in vacuo. The colorless glass was crystallized by solution in 10 cc. of absolute alcohol and addition of heptane to turbidity; yield 2.75 g. (63 or 60% based on II), m.p. 101–104°.

In a pilot run the yield was 52% over-all from II, m.p. 102–106°. Recrystallization from absolute ethanol–heptane gave hygroscopic white crystals, m.p. 103–106°. The analytical data showed that the compound was slightly hydrated.

Anal. Calcd. for $C_{21}H_{26}N_6O_7S$: C, 49.8; H, 5.20; N, 16.6. Found: C, 49.1; H, 5.58; N, 16.1.

The compound had $\lambda_{max}^{pH\ 1.7}$ 291 mμ (ε 16,600) and only end absorption in 0.1 *N* NaOH. The infrared spectrum (Nujol mull) showed OH–NH absorption at 2.83, 3.12 and 3.20 μ, –CONH– at 5.89 μ, C=N at 6.18 μ and sulfonate at 8.53 μ.

3,5′-Cyclo-6-dimethylamino-9-(3′-amino-3′-deoxy-β-D-ribofuranosyl)-purine Bromide Hydrobromide.—To a solution of 2.00 g. of the preceding carbobenzoxy derivative in 8.8 cc. of glacial acetic acid was added 3.3 cc. of 30% hydrogen bromide in acetic acid.[13] An amorphous solid began to separate after 10 minutes. After 1.5 hours the mixture was diluted with 10 cc. of dry ether. The solid was collected on a sintered-glass filter and washed with dry ether. The solvent wet solid was stirred immediately with 10 cc. of absolute alcohol on the filter, causing the amorphous solid to crystallize rapidly. The solvent was removed and the product washed thrice with acetone; yield 1.28 g. (74%) of white crystals, m.p. 216–218° dec., $[\alpha]^{24}D$ −53.9° (1.7% in H_2O).

Anal. Calcd. for $C_{12}H_{18}Br_2N_6O_2$: C, 32.9; H, 4.14; N, 19.2. Found: C, 33.0; H, 4.31; N, 18.9.

This compound had $\lambda_{max}^{pH\ 1.7}$ 290 mμ (ε 18,000), $\lambda_{max}^{pH\ 14}$ 275 mμ (ε 6470) (inflection) in the ultraviolet. The infrared spectrum (Nujol mull) showed OH–NH absorption at 2.92 μ, N^+ absorption at 3.75, 3.87, 4.10 and 5.04 μ and C=N absorption at 6.07 and 6.15 μ.

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[CONTRIBUTION FROM THE CHEMICAL AND BIOLOGICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

Puromycin. Synthetic Studies. XI. D-Ribofuranosyl Derivatives of 6-Dimethylaminopurine

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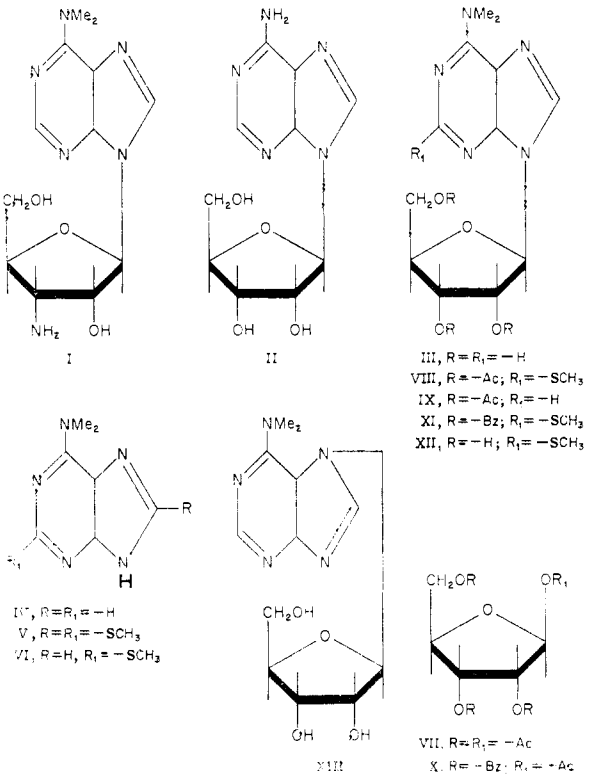
The puromycin analogs, 6-dimethylamino-9-β-D-ribofuranosylpurine (III), 2-methylmercapto-6-dimethylamino-9-β-D-ribofuranosylpurine (XII) and 6-dimethylamino-7-β-D-ribofuranosylpurine (XIII) have been synthesized. Tetra-*O*-acetyl-β-D-ribofuranose (VII), one of the two ribofuranose derivatives used for these syntheses,was separated from tetra-*O*-acetyl-D-ribopyranose by partition chromatography.

The aminonucleoside derived from the antibiotic puromycin has been shown[1] to be 6-dimethylamino-9-(3′-amino-3′-deoxy-β-D-ribofuranosyl)-purine (I). In view of the resemblance of this compound to adenosine (II) it seemed of interest to investigate whether the biological activities[1] of I were due to the presence of an amino function in the sugar moiety or to the methylation of the amino group on the purine nucleus. It was thought that a partial answer to this question might be found with the synthesis of the adenosine analog, 6-dimethylamino-9-β-D-ribofuranosylpurine (III).

Baker, Joseph and Schaub[2a] have studied the condensation of tetra-*O*-acetyl-α-D-glucopyranosyl bromide with the mercuric chloride salts[3] of 6-dimethylaminopurine (IV), 2,8-bis-methylmercapto-6-dimethylaminopurine (V) and 2-methylmercapto-6-dimethylaminopurine (VI). They were able to show by comparison of the ultraviolet spectra of the condensation products with those of unequivocally synthesized 7- and 9-alkyl substituted 6-dimethylaminopurines,[2b] that glucosidation took place in the 9-position only with the 2-methylmercapto derivative VI. The other two compounds (IV and V) yielded 7-glucosylpurine derivatives. Accordingly, it was decided to use the mercuric chloride salts of VI for the synthesis of III.

Todd and his co-workers have made extensive use



of 1,2,3,5-tetra-*O*-acetyl-D-ribose (VII) in their elegant nucleoside syntheses.[4] Recently the prepara-

(1) B. R. Baker, J. P. Joseph and J. H. Williams, paper VII of this series, THIS JOURNAL, **76**, 2838 (1954). Compound I was active against *Trypanosoma equiperdum* in mice and also against the transplanted mammary adenocarcinoma of the C3H mouse.

