Nucleosides from 3-Deoxy-3-methylamino-D-ribofuranose[1]

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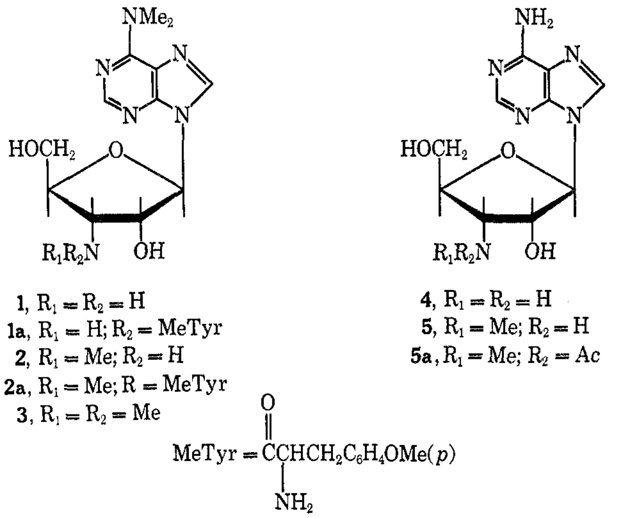
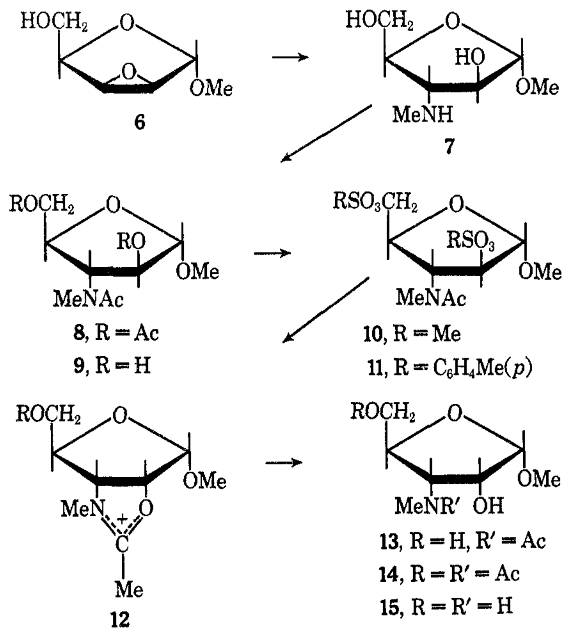
A number of 9-(3-deoxy-3-methylamino-β-D-ribofuranosyl)-6-substituted purines have been prepared with the 6 substituent being amino, dimethylamino (**2**), oxygen, and sulfur (**31**). Compound **31** is the first example of a nucleoside with purine-6-thione bonded to an amino sugar. Compound **2** was further substituted at the 3′-methylamino position with a *p*-methoxyphenyl-L-alanyl group to give 3′-*N*-methylpuromycin (**2a**). Eschweiler–Clarke methylation, carried out for the first time on a nucleoside, of the 6-dimethylaminopurine nucleoside **2** gave the 3′-deoxy-3′-dimethylamino-D-ribofuranose derivative **3**. The key intermediate required for the nucleoside condensations, 1,2,5-tri-*O*-acetyl-3-deoxy-3-(*N*-methylacetamido)-D-ribofuranose (**20**) was prepared from methyl 2,3-anhydro-α-D-lyxofuranoside (**6**) by a sequence of seven steps that included an intramolecular displacement by an *N*-methylacetamido neighboring group.

Puromycin (**1a**), an antibiotic with antitumor activity,[2] has been used as an important biochemical tool in the study of protein synthesis. The amino nucleoside **1** from puromycin and its adenine analog **4** also exhibit antitumor[3a,b] and other biological activity.[3c] In view of the great interest in the potential biological activity of puromycin analogs,[4] we have synthesized some 3′-*N*-methyl derivatives of **1** and **4** (*e.g.* **2**, **3**, and **5**) as well as 3′-*N*-methylpuromycin (**2a**).



The 3-deoxy-3-methylamino-D-ribofuranose moiety was prepared from the epoxide **6**[5] by the method (see Scheme I) used for 3-deoxy-3-aminoribose.[5] Aqueous methylamine cleaved **6** at the 3 position to give **7** with no detectable opening at C-2. Acetylation to **8** and selective deacylation gave crystalline **9**. In **9** the *N*-methylacetamido group existed in *cis* and *trans* forms according to the nmr spectrum.[6] Upon raising the

SCHEME I



temperature, the two *N*-acetyl signals collapsed to one signal. A number of the other *N*-methylacetamides also showed two forms, but the nmr spectra have not been examined at higher temperatures. While sulfonation of **9** with methanesulfonyl chloride afforded syrupy **10**, *p*-toluenesulfonyl chloride gave crystalline, stable **11** in good yield. Inversion of **11** at C-2 on treatment with sodium acetate in hot aqueous 2-methoxyethanol proceeded *via* the oxazolinium ion **12**. No relatively stable uncharged imidazoline intermediate[5] was possible with this amide. This appears to be the first carbohydrate example of a neighboring group participation reaction utilizing an N,N-disubstituted amide.[7,8] The inversion proceeded very cleanly,

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(1) This work was carried out under the auspices of Chemotherapy, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. PH-43-64-500. The opinions expressed here are those of the authors and not necessarily those of Chemotherapy.

(2) B. L. Hutchings in "Chemistry and Biology of Purines. CIBA Foundation Symposium," G. E. W. Wolstenholme and C. M. O'Connor, Ed., Little, Brown and Co., Boston, Mass., 1957.

(3) (a) B. R. Baker, R. E. Schaub, and H. M. Kissman, *J. Amer. Chem. Soc.*, **77**, 5911 (1955); (b) N. N. Gerber and H. A. Lechevalier, *J. Org. Chem.*, **27**, 1731 (1962); (c) J. T. Truman and S. Frederiksen, *Biophys. Biochim. Acta*, **182**, 36 (1969).

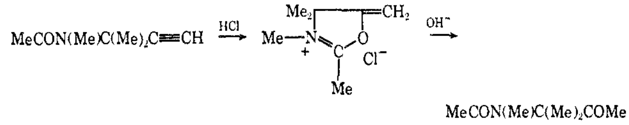
(4) See L. V. Fisher, W. W. Lee, and L. Goodman, *J. Med. Chem.*, **13**, 775 (1970), and references there.

(5) B. R. Baker, R. E. Schaub, and J. H. Williams, *J. Amer. Chem. Soc.*, **77**, 7 (1955).

(6) (a) H. Paulson and K. Todt, *Chem. Ber.*, **100**, 3385 (1967), have reported a carbohydrate amide showing two forms in its nmr spectrum. (b) R. C. Neumann, Jr., and V. Jonas, *J. Amer. Chem. Soc.*, **90**, 1970 (1968), have studied the hindrance to internal rotation of *N,N*-dimethylacetamide-d_6 by nmr.

(7) See L. Goodman, *Advan. Carbohyd. Chem.*, **22**, 109 (1967), for a recent review on participation reactions in sugars.

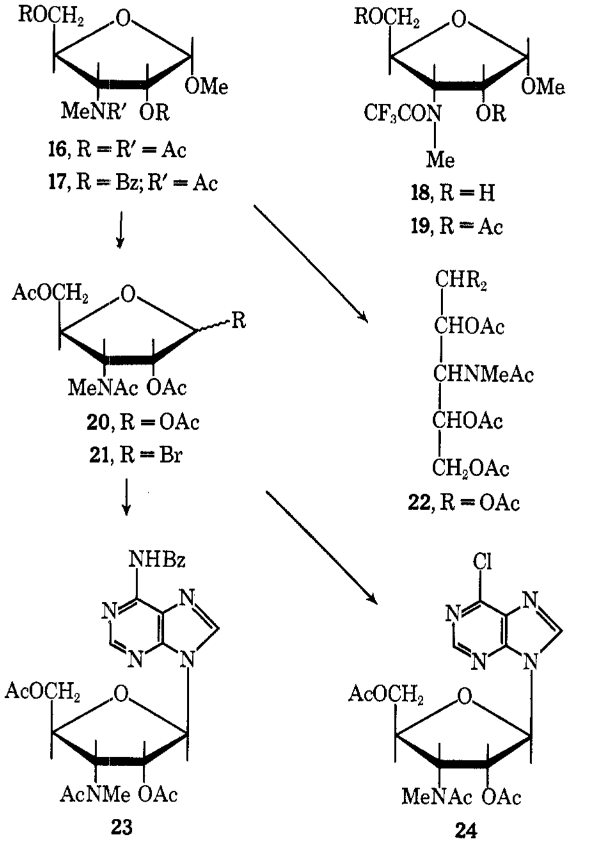
(8) N. R. Easton and R. D. Dillard, *J. Org. Chem.*, **28**, 2465 (1963), have reported the following tertiary amide participation reaction



for acetylation of the reaction mixture (**13**–**15**) gave only the syrupy ribose derivative **16**; none of the arabinoside **8** could be detected (limit of detection, <0.5%) by glc. Selective deacylation of **16** gave crystalline **13** which was unlike the arabinoside **9** in all its properties, but also like compound **9** showed two isomeric forms by nmr. Hot sodium hydroxide hydrolyzed **13** to **15** which was analyzed as the crystalline hydrochloride.

