[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

PUROMYCIN. SYNTHETIC STUDIES. V. 6-DIMETHYLAMINO-9-(2′-ACETAMINO-β-D-GLUCOPYRANOSYL)PURINE

B. R. BAKER,[1] JOSEPH P. JOSEPH, ROBERT E. SCHAUB, AND JAMES H. WILLIAMS

Received June 28, 1954

Puromycin has been shown to be a derivative of 6-dimethylamino-9-(3′-aminoribosyl)purine (1). In a previous paper (2) a method was described for the glycosidation of 6-dimethylaminopurine on the 9-position *via* the 2-methylmercapto derivative. Since a search of the literature revealed no example of the glycosidation of a purine with an amino sugar, it would be necessary to solve this problem before a total synthesis of the antibiotic could be effected. The proper blocking group and activation for the coupling of D-glucosamine, as a model amino sugar, with a purine has now been successfully completed.

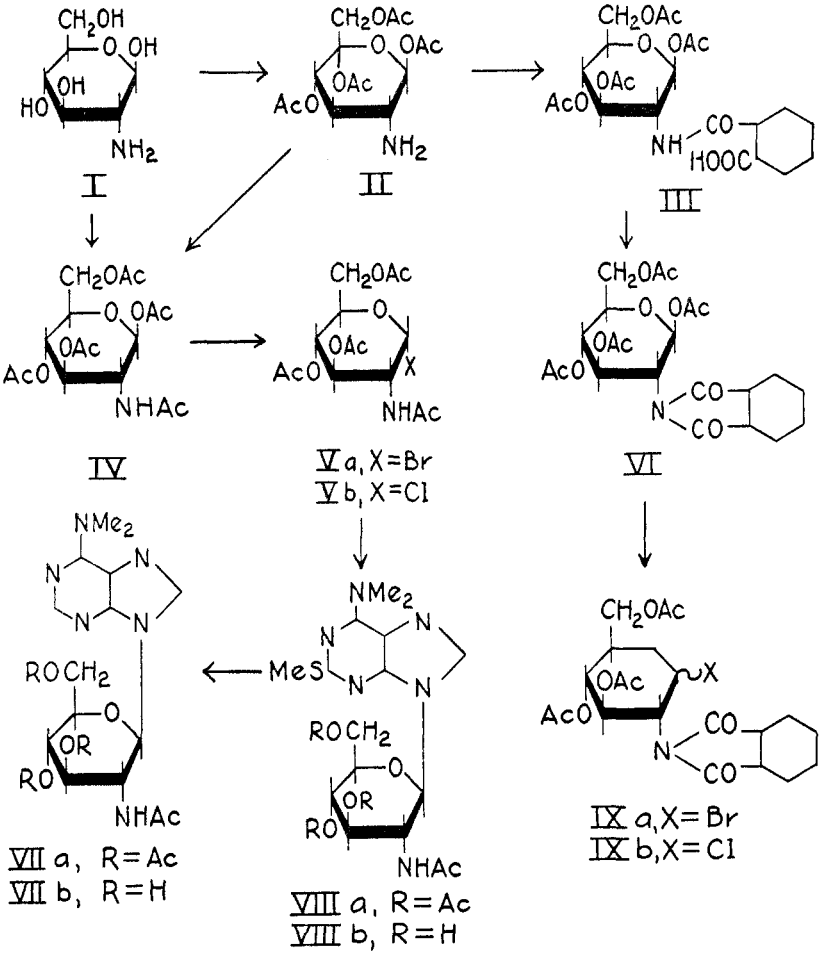
A derivative of D-glucosamine (I) suitable for variation of the N-blocking group is 1,3,4,6-tetraacetyl-2-amino-β-D-glucopyranose (II) prepared by the elegant method of Bergmann and Zervas (3). This derivative was then N-blocked by acetyl (IV), phthalyl (VI), or carbobenzoxy. The introduction of the phthalyl blocking group by the standard method of direct fusion of the base, II, with phthalic anhydride was unpromising. This difficulty was circumvented by treatment of the base, II, with phthalic anhydride in boiling chloroform which formed the crystalline phthalamic acid, III, in 85% yield. The ring closure to the phthalimido derivative, VI, did not proceed readily with boiling acetyl chloride. A new and milder method for cyclization of phthalamic acids was devised. Treatment of the phthalamic acid, III, in chloroform with triethylamine and ethyl chlorocarbonate at 0° gave a mixed anhydride (4) which cyclized at room temperature in 2 hours to the desired phthalimido derivative, VI, in 74–81% yield.[2]