(2) (a) B. R. Baker, J. P. Joseph and R. E. Schaub, paper IV of this series, *J. Org. Chem.*, **19**, 1780 (1954); (b) B. R. Baker, R. E. Schaub and J. P. Joseph, *ibid.*, **19**, 638 (1954).

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

(4) The work of this group has been reviewed by G. W. Kenner, "Progress in the Chemistry of Organic Natural Products," Vol. VIII, Springer Verlag, Vienna, 1951, 108 ff.; *cf.* reference 6a.

tion of this tetraacetate has been simplified by Zinner,[5] who acetylated D-ribose at elevated temperatures to obtain a mixture of β-D-ribofuranose and β-D-ribopyranose tetraacetates which was separated by fractional crystallization. He reported a m.p. of 82° and a specific rotation of $[\alpha]^{24}D$ −12.6° (chloroform), but these values were at variance with constants previously cited for this compound.[6a,b] In our hands the use of Zinner's method afforded first the furanose derivative with a m.p. of 56° and the specific rotations $[\alpha]^{24}D$ −12.4° (chloroform), and $[\alpha]^{24}D$ −15.2° (methanol). This compound could be separated readily from the accompanying ribopyranose tetraacetate. In a later preparation, a compound with m.p. 81–82° and a rotation of $[\alpha]^{24.5}D$ −12.9° (chloroform), *i.e.*, with the characteristics described by Zinner[5] for the furanose derivative, was obtained and since that time we have never been able to isolate the lower melting form again. This phenomenon has also been observed in other laboratories.[7] Separation of the furanose derivative with m.p. 81–82° from the pyranose tetraacetate (m.p. 110°) by fractional crystallization was found to be very difficult[8a] and a procedure was worked out by which these two compounds could be separated by partition chromatography on Celite columns with the system, water:methanol:heptane:benzene (1:2:3:0.6 by volume).[8b] With this solvent system, the furanose derivative was eluted somewhat faster than the pyranose derivative. Although quantities of 31 g. of mixed tetraacetates have been handled in this manner, the method is more efficient when applied to smaller amounts.

The D-ribofuranose tetraacetate thus obtained was converted to a non-crystalline, chloroaceto sugar with ethereal hydrogen chloride.[9] The latter was not purified but was allowed to react with a mixture of Celite and 2-methylmercapto-6-dimethylaminopurine mercuric chloride (VI) in boiling xylene[2a] to yield a gummy reaction product (VIII) whose ultraviolet spectrum showed by comparison with that of 2-methylmercapto-6-dimethylamino-9-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-purine[2a] that the ribose moiety had entered the 9-position of the purine ring. Desulfurization of the crude reaction product with Raney nickel[10] yielded non-crystalline IX. This could be *O*-deacetylated with catalytic amounts of sodium methoxide in methanol to a white solid, which after recrystallization from acetone analyzed correctly for the nucleoside derivative III. The compound was obtained in 26% yield over-all from β-D-ribofuranose tetraacetate.

Evidence for the β-configuration in compound III, which had a specific rotation of $[\alpha]^{25}D$ −62.6° (water), was adduced from the molecular rotation value ($[M]^{24}D$ −5640) of the periodate cleavage product (not isolated) obtained from III. The value is in satisfactory agreement with the molecular rotation ($[M]^{24}D$ −4827) of the periodate oxidation product obtained from the puromycin aminonucleoside (I)[11a] and since the latter has been shown to have the β-configuration[11a,b] it follows that the nucleoside III also should have this configuration.

In spite of recent improvements[5] in the synthesis of VII, it is still rather difficult to prepare this compound on a larger scale (*i.e.*, molar quantities). Therefore, we were interested in finding a more easily accessible D-ribofuranose derivative which would permit us to synthesize the nucleoside III in amounts large enough for thorough biological testing. It was thought that the 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribose (X) which Weygand and Wirth[12] had obtained from adenosine and which was synthesized recently by Ness, Diehl and Fletcher[13] from D-ribose would serve this purpose. The synthesis from D-ribose[13] was used here with a few alterations (*cf.* Experimental section) designed to make the method more attractive for large scale preparations.[14]

The condensation of the chloro sugar, obtained from X with ethereal hydrogen chloride, as described above for the D-ribofuranose tetraacetate, with the mercuric chloride salt of 2-methylmercapto-6-dimethylaminopurine (VI) in refluxing xylene proceeded smoothly and yielded, after desulfurization and *O*-debenzoylation with catalytic amounts of methanolic sodium methoxide, a crystalline solid which was shown to be identical with III as prepared by the first route. The compound was obtained in 39% yield over-all from X. When the reaction sequence was changed and the crude 2-methylmercapto-6-dimethylamino-9-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-purine (XI) was *O*-debenzoylated directly, there was obtained 2-

(5) H. Zinner, *Chem. Ber.*, **83**, 153 (1950).

(6) (a) G. A. Howard, B. Lythgoe and A. R. Todd, *J. Chem. Soc.*, 1052 (1947), reported a m.p. of 58° and a specific rotation of $[\alpha]^{25}D$ +20° (chloroform). (b) The constants given by H. Bredereck and E. Hoepfner, *Chem. Ber.*, **81**, 51 (1948), are m.p. 56° and $[\alpha]^{20}D$ −3.6° (methanol).

(7) J. Davoll, G. B. Brown and D. W. Visser, *Nature*, **170**, 64 (1952), have suggested that the change in m.p. which in their case was accompanied by a change in specific rotation (from $[\alpha]^{20}D$ −3.6 to −13.5° (in methanol) could be explained by structural isomerism. K. R. Farrar, *ibid.*, **170**, 896 (1952), did not find any difference in specific rotation between the high and low melting forms and she attributed the phenomenon to simple dimorphism. Our own results seem to bear out the findings of the last mentioned author. For crystallographic data *cf.* A. L. Patterson and B. P. Groshens, *ibid.*, **173**, 398 (1954).

(8) (a) Zinner[5] states only that the two isomers were separated by fractional crystallization from methanol. We were unable to effect any practical separation in a seven-step triangular crystallization from that solvent. An improvement in the preparation of the furanose derivative has been reported recently by A. W. Johnson, G. W. Miller, J. A. Mills and A. R. Todd, *J. Chem. Soc.*, 3061 (1953). Dr. George B. Brown was kind enough to inform us that he had been able to evolve a fractional crystallization method for the separation of the mixed acetates and that he has used this method on 500-g. batches. His procedure will be published in a future issue of "Biochemical Preparations," John Wiley and Sons, Inc., New York, N. Y. (b) Since then, this quadruple solvent system has been found to be applicable to the partition chromatography of a large variety of water-soluble and insoluble substances in the carbohydrate, steroid and alkaloid fields simply by a change of the proportion in which the four solvents are used.