For the nucleoside condensations, the blocked methyl riboside **16** needed to be converted to the 1-*O*-acetate **20** or the halo sugar **21** (see Scheme II). The

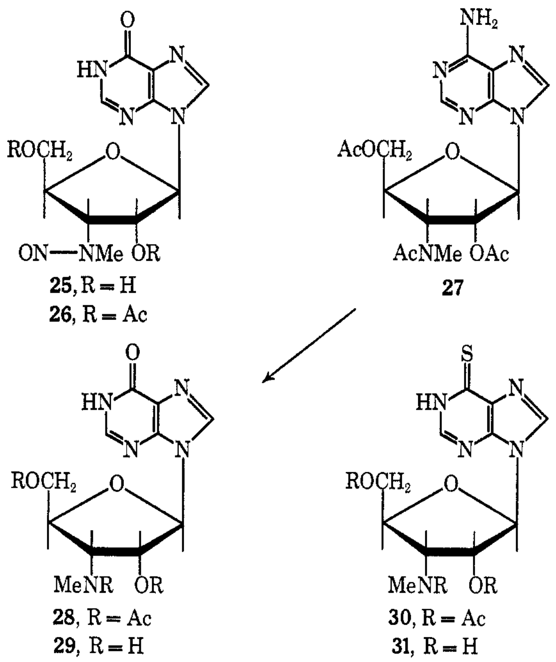
SCHEME II



acetolysis of **16** did not proceed in high yields, but **20** could be obtained in reproducible yields under carefully controlled conditions. The acyclic aldehyde diacetate **22**, one of the acetolysis by-products, could be isolated and characterized after being carried through the nucleoside condensation. The use of other blocking groups as in **17** and **19** was considered but was not found to be advantageous. Chloromercuri-6-benzamidopurine was condensed with the 1-*O*-acetate **20** by the titanium tetrachloride method[9] to afford the crystalline blocked nucleoside **23**. The combined yield of **23** and acyclic **22** was over 80%. An attempt to prepare the bromo sugar **21** gave a precipitate[10] which, when condensed with chloromercuri-6-benzamidopurine, gave a poorer yield of **23** than the first method. Heating **23** with 1.5 equiv of sodium methoxide in methanol for 8 hr gave the completely deblocked nucleoside **5** in high yield. The *N*-acetyl group was relatively easy to remove from this N,N-disubstituted amide in contrast to other monosubstituted amides on nucleosides.[11] In fact, attempts to hydrolyze **23** selectively to the 3′-*N*-acetyl derivative **5a** always gave some **5** also.

The chloropurine nucleoside **24** would seem to be a versatile intermediate for other nucleosides. The fusion of the 1-*O*-acetate **20** with 6-chloropurine afforded **24** in better yield than reaction of **20** with chloromercuri-6-chloropurine in the presence of titanium tetrachloride. The noncrystalline **24**, accompanied by small amounts of another nucleoside and the acetolysis by-products, could be converted to the crystalline **5**. The yields of **5** from the 1-*O*-acetate **20** *via* either **23** or **24** were equal. This established the amount of **24** present in the crude mixtures which were not readily purified and decomposed slowly on ordinary storage (probably because the acetolysis by-products gradually reacted with the chloropurine). In the future, it may be worthwhile to purify **24** by column chromatography to improve its shelf life.

The hypoxanthine nucleoside **29** could not be obtained by direct nitrosation of **5**; the product was the nitroso derivative **25** which was characterized as the



crystalline diacetate **26**. To prevent 3′-*N*-nitrosation, **5** was first converted to the triacetyl derivative **27** which reacted with nitrous acid to afford **28**; deacylation gave the desired **29**. Attempts to convert the triacetyl hypoxanthine nucleoside **28** to the chloronucleoside **24** by treatment with thionyl chloride and *N*,*N*-dimethylformamide (DMF)[12] gave mainly decomposition products with little or none of the chloro nucleoside **24**.

The mercaptopurine nucleoside **31** could be obtained by several routes, but in relatively poor yield. Thus,

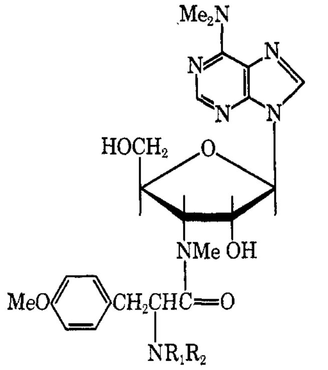
(9) (a) B. R. Baker, R. E. Schaub, J. P. Joseph, and J. H. Williams, *J. Amer. Chem. Soc.*, **77**, 12 (1955); (b) D. H. Murray and J. Prokop, *J. Pharm. Sci.*, **54**, 1468 (1965).

(10) This may be the insoluble HBr salt of the weakly basic amide group (see ref 9a for a similar insoluble salt) of **20** with perhaps some being converted to **21** or its salt.

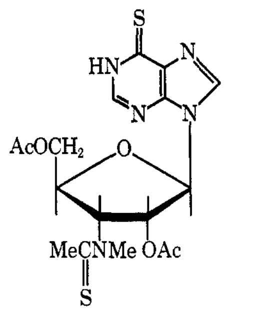
(11) (a) B. R. Baker and R. E. Schaub, *J. Amer. Chem. Soc.*, **77**, 2396 (1955); (b) M. L. Wolfrom, P. J. Conigliaro, and E. J. Soltes, *J. Org. Chem.*, **32**, 653 (1967), discussed the removal of *N*-acetyl groups and the choice of other N-blocking groups for amino sugar nucleoside synthesis. (c) K. A. Watanabe, J. Beránek, H. A. Friedman, and J. J. Fox, *ibid.*, **30**, 2735 (1965), have converted *N*-acetyls of nucleosides to *N*-thioacetyls for easier removal.

(12) J. Pliml and F. Šorm, *Collect. Czech. Chem. Commun.*, **28**, 546 (1963).

thiation of the acetylated hypoxanthine nucleoside **28** with phosphorus pentasulfide in hot pyridine afforded the crystalline 3′-thioacetamido-6-mercaptopurine nucleoside **34**. Deacylation in refluxing methanolic



32, R_1 = Cbz; R_2 = H
33, R_1; R_2 = Me_2C=



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sodium methoxide under various conditions was either incomplete or gave **31** accompanied by some by-products. The chloropurine nucleoside **24** could be treated with either thiourea or sodium hydrogen sulfide, preferably with the latter, to give the desired **31** after deacylation. Compound **31** sometimes required purification *via* the lead salt since **31** was not as readily crystallized as **2** or **5** from the reaction mixtures that contained appreciable amounts of by-products. Compound **31** is the first example of a mercaptopurine nucleoside of an amino sugar.

Reaction of the chloropurine nucleoside **24** with hot methanol and dimethylamine readily afforded, after sodium methoxide treatment, the dimethylaminopurine nucleoside **2**. Omission of the sodium methoxide step resulted in incomplete 3′-*N*-deacylation. The nucleoside **2** was coupled to *N*-benzyloxycarbonyl-*p*-methoxy phenyl-L-alanine[13] by the dicyclohexylcarbodiimide–*N*-hydroxysuccinimide method[14] to afford the blocked nucleoside peptide **32** in excellent yield. Other coupling methods gave much less or no **32**. Hydrogenolysis readily yielded **2a** which is 3′-*N*-methylpuromycin. Attempts to crystallize **2a** from acetone afforded the crystalline azomethine derivative **33**. This was stable in acetone or as a crystalline solid. In other solvents, it reverted back to **2a**.

