II, Compound 8).—A mixture of 9.25 g. (0.0685 mole) of N-methyl-2,6-dimethylaniline, 33.4 g. (0.137 mole) of 1,6-dibromohexane and 50 mg. of potassium iodide was heated in an oil-bath at 140° for 25 minutes. After addition of 100 ml. of water, the cooled mixture was made alkaline with 6 *N* sodium hydroxide and promptly extracted with three 100-ml. portions of ether. The combined ether extracts were dried (magnesium sulfate), filtered, the ether removed and the residue distilled. The product, 7.1 g. (35%), boiled at 146–154° (0.5 mm.).

N-Methyl-(3-[N-methyl-2,6-dimethylanilino]-propyl)-piperidinium Bromide (Table II, Compound 3).—A mixture of 1.79 g. (0.007 mole) of N-(3-bromopropyl)-N-methyl-2,6-dimethylaniline (Table II, compound 1) and 0.73 g. (0.0074 mole) of N-methylpiperidine in 5 ml. of acetonitrile was heated under reflux for 1 hr. When cool, 0.95 g. (38%) of colorless crystals was filtered off, washed with ethyl acetate and dried *in vacuo*, m.p. 185–187.5°.

Anal. Calcd. for $C_{18}H_{31}BrN_2$: C, 60.8; H, 8.7; N, 7.9; Br, 22.5. Found: C, 60.9; H, 8.8; N, 7.9; Br, 22.6.

N-Methyl-N-β-phenethyl-2,6-dimethylaniline.—A mixture of 13.6 g. (0.1 mole) of N-methyl-2,6-dimethylaniline and 37 g. (0.2 mole) of 2-bromoethylbenzene and 100 mg. of potassium iodide was heated in an oil-bath maintained at 140° for 0.5 hr. When cool, the crystalline mass was dissolved in 100 ml. of water, the solution made alkaline with 6 *N* sodium hydroxide and extracted with three 100-ml. portions of ether. The combined ether extracts were dried (magnesium sulfate), filtered, the ether removed and the residue distilled. The product, 8.3 g. (35%), boiled at 122–128° (0.1–0.2 mm.).

Anal. Calcd. for $C_{17}H_{21}N$: C, 85.3; H, 8.8; N, 5.9. Found: C, 85.1; H, 8.9; N, 5.8.

Acknowledgment.—The authors are grateful to Dr. G. Ungar and his staff for the pharmacologic evaluation of the compounds herein described.

YONKERS, NEW YORK

[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

Synthesis of Potential Anticancer Agents. XIV. Ribosides of 2,6-Disubstituted Purines

BY HOWARD J. SCHAEFFER AND H. JEANETTE THOMAS

RECEIVED FEBRUARY 15, 1958

The syntheses of several new 2-substituted-6-methoxy- and 2-substituted-6-aminopurine ribosides have been accomplished.

In an earlier paper of this series,[1] we discussed the reasons for our interest in the area of purine ribosides as potential anticancer agents, with special reference to certain 6-substituted purine ribosides. In a continuation of our studies, we have now prepared a representative number of 2,6-disubstituted purine ribosides for biological evaluation.

Because of the recently demonstrated[2] differences in the reactivity of the chlorine atoms in 2,6-dichloropurine, we selected 2,6-dichloro-9-β-D-ribofuranosylpurine (IIIc) as the key intermediate for the syntheses of some 2,6-disubstituted purine ribosides. Since the 6-chlorine atom is much more reactive than the 2-chlorine atom in the free purine, it is logical to assume that the chlorine atoms of the corresponding riboside (IIIc) would show a similar difference in reactivity. Thus, monosubstitution of 2,6-dichloropurine riboside by a nucleophilic reagent should yield a 6-substituted product which, after isolation, should be capable of undergoing further substitution of the 2-position with a variety of nucleophilic reagents. In this way, a useful method for the preparation of a wide variety of 2,6-disubstituted purine ribosides would be available.