(9) J. Davoll, B. Lythgoe and A. R. Todd, *J. Chem. Soc.*, 967 (1948).

(10) R. Mozingo, D. E. Wolf, S. A. Harris and K. Folkers, THIS JOURNAL, **65**, 1013 (1943).

(11) (a) C. W. Waller, P. W. Fryth, B. L. Hutchings and J. H. Williams, N. Y. Meeting-in-miniature, Feb., 1954, to be published; (b) B. R. Baker and J. P. Joseph, paper X of this series, THIS JOURNAL, **77**, 15 (1955).

(12) F. Weygand and F. Wirth, *Chem. Ber.*, **85**, 1000 (1952).

(13) R. K. Ness, H. W. Diehl and H. G. Fletcher, Jr., THIS JOURNAL, **76**, 763 (1954).

(14) We would like to thank Dr. Fletcher for sending us a copy of his manuscript[13] prior to publication.

methylmercapto-6-dimethylamino-9-β-D-ribofuranosylpurine (XII) as a crystalline solid in 63% over-all yield from X. This nucleoside derivative also was needed for biological testing. Its structure was established by analysis and Raney nickel desulfurization to III. The first mentioned reaction sequence, *i.e.*, desulfurization followed by *O*-debenzoylation, is to be preferred for the synthesis of III.

The increased yield of III obtained through the use of the tri-*O*-benzoyl-D-ribofuranose derivative X indicates that in this type of reaction benzoyl groups are better than acetyl groups as blocking functions. Higher yields in the condensation reactions and the greater ease of preparing large amounts of X (as compared to VII) make this compound a valuable intermediate for the synthesis of ribonucleosides.

As mentioned previously Baker, Joseph and Schaub[2a] have found that the condensation of the mercuric chloride salts of 6-dimethylaminopurine (IV) and of 2,8-bis-methylmercapto-6-dimethylaminopurine (V) with tetra-*O*-acetyl-D-glucopyranosyl bromide afforded 6-dimethylamino-7-D-glucosylpurine derivatives. It seemed of interest to apply this information to the synthesis of 6-dimethylamino-7-β-D-ribofuranosylpurine (XIII). Surprisingly enough, the condensation of IV with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride yielded after debenzoylation, not a 7-substituted purine derivative but rather the 9-substituted compound III. The substance was obtained in 46% yield over-all from X and this method actually represented the best synthesis of III. The difference in the course of condensation of IV and tetra-*O*-acetyl-D-glucopyranosyl bromide as against IV and tri-*O*-benzoyl-D-ribofuranosyl chloride might be attributed tentatively to steric considerations. The three obvious differences between the two sugar derivatives are the size of the blocking groups (benzoyl *vs.* acetyl), the ring size and the configuration around the third carbon atom. That the first mentioned difference was not the predominant cause for the failure of the ribose derivative to enter the 7-position of the purine IV was shown by an experiment with tri-*O*-acetyl-D-ribofuranosyl chloride. This compound condensed with IV under the usual conditions in the 9-position to give after *O*-deacetylation a 25% yield of III. It is hoped that studies, which are now in progress, of the condensation of IV with other sugar derivatives will make it possible to decide which of the two remaining factors causes substitution to take place in the 9-position.

Reaction of the mercuric chloride salt of 2,8-bis-methylmercapto-6-dimethylaminopurine (V) with tri-*O*-benzoyl-D-ribofuranosyl chloride led, after desulfurization and *O*-debenzoylation, to a mixture of products whose ultraviolet spectrum indicated the presence of both 7- and 9-substituted purine derivatives.[2b] It was possible to separate this mixture by fractional crystallization into lower melting (179–180°) and higher melting (198–200°) components. Ultraviolet data showed the former (λ_{max} 274 mμ, ε 18750 in ethanol) to be the 9-substituted derivative III, an identification which was confirmed by a mixed m.p. with an authentic sample of III. The higher melting substance was isomeric with III and had the ultraviolet spectrum of a 7-substituted 6-dimethylaminopurine derivative[2b] (λ_{max} 298 mμ, ε 17720 in ethanol); it was assigned structure XIII. The β-configuration in this compound ($[\alpha]^{24.5}D$ −85.5° in 60% ethanol) was not rigidly established by periodate cleavage as was done for III, but was assumed from the large negative value of the specific rotation. This configuration would be in line with the rule postulated by Baker, Joseph and Schaub[15] which states that the purine will enter the sugar ring from the opposite side of the 2-group regardless of the configuration at C_1–C_2. Separation of the two isomers, III and XIII, has been simplified by partition chromatography on Celite from an ethyl acetate–water system. Inspection by ultraviolet spectroscopy of aliquots taken from the percolate fractions showed that the 9-isomer III was the first one to be eluted from the column. It was followed by some fractions which contained no purine derivatives and finally by the 7-isomer XIII.

The results obtained in these condensation reactions seem to indicate that in the case of V the forces which generally direct the entering sugar moiety into the 7-position of the purine nucleus, are strong enough to overcome, at least partially, the steric strain which seems to be involved in the formation of a 6-dimethylamino-7-β-D-ribofuranosylpurine derivative. This is especially interesting because an examination of Catalin models[16] shows that the presence of a methylmercapto group in the 8-position actually makes the 7-position even more inaccessible.

Biological testing showed that the three nucleoside derivatives, 6-dimethylamino-9-β-D-ribofuranosylpurine (III), 6-dimethylamino-7-β-D-ribofuranosylpurine (XIII) and 2-methylmercapto-6-dimethylamino-9-β-D-ribofuranosylpurine (XII) were inactive against *Trypanosoma equiperdum* in mice.[17a] Only compound III showed activity against the transplanted mammary adenocarcinoma of the C_3H mouse.[17b] It was found to be less active *in vivo* than the puromycin aminonucleoside (I)[1] but its *in vitro* activity (tissue culture)[17c] was four times as high as that of I. These changes in activity resulting from the substitution of a D-ribofuranosyl moiety for the 3-amino-3-deoxy-D-ribofuranosyl grouping indicate that the dimethyladenine structure is not the sole cause for the antibiotic properties of I.

Experimental[18]

Tetra-*O*-acetyl-β-D-ribofuranose (VII). (a) High Melting Product.—The acetylation of D-ribose with boiling acetic anhydride and sodium acetate was carried out as described by Zinner.[5] The crude reaction product was usually recrystallized once from methanol to give over-all yields of approximately 50%, and the mixture of D-ribofuranose and

(15) B. R. Baker, J. P. Joseph and R. E. Schaub, paper V of this series, *J. Org. Chem.*, **19**, 1786 (1954).