By proper modification of the literature procedure (5), the conversion of D-glucosamine β-pentaacetate (IV) to α-bromoaceto-D-glucosamine (Va) was increased from 42 to 55%. Attempts to condense this bromo sugar derivative with the chloromercury salt of 2-methylmercapto-6-dimethylaminopurine (2) in boiling xylene, toluene, or benzene did not lead to any of the nucleoside derivative (VIIIa), but decomposition of the bromo sugar took place with consequent formation of the free purine base. Similar results were obtained with the crystalline 1-bromo-2-phthalimido-3,4,6-triacetyl-D-glucopyranoside (IXa). Since the bromo phthalylglucosamine, IXa, obviously decomposes at its m.p. of 120° and α-bromoaceto-D-glucosamine (Va) has no definite m.p., but gradually decomposes, the difficulties in the coupling reaction were attributed to the instability

[1] To whom inquiries concerning this paper should be directed.

[2] This two step procedure for the conversion of amines containing other sensitive functional groups to their phthalyl derivatives appears to be general. For example, ethyl 3,3-diethoxyalanate can be converted to ethyl 2-phthalimido-3,3-diethoxypropionate in 64% yield by this mild method. Other examples will be published in future papers.

of these two bromo sugars to heat, since pure α-bromoacetoglucose could be heated at 150° in a capillary tube without evidence of any rapid decomposition.



The observation that chloroaceto-D-ribofuranoside would stand the rigors of this type of coupling reaction much better than bromoaceto-D-ribofuranoside (6) led to investigation of the α-chloro-D-glucosamine derivatives, Vb and IXb. Reaction of β-pentaacetyl-D-glucosamine (IV) with ethereal hydrogen chloride containing about 20% of acetic anhydride gave 81–84% yields of the crystalline chloro sugar, Vb, m.p. 124° dec., which probably had the α-configuration. Since this chloro sugar obviously decomposed at 124°, toluene was selected as the solvent for the coupling reaction and a 47% yield of crystalline nucleoside acetate, VIIIa, was obtained. The N-phthalyl D-glucosamine (VI) reacted with ethereal hydrogen chloride to give a chloro sugar, IXb, as a glass. However, no appreciable nucleoside was formed when the crude IXb was reacted with chloromercury purine as shown by u.v. analysis.

When VIIIa was O-deacetylated with methanolic ammonia or sodium methoxide, the crystalline nucleoside, VIIIb, was obtained in good yield. Desulfurization of VIIIa afforded 6-dimethylamino-9-(2′-amino-D-glucopyranosyl)purine tetraacetate (VIIa) as a glass in 76% yield. That desulfurization had taken place and that the glycosidic link was still present was proven by the typical (2) u.v. spectra of VIIa. O-Deacetylation of VIIa formed 6-dimethylamino-9-(2′-acetamino-D-glucopyranosyl)purine (VIIb) as an analytically pure glass.

Since this is the first example of a synthetic nucleoside from D-glucosamine, it was of interest to establish the α- or β-configuration of the sugar. Unfortunately, the N-acetyl groups of VIIb or VIIIb were resistant to alkaline hydrolysis and the free aminonucleosides could not be obtained in order to use the type of determination employed on adenosine (7) to establish the configuration. However, there are a number of inferences which would strongly point to the β-configuration for these nucleosides. The configuration of the 1-linkage appears to depend on the position of the 2-group; that is, the purine, in all known cases, is on the opposite side of the sugar ring from the 2-group. For example, with D-glucopyranose (7), D-galactopyranose (11), D-xylofuranose (8), and D-ribofuranose (6), where the 2-group is down, the purine approaches from the top side to give β-nucleosides. In contrast a purine will approach the bottom side of D-arabinofuranose (10) and D-arabinopyranose (11), where the 2-group is up, to give α-nucleosides.