Treatment of **2** with formaldehyde and formic acid gave the crystalline 3′-dimethylamino nucleoside **3**. This is apparently the first time that the Eschweiler–Clarke methylation procedure[15a] has been applied to a nucleoside, although it has been employed with aminosugars.[15b] That **3** cannot undergo 3′-*N*-acylation may make it an interesting analog of the puromycin nucleoside **1**.

All the nucleosides have been assigned as β anomers on the basis that **5**, predictably the β anomer when produced from the bromo sugar **21** and chloromercuri-6-benzamidopurine,[16] was the same when prepared from the chloropurine nucleoside **24**. If **24** and **5** are β anomers, so must be all the other nucleosides derived from them. This conclusion is supported by circular dichroism (CD) measurements[17] showing that **2**, **3**, and **5** have the same anomeric configuration as **1**, which is known to be the β anomer.[18] In addition, Eschweiler–Clarke methylation of **1** gave the same product, **3**, obtained from **2**.

Experimental Section[19]

Methyl 3-Deoxy-3-methylamino-α-D-arabinofuranoside (7).—Methyl 2,3-anhydro-α-D-lyxofuranoside **6**[5] (3.00 g, 20.5 mmol) and 21 ml of anhydrous methylamine were heated in a bomb at steam bath temperature for 28 hr. After evaporation for 20 hr at 60°, there was left 3.66 g (100%) of **7** as a homogeneous syrup, R_f 0.58 in solvent TA. This was immediately used in the next step. The use of 40% aqueous methylamine was more convenient and gave the same results.

A 1.31-g portion of **7** from another run was dissolved in an equivalent amount of 1 *N* HCl (7.43 ml) and evaporated to give 1.57 g (100%) of the hydrochloride of **7**, mp 120–122.5°. Crystallization from 100 ml of acetonitrile gave 1.29 g (84%) of white crystals of **7**·HCl: mp 126–127°; $[\alpha]^{20}D$ 99° (*c* 1.0, H_2O); nmr (D_2O) δ 5.10 (s, 1, H-1), 3.44 (s, 3, OCH_3), and 2.87 (s, 3, NCH_3); R_f 0.47 in solvent TB.

Anal. Calcd for $C_7H_{15}NO_4 \cdot HCl$: C, 39.4; H, 7.55; Cl (ionic), 16.6; N, 6.56. Found: C, 39.6; H, 7.64; Cl (ionic), 16.3; N, 6.58.

Methyl 3-Deoxy-2,5-di-*O*-acetyl-3-*N*-methylacetamido-α-D-arabinofuranoside (8).—The above 3.66 g of **7** was stirred with 23.2 ml of acetic anhydride and 50 ml of pyridine at room temperature for 24 hr to give, after work-up and thorough drying *in vacuo*, 5.12 g (82%) of **8** as a syrup: $[\alpha]^{24}D$ +89° (*c* 0.87, $CHCl_3$); nmr ($CDCl_3$) δ 5.10 (m, 2, H-2 and H-3), 4.95 (s, 1, H-1), 4.23 (m, 3, H-4 and 2 H-5), 3.44 (s, 3, OCH_3), 3.07 (s, 2.3, N-CH_3 one form), 2.95 (s, 0.7, N–CH_3 another isomer), and 2.12 (s, 3, $NCOCH_3$); R_f 0.73 in solvent TC.

Anal. Calcd for $C_{13}H_{21}NO_7$: C, 51.5; H, 6.98; N, 4.62. Found: C, 51.2; H, 7.01; N, 4.26.

Methyl 3-Deoxy-3-*N*-methylacetamido-α-D-arabinofuranoside (9).—A 10.2 g (33.7 mmol) portion of **8** in 50 ml of dry methanol containing 3 ml of 1 *N* sodium methoxide in methanol was kept overnight, neutralized with acetic acid and filtered to give 3.34 g of **9**, mp 155–156°, and a second crop of 2.43 g of **9**, mp 152–154° (total yield 78%).

A sample from an earlier run was recrystallized from ethanol to give the analytical sample of **9**: mp 155–156°; $[\alpha]^{23}D$ +89° (*c* 0.99, H_2O); nmr (D_2O) δ 5.05 (d, 1, $J_{1,2}$ = 2 Hz, H-1), 3.55 (s, 3, OCH_3), 3.15 and 2.99 (both s, 3, N–CH_3, two forms), 2.30 and 2.25 (both s, 3, NAc, two forms); at 95° the protons of the NAc group had collapsed to a singlet at 2.25, but the two N–CH_3 peaks were only slightly changed; R_f 0.13 in solvent TD.

Anal. Calcd for $C_9H_{17}NO_5$: C, 49.3; H, 7.82; N, 6.39. Found: C, 49.5; H, 7.84; N, 6.15.

Further recrystallizations did not change the rotation or

(13) (a) R. P. Rivers and J. Lerman, *J. Endocrinol.*, **5**, 223 (1948); (b) H. E. Carter and J. W. Hinman, *J. Biol. Chem.*, **178**, 403 (1949).

(14) (a) F. Weygand, D. Hoffman, and E. Wünsch, *Z. Naturforsch.*, **21b**, 426 (1966); (b) J. E. Zimmerman and G. W. Anderson, *J. Amer. Chem. Soc.*, **89**, 7151 (1967).

(15) (a) M. L. Moore in "Organic Reactions" Vol. V, R. Adams, *et al.*, Ed., Wiley, New York, N. Y., 1949, p 301; (b) C. Richardson, *J. Chem. Soc.*, 5364 (1964).

(16) B. R. Baker in ref 2, pp 120–129.

(17) R. H. Iwamoto, *et al.*, manuscript in preparation, describing CD studies of a number of nucleosides.

(18) C. W. Waller, P. W. Fryth, B. L. Hutchings, and J. H. Williams, N. Y. Meeting in Miniature, Feb 1954.

(19) Melting points were determined on a Fisher–Johns apparatus and are corrected. Optical rotations were obtained with a Perkin-Elmer Model 141 automatic polarimeter; nmr, with a Varian A60 or HA 100; CD, with a Jasco Model ORD/UV-5, Sproule Scientific SS 107 CD modification. Evaporations were carried out *in vacuo* at or below 45° unless specified otherwise. Anhydrous magnesium sulfate was used as drying agent. Celite is a diatomaceous earth product of Johns–Manville. Glc was run on a Varian 2100-20. Paper chromatograms were run by the descending technique on Whatman No. 1 paper in these solvent systems: PA, *n*-butyl alcohol–water (saturated); PC, 5% aqueous disodium hydrogen phosphate, pH 8.9; PE, *n*-butyl alcohol–acetic acid–water (5:2:3); PF, *t*-butyl alcohol–water (5:1); PG, 3% aqueous ammonium chloride; PP, aqueous saturated ammonium sulfate–2-propanol–water (2:28:70). Tlc was run on silica gel HF (E. Merck AG Darmstadt) in these solvent systems: TA, methanol–ethyl acetate (4:6); TB, methanol; TC, ethanol–ethyl acetate (1:9); TD, chloroform–methanol (19:1); TE, same (4:1); TF, same (9:1). The spots were detected under uv light or by iodine vapor and reported as R_f or R_{Ad} in relation to solvent front or adenine, respectively.

melting point of **9**. Its 2,5-di-*O*-*p*-nitrobenzoate (**9**, R = $OCC_6H_4NO_2$-*p*) had mp 150–151°, $[\alpha]^{24}D$ +16.6° (*c* 0.99, $CHCl_3$).

Anal. Calcd for $C_{22}H_{23}N_3O_{11}$: C, 53.4; H, 4.48; N, 8.12. Found: C, 53.6; H, 4.61; N, 8.25.

Methyl 3-Deoxy-3-(*N*-methylacetamido)-2,5-di-*O*-*p*-toluenesulfonyl-α-D-arabinofuranoside (11).—To a cold (0°) stirred solution of 8.37 g (40 mmol) of the arabinofuranoside (**9**) in 200 ml of dry pyridine was added 30.5 g (160 mmol) of *p*-toluenesulfonyl chloride. After stirring at 0° for 1 hr, the solution was stored at 5°, protected from moisture, for 65 hr. The solution was cooled to 0°, diluted with 20 ml of ice water, and stirred at 0° for 15 min. The mixture was then poured into 600 ml of cold water and extracted with two 100-ml portions of chloroform. The chloroform extracts were washed with 150 ml of saturated sodium bicarbonate solution and with two 200-ml portions of water. After drying, the chloroform solution was treated with charcoal and evaporated; the residue was suspended in 50 ml of toluene and reevaporated to a reddish-white solid, 19.9 g. The crude product was dissolved in 300 ml of preheated methanol and cooled to 5° to afford **11** as yellowish-white fibrous needles, 15.4 g (73%), mp 132.5–133.5°; R_f 0.65 in solvent TD. The product from another run was triturated with methanol to afford the analytical sample of **11** as white needles, mp 134–135°.

