; N, 23.22; Cl, 11.75. Found: C, 40.15; H, 4.15; N, 23.02; Cl, 11.12.

5-(6-Aminopurin-9*H*-9-yl)-2(*S*),3(*R*),4(*R*)-trihydroxyvaleric Acid Isobutyl Ester (XIII).—Through the suspension of IV (3.9 g, 13.8 mmol) in isobutyl alcohol (250 ml), HCl gas was bubbled for 15 min under ice cooling. The mixture was kept at 100 110° for 45 hr and evaporated *in vacuo* to give a pale brown solid, which was washed with ether and dissolved in isobutyl alcohol (500 ml). To the solution was added Amberlite IR-45 (22 g, OH^- form), and this was stirred for 20 hr at room temperature. Amberlite IR-45 was filtered off, and the filtrate was concentrated to 20 ml, to which was added, ether to precipitate XIII (2.52 g, 54%), mp 164° dec. Recrystallization from isobutyl alcohol afforded a colorless, crystal powder: mp 166° dec; $[\alpha]^{26}_{\mathrm{D}}$ +19.3° (*c* 0.70, DMSO); ir (Nujol) 1720 cm^{-1} (–CO).

Anal. Calcd for $C_{14}H_{21}O_5N_5$: C, 49.55; H, 6.24; N, 20.64. Found: C, 48.99; H, 5.93; N, 20.94.

5-(6-Aminopurin-9*H*-9-yl)-2(*R*),3(*R*),4(*R*)-trihydroxyvaleric Acid Isobutyl Ester (XII).—The solution of XI (0.72 g, 2.39 mmol) in H_2O was adjusted to pH 8 with $NaHCO_3$ to afford 5-(6-aminopurin-9*H*-9-yl)-D-ribono-1,4-lactone (0.41 g, 55%), mp 232° dec, ir (Nujol) 1768 cm^{-1} (–CO). A suspension of this lactone (0.33 g, 1.25 mmol), Et_3N (0.31 ml), and AcOH (0.10 ml) in isobutyl alcohol (70 ml) was stirred at room temperature for 18 hr and then at 85° for 24 hr. The reaction mixture was filtered and evaporated to dryness *in vacuo* to give a colorless solid, which was washed with ether, 0.32 g (76%), mp 227° dec. Recrystallization from isobutyl alcohol and a small amount of H_2O afforded colorless crystals of XII: mp 231° dec (slightly changed at 180°); $[\alpha]^{26}_{\mathrm{D}}$ +12.4° (*c* 0.65, DMSO); ir (Nujol) 1735 cm^{-1} (–CO).

Anal. Calcd for $C_{14}H_{21}O_5N_5 \cdot {}^1/_4H_2O$: C, 48.89; H, 6.30; N, 20.37. Found: C, 49.00; H, 6.33; N, 20.18.

5-(6-Aminopurin-9*H*-9-yl)-5-deoxy-1,2-*O*-isopropylidene-D-xylo-

---

(10) This sample was not hygroscopic, but it became so after being dried at 50–60°.

furanose (XVIa).—The sodium salt of adenine prepared from adenine (3.78 g), sodium hydride (1.05 g, 64% oil dispersion), and 1,2-*O*-isopropylidene-5-*O*-tosyl-D-xylofuranose (XIV) (9.53 g) in DMF (120 ml) was heated at 100–120° for 20 hr. After removal of the solvent *in vacuo*, the residue was extracted with hot chloroform repeatedly. The combined extracts were evaporated and the residue was triturated with *n*-hexane. The resulting solid was recrystallized from chloroform. XVIa was obtained as colorless needles (2.41 g): mp 208–210°; $[\alpha]^{25}\mathrm{D}$ +20.6° (*c* 1.8, MeOH); uv max (MeOH) 262 nm (pH 7 and 12); nmr (DMSO-d_6) τ 1.90 (s, 1 H), 1.95 (s, 1 H, C_2 H, C_8 H of purine), 2.78 (broad s, 2 H, $-NH_2$), 4.27–4.25 (m, 2 H), 5.55–5.67 (m, 4 H), 6.03 (s, 1 H), 8.75 (s, 3 H), 8.85 (s, 3 H, $>CMe_2$).

Anal. Calcd for $C_{13}H_{17}N_5O_4$: C, 50.81; H, 5.58; N, 22.79. Found: C, 50.48; H, 5.73; N, 22.47.