(16) These models, which are produced by Catalin Ltd., Waltham Abbey, Essex, England, are similar to the Fisher–Taylor–Hirschfelder models.

(17) Private communications from (a) Dr. R. Hewitt, (b) Dr. J. J. Oleson and (c) Dr. P. A. Eichorn, all of these laboratories.

(18) Melting points were taken on a Kofler micro hot-stage and are corrected. Ultraviolet absorption spectra were determined on a Cary recording spectrophotometer and infrared absorption spectra on a Perkin–Elmer double beam spectrophotometer, model 21.

D-ribopyranose tetraacetates thus obtained was separated on a Celite column as follows.

Methanol–heptane was chosen as the basic solvent system for the partition chromatogram. Water was added to this system so that the lower phase would be held by the Celite packing and benzene was added in order to increase the solubility of the tetraacetates in the upper and moving phase. After some experimentation, the system water: methanol:heptane:benzene (1:2:3:0.6 by volume) was found to give the best results. A column (2.1 cm. i.d. × 57 cm. length) was packed in uniform layers with 75 g. of Celite,[19] which had been intimately mixed with 37.5 ml. of the lower phase of the solvent system just described to give an almost dry powder. The tetraacetate mixture (0.5 g.) was dissolved, with addition of a small amount of extra methanol, in 6 ml. of the same phase and this solution was mixed thoroughly with 12 g. of Celite which was in turn packed on top of the column. This column, whose hold back volume[20] was 100 ml. was then developed with the upper phase and the percolate was collected in 5-ml. fractions. The solid content of each fraction was determined by evaporation of the solvent and the m.p.'s of the solids from approximately every fifth fraction were determined. No solids were eluted in the first 70 fractions (3.5 h.b.v.) and the solids in fractions 70–113 (3.5–5.5 h.b.v.) had melting points which varied from 77.5 to 80°. These were considered to be pure VII[21] and were combined to yield 237 mg. Fractions 114–125 yielded solids which melted over a range from about 65–75°. The combined "mixed" solids from these fractions weighed 78 mg.; they were set aside and used in another run. Fractions 126–150 (6–7.5 h.b.v.) afforded solids which melted from 107–110° and when combined represented 116 mg. of pure pyranose derivative. The weight of all the solids eluted off the column was 431 mg. or 86% of the starting material.

In a larger run, 31.8 g. of mixed tetraacetates was partitioned on a column (7.8 cm. i.d. × 120 cm. length) containing 1700 g. of Celite which had been wetted with 850 ml. of the lower phase. The column, which had a h.b.v. of 3360 ml., was developed with the upper phase as before and 300-ml. fractions were collected. Solid material began to be eluted as in the first column after 3.5 h.b.v. and the solids from fractions 8–25 (3.5–5.5 h.b.v.) were pooled and recrystallized once from methanol to yield 10.39 g. of pure furanose derivative. Fractions 26–39 contained 14.81 g. of mixed tetraacetates. These were set aside to be repartitioned in another experiment. Fractions 40–50 (8th h.b.v.) yielded 3.7 g. of the pyranose derivative. The total solids (28.8 g.) represented a material recovery of 90%. The large amount of mixed tetraacetates obtained in this experiment indicated that the column had been overloaded.

The D-ribofuranose tetraacetate obtained in these runs and recrystallized from methanol had a m.p. 81–82° and $[\alpha]^{24.5}D$ −12.9° (*c* 2.05 in chloroform) (lit.[5] m.p. 82°, $[\alpha]^{24}D$ −12.6° (*c* 12.83 in chloroform).

(b) Low Melting Product.—The first two preparations of VII according to the method of Zinner[5] yielded mixtures of tetraacetates which could be separated quite well by crystallization from methanol. The less soluble pyranose derivative was isolated first (m.p. 95–100°) and further evaporation and cooling in a Dry Ice–ethanol-bath yielded a crystalline solid, which after one more crystallization from methanol melted at 56–57°. It had the following specific rotations: $[\alpha]^{24}D$ −12.04° (*c* 2.16 in chloroform), $[\alpha]^{24}D$ −15.22° (*c*, 2.10 in methanol) and was obtained as large chunky crystals in approximately 23% yield from D-ribose. The third time the acetylation reaction was carried out, there was isolated instead of this compound, the high melting substance which has been described under (a). A sample of large crystals of the low melting material which had been kept in a loosely covered vessel in the laboratory for almost a year, now has a m.p. of 74–80°. No obvious change has taken place in the shape of the crystals but they have become milky and pulverize readily on touching.