Anal. Calcd for $C_{23}H_{29}NO_9S_2$: C, 52.4; H, 5.54; N, 2.66; S, 12.2. Found: C, 52.5; H, 5.65; N, 2.84; S, 12.1.

Crystalline **11** can be kept at 5° for 1 year without decomposition. A chloroform solution of **11** showed two new spots by tlc after 1 week. A refluxing absolute ethanol solution of **11** is 50% decomposed after 30 min, and 90% after 1 hr. By ir, one decomposition product may be the toluenesulfonic acid salt of methyl 2-*O*-acetyl-3-deoxy-3-methylamino-5-*O*-tosyl-α-D-ribofuranoside.

The dimesyl sugar **10** could be prepared by the same procedure as a homogeneous oil which was unstable.

Methyl 2,5-Di-*O*-acetyl-3-deoxy-3-(*N*-methylacetamido)-α-D-ribofuranoside (16).—A stirred suspension of 15.8 g (30 mmol) of the ditosylate **11** and 12.3 g (150 mmol) of anhydrous sodium acetate in 200 ml of 95% aqueous 2-methoxyethanol was heated at reflux for 21 hr. The solution was evaporated; the residue was suspended in 75 ml of toluene and reevaporated. A suspension of the residue in a mixture of 50 ml of acetic anhydride and 100 ml of dry pyridine was stirred and heated at 100° for 1 hr. The mixture was worked up to leave 8.42 g (93%) of **16** as an orange-yellow syrup: $[\alpha]^{22}D$ +163° (*c* 0.61, $CHCl_3$); ir (neat) 5.71 (C=O ester), 6.02 (C=O amide), 8.10 μ (ester); nmr ($DCCl_3$) δ 5.14 (m, 3, H-1, 2,3), 4.25 (m, 3, H-4 and 2 H-5), 3.48 and 3.45 (both s, 3, OCH_3), 3.09 and 2.97 (both s, 3, N–CH_3), 2.14 and 2.10 (both s, 9, 3 $COCH_3$); glc (packing: 5% STAP on 80–100 Chromosorb W, acid washed, 6 ft × 2 mm; column temperature 215°; injection temperature 240°; H_2 flame detector temperature 300°; flow rate, 26 ml/min of He) retention time 250 sec (99.2%) for **16**; no **8**, retention time 228 sec was detected (limit of detection, 0.5%); a minor unidentified peak (0.8%) occurred at a retention time of 296 sec; R_f 0.50 in solvent TD.

Anal. Calcd for $C_{13}H_{21}NO_7 \cdot {}^1/_4H_2O$: C, 50.7; H, 7.04; N, 4.55. Found: C, 50.8; H, 7.07; N, 4.55.

Methyl 3-Deoxy-3-(*N*-methylacetamido)-α-D-ribofuranoside (13).—A cold (0°) solution of 8.29 g (27.4 mmol) of the triacetate **16** in 150 ml of methanol was saturated with ammonia, allowed to stand at 25° for 16 hr, and evaporated. Crystallization of the product from 65 ml of ethyl acetate afforded 4.49 g (75%) of **13**, mp 107.5–109°. Recrystallization from ethyl acetate gave analytically pure **13**, melting point unchanged; $[\alpha]^{19}D$ +221° (*c* 0.99, H_2O); nmr (D_2O) δ 5.08 (d, 1, $J_{1,2}$ = 4.5 Hz, H-1), 3.48 (s, 3, OCH_3), 3.12 and 2.97 (both s, 3, N–CH_3), and 2.18 (s, 3, $NCOCH_3$); R_f 0.12 in solvent TD.

Anal. Calcd for $C_9H_{17}NO_5$: C, 49.3; H, 7.82; N, 6.39. Found: C, 49.5; H, 8.02; N, 6.47.

Methyl 3-Deoxy-3-(methylamino)-α-D-ribofuranoside Hydrochloride (15·HCl).—A solution of 7.84 g (25.8 mmol) of the triacetate **16** in 78 ml of 1.0 *N* sodium hydroxide was heated on the steam bath for 15 hr. The solution was cooled to 0°, acidified with 104 ml of 1.0 *N* hydrochloric acid, treated with charcoal, and evaporated. The residue was triturated with 75 ml of hot absolute ethanol; the sodium chloride was removed by filtration and washed with two 20-ml portions of absolute ethanol. The combined ethanol solution was evaporated; the residue was crystallized from 40 ml of hot absolute ethanol, to afford 4.60 g (83%) of **15**·HCl as white needles, mp 120–121.5°. The mother liquors gave an additional 0.68 g of **15**·HCl [total 5.28 g (95%)], mp 120–121°. The analytical sample of **15**·HCl, recrystallized from absolute ethanol, had mp 120.5–121.5°: $[\alpha]^{20}D$ +112° (*c* 0.99, H_2O); nmr (D_2O) δ 5.11 (d, 1, $J_{1,2}$ = 4 Hz, H-1), 3.48 (s, 3, OCH_3), and 2.83 (s, 3, NCH_3); R_f 0.29 in solvent TB.

Anal. Calcd for $C_7H_{15}NO_4 \cdot HCl$: C, 39.4; H, 7.55; Cl (ionic), 16.6; N, 6.56. Found: C, 39.5; H, 7.54; Cl (ionic), 16.2; N, 6.48.

Methyl 2,5-Di-*O*-benzoyl-3-deoxy-3-(*N*-methylacetamido)-α-D-ribofuranoside (17).—A solution of 3.16 g (14.4 mmol) of the acetamidoribofuranoside (**13**) in 30 ml of dry pyridine was treated with 3.7 ml (31.8 mmol) of benzoyl chloride and kept at 25° for 17 hr, to leave, after work-up, 5.53 g (90%) of **17** as a pale yellow gum. For analysis, a sample was dried at 100° (0.1 Torr) for 15 hr; $[\alpha]^{16}D$ +98° (*c* 1.88, $CHCl_3$); R_f 0.70 in solvent TD.

Anal. Calcd for $C_{23}H_{25}NO_7$: C, 64.6; H, 5.90; N, 3.27. Found: C, 64.3; H, 6.00; N, 3.40.

Attempts to prepare the 1-*O*-acetate derived from **17** by treatment with acetic anhydride, acetic acid, and sulfuric acid, resulted in some replacement of benzoyl by acetyl according to nmr data.

Methyl 3-Deoxy-3-(*N*-methyltrifluoroacetamido)-α-D-ribofuranoside (18).—A solution of 2.14 g (10 mmol) of the aminoribofuranoside hydrochloride **15**·HCl in 10 ml of trifluoroacetic anhydride was allowed to stand at 5° for 15 hr and then evaporated. The residue was dissolved in 50 ml of methanol, refluxed for 25 min, and then evaporated to a crystalline residue. The product was dissolved in 10 ml of hot methanol, diluted with 50 ml of hot chloroform, and allowed to cool to afford 2.11 g (73%) of **18** as white fibrous needles, mp 153–154.5°. The mother liquors yielded an additional 0.47 g [total 2.58 g (88%)], mp 153–154°. For analysis, a sample was recrystallized from methanol-chloroform (1:5) to give **18**, melting point unchanged: ir (Nujol) 3.06 (OH), 5.90 μ (amide); $[\alpha]^{16}D$ +83° (*c* 0.84, H_2O); R_f 0.10 in TE.

Anal. Calcd for $C_9H_{14}F_3NO_5$: N, 5.13. Found: N, 4.97.

Attempts to convert **18** to the diacetyl **19** with acetic anhydride in pyridine resulted in conversion to the triacetyl sugar **16** according to ir data.