Bristow and Lythgoe (10) have explained these results by assuming that the haloacetosugars fortuitously have a 1,2-*cis* configuration in all cases and the purines enter with a simple Walden inversion. Since some of these haloacetosugars were probably anomeric mixtures used as oils of unknown configuration (8–10), and since sometimes the 1,2-*trans*-haloacetosugar is the stable form (13), another explanation would appear to be more general. One cannot question the fact that if the halosugars have the 1,2-*cis* configuration, the purine will enter with simple Walden inversion to give a 1,2-*trans*-configuration. However, the 1,2-*trans*-halosugars could react with a purine by double Walden inversion to give the 1,2-*trans*-configuration. If it is logically assumed that the large purine ion cannot approach from the same side as the 2-group in a 1,2-*trans* system, then it follows that the purine could enter from the opposite side of the 2-group by double Walden inversion. There are two obvious ways in which this might happen. The 1-halo group can be inverted by attack of halogen ion[3] to give a 1,2-*cis*-halosugar or double Walden inversion can be obtained by neighboring participation of the 2-group *via* an *ortho* ester ion (9, 13). This explanation would then state that overall, the purine would enter the sugar ring from the opposite side of the 2-group regardless of the relative configuration at C_1–C_2.[4]

[3] It has been shown that α-bromoacetoglucose reacts with silver chloride to give β-chloroacetoglucose (12).

[4] This mechanism could be established by reaction of crystalline β-bromo-D-ribopyranoside tribenzoate (13) or β-chloroacetoglucose (12) with a heavy metal salt of a purine such as silver theophylline. If the explanation of Bristow and Lythgoe (10) is correct, that is

Similarly, α-chloroaceto-D-glucosamine would be expected to give a β-nucleoside by a single Walden inversion. However, β-chloroaceto-D-glucosamine would be expected to form an oxazoline (22) at C_1–C_2 in place of an *ortho* ester ion which can be obtained with sugars having a *trans*-2-acetate group. This oxazoline could either be inert to an approaching purine ion, in which case no nucleoside would be obtained, or the purine ion could open the oxazoline by a second Walden inversion with formation of a β-nucleoside with overall retention of configuration. Thus, the D-glucosamine nucleoside (VIII) could be expected to have the β-configuration.

Acknowledgement. The authors wish to thank L. Brancone and staff for the microanalyses, W. Fulmor and staff for the spectra and rotations, and W. McEwen and staff for large scale preparation of some of the intermediates.

EXPERIMENTAL

2-Carbobenzoxyamino-β-D-glucopyranose tetraacetate. To a stirred mixture of 500 mg. of 1,3,4,6-tetraacetyl-β-D-glucosamine (II) hydrochloride (3), 5 cc. of water, 4 cc. of chloroform, and 0.33 g. of sodium bicarbonate cooled in an ice-bath was added 0.51 cc. of 70% carbobenzoxy chloride. After 15 minutes the layers were separated and the aqueous phase was extracted with chloroform. The combined chloroform extracts, dried with magnesium sulfate, were evaporated to dryness *in vacuo*. Trituration of the solid residue with heptane gave 340 mg. (55%) of product, m.p. 146–148°.

Bromund and Herbst (14) have recorded m.p. 151° for this compound prepared in a different manner.

2-Amino-β-D-glucopyranose pentaacetate (IV). A mixture of 5.0 g. of II hydrochloride (3), 50 cc. of chloroform, 1.73 g. of anhydrous sodium acetate, and 25 cc. of water was stirred until solution was complete. After the addition of 2 cc. of acetic anhydride, the mixture was stirred for 15 minutes. The separated chloroform layer, dried with magnesium sulfate, was evaporated to dryness *in vacuo*. Trituration of the residue with heptane gave 4.2 g. (81%) of white solid, m.p. 178–180°.

The above procedure is considered to be more convenient than that described by Bergmann and Zervas (3) which involves acetic anhydride and anhydrous sodium acetate at the b.p. They record a yield of 90% and m.p. 187° for the pure material. In this laboratory their procedure gave a 58% yield.