1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose (X).[13]—To 825 ml. of anhydrous methanol was added 37.5 g. (0.25 mole) of D-ribose and 11 ml. of dry methanolic hydrogen chloride (containing 3.3 g. of the gas). The clear solution was stirred at room temperature for 90 minutes[22] and the reaction was then quenched by the addition of 75 ml. of anhydrous pyridine. The reaction mixture was freed from solvents *in vacuo* with the bath temperature below 45° and to the residue was added another 75-ml. portion of pyridine. Evaporation was continued until there remained a yellow, somewhat fluid sirup which was dissolved in 200 ml. of methylene chloride and 440 ml. of pyridine. The solution was cooled in ice and benzoyl chloride (146 ml., 1.25 moles) was added slowly with shaking over a period of 10 minutes. The mixture was allowed to stand for 48 hours at 3° and was then poured into 1000 ml. of water. The resulting layers were separated and the aqueous phase was extracted with three 100-ml. portions of chloroform. The combined extracts were in turn washed with two 100-ml. portions of saturated sodium bicarbonate solution and finally with 100 ml. of water. The washings were back-extracted three times with 25-ml. portions of chloroform and the combined extracts were dried over magnesium sulfate, filtered and evaporated under reduced pressure. Last traces of pyridine in the residue were removed by codistillation with toluene *in vacuo*. This left 166 g. of a dark brown oil which was dissolved in 500 ml. of 30% hydrobromic acid in acetic acid[23] and the solution was stirred at room temperature for 30 minutes after which time 350 ml. of glacial acetic acid was added and the mixture was cooled to 8° (internal temperature) in an ice–salt-bath. Stirring and cooling were continued while 250 ml. of water was added dropwise at a rate which kept the internal temperature between 7–11° (37 minutes). The mixture was removed from the cooling bath and stirring was continued for another 23 minutes. The non-homogeneous reaction mixture was then poured into 4 l. of water and this was extracted with five 300-ml. portions of chloroform. These extracts were in turn washed five times with 200-ml. portions of saturated sodium bicarbonate solution and the washings were back-extracted with three 75-ml. portions of chloroform. The combined extracts were dried over magnesium sulfate, filtered and evaporated *in vacuo* to a volume of about 300 ml. To this solution was added an equal volume of pyridine and 70 ml. of acetic anhydride. The mixture was kept for 2 days at room temperature and was then evaporated *in vacuo* to about 150 ml., with the bath temperature not going above 40°. This solution was poured into 500 ml. of water and 200 ml. of chloroform and after separation of the resulting layers the aqueous phase was extracted five times with 50-ml. portions of chloroform. The extracts were washed three times with 50-ml. portions of saturated sodium bicarbonate solution and the washings were extracted with another 40 ml. of chloroform. The combined extracts were dried over magnesium sulfate and filtered. The dark filtrate was freed from solvents *in vacuo*, the last traces of pyridine being again removed by evaporation with toluene. The brown residue crystallized partially on trituration with 300 ml. of ethanol and more crystals could be obtained from the filtered solution on standing in the cold overnight (combined solids weighed 78.3 g., m.p. 122–126°). An additional small amount of crystalline material (2.53 g., m.p. 114–118°) could be obtained by partial evaporation of the mother liquor. Complete evaporation *in vacuo* left 41 g. tarry material which was not further investigated. The combined solid fractions were recrystallized from ethanol–ethyl acetate (5:2) with Darco and there was obtained 71.8 g. (57% from D-ribose) of white crystalline solid, m.p. 126–128°. Rotation and combustion values were obtained from material prepared in a previous run which had been recrystallized once more from ethanol; m.p. 126–129°, $[\alpha]^{25}D$ +35.4° (*c* 1.38 in chloroform), $[\alpha]^{23}D$ +23.8° (*c*, 2.10 in pyridine).[24]

(19) Celite 545, a product of the Johns–Manville Corporation, was washed with 6 *N* hydrochloric acid and then with distilled water until the washings were neutral, and finally with methanol. The substance was dried in air to give a fluffy powder.

(20) Hold back volume (h.b.v.) is defined as the volume of solvent necessary to fill the column.

(21) The m.p. is a sufficient indication of purity in this case, because contamination with even small amounts of the pyranose tetraacetate causes a very obvious depression. The m.p. of pure D-ribofuranose tetraacetate is 81–82° and that of pure D-ribopyranose tetraacetate is 110°.[5]

(22) P. A. Levene, A. L. Raymond and R. T. Dillon, *J. Biol. Chem.*, **95**, 699 (1932), found that after this time 93% of the D-ribose was present as methyl D-ribofuranoside.

(23) Eastman Kodak Company.

(24) Previously reported values are: m.p. 128–129°, $[\alpha]^{20}D$ +23.9° (pyridine),[12] and m.p. 130–131° $[\alpha]^{20}D$ +44.2° (chloroform).[13]

A threefold increase in the size of the reaction afforded approximately the same yield of product.

2-Methylmercapto-6-dimethylamino-9-(2',3',5'-tri-*O*-benzoyl-β-D-ribofuranosyl)-purine (XI).—A sample of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose (X) (5.05 g., 10 mmoles), which had been dried *in vacuo* at 74° for 2 hours, was added to 150 ml. of a cold solution of ethereal hydrogen chloride[9] (saturated at 0°) and the solution was allowed to stand in a closed vessel at −3° for 7 days.[25] The solvent was then removed *in vacuo* at room temperature and the residual gum was dissolved in 30 ml. of anhydrous benzene and the solvent was again evaporated *in vacuo*. This procedure was repeated twice and the gummy tri-*O*-benzoyl-D-ribofuranosyl chloride was then dissolved in 35 ml. of benzene and added to an azeotropically dried suspension of 2-methylmercapto-6-dimethylaminopurine (VI) mercuric chloride, which had been deposited on Celite[2a] (9.2 g. of the mixture containing 4.4 g., 10 mmoles, of the purine salt), in 125 ml. of xylene. Another 45 ml. of mixed solvents was removed from the stirred mixture by distillation and stirring and refluxing were continued for 3 hours. The hot solution was filtered and the filtrate was evaporated to residue *in vacuo*. The Celite precipitate was washed with three 30-ml. portions of hot chloroform and the washings plus another 50 ml. of chloroform were added to the residue from the xylene filtrate. This solution was freed from traces of solid by filtration and was then washed twice with 15-ml. portions of a 30% aqueous potassium iodide solution and finally with 15 ml. of water. The dark solution was dried and partially decolorized with magnesium sulfate and Darco. After filtration it was evaporated *in vacuo* and the dark residue was dissolved in 150 ml. of ether and decanted from a small amount of insoluble gum, which was discarded. The solution was again partially decolorized with Darco and was evaporated to residue under reduced pressure, finally with heating on the steam-bath. This left 6.76 g. of a light brown glass whose maximum purity was 85% by ultraviolet absorption analysis.[2a] This would indicate a maximum yield of 88% from X. The material was not characterized further but was used as such in subsequent reactions.

2-Methylmercapto-6-dimethylamino-9-β-D-ribofuranosylpurine (XII).—The 6.7 g. of crude XI obtained in the previous experiment was dissolved in 50 ml. of anhydrous methanol containing 1.5 ml. of 1 *N* methanolic sodium methoxide and the dark yellow solution was allowed to reflux on the steam-bath for 70 minutes.[26] Evaporation of this solution under reduced pressure left a tan solid residue which was extracted by trituration with three 70-ml. portions of boiling chloroform. The combined extracts were clarified with Darco and freed from solvent *in vacuo* to leave a slightly discolored solid which could be decolorized by trituration with ether to yield, after drying, 2.17 g. (63% from X) of white crystalline material, m.p. 172–173°. For analysis, a small amount of this substance was recrystallized once from 1,2-dimethoxyethane; m.p. 173–174°, $[\alpha]^{24}D$ −43.4° (*c* 1.63 in methanol). The compound showed the following absorption maxima in the ultraviolet: $\lambda_{max}^{ethanol}$ 248 mμ (ε 21300) and 288 mμ (ε 17600) at *p*H 7, and 247 mμ (ε 20350) and 288 mμ (ε 17050) at *p*H 14. In the infrared, the substance showed strong C=N absorption at 6.24 μ and OH absorption at 2.97 μ (KBr window).