Acetolysis of Methyl 3-Deoxy-2,5-di-*O*-acetyl-3-(*N*-methylacetamido)-α-D-ribofuranose (16).—To a cold (0°) stirred solution of 15.00 g (49.5 mmol) of the methyl riboside (**16**) in 70 ml each of acetic anhydride and acetic acid was added 8.25 ml (148.5 mmol) of sulfuric acid dropwise over a 1-hr period. The solution was stirred and protected from moisture at 25° for 23 hr. The reaction mixture was cooled to 0°, 26.0 g (317 mmol) of anhydrous sodium acetate was added, and the mixture was stirred at 25° for 30 min and then evaporated (≤30°). The residue was suspended in 200 ml of methanol and reevaporated; the evaporation with methanol was repeated. A solution of the residue in 200 ml of chloroform was washed with two 300-ml portions of saturated sodium bicarbonate solution and with two 50-ml portions of water. The dried chloroform solution was treated with charcoal and evaporated to leave 14.0 g of a pale yellow syrup. [The product was a mixture of ~29% of **16**, ~55% of **20**, ~11% of aldehyde (*e.g.*, **22**, R_2 = O), and ~5% of other products as estimated by nmr analysis; the yield of **20** was 47%.] The above product mixture was treated a second time with 5.90 ml (106 mmol) of sulfuric acid in 50 ml each of acetic acid and acetic anhydride at 25° for 23 hr; the mixture was worked up as described above to leave 12.6 g of a pale yellow syrup. [This product was a mixture of ~11% of **16**, ~63% of the 1-*O*-acetate (**20**), ~7% of the aldehyde (**22**, R_2 = 0), and ~19% of the aldehyde diacetate (**22**); the yield of **20** was 48%]: ir (neat) 5.70 (C=O, ester), 6.02 (C=O, amide), 8.12 μ (acetate); nmr ($CDCl_3$) δ 9.49 (s, CHO), 6.15 (H-1 of **20**), and various amounts of H-1 of **22**, 1-OCH_3 of **16**, and $COCH_3$ (for δ values see under particular compound) which were used to estimate mixture composition; R_f 0.40 and 0.60 in solvent TD.

Various acetolysis conditions were studied and found less satisfactory than the above. For example, pouring the acetolysis mixture into ice water[20] in the work-up gave little or no chloroform soluble product.

9-[2,5-Di-*O*-acetyl-3-deoxy-3-(*N*-methylacetamido)-β-D-ribofuranosyl]-6-benzamidopurine (23).—Using a literature procedure,[9b] 22.6 g (47.6 mmol) of chloromercuri-6-benzamidopurine (35.3 g of a 36% Celite mixture) and 7.94 g (24.0 mmol)

(20) K. J. Ryan and E. M. Acton in "Synthetic Procedures in Nucleic Acid Chemistry," Vol. 1, W. W. Zorbach and R. S. Typson, Ed., Interscience, New York, N. Y., 1968, p 165.

of the tetraacetate **20** (12.6 g of a 63% pure sample) in 1,2-dichloroethane were treated with 5.25 ml (47.7 mmol) of titanium tetrachloride in the same solvent and refluxed for 22 hr, then worked up to give 11.4 g of **23** as a foam. Crystallization from 20 ml of warm alcohol diluted with 200 ml of warm water gave 5.66 g (46%) of **23** as fibrous needles, mp 95.5–98.5°. Recrystallization from water gave the analytical sample of **23**: mp 96.5–99.5°; $[\alpha]^{20.5}D$ −27° (*c* 0.99, EtOH); ir 5.71 (C=O, acetate) 5.87 (C=O, benzamide), 6.02 (C=O, acetamide), 6.22, 6.32 (purine), 8.14 μ (ester); uv max (pH 1) 252 mμ (ε 11,400), 291 (26,300); (EtOH) 231 mμ (ε 13,200), 253 sh (~11,700), 262 sh (~13,100), 279 (21,300); (pH 13) 303 mμ (ε 13,900); nmr ($DCCl_3$) δ 9.64 (s, 1, NHBz), 8.71 and 8.23 (both s, 2, H-2/H-8), 8.04 and 7.5 (both m, 5, C_6H_5CO), 6.40 (d, 1, $J_{1',2'}$ = 4 Hz, H-1'), 3.11 and 3.06 (both s, NCH_3); R_f 0.30 in solvent TD.

Anal. Calcd for $C_{24}H_{26}N_6O_7$: C, 56.5; H, 5.13; N, 16.5. Found: C, 56.3; H, 5.33; N, 16.3.

1,1,2,4,5-Penta-*O*-acetyl-3-deoxy-3-(*N*-methylacetamido)-D-ribose (22).—The aqueous ethanolic mother liquors, from the crystallization of the 6-benzamidonucleoside (**23**), were concentrated to approximately 75 ml and then extracted with six 35-ml portions of ether. The combined ether extract was washed with 20 ml of water, dried, treated with charcoal, and evaporated to a partially crystalline residue, 1.69 g. The residue was dissolved in 10 ml of hot benzene, diluted with 40 ml of hot cyclohexane, filtered, and allowed to cool to afford 0.95 g (40%) of light yellow crystals, mp 112.5–115.5°. Recrystallization from benzene–cyclohexane (1:4) gave the analytical sample of **22**: mp 115–116.5°; $[\alpha]^{20}D$ +41° (*c* 1.99, $CHCl_3$); ir (Nujol) 5.61, 5.70 (C=O, ester), 6.02 (C=O, amide), 8.00, 8.10, 8.20 μ (COOR); nmr ($CDCl_3$) δ 6.85 (d, $J_{1,2}$ = 7 Hz, H-1), 3.17 (s, 3, NCH_3), 2.08 and 2.04 (both s, 18 $COCH_3$); R_f 0.64 in solvent TD.

Anal. Calcd for $C_{18}H_{27}NO_{11}$: C, 49.9; H, 6.28; N, 3.23. Found: C, 50.2; H, 6.51; N, 3.34.

9-[2,5-Di-*O*-acetyl-3-deoxy-3-(*N*-methylacetamido)-β-D-ribofuranosyl]-6-chloropurine (24).—A mixture of 3.09 g (20 mmol) of 6-chloropurine and 6.27 g (19 mmol) of the tetraacetate **20** [11.0 g of a 57% pure sample of **20**] was stirred and heated in an oil bath at 135–140°, 0.100 g of *p*-toluenesulfonic acid monohydrate was added, and the flask was evacuated to 0.25 Torr. The melt was stirred at 135–140° (0.25 Torr) for 20 min and then cooled. A solution of the fusion product in 150 ml of methylene chloride was washed with 25 ml of saturated sodium bicarbonate solution and with two 25-ml portions of water. The dried organic solution was treated with charcoal and evaporated to a foam, 11.80 g (uv indicated a purity of approximately 60%): uv max (EtOH) 250 mμ sh (ε 4460), 264 (5960); R_f 0.40 [chloronucleoside (**24**)], 0.48 and 0.63 (acetolysis by-products) in solvent TD.

9-(3-Deoxy-3-methylamino-β-D-ribofuranosyl)adenine (5).—A solution of 5.66 g (11.1 mmol) of the 6-benzamidonucleoside (**23**) and 17 ml of 1.0 *M* methanolic sodium methoxide in 225 ml of methanol was stirred and refluxed for 8 hr, during which time the aminonucleoside (**5**) crystallized from the reaction mixture. The mixture was cooled and adjusted to pH 8–9 with acetic acid; the crystalline precipitate was collected and washed with four 5-ml portions of methanol and three 5-ml portions of methylene chloride to afford 2.74 g (89%) of **5**, mp 244–247° dec. An additional 0.14 g [total 2.88 g (93%)] of **5**, mp 243–245°, was obtained from the mother liquors. The analytical sample of **5**, recrystallized twice from water, had mp 247.5–250° dec: $[\alpha]^{19}D$ −103° (*c* 1.00, 1.0 *N* NaOH); uv max (pH 1) 206 mμ (ε 22,100), 256 (14,800); (pH 7) 207 mμ (ε 20,400), 259 (15,100); (pH 13) 259 mμ (ε 15,200); nmr (DMSO-d_6, D_2O exchanged) δ 8.39 and 8.15 (both s, 2, H-2 and H-8), 5.95 (d, $J_{1',2'}$ = 3 Hz, H-1'), 2.32 (s, 3, NCH_3); R_f 0.37 in solvent TB; R_{Ad} 0.79, 1.56, and 0.78 in solvents PA, PC, and PE, respectively.

Anal. Calcd for $C_{11}H_{16}N_6O_3$: C, 47.1; H, 5.76; N, 30.0. Found: C, 46.9; H, 5.93; N, 30.1.

Attempts to selectively deacylate **23** at room temperature to the 3'-*N*-acetyl derivative (**5a**) of **5** were not successful. Treatment with 1 equiv of sodium methoxide in methanol for 16 hr gave **5a**:**5** in the ratio of 1:1; 0.2 equiv for 45 hr, a ratio of 9:1.

Treatment of the chloropurine **24** with methanolic ammonia at 100° for 15 hr followed by methanolic sodium methoxide deacylation as above gave **5** in 43% yield overall from **20**; the same yields as *via* **23** to **5** are obtained from **20**.