5-(6-Aminopurin-9*H*-9-yl)-5-deoxy-1,2-*O*-isopropylidene-3-acetoxy-D-xylofuranose (XVIb).—The sodium salt of adenine (1.65 g) and 1,2-*O*-isopropylidene-3-*O*-acetyl-5-*O*-tosyl-D-xylofuranose (XV) (4.14 g) in DMF (50 ml) were heated at 100° for 10 hr. The solvent was removed under reduced pressure, and the residue was triturated with ether, taken up with chloroform, filtered, and evaporated. The residue was recrystallized from ethyl acetate. XVIb was obtained as colorless prisms (0.9 g): mp 201–202°; ir (Nujol) 1734, 1650, 1600 cm^{-1}; nmr ($CDCl_3$) τ 1.70 (s, 1 H), 2.10 (s, 1 H), 3.80 (broad s, 2 H, $-NH_3$), 4.04 (d, 1 H), 5.28–5.72 (m, 4 H), 7.92 (s, 3 H, $-COCH_3$), 8.56 (s, 3 H), 8.72 (s, 3 H, $>CMe_2$). *Anal.* Calcd for $C_{15}H_{19}N_5O_5$: C, 51.57; H, 5.48; N, 20.05. Found: C, 51.30; H, 5.52; N, 19.81.

4-(6-Aminopurin-9*H*-9-yl)-2(*S*),3(*R*)-dihydroxybutylic Acid (XVIII).—A solution of XVIa (1.5 g) in 1% HCl (50 ml) was warmed at 60° for 2.5 hr. After cooling, the solution was passed through a column of Amberlite IR-45. The eluates were spin evaporated *in vacuo* to dryness. The residue was taken up with $CHCl_3$, dried, and evaporated to give XVII as a powder (744 mg), nmr (DMSO-d_6) τ 1.85 (s, 1 H), 1.91 (s, 1 H, C_2 H, C_8 H of purine), 2.80 (broad s, 2 H, $-NH_2$), 4.10–6.20 (m, 8 H). A suspension of XVII (700 mg) in dilute NaOH solution (312 mg, 140 ml) was shaken with oxygen at room temperature for 30 hr. The resulting clear solution was passed through a column of Amberlite IR-120 to absorb the product. The column was eluted with dilute NH_4OH solution. The eluate was condensed under reduced pressure at 50–60°. The condensed solution (about 3 ml) was acidified with HCOOH, then the precipitates were collected and washed. XVIII was obtained as a colorless powder (320 mg): mp 300° dec; $[\alpha]^{25}\mathrm{D}$ +66.4° (*c* 1.1, 1 *N* NaOH); ir 3500–3200 (broad, OH), 3200, 3080 (NH), 1660 cm^{-1} (COOH); λ_{max} (H_2O) 261 nm, 259 (H^+), 263 (OH^-).

Anal. Calcd for $C_9H_{11}N_5O_4$: C, 42.69; H, 4.38; N, 27.67. Found: C, 42.53; H, 4.52; N, 27.34.

Methyl 3-Aminocarbonyl-2,3-diacetoxypropionate (XIX).—This amido ester was synthesized from L-tartaric acid using a method similar to that of Yokoo, *et al.*,[11] as a colorless, crystalline powder: mp 147–148°; ir (Nujol) 3340 (NH), 1770, 1745 (–CO), 1680 cm^{-1} (–CONH).

Anal. Calcd for $C_9H_{13}O_7N$: C, 43.73; H, 5.30; N, 5.67. Found: C, 44.11; H, 5.41; N, 5.72.

Methyl 3-Cyano-2,3-diacetoxypropionate (XX).—The amido ester XIX (10 g) was refluxed with $POCl_3$ (45 ml) for 30 min. The excess $POCl_3$ was removed by distillation *in vacuo*. The residue was poured into ice–water saturated with Na_2CO_3 and extracted with ether and $CHCl_3$. The extracts were dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was recrystallized from benzene–petroleum ether to give colorless needles: mp 74–74.5°; 7 g (73%); ir (Nujol) 2210 (CN), 1768, 1755 cm^{-1} (CO).

Anal. Calcd for $C_9H_{11}O_6N$: C, 47.16; H, 4.48; N, 6.11. Found: C, 47.33; H, 4.83; N, 6.11.