Anal. Calcd. for $C_{13}H_{19}N_5O_4S$: C, 45.74; H, 5.61; N, 20.52; S, 9.38. Found: C, 45.90; H, 5.70; N, 20.65; S, 9.58.

6-Dimethylamino-9-(2',3',5'-tri-*O*-acetyl-β-D-ribofuranosyl)-purine (IX).—Dry tetra-*O*-acetyl-β-D-ribofuranose (VII) (3.18 g., 10 mmoles) was dissolved in 75 ml. of anhydrous ethereal hydrogen chloride (saturated at 0°) and the solution was allowed to stand at −3° for 3 days. It was then worked up as described for tri-*O*-benzoyl-D-ribofuranosyl chloride, and the gummy chloro sugar was dissolved in 50 ml. of anhydrous xylene and added to an azeotropically dried suspension of VI mercuric chloride, which had been deposited on Celite[2a] (8 g. of the mixture containing 3.83 g., 8.65 mmoles of the purine salt) in 70 ml. of xylene. The stirred mixture was allowed to reflux for 3.5 hours and was then worked up as described for the preparation of XI. There was obtained 3.72 g. of crude VIII which was approximately 68% pure by ultraviolet analysis.[2a] This was not further purified but was dissolved in 200 ml. of methanol and stirred under reflux with approx. 9 g. of Raney nickel[10] for 1 hour. The suspension was filtered through Celite and the precipitate was washed three times with 50-ml. portions of boiling methanol. The combined filtrates were evaporated *in vacuo* to yield 2.42 g. of IX (ultraviolet analysis indicated a maximum purity of 63%[2a]) which showed absorption peaks in the ultraviolet $\lambda_{max}^{ethanol}$ 267 mμ (*p*H 1), 273 mμ (*p*H 7), 276 mμ (*p*H 14). A small amount of the material was converted to a picrate with ethanolic picric acid and was recrystallized from that solvent; m.p. 172–173°.

Anal. Calcd. for $C_{24}H_{26}N_8O_{14}$: C, 44.31; H, 4.03; N, 17.23. Found: C, 44.24; H, 4.37; N, 17.47.

6-Dimethylamino-9-β-D-ribofuranosylpurine (III). (A) From 6-Dimethylamino-9-(2',3',5'-tri-*O*-acetyl-β-D-ribofuranosyl)-purine (IX).—The crude triacetate IX (2.3 g.) which had been obtained in one experiment from 3.18 g. (10 mmoles) of tetra-*O*-acetyl-D-ribofuranose (VII) was dissolved in 40 ml. of anhydrous methanol containing 0.4 ml. of methanolic sodium methoxide[26] and the dark solution was allowed to reflux for 1 hour and was then evaporated to residue under reduced pressure. The light brown solid was taken up in hot methyl ethyl ketone containing just enough methanol to effect solution. After treatment with Darco and filtration, the solution was concentrated on the steam-bath until cloudy. A white, fibrous substance crystallized out on cooling and was filtered off, washed with a few drops of anhydrous acetone and several portions of ether. The dried material weighed 643 mg., m.p. 174–175°. Further evaporation of the mother liquor yielded another 290 mg. of material with the same m.p. The 933 mg. thus obtained represent an over-all yield of 32% from VII. Material of analytical purity was obtained in 26% over-all yield in another run by three additional recrystallizations from acetone, m.p. 183–184°, with ultraviolet absorption maxima at $\lambda_{max}^{ethanol}$ 268 mμ, (ε 18460 at *p*H 1), 274 mμ (ε 18750 at *p*H 7), 276 mμ (ε 18520 at *p*H 14). In the infrared, the substance shown O–H absorption at 291 μ and 3.02 μ and C=N absorption at 6.17 μ (Nujol mull). Its specific rotation was $[\alpha]^{25}D$ −62.6° (*c* 2.63 in water).

Anal. Calcd. for $C_{12}H_{17}N_5O_4$: C, 48.80; H, 5.80; N, 23.72. Found: C, 49.11; H, 5.90; N, 23.43.

The molecular rotation of the periodate cleavage product of III[11a] was obtained by dissolving 67.93 mg. of this compound in 2 ml. of 0.5 *N* periodic acid and bringing the volume to 10 ml. with sodium acetate–acetic acid buffer (*p*H 4). The specific rotation of this solution after the reaction had gone to completion was $[\alpha]^{24}D$ −19.98° (*c* 0.67 calcd. as the cleavage product $C_{12}H_{15}N_5O_4$, mol. weight 293.28). From this, the molecular rotation was found to be $[M]^{24}D$ −5640.

(B) From 2-Methylmercapto-6-dimethylamino-9-(2',3',5'-tri-*O*-benzoyl-β-D-ribofuranosyl)-purine (XI).—Crude XI (2.93 g. of gum which had been obtained from 2.52 g., 5 mmoles of the tribenzoyl ribose derivative X) was dissolved in 200 ml. of methanol and was stirred and refluxed with approx. 9 g. of Raney nickel[10] for 1.5 hours. The solution was filtered through Celite while hot and the catalyst was washed three times with 50-ml. portions of hot methanol. Filtrate and washings were evaporated to residue under reduced pressure, and the remaining gum was dissolved in chloroform and evaporated once more in order to ensure complete removal of water. This left 1.74 g. of a light yellow gum which was not further purified but was dissolved in 40 ml. of absolute methanol containing 0.4 ml. of 1 *N* methanolic sodium methoxide[25] and refluxed for 45 minutes. The yellow solution was filtered through Darco and was evaporated *in vacuo*. The residue was crystallized from hot acetone to yield (in several fractions) a total of 577 mg. of solid (39% over-all from X), m.p. 179–182°. A sample which was recrystallized from acetone had m.p. 181–183° and did not depress the m.p. of authentic III (obtained under (A)) on

(25) In other preparations it was found that a reaction period of 3 days is quite sufficient; *cf.* reference 9.

(26) These catalytic *O*-deacylations were always started with a volume of 1 *N* sodium methoxide solution corresponding to 1% of the volume of solvent used. The alkalinity of the reaction mixture was checked after 30 minutes of reflux and another portion of the methoxide solution was added if the *p*H had fallen below 8 (Alkacid Test Paper) and reflux was resumed for 20 minutes when the *p*H was checked again. The addition of methoxide solution was continued until the mixture remained basic throughout a 20–30 minute reflux period. In these descriptions, only the total amount of methoxide solution and reflux time are given.

admixture. Identity with III was shown also by infrared spectroscopy.