Direct acetylation of D-glucosamine hydrochloride to IV according to the procedure of DeBruyn and VanEckenstein (15) gave only a 10% yield, m.p. 180–181°. They record m.p. 184°, but do not mention the yield.

2-(o-Carboxybenzamido)-β-D-glucopyranose tetraacetate (III). To a solution of 2.7 g. of II (3) in 27 cc. of chloroform was added a solution of 1.2 g. of phthalic anhydride in 10 cc. of chloroform. The solution was refluxed for 30 minutes, cooled, and extracted with three 10-cc. portions of saturated sodium bicarbonate. The combined aqueous extracts were clarified by filtration through Celite, then acidified with 1 *N* hydrochloric acid, and chilled. The product was collected and washed with water; yield, 3.3 g. (85%) of white crystals, m.p. 181–182° (gas). No suitable solvent for recrystallization could be found.

Anal. Calc'd for $C_{22}H_{25}NO_{12}$: C, 53.3; H, 5.10; N, 2.83.
Found: C, 53.0; H, 5.40; N, 2.79.

---

the purine enters with one inversion, then α-nucleosides should be obtained in both cases. However, if the new hypothesis is correct, β-nucleosides should be obtained by double Walden inversion.

A referee has pointed out that Fox and Goodman (23) have condensed both α- and β-chloroacetoglucopyranose with 2,4-diethoxypyrimidine and obtained the same β-nucleoside in both cases.

2-Phthalimido-β-D-glucopyranose tetraacetate (VI). To a solution of 8.1 g. of III and 2.3 cc. of triethylamine in 81 cc. of chloroform cooled in an ice-bath was added 1.6 cc. of ethyl chlorocarbonate. The solution was allowed to stand at room temperature for 1½ hours, carbon dioxide evolution being complete in 1 hour. (There was no gas evolution, indicative of ring closure, at 0°). The solution was washed with excess aqueous sodium bicarbonate, then dried with magnesium sulfate, and evaporated to dryness *in vacuo*. The glassy residue was crystallized from methanol; yield, 5.7 g. (74%), m.p. 187–189°. In three similar runs the yields were 76–81%. Recrystallization from ethyl acetate gave white crystals, m.p. 199–200°.

Anal. Calc'd for $C_{22}H_{23}NO_{11}$: C, 55.4; H, 4.86; N, 2.93.
Found: C, 54.5, 54.1; H, 5.46, 4.83; N, 2.93.

The normal dehydration procedure for conversion of an amic acid to an imide by refluxing in acetyl chloride for 15 minutes (16), gave 55% of unchanged III and no crystalline product could be isolated from the bicarbonate insoluble fraction.

α-Bromoaceto-D-glucosamine (Va). A solution of 1.00 g. of IV in 1.0 cc. of acetic anhydride and 3.5 cc. of 30% hydrogen bromide in acetic acid was allowed to stand in a stoppered flask for 24 hours. After dilution with 50 cc. of chloroform and chilling in an ice-bath, the solution was washed successively with two 10-cc. portions of ice-cold water and two 10-cc. portions of ice-cold saturated aqueous sodium bicarbonate. The organic layer, quickly dried with magnesium sulfate, was evaporated almost to dryness *in vacuo*. Addition of 2 cc. of ethyl acetate gave 590 mg. (55%) of product which chars at 150–180°, but does not melt.

Without the acetic anhydride, the yield was 43–47%, whereas acetic anhydride saturated with hydrogen bromide gave only 22%. At the end of two hours in the above described reaction, the yield was 33%. Moggridge and Neuberger (5) record a similar lack of m.p., but do not record the yield of product.

N-Phthalyl 1-α-(?)-bromo-D-glucosamine-3,4,6-triacetate (IXa). Treatment of 4.3 g. of VI with 3.1 cc. of acetic anhydride and 12.5 cc. of 30% hydrogen bromide in acetic acid as described for Va gave on evaporation of the chloroform solution a thick oil. Crystallization from 50 cc. of dry ether afforded 3.2 g. (72%) of product, m.p. 117–118° dec. In four other runs the yields were 70–73%. One sample, m.p. 120–121° dec., was dried in a vacuum desiccator over potassium hydroxide and concentrated sulfuric acid for analysis.