9-[2,5-Di-*O*-acetyl-3-deoxy-3-(*N*-nitrosomethylamino)-β-D-ribofuranosyl]hypoxanthine (26).—A solution of 1.40 g (5.0 mmol) of the aminonucleoside **5** and 2.07 g (30 mmol) of sodium nitrite in 10 ml of acetic acid and 30 ml of water was kept at 25° for 24 hr and then evaporated. The residue of **25** was acetylated with 10 ml of acetic anhydride in 50 ml of pyridine at 25° for 23 hr and evaporated. The residue was triturated several times with water (5-ml portions), three times with methanol (4-ml portions), and dried to afford 1.82 g (92%) of **26**, mp 244–245.5° dec. Two recrystallizations from water gave the analytical sample of **26**: mp 247.5–249° dec; $[\alpha]^{20}D$ −36° (*c* 0.99, pyridine); uv max (pH 1) 243 mμ (ε 17,600); (pH 7) 242 mμ (18,000); (pH 13) 252 mμ (18,000); R_f 0.34, in solvent TF; R_{Ad} 2.18 and 1.43 in solvents PC and PE, respectively.

Anal. Calcd for $C_{15}H_{18}N_6O_7$: C, 45.7; H, 4.60; N, 21.3. Found: C, 45.7; H, 4.79; N, 21.1.

9-[2,5-Di-*O*-acetyl-3-deoxy-3-(*N*-methylacetamido)-β-D-ribofuranosyl]adenine (27).—A suspension of 2.80 g (10 mmol) of the aminonucleoside **5** and 5.0 ml (53 mmol) of acetic anhydride in 100 ml of pyridine was stirred at 25° for 4 hr, during which time **5** dissolved. After the solution was worked up the residue was crystallized from 220 ml of absolute ethanol to give 2.93 g (72%) of **27** as white crystals, mp 222.5–224.5°. The mother liquors gave another 0.73 g [total 3.66 g (90%)] of **27**, mp 220–223°. A recrystallization from absolute ethanol afforded the analytical sample of **27**: mp 224–225.5°; $[\alpha]^{21.5}D$ −15° (*c* 0.99, pyridine); uv max (pH 1) 257 mμ (ε 13,800); (pH 7) 259 mμ (ε 13,900); (pH 13) 260 mμ (ε 14,200); R_f 0.70 in solvent TE; R_{Ad} 1.39, 1.95, and 1.38 in PA, PC, and PE, respectively.

Anal. Calcd for $C_{17}H_{22}N_6O_6 \cdot {}^1/_4H_2O$: C, 49.7; H, 5.52; N, 20.5. Found: C, 49.8; H, 5.60; N, 20.6.

9-[2,5-Di-*O*-acetyl-3-deoxy-3-(*N*-methylacetamido)-β-D-ribofuranosyl]hypoxanthine (28).—A 2.80 g (10 mmol) portion of **5** was acetylated as before, but the product **27** was immediately treated with 2.76 g (40 mmol) of sodium nitrite in 10 ml of acetic acid and 30 ml of water by the procedure used for **26**. Crystallization of the product, **28**, from 100 ml of methanol gave 3.06 g (75%) of **28** as white crystals, mp 239–241°, with a second crop of 0.37 g (total 84%), mp 238–240°. Recrystallization from methanol afforded the analytical sample of **28**: mp 240–241°; $[\alpha]^{21.5}D$ −24° (*c* 0.92, pyridine); uv max (pH 1) 248 mμ (ε 12,100); (pH 7) 248 mμ (ε 12,300); (pH 13) 253 mμ (ε 13,500); R_f 0.54 and 0.22 in solvents TE and TF, respectively; R_{Ad} 1.02, 2.38, and 1.25 in solvents PA, PC, and PE, respectively.

Anal. Calcd for $C_{17}H_{21}N_5O_7$: C, 50.1; H, 5.20; N, 17.2. Found: C, 50.1; H, 4.94; N, 17.3.

9-(3-Deoxy-3-methylamino-β-D-ribofuranosyl)hypoxanthine (29).—A solution of 2.04 g (5.00 mmol) of the triacetyl **28** and 7.5 ml of 1.0 *N* methanolic sodium methoxide in 100 ml of methanol was refluxed for 8 hr, neutralized with acetic acid, and evaporated. Crystallization of the residue from 50 ml of methanol gave 1.01 g (72%) of **29** as white crystals, mp 217–219° dec, and a second crop, 0.09 g (total 79%), mp 215.5–219° dec. Recrystallization from the same solvent yielded the analytical sample of **29**: mp 218–219.5° dec; $[\alpha]^{22}D$ −25° (*c* 0.97, H_2O); uv max (pH 1) 249 mμ (ε 12,000); (pH 7) 249 mμ (ε 12,400); (pH 13) 254 mμ (ε 13,300); R_f 0.32 in solvent TB, R_{Ad} 0.33, 2.15, and 0.60 in solvents TA, TC, and TE, respectively.

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 47.0; H, 5.38; N, 24.9. Found: C, 47.1; H, 5.48; N, 25.1.

9-[2,5-Di-*O*-acetyl-3-deoxy-3-(*N*-methylacetamido)-β-D-ribofuranosyl]-6-mercaptopurine (30).—A solution of 0.705 g (1.65 mmol) of the chloronucleoside **24** (1.31 g of 54% pure **24**), 0.19 g (2.48 mmol) of thiourea, and 0.27 ml (3.35 mmol) of pyridine in 25 ml of absolute ethanol was refluxed for 10 hr and evaporated and the residue triturated with ether to give 0.372 g (54%) of chromatographically pure, amorphous **30**. Crystallization from absolute ethanol gave two crops of **30**, 0.136 g (20%) of mp 210.5–212.5° dec and 0.036 g (total 25%) of mp 186–190° dec. Recrystallization of the first crop afforded **30**: mp 215.5–217.5° dec; $[\alpha]^{20}D$ −58° (*c* 0.49, pyridine); uv max (pH 1) 227 mμ sh (ε 9850), 321 (23,500); (pH 7) 228 mμ sh (ε 9500), 319 (20,500); (pH 13) 235 mμ sh (ε 14,600), 311 (22,200); R_f 0.42 in solvent TF.

Anal. Calcd for $C_{17}H_{21}N_5O_6S$: C, 48.2; H, 5.00; N, 16.5; S, 7.57. Found: C, 47.9; H, 4.87; N, 16.5; S, 7.13.

Reaction of **24** with excess thiourea in hot ethanol without pyridine cleaved the nucleoside product to 6-mercaptopurine. With 1.5 mol of thiourea and 2 of pyridine, crystalline **30** could be obtained in 23% yield together with 30% 6-mercaptopurine. On larger scale, the yield of **30** was not reproducible. With larger excesses of pyridine, the product **30**, though present, could not be isolated. Replacement of pyridine with sodium bicarbonate resulted mostly in de-O-acylation of **24**.

9-(3-Deoxy-3-methylamino-β-D-ribofuranosyl)-6-mercaptopurine (31).—To a solution of 1.31 g (3.08 mmol) of the chloronucleoside **24** (2.30 g of 57% pure **24**) in 40 ml of methanolic hydrogen sulfide was added 9.3 ml of 1.0 *M* methanolic sodium hydrogen sulfide. The solution was refluxed for 1 hr during which time hydrogen sulfide was bubbled through the mixture. Then nitrogen was bubbled through the refluxing mixture for 15 min, 6.2 ml of 1.0 *M* methanolic sodium methoxide was added, and refluxing under nitrogen was continued for 7 hr more. After cooling, the mixture was adjusted to pH 7–8 with acetic acid to afford 0.43 g of **31**. Crystallization from water yielded 0.21 g (23%) of **31**, mp 221–223° dec. A further crystallization gave the analytical sample of **31**: mp 228–230.5° dec; $[\alpha]^{19}D$ −93° (*c* 0.46, 0.1 *N* NaOH); uv max (pH 1) 224 mμ (ε 9500), 321 (23,900); (pH 7) 229 mμ (ε 11,200), 315 (21,600); (pH 13) 232 mμ (ε 16,400), 310 (26,800); R_f 0.50 in solvent TB; R_{Ad} 1.88 and 0.73 in solvents PC and PE, respectively.

Anal. Calcd for $C_{11}H_{15}N_5O_3S$: C, 44.4; H, 5.09; N, 23.6; S, 10.8. Found: C, 44.5; H, 5.16; N, 23.3; S, 10.7.