(C) From the Condensation of 6-Dimethylaminopurine (IV) with Tri-*O*-benzoyl-D-ribofuranosyl Chloride.—The chloro sugar obtained as described above (preparation of XI) from 2.52 g. (5 mmoles) of X was added in 20 ml. of anhydrous benzene to an azeotropically dried suspension of 6-dimethylaminopurine (IV) mercuric chloride on Celite[2a] (3.24 g. of the mixture containing 1.99 g., 5 mmole of the purine salt) in 60 ml. of xylene. An additional 35 ml. of mixed solvents was distilled out of the stirred mixture and stirring and refluxing were continued for 3 hours. The solution was processed as described under the preparation of IX to afford 2.57 g. of light yellow gum which had 83% maximum purity by ultraviolet analysis.[2a] The gum was not further purified but was dissolved in 100 ml. of absolute methanol containing 1 ml. of 1 *N* methanolic sodium methoxide[26] and the solution was allowed to reflux for 50 minutes. It was freed from solvent *in vacuo* and the residue was taken up in 100 ml. of hot acetone and decanted from a small amount of insoluble gum. It was concentrated to a volume of 20 ml. and ether was added to this solution until it became cloudy. A white precipitate which formed on standing was filtered off (it contained mostly sodium salts and was discarded) and the filtrate was further concentrated by evaporation to yield, on cooling, several fractions of crystalline material which were combined to afford 678 mg. (46% over-all from X) of compound with m.p. 178–180° (undepressed by III).

(D) From the Condensation of IV with Tri-*O*-acetyl-D-ribofuranosyl Chloride.—The chloro sugar obtained from 1.59 g. (5 mmoles) of VII was condensed with IV mercuric chloride (5 mmoles of purine salt) as described under (C). The crude triacetate IX was isolated as 1.32 g. of yellow gum which had a maximum purity of 66% by ultraviolet analysis.[2a] The gum was dissolved in 40 ml. of absolute methanol containing 0.4 ml. of 1 *N* methanolic sodium methoxide[26] and the orange solution was refluxed for 45 minutes. The solvent was removed under reduced pressure and the residue was taken up in a mixture of 80 ml. of acetone and 15 ml. of methanol and decolorized by filtration through Darco. The filtrate was evaporated again *in vacuo* and the residue was crystallized from hot acetone. The acetone insoluble material which contained sodium salts was discarded. There was obtained 368 mg. (25% over-all from VII) of white crystalline solid m.p. 182–183° which did not depress the m.p. of an authentic sample of III on admixture.

(E) From 2-Methylmercapto-6-dimethylamino-β-D-ribofuranosylpurine (XII).—To a solution of 112 mg. (0.328 mmole) of XII in 25 ml. of ethanol was added approx. 300 mg. of Raney nickel[10] and the suspension was stirred and refluxed for 1 hour. Inspection of an aliquot by ultraviolet spectroscopy (*i.e.*, extinction at the 248 mμ peak) showed that only approximately 25% of the compound had been desulfurized. The mixture was filtered and the catalyst was washed with a small amount of ethanol. Freshly prepared catalyst (300 mg. approx.) was added and the mixture was again stirred and refluxed. Aliquots were removed at periodic intervals and checked in the spectrophotometer at 248 and 274 mμ. The solution was again filtered after 1.5 hours (57% desulfurized) and the catalyst was washed with ethanol. Another batch of catalyst (300 mg. approx.) was added to filtrate and washings; and the reaction was allowed to proceed for 6 hours.[27] Spectrophotometric inspection of an aliquot showed that the band at 248 mμ had completely vanished by this time. Therefore, the solution was filtered and the catalyst was washed with hot ethanol. Filtrate and washings were evaporated *in vacuo* and the residual crystalline solid was triturated with ether and collected. After drying, it weighed 53 mg. (55% from XII) and had a m.p. 180–181°. This was not depressed by admixture of an authentic sample of III.

6-Dimethylamino-7-β-D-ribofuranosylpurine (XIII).—Tri-*O*-benzoyl-D-ribofuranosyl chloride, prepared from 2.52 g. (5 mmoles) of X (*cf.* preparation of XI), in 25 ml. of anhydrous benzene was added to an azeotropically dried suspension of 2,8-bis-methylmercapto-6-dimethylaminopurine (V) mercuric chloride on Celite[2a] (4.2 g. of the mixture containing 2.44 g., 5 mmoles of the purine salt) in 60 ml. of xylene. Some 30 ml. of mixed solvents was removed from the stirred reaction mixture by distillation and stirring and refluxing were continued for 3.5 hours. The reaction mixture was then worked up as described for XI and there was obtained 2.1 g. of a light yellow glass which showed broad absorption between 270–300 mμ in the ultraviolet, thus indicating the presence of both 9- and 7-substituted 6-dimethylaminopurine derivatives.

The mixture was dissolved in 30 ml. of ethyl acetate and to the solution was added 150 ml. of ethanol and approx. 9 g. of Raney nickel catalyst.[10] The stirred suspension was allowed to reflux for 3 hours and was then filtered through a layer of Celite. The catalyst was washed with several portions of hot ethanol, and washings and filtrate were evaporated *in vacuo*. The residue was taken up in 100 ml. of chloroform and was washed with two 15-ml. portions of water in order to remove unreacted 6-dimethylaminopurine. The washings were back-extracted with 15 ml. of chloroform and the combined extracts were dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was a white glass which weighed 2.02 g. after drying *in vacuo* over P_2O_5.

The material was *O*-debenzoylated by allowing it to reflux in 60 ml. of absolute methanol containing 1.2 ml. of 1 *N* methanolic sodium methoxide for 65 minutes.[26] The brown solution was freed from solvent *in vacuo* and the residue was triturated with a small amount of ether in order to remove methyl benzoate. The remaining solid was heated with 180 ml. of anhydrous acetone and filtered from insoluble sodium salts, which were discarded. The acetone solution was partially decolorized with Darco and concentrated in several stages. The solid fractions which could be collected at each stage on cooling had m.p.'s which varied from 135 to 193°. Altogether, there were collected five fractions of solid material (combined weight 393 mg.) all of which contained 7- and 9-substituted 6-dimethylaminopurine derivatives (ultraviolet spectra). Separation of these isomers was effected by treating each solid fraction first with hot ethyl acetate and then crystallizing the material which was not soluble in that solvent from hot acetone. The solid which first crystallized out of this acetone solution (m.p. 193–200°) could be shown to be almost pure 7-isomer by its ultraviolet absorption spectrum. Evaporation of the ethyl acetate solution to a small volume yielded solid material which was again crystallized from acetone to give first a small amount of 7-isomer and then mostly 9-isomer (m.p. 174–183°). All solid fractions were checked by ultraviolet spectroscopy and identical fractions were combined for a final recrystallization from acetone. There were isolated 128 mg. of the 7-isomer XIII and 250 mg. of the 9-isomer III. The total amount of pure solids (378 mg.) represents 25% over-all yield from X.