Anal. Calc'd for $C_{20}H_{20}BrNO_9$: C, 48.2; H, 4.22; Br, 16.1.
Found: C, 48.1; H, 4.49; Br, 14.4.

Another sample was recrystallized from chloroform and dry ether and then melted at 122–123° dec., but gave poorer combustion values.

α(?)-Chloroaceto-D-glucosamine (Vb) (*A*). A solution of 6.2 g. of IV in 104 cc. of dry ether saturated with hydrogen chloride at 0° and 18.7 cc. of acetic anhydride was allowed to stand in a stoppered flask at 3° for 3 days. The solution was concentrated *in vacuo* to remove the ether (bath 15°). The residual solution was dissolved in 75 cc. of chloroform and processed according to the method used for Va. Crystallization from dry ether gave 5.0 g. (86%) of white crystals, m.p. 125–126° dec. In a pilot run the yield was 1.02 g. (54%), m.p. 123–124° dec. The yield is probably lower in this case due to the necessarily larger ratio of solvent used for crystallization. No suitable solvent for recrystallization could be found.

Anal. Calc'd for $C_{14}H_{20}ClNO_8$: C, 46.0; H, 5.52; N, 3.83; Cl, 9.72.
Found: C, 46.6; H, 5.69; N, 3.80; Cl, 10.4.

Treatment of VI in a similar manner gave IXb as a gum in 87% yield which could not be crystallized.

(*B*). To a solution of 0.75 g. of IV in 9 cc. of chloroform was added 0.26 cc. of titanium tetrachloride (17). A yellow-green precipitate formed which gradually dissolved during a 3½ hour reflux of the solution. The solution was processed as described in part *A*. Crystallization from 5 cc. of dry ether gave 0.31 g. (44%) of product, m.p. and mixture m.p. with preparation *A*, 125–126° dec. The yield would no doubt be higher on a larger scale (see preparation *A*).

2-Methylmercapto-6-dimethylamino-9-(2'-amino-β-D-glucopyranosyl)purine tetraacetate (VIIIa). A stirred mixture of 6.5 g. of chloromercury-2-methylmercapto-6-dimethylamino-

purine (2), 8 g. of Celite, and 500 cc. of toluene was distilled until anhydrous. After the addition of 6.7 g. of Vb, the mixture was stirred and refluxed for 20 hours, then filtered. The filter cake was thoroughly washed with 150 cc. of hot alcohol in portions. The combined filtrate and washings were evaporated to dryness *in vacuo*. The residue was dissolved in a mixture of 60 cc. of chloroform and 30 cc. of 30% potassium iodide by warming. Some insoluble material was removed by filtration and washed with chloroform. The organic solution, dried with magnesium sulfate, was evaporated to dryness *in vacuo*. Crystallization from 10 cc. of methanol gave 3.7 g. (47%) of product, m.p. 231–233°. Recrystallization from absolute alcohol gave white crystals, m.p. 238–240°, $[\alpha]_D^{24}$ +8.5° (1.8% in $CHCl_3$).

Anal. Calc'd for $C_{22}H_{30}N_6O_8S$: C, 49.1; H, 5.62; N, 15.6.
Found: C, 48.8; H, 5.60; N, 15.8.

This compound was a 9-glycosyl derivative of 2-methylmercapto-6-dimethylaminopurine as shown by its u.v. spectra in 10% alcohol (18); *pH* 1, λ_{max} 242.5 mμ (ε 17,900), λ_{max} 277.5 mμ (ε 19,300); *p*H 7, λ_{max} 249 mμ (ε 26,700), λ_{max} 284 mμ (ε 18,800); *p*H 14, λ_{max} 250 mμ (ε 26,700), λ_{max} 286 mμ (ε 18,500). Numerous attempts to prepare this compound from α-bromoaceto-D-glucosamine in boiling benzene, toluene, xylene, or dimethyl-formamide (100°) resulted only in decomposition of mercury salt into the unalkylated purine. Similar results were obtained with N-phthalyl α-bromoaceto-D-glucosamine whereas the corresponding chloro compound failed to give any glycosidation as shown by u.v. analysis.