4-Amino-2(*R*),3(*S*)-dihydroxybutyric acid (XXI).—The nitrile XX (6.5 g) in MeOH (100 ml) was reduced at 80° for 6 hr in an autoclave in the presence of Raney Co (3 g) at an initial pressure of hydrogen of 85 atm. The reaction mixture was filtered, and the filtrate was spin evaporated *in vacuo*. The residue, dissolved in 6 *N* HCl (40 ml), was refluxed for 2.5 hr, and the HCl solution was distilled off. The remaining water was azeotropically removed by benzene. To the residue dissolved in MeOH (40 ml) was added pyridine (2 ml) to give a crude precipitate of XXI. Recrystallization of the crude XXI from H_2O afforded colorless crystals: 2.7 g (71%); mp 222–224° dec (lit.[9] mp 221–222° dec); $[\alpha]^{25}\mathrm{D}$ +43° (*c* 0.7, H_2O).

4-(4-Amino-5-nitropyrimidin-6′-yl)amino-2(*R*),3(*S*)-dihydroxybutyric Acid (XXII).—XXI (620 mg), 4-amino-6-chloro-5-nitropyrimidine (715 mg), KOH (258 mg), K_2CO_3 (475 mg), H_2O (10 ml), and acetone (5 ml) were mixed and refluxed for 1 hr. After cooling, the crystals which separated were collected and dried, mp 233–235° dec. A 952-mg quantity of the potassium salt of XXII was obtained: λ_{max} (H_2O) 347 nm; ir (Nujol) 1645 cm^{-1} (COOH); free acid mp 218–220° dec.

4-(4,5-Diaminopyrimidin-6-yl)amino-2(*R*),3(*S*)-dihydroxybutyric Acid (XXIII).—XXII (1.07 g) dissolved in H_2O (40 ml) was reduced in the presence of Raney Ni (2 ml) at an initial hydrogen pressure of 25 psi. The catalyst was filtered off, and the filtrate was adjusted to pH 4 with HCOOH. The crystals separated were collected and washed: mp >300°; 680 mg (84.3%); λ_{max} (H_2O) 286 nm, 279 (H^+), 289 (OH^-); ir (Nujol) 3350 (NH) 1640 cm^{-1} (COOH).

4-(6-Amino-8-mercaptopurin-9*H*-9-yl)-4-deoxy-L-threonic Acid (XXIV).—XXIII (670 mg) dissolved in DMF (180 ml), pyridine (10 ml), and CS_2 (5 ml) was refluxed for 2 hr, and spin evaporated *in vacuo*. The residue was triturated with H_2O to give XXIV: mp >300°; 475 mg (60.6%); λ_{max} (H_2O) 305 nm, 306 (H^+), 301 (OH^-).

4-(6-Aminopurin-9*H*-9-yl)-4-deoxy-L-threonic Acid (XXV).—XXIV (866 mg) dissolved in 3% NH_4OH (30 ml) was refluxed for 3.5 hr in the presence of Raney Ni (5 ml). The mixture was filtered. The filtrate was spin evaporated *in vacuo* and adjusted to pH 3 with 6 *N* HCl to give colorless crystals of XXV, mp 300° dec (lit.[8] mp 297° dec), $[\alpha]^{28}\mathrm{D}$ −67° (*c* 1.0, 1 *N* NaOH). The uv and ir spectra of this compound were identical with those of an authentic sample of XVIII.

Acknowledgment.—The authors are indebted to Mr. M. Yamazaki, director of this laboratory, for his generous support and encouragement; we are also grateful to Dr. S. Saito and Dr. M. Mizoguchi for advice and useful suggestions. Thanks are due to the staff of the analytical section presided over by Dr. K. Kotera for elemental and spectral analyses.

Registry No.—I (R = R′ = Me), 7595-86-0; I (R = Ph; R = H), 40518-91-0; IIa, 29789-10-4; IIb, 40518-93-2; III, 29789-11-5; IV, 29973-43-1; V, 32087-60-8; VI, 40518-97-6; VIIa, 40518-98-7; VIIb, 40518-99-8; VIII, 40519-00-4; IX, 29789-12-6; X, 29789-14-8; XI, 40519-03-7; XII, 40519-04-8; XIII, 40519-05-9; XIV, 20513-95-5; XV, 33156-03-5; XVIa, 40519-08-2; XVIb, 40519-09-3; XVII, 40519-10-6; XVIII, 28617-16-5; XIX, 40519-12-8; XX, 40519-13-9; XXI, 40519-14-0; XXII, 33171-94-7; XXII potassium salt, 40429-84-3; XXIII, 40429-85-4; XXIV, 40429-86-5; XXV, 28617-17-6; 1,2:3,5-di-*O*-benzylidene-D-glucofuranose, 22164-08-5; *p*-toluenesulfonnylchloride, 98-59-9; adenine, 73-24-5.

---

(11) A. Yokoo and S. Akutagawa, *Bull. Chem. Soc. Jap.*, **35**, 644 (1962).