In subsequent runs it was possible to separate these two isomers by *partition chromatography* on Celite. Preliminary experiments showed that the distribution coefficients of the two compounds in ethyl acetate–water system, as determined by ultraviolet spectroscopy, were as follows: D.C. ethyl acetate/water = 0.089 for the 7-isomer and 0.199 for the 9-isomer. These figures indicated that the 9-isomer would travel sufficiently faster in the moving phase (ethyl acetate) to be separated efficiently from the 7-isomer. Distilled water and C.P. ethyl acetate were saturated with each other and 124 mg. of a mixture of III and XIII was dissolved with warming (35°) in the 7 ml. of the aqueous phase. A column (3 cm. I.D. × 60 cm. length) was packed in uniform layers with 150 g. of Celite[19] which had been thoroughly mixed with 75 ml. of the aqueous phase to give an almost dry powder. The solution containing the nucleoside mixture was also mixed with 15 g. of Celite which was in turn packed on top of the column (column height 50 cm.). The column which had a h.b.v.[20] of 250 ml. was developed with the organic phase and the percolate was collected in 20-ml. fractions. An aliquot from every fifth fraction was checked in the spectrophotometer at 278 mμ (λ_{max} of 9-isomer[26]) and at 298 mμ (λ_{max} of 7-isomer[26]). When optical densities times dilutions at these two wave lengths were plotted against fraction numbers, there were obtained two curves which showed that fractions 5–30 (0–2.5 h.b.v.) contained the 9-isomer and that fractions 40–80 (3.5–6.5 h.b.v.) contained the 7-isomer. Fractions 30–40 and fractions 81–120

(27) Since this reaction has only been run once, it is not clear whether the inordinate length of time necessary to effect complete desulfurization is due to the nature of the compound (*i.e.*, the presence of free hydroxyl groups in the sugar moiety) or to a particularly weak batch of Raney nickel catalyst.

showed practically no purine absorption in the ultraviolet and were discarded. Evaporation of pooled identical fractions *in vacuo* yielded 27.2 mg. of III, m.p. 180–182° and 61 mg. of XIII, m.p. 189–191°. A sample of XIII obtained in a similar partition chromatogram and recrystallized from hot ethyl acetate with just enough methanol to effect solution had a m.p. 200–201° after drying *in vacuo* for 3 hours at 110°; $[\alpha]^{24.5}D$ −85.5° (*c* 0.415 in 60% ethanol). In the ultraviolet the compound showed the following maxima: $\lambda_{max}^{ethanol}$ 291 mμ (ε 22400 at *p*H 1), 298 mμ (ε 17720 at *p*H 7), 298 mμ (ε 17480 at *p*H 14).

Anal. Calcd. for $C_{12}H_{17}N_5O_4$: C, 48.80; H, 5.80; N, 23.72. Found: C, 49.17; H, 6.05; N, 23.74.

The compound was somewhat hygroscopic and a sample which had not been dried as well as the one just described, analyzed for a semihydrate, m.p. 199–200°.

Anal. Calcd. for $C_{12}H_{17}N_5O_4{}^1/_2H_2O$: C, 47.36; H, 5.96; N, 23.02. Found: C, 47.67; H, 6.07; N, 23.28.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & COMPANY]

Compounds Related to Chloromycetin.[1] 1-Biphenylyl and Ring-substituted 1-Biphenylyl-2-dichloroacetamido-1,3-propanediols

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The preparations of 4′-bromo- and 4′-methyl-1-biphenylyl-2-dichloroacetamido-1,3-propanediol are described. DL-*threo*-1-Biphenylyl-2-amino-1,3-propanediol was resolved by the fractional crystallization of a salt of dextrorotatory phenylethylsuccinic acid to obtain the D-*threo* intermediate base for use in preparing the biologically active dichloroacetamide.

An extensive group of compounds related to Chloromycetin in which the nitro group in the *para* position is replaced by various types of organic radicals, has now been described in the literature. The substituents include the halogens: iodine,[2-4] bromine,[2,3] chlorine[2,3,5] and fluorine.[2,3] Compounds have also been prepared with methoxy and phenoxy,[6] methyl,[7] cyano,[8] acylamido and aroylamido,[9] alkylmercapto and arylmercapto,[10] alkylsulfonyl[10] and trifluoromethyl[11] groups in the *para* position.

Although Colonna and Runti prepared 1-biphenylyl-2-acetamido-1,3-propanediol,[12] conversion to the dichloroacetamide was not reported by these workers. Bambas in a patent[13] has described the synthesis of the latter compound. Further details in the preparation of D- and DL-*threo*-1-biphenylyl-2-dichloroacetamido-1,3-propanediol as well as the 4′-methyl and 4′-bromo related compounds are reported in this paper. The procedure developed by Long and Troutman[14] as a method for the preparation of Chloromycetin, or a slight modification of this approach first described in the literature by Sorm and co-workers,[5] proved useful in synthesizing these compounds. According to the first method α-acetamido-β-hydroxymethylacetophenones are reduced to the corresponding phenylacetamidopropanediols. The amino group is then liberated by hydrolysis, the free base is resolved, and the D-threo isomer converted to the dichloroacetamide. If dichloroacetamidoacetophenones are used instead of acetamides, reduction leads directly to the racemic substituted 1-phenyl-2-dichloroacetamido-1,3-propanediols. A disadvantage in the latter approach may lie in the fact that the presence of labile halogens limits the reducing agents which can be used. Meerwein–Ponndorf–Verley conditions have been found useful in the reduction of such dichloroacetamides but these conditions usually lead to the formation of one diastereoisomer in much greater quantity than the other. In some cases only one of the two possible racemates has been isolated. Fortunately when both isomers were obtained, the compound which predominated had some antibacterial activity, while the isomer formed in lower yield always proved to be virtually inactive under the conditions of our testing program.[15]

On the other hand, it was advantageous to have the α-dichloroacetamido-β-hydroxymethylacetophenone intermediates for investigation as possible antifungal agents. These compounds are related to α-dichloroacetamido-β-hydroxymethyl-*p*-nitroacetophenone, a compound prepared by Long and Troutman and found by Hillegas to be very effective in inhibiting the growth of certain fungi.[16]

The reduction of α-dichloroacetamido-β-hydroxymethyl-4′-methylphenylacetophenone using Meer-

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