2-Methylmercapto-6-dimethylamino-9-(2′-acetamino-β-D-glucopyranosyl)purine (VIIIb). (*A*). A mixture of 250 mg. of VIII, 5 cc. of methanol, and 0.05 cc. of 1 *N* methanolic sodium methoxide was refluxed for ½ hour, solution taking place at the b.p. The solution was evaporated to dryness *in vacuo*. Trituration with methanol gave 160 mg. (84%) of product, m.p. 245–247° dec., $[\alpha]_D^{24}$ +23.3° (1.4% in pyridine).

Anal. Calc'd for $C_{16}H_{23}N_6O_5S \cdot H_2O$: C, 44.7; H, 5.82; N, 19.5; H_2O, 4.2.
Found: C, 44.9; H, 6.01; N, 19.3; H_2O, 4.7 (K. Fischer).

In a larger run the yield was 92% (1.06 g.), m.p. 246–247° dec.

(*B*). A solution of 100 mg. of VIII in 50 cc. of methanol was saturated with ammonia at 0° and kept at 3° for 3 days. The solution was evaporated to dryness *in vacuo*. Crystallization from methanol gave 60 mg. (78%) of product, m.p. 240–241° dec., which gave no depression in m.p. when mixed with preparation *A*.

6-Dimethylamino-9-(2′-amino-β-D-glucopyranosyl)purine tetraacetate (VIIa). A solution of 800 mg. of VIIIa in 80 cc. of absolute alcohol was refluxed with 1 teaspoon of desulfurizing Raney nickel (19) for 2 hours, then filtered hot through Celite. The combined filtrates and washings were evaporated to dryness *in vacuo* leaving 590 mg. (81%) of a glass which could not be crystallized. That desulfurization had taken place and the side chain was still present was shown by the typical u.v. spectra (18) in 10% alcohol: *p*H 1, λ_{max} 267 mμ (ε 18,200); *p*H 7, λ_{max} 275 mμ (ε 18,200); *p*H 14, λ_{max} 275 (ε 17,400).

6-Dimethylamino-9-(2′-acetamino-β-D-glucopyranosyl)purine (VIIb). A solution of 570 mg. of VIIa in 11 cc. of methanol and 0.12 cc. of 1 *N* sodium methoxide was refluxed for 1 hour, then evaporated to dryness *in vacuo* leaving 0.437 g. (102%) of a glass which could not be crystallized. For analysis a sample was dissolved in absolute alcohol, treated with Norit and evaporated.

Anal. Calc'd for $C_{15}H_{22}N_6O_5 \cdot \frac{1}{2}H_2O$: C, 47.9; H, 6.18; N-Ac, 11.4.
Found: C, 47.8; H, 6.28; N-Ac, 11.9.

This compound had amide bands at 6.00 and 6.45 μ, C=N absorption at 6.20 μ, OH and NH bands at 3.02 μ, but no ester carbonyl bands in the infrared. When heated at 100° with 0.5 *N* barium hydroxide for 1 hour (20) the compound was recovered unchanged as shown by its infrared spectrum.

Ethyl 2-(o-carboxybenzamido)-3,3-diethoxypropionate. To a hot filtered solution of 4.8 g. of phthalic anhydride in 50 cc. of benzene was added 6.7 g. of ethyl β,β-diethoxyalanate (21). Heat was evolved. After standing about 3 hours, the solution was evaporated *in vacuo*. The residue was dissolved in ethyl acetate and heptane was added to turbidity. On standing overnight the solution deposited 7.0 g. (73%) of white crystals, m.p. 94–96°. Recrystallization from benzene-heptane did not change the m.p.

Anal. Calc'd for $C_{17}H_{23}NO_7$: C, 57.9; H, 6.56; N, 3.97.
Found: C, 58.6; H, 6.62; N, 4.10.

By extraction of the mother liquor from the 7.0 g. with aqueous sodium bicarbonate and acidification with acetic acid was obtained an additional 0.5 g. (5%), m.p. 94–96°.