9-[2,5-Di-O-acetyl-3-deoxy-3-(N-methylthioacetamido)-β-D-ribofuranosyl]-6-mercaptopurine (34).—To a stirred suspension of 1.70 g (4.17 mmol) of the triacetate **28** in 85 ml of dry pyridine was added 3.80 g (17 mmol) of phosphorus pentasulfide. The mixture was stirred vigorously and refluxed for 4 hr. The two-phase reaction mixture was evaporated and the residue was triturated with a solution of 2.86 g (34 mmol) of sodium bicarbonate in 40 ml of water. The precipitate was collected and washed with water to yield 1.32 g of **34**. Crystallization from 50 ml of ethanol gave 0.95 g (52%) of a crystalline powder, mp 191–196° dec, and an additional 0.15 g (total 60%), mp 185–191° dec. The analytical sample of **34**, recrystallized from water, had mp 207.5–209.5° dec: $[\alpha]^{21.5}D$ −93° (*c* 1.00, pyridine); uv max (pH 1) 223 mμ sh (ε 13,300), 272 (17,300), 321 (26,000); (EtOH) 228 mμ sh (ε 10,700), 275 (16,900) 324 (24,200); (pH 13) 235 mμ sh (ε 25,100) 311 (24,400); R_f 0.47 in solvent TF; R_{Ad} 1.55, 1.72, and 1.52 in solvents PA, PC, and PE, respectively.

Anal. Calcd for $C_{17}H_{21}N_5O_5S_2$: C, 46.5; H, 4.82; N, 15.9; S, 14.6. Found: C, 46.1; H, 4.86; N, 15.9; S, 14.5.

9-[3-Deoxy-3-methylamino-β-D-ribofuranosyl)-6-dimethylamino]purine (2).—Treatment of 5.85 g (13.7 mmol) of the chloronucleoside **24** (9.76 g of a 60% pure sample of **24**) with 15 ml of anhydrous dimethylamine in 150 ml of methanol in a bomb at 100° for 2 hr followed by deacylation with methanolic sodium methoxide (as for **5**) afforded crude **2**. Crystallization from 40 ml of water gave 2.65 g (63%) of **2** as white crystals, mp 215–216.5°, with a second crop of 0.20 g (total 68%), mp 213–215°. Recrystallization from water afforded **2**: mp 216.5–218°; $[\alpha]^{23}D$ −52° (*c* 0.97, EtOH); uv max (pH 1) 208 mμ (ε 20,100), 267 (19,200); (pH 7) 214 mμ (ε 17,100) and 275 (19,400); (pH 13) 275 mμ (ε 19,700); R_f 0.42 in solvent TB; R_{Ad} 1.47, 1.89, and 1.00, in solvents PA, PC, and PE, respectively; nmr (DMSO-d_6) δ 8.28 and 8.10 (both s, 2, H-8, H-2), 5.89 (d, 1, $J_{1,2}$ = 3 Hz, H-1'), 3.31 [s, 6, N^6-$(CH_3)_2$], 2.20 (s, 3, $HNCH_3$).

Anal. Calcd for $C_{13}H_{20}N_6O_3$: C, 50.6; H, 6.54; N, 27.3. Found: C, 50.7; H, 6.69; N, 27.1.

9-{3-Deoxy-3-[N-(benzyloxycarbonyl-p-methoxyphenyl-L-alanyl)methylamino]-β-D-ribofuranosyl}-6-dimethylaminopurine (32).—To a cooled (0°) stirred solution of 1.43 g (4.64 mmol) of the 3'-methylaminonucleoside (**2**), 1.61 g (4.9 mmol) of *N*-benzyloxycarbonyl-*p*-methoxyphenyl-L-alanine,[13] and 0.565 g (4.9 mmol) of *N*-hydroxysuccinimide in 45 ml of dry DMF was added 1.01 g (4.9 mmol) of dicyclohexylcarbodiimide. The solution was stirred at 0° for 30 min and then at 25° for 3 days, protected from moisture. The reaction mixture was filtered, the dicyclohexylurea was washed with ethyl acetate, and the combined filtrate was evaporated. A solution of the residue in 40 ml of ethyl acetate was cooled at 0° for 1 hr and then filtered to remove the precipitated dicyclohexylurea. The filtrate was diluted to 100 ml with ethyl acetate and then washed successively with 25-ml portions of water, one-half saturated sodium bicarbonate solution, and two portions of water. The dried ethyl acetate solution was treated with charcoal and evaporated; the residual syrup was azeotroped with several 20-ml portions of methylene chloride to leave 2.79 g (91%, calcd as **32**·$^1/_2CH_2Cl_2$) of a pale yellowish-white solid foam: nmr (DCl_3) δ 8.17 (s, 1, $NHCO_2R$), 8.03 (s), and 7.85 (s, H-8, H-2), 7.25 (s, C_6H_5), 6.94 (q, $MeOC_6H_4$), 6.13 (d, H-1'), 5.27 (s, CH_2Cl_2) and remainder of spectrum compatible with structure of **32**; R_f 0.32 in solvent TD.

9-{3-Deoxy-3-[N-(p-methoxyphenyl-L-alanyl)methylamino]-β-D-ribofuranosyl}-6-dimethylaminopurine (3'-N-methylpuromycin) (2a).—A 2.08-g (3.14 mmol) sample of the amino acid nucleoside **32** and 0.31 g of 5% palladium on carbon in 50 ml of ethanol was stirred under hydrogen, 1 atmosphere, at 25° for 20 hr. After filtration through Celite, the filtrate was evaporated. The residue was dissolved in 10 ml of ethanol, diluted with 25 ml of water, and allowed to stand 1 day to precipitate the last traces of dicyclohexylurea. After filtration the filtrate was concentrated to about 20 ml, and extracted with three 20-ml portions of methylene chloride. The combined extracts were washed with two 10-ml portions of water, dried, treated with charcoal, and evaporated to a solid foam. This was dissolved in 50 ml of hot benzene, filtered, and allowed to crystallize at 25°. The very fine needles were collected, washed with benzene, and dried at 56° (0.1 Torr) for 15 hr to give 1.34 g (81% as **2a**·$^1/_2C_6H_6$) with mp 98–108°. Recrystallization from benzene did not change the melting point of **2a**·$^1/_2C_6H_6$: $[\alpha]^{19}D$ +30° (*c* 0.97, EtOH); uv max (pH 1) 268 mμ (ε 20,100); (EtOH) 213 mμ sh (ε 27,400), 276 (20,600); (pH 13) 276 mμ (ε 20,300); nmr ($DCCl_3$) δ 8.13 and 7.90 (both s, 2, H-8, H-2), 6.91 (q, 4, $MeOC_6H_4$), 5.86 (d, 1, $J_{1',2'}$ = 5.5 Hz, H-1'), remainder of spectrum showed overlapping with discernible singlets at δ 3.76 (OCH_3), 3.46 [$N^6(CH_3)_2$], and 2.90 ($N^{3'}CH_3$) as well as 0.5 C_6H_6 at δ 7.34; R_f 0.31 in solvent TE; R_{Ad} 1.65 in solvent PA.

Anal. Calcd for $C_{23}H_{31}N_7O_5$·$^1/_2C_6H_6$: C, 59.5; H, 6.53; N, 18.7. Found: C, 59.3; H, 6.25; N, 18.5.

9-{3-Deoxy-3-[N-(N-isopropylidene-p-methoxyphenyl-L-alanyl)methylamino]-β-D-ribofurnaosyl}-6-dimethylaminopurine (33).—A 0.181-g (0.37 mmol) sample of 3'-*N*-methylpuromycin (**2a**) was dissolved in 2 ml of acetone and allowed to stand at 25° (crystals began to form after approximately 15 min) for 17 hr. The fine white fibrous needles were collected, washed with acetone, and dried to give 0.149 g (76%) of **33**, mp 164–168°. For analysis, a sample was recrystallized from acetone and dried at 56° (0.15 Torr) for 15 hr: mp 166.5–170.5°; $[\alpha]^{19}D$ +5° (*c* 0.98, EtOH); after 17 hr at 25° the solution had $[\alpha]^{19}D$ +30°; like **2a**; ir (Nujol) 6.00 μ (C=N); uv max (pH 1) 268 mμ (ε 20,800); (EtOH) 213 mμ (ε 27,000), 276 (21,100); (pH 13) 276 mμ (ε 20,900); nmr ($DCCl_3$) δ 2.11 [s, 6, N=$C(CH_3)_2$]; remainder of spectrum like that of **2a**; **33** had the same chromatographic behavior as **2a**.