Ethyl 2-phthalimido-3,3-diethoxypropionate. To a solution of 543 mg. of the preceding phthalamic acid in 3 cc. of chloroform and 0.21 cc. of triethylamine was added 0.15 cc. of ethyl chlorocarbonate. The evolution of carbon dioxide was complete in about 12 minutes. After dilution with 7 cc. of chloroform, the solution was washed with excess aqueous sodium bicarbonate, dried with magnesium sulfate, and evaporated to dryness *in vacuo*. Trituration with petroleum ether gave 420 mg. (82%) of product, m.p. 90–92°. Recrystallization from heptane afforded white crystals, m.p. 93–95°.

Anal. Calc'd for $C_{17}H_{21}NO_6$: C, 61.0; H, 6.31; N, 4.18.
Found: C, 61.3; H, 6.46; N, 4.33.

An attempt to prepare this product by cyclization of the phthalamic acid with boiling acetyl chloride (16) gave a gum which could not be crystallized.

SUMMARY

A synthesis of 6-dimethylamino-9-(2′-acetamino-β-D-glucopyranosyl)purine and its 2-methylmercapto derivative from D-glucosamine has been described. These are the first known examples of the syntheses of nucleosides containing an amine function in the sugar moiety, thus serving as model compounds for the total synthesis of puromycin.

A mechanism for the condensation of purine salts with haloacetosugars is proposed whereby a nucleoside with a 1,2-*trans*-configuration in the sugar moiety is obtained regardless of the configuration of the haloacetosugar.

PEARL RIVER, NEW YORK

REFERENCES

(1) WALLER, FRYTH, HUTCHINGS, AND WILLIAMS, *J. Am. Chem. Soc.*, **75**, 2025 (1950).
(2) BAKER, JOSEPH, AND WILLIAMS, Paper IV of this series, **19**, 1780 (1954).
(3) BERGMANN AND ZERVAS, *Ber.*, **64**, 975 (1931).
(4) BOISSONNAS, *Helv. Chim Acta*, **34**, 874 (1951).
(5) MOGGRIDGE AND NEUBERGER, *J. Chem. Soc.*, 745 (1938).
(6) DAVOLL, LYTHGOE, AND TODD, *J. Chem. Soc.*, 967 (1948).
(7) DAVOLL, LYTHGOE, AND TODD, *J. Chem. Soc.*, 833 (1946).
(8) CHANG AND LYTHGOE, *J. Chem. Soc.*, 1992 (1950).
(9) FRUSH AND ISBELL, *J. Natl. Bur. Standards*, **27**, 413 (1941).
(10) BRISTOW AND LYTHGOE, *J. Chem. Soc.*, 2306 (1949).
(11) LYTHGOE AND TODD, *J. Chem. Soc.*, 592 (1944).
(12) SCHLUBACH, *Ber.*, **59**, 840 (1926).
(13) NESS, FLETCHER, AND HUDSON, *J. Am. Chem. Soc.*, **73**, 959 (1951).
(14) BROMUND AND HERBST, *J. Org. Chem.*, **10**, 267 (1945).
(15) DEBRUYN AND VANECKENSTEIN, *Rec. trav. chim.*, **18**, 77 (1899).
(16) HOOGEWERF AND VANDORP, *Rec. trav. chim.*, **13**, 93 (1894); GABRIEL AND COLMAN, *Ber.*, **45**, 1643 (1912).
(17) PACSU, *Ber.*, **61**, 1508 (1928).
(18) BAKER, SCHAUB, AND JOSEPH, *J. Org. Chem.*, **19**, 638 (1954), Paper II of this series.
(19) MOZINGO, WOLF, HARRIS, AND FOLKERS, *J. Am. Chem. Soc.*, **65**, 1013 (1943).
(20) WOLFROM AND ANNO, *J. Am. Chem. Soc.*, **75**, 1038 (1953).
(21) BROWN, *Chemistry of Penicillin* (CLARKE, *et al.*) (Princeton University Press), 1949, p. 512.
(22) MCCASLAND, CLARK, AND CARTER, *J. Am. Chem. Soc.*, **71**, 637 (1949).
(23) FOX AND GOODMAN, *J. Am. Chem. Soc.*, **73**, 3256 (1951).