Anal. Calcd for $C_{26}H_{35}N_7O_5$·H_2O: C, 57.5; H, 6.86; N, 18.0. Found: C, 57.8; H, 6.80; N, 18.1.

9-[3-Deoxy-3-(dimethylamino)-β-D-ribofuranosyl]-6-dimethylaminopurine (3).—A solution of 0.925 g (3.00 mmol) of **2** in 5 ml of 88% formic acid and 5 ml of 37% aqueous formaldehyde was stirred and heated at reflux for 10 min (CO_2 evolution had ceased after ~8 min) and then evaporated. After adding and evaporating successively three 10-ml portions of water, the gelatinous residue was dissolved in 30 ml of water and filtered through Celite, and the filter was washed with water. The combined filtrates, about 40 ml, were adjusted to pH 9.5 with 1.0 *N* sodium hydroxide (4.9 ml needed), and evaporated. A solution of the residue in 10 ml of hot water gave, after standing at 5°, 0.645 g (67%) of **3**, mp 184–185°, and a second crop of 0.112 g (total 78%), mp 183.5–185°. Recrystallization of 0.15 g of **3** from 1 ml of water afforded, after drying at 56° and 0.15 Torr for 15 hr, 0.132 g of **3**: mp 184.5–186°; $[\alpha]^{22}D$ −27° (*c* 1.00, H_2O); uv max (pH 1) 209 mμ (ε 17,700), 267 (18,600); (pH 7) 214 mμ (ε 16,100), 275 (19,000); (pH 13) 276 mμ (ε 18,700); nmr (D_2O) δ 8.00 and 7.74 (both s, 2, H-8, H-2), 5.86 (d, 1, $J_{1',2'}$ = 3.5 Hz, H-1'), 3.07 [s, 6, $N^6(CH_3)_2$], 2.42 [s, 6, $N^{3'}(CH_3)_2$]; R_{Ad} 1.39, 1.96, and 1.64 in solvents PF, PG, and PP, respectively, where **2**, on the same sheet, had R_{Ad} 1.33, 1.91, and 1.70, respectively.

Anal. Calcd for $C_{14}H_{22}N_6O_3$: C, 52.2; H, 6.88; N, 26.1. Found: C, 52.2; H, 7.20; N, 26.0.

Registry No.—**2**, 25787-40-0; **2a**, 25787-41-1; **3**, 25787-42-2; **5**, 25787-43-3; **7** HCl, 25787-44-4; **8**, 25787-45-5; **9**, 25787-46-6; **11**, 25787-47-7; **13**, 25787-48-8; **15** HCl, 25787-49-9; **16**, 25787-50-2; **17**, 25787-51-3; **18**, 25787-52-4; **22**, 25787-53-5; **23**, 25787-54-6; **24**, 25834-69-9; **26**, 25834-70-2; **27**, 25834-71-3; **28**, 25787-55-7; **29,** 25787-56-8; **30,** 25787-57-9; **31,** 25791-57-5; **32,** 25791-58-6; **33,** 25791-59-7; **34,** 25791-60-0; 3-deoxy-3-methylamino-D-ribofuranose, 25791-61-1.

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2-Phenylaspartic Acid Derivatives from β-Lactams

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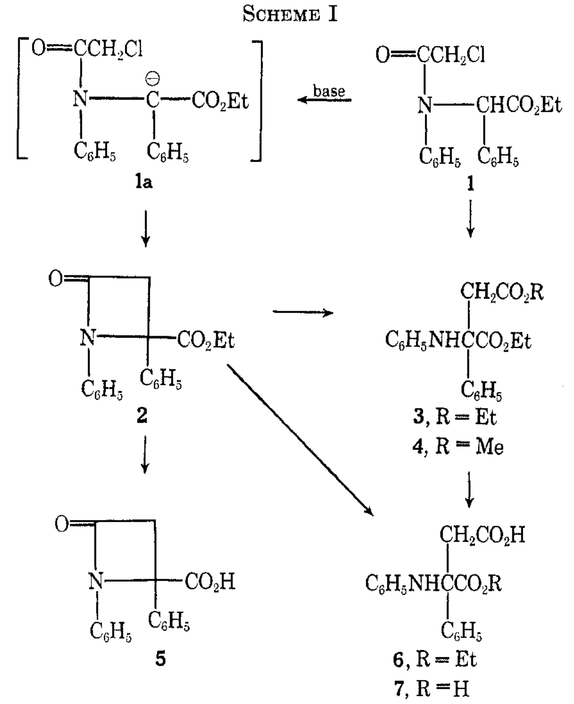
Intramolecular cyclization of an *N*-chloroacetyl-2-phenylglycine ethyl ester occurs in the presence of various bases to produce the corresponding 2-phenyl-4-oxoazetidine. A similar cyclization of the *N*-(3-chloropropionyl) homolog to an oxopyrrolidine has been observed. The facile ring cleavage of the oxoazetidines yielded a series of novel 2-phenylaspartic acid derivatives. Large geminal coupling constants from the pmr spectra of the *N*-phenyl- and *N*-benzyl-2-phenylaspartic acid derivatives support restricted rotational conformations for these compounds.

When *N*-chloroacetyl-*N*,2-diphenylglycine ethyl ester (**1**)[1] reacts with sodium cyanide, ethyl 4-oxo-1,2-diphenylazetidine-2-carboxylate (**2**)[2] is formed in good yield, rather than the *N*-cyanoacetyl derivative. Although **1** fails[1] to yield **2** in the presence of triethylamine, the reaction is successful[2] when carried out in the presence of basic anion exchange resin. Sheehan and Bose[3] report the intramolecular cyclization of diethyl *N*-arylhaloacetamidomalonates in the presence of triethylamine to 1-aryl-2,2-dicarbethoxy-4-oxoazetidines. Similarly, Deshpande, Mukerjee, and Dey[1,4] prepare 2,2-dicarbethoxy-1-phenyl-3-phthalimidomethyl-4-oxoazetidine from diethyl *N*-(3-phthalimido)-2-bromo-*N*-phenylpropionamidomalonate.

Sodium cyanide is apparently a strong enough base to form the carbanion (**1a**) which by intramolecular nucleophilic displacement of Cl gives **2**. Other bases (*e.g.*, NaH, NaOR, NaOAc, and NH_3) behave similarly, and may be preferred cyclization reagents (Scheme I).

SCHEME I



1,4-Diethyl *N*,2-diphenylaspartate (**3**) was obtained in 84% yield by the addition of an excess (1.3 equiv) of NaOEt to **1** in EtOH. When 1 equiv of NaOEt was added rapidly to **1**, compound **3** was the major reaction product. The localized excess of NaOEt presumably opens up the initially formed azetidine ring to give **3** and a lesser amount (26%) of **2**. As expected, when **2** was treated with NaOMe–MeOH the analogous ester, 1-ethyl 4-methyl *N*,2-diphenylaspartate (**4**), was obtained.

Mild hydrolysis[2-4] of **2** (1 equiv) at room temperature in a 0.5% solution of KOH (1 equiv) in 95% EtOH produced the azetidinecarboxylic acid **5**. When the reaction was repeated with MeOH as solvent, the chief product was the ring-opened diester **4** with only a minor amount of **5** being isolated. Refluxing **3** for 5 min in a 1.6% NaOH (2.4 equiv) aqueous EtOH solution allowed selective hydrolysis of the 4-carbethoxy group, giving an 80% yield of 1-ethyl *N*,2-diphenylaspartate (**6**). Compound **6** was prepared by: (a) selective hydrolysis of **3** with hot dilute H_2SO_4, or (b) the ring cleavage of **2** with concentrated H_2SO_4. More drastic hydrolysis of either **2** or **3** with excess NaOH in refluxing aqueous dioxane produced *N*,2-diphenylaspartic acid (**7**).

Other investigators[3] obtained *N*-phenylaspartic acid by hydrolysis of 2,2-dicarbethoxy-1-phenyl-4-oxoazetidine with KOH, followed by decarboxylation. The dimethyl ester was obtained[3] by treatment with diazomethane. α esters are less readily available than β or γ esters of monoaminodicarboxylic acids. Klieger and Gibian[5] found that benzyloxycarbonyl-L-glutamic acid anhydride reacts with ROH in the presence of dicyclohexylamine to produce the α ester dicyclohexylammonium salt. The α esters may also be prepared[6] by taking advantage of the difference in the dissociation constants of the α- and γ-carboxyl groups of *N*-acylglutamic acids. The reaction is carried out

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