Condensation of bis-(2,6-dichloropurinyl)-mercury (I) with 2,3,5-tri-*O*-benzoylribofuranosyl chloride (IIa)[3] proceeded in high yield, and the blocked nucleoside IIIa, which was isolated as a glass, was shown to be fairly pure by its elemental analysis. The proof of structure of the crude nucleoside IIIa will be described later in the paper. The next step in our synthetic scheme was the removal of the *O*-benzoyl blocking groups from the crude nucleoside IIIa. In an earlier paper of this series,[4] it was demonstrated that *O*-benzoyl blocking groups may be removed from several 6-chloropurine blocked nucleosides with methanolic ammonia at 0° in 24 hours without concomitant replacement of the 6-chloro group. However, when we allowed IIIa to react with methanolic ammonia at 0° for 18 hours a complex reaction mixture resulted which was shown by paper chromatography to contain at least four materials. Elution of the spot having an R_{ad} 1.00[5] from the chromatogram and determination of its ultraviolet spectrum indicated by comparative studies with an authentic sample[6] that the material was 6-amino-2-chloropurine-9-β-D-ribofuranosylpurine.[7a,b] Since it is known[8] that the removal of the acetyl blocking group proceeds at a much faster rate than the removal of the benzoyl blocking group, we attempted to prepare IIIc by a procedure which employs the more easily removed acetyl blocking group. Condensation of bis-(2,6-dichloropurinyl)-mercury (I) with 2,3,5-tri-*O*-acetylribofuranosyl chloride (IIb)[9a,b,10] proceeded smoothly; the blocked nucleoside IIIb was allowed to react with excess

(1) Affiliated with Sloan-Kettering Institute. This work was supported by funds from the C. F. Kettering Foundation and the National Institutes of Health, Grant Number CY-2942. Part XIII. J. A. Johnson, Jr., H. J. Thomas and H. J. Schaeffer, THIS JOURNAL, **80**, 699 (1958).

(2) J. A. Montgomery and L. B. Holum, *ibid.*, **79**, 2185 (1957).

(3) H. M. Kissman, C. Pidacks and B. R. Baker, *ibid.*, **77**, 18 (1955).

(4) B. R. Baker, K. Hewson, H. J. Thomas and J. A. Johnson, Jr., *J. Org. Chem.*, **22**, 954 (1957).

(5) Paper chromatograms were developed with butanol saturated with water by the descending technique on Whatman No. 1 paper. Adenine was employed as a standard and was assigned R_{ad} 1.00.

(6) This sample of IVa was furnished by Dr. G. B. Brown of the Sloan-Kettering Institute; see also *J. Org. Chem.*, **23**, 125 (1958).

(7) (a) This experiment was performed by Dr. J. A. Johnson, Jr.; (b) J. Davoll, B. Lythgoe and A. R. Todd, *J. Chem. Soc.*, 1685 (1948).

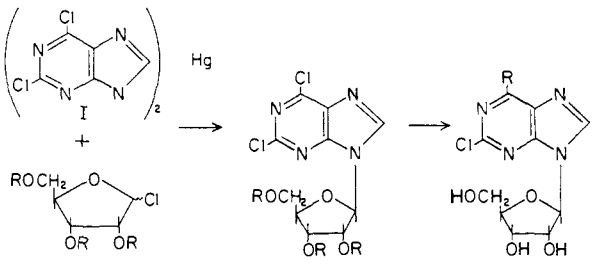
(8) K. Kindler, *Ann.*, **452**, 90 (1927); *Ber.*, **69B**, 2792 (1936).

(9) (a) J. Davoll, B. Lythgoe and A. R. Todd, *J. Chem. Soc.*, 967 (1948); (b) H. Zinner, *Ber.*, **83**, 153 (1950).

(10) E. Fischer and B. Helferich, *ibid.*, **47**, 210 (1914).

methanolic ammonia at 0° for only two hours.[7a]

CHART I



IIa, R = C_6H_5CO- IIIa, R = C_6H_5CO- IVa, R = NH_2-
IIb, R = CH_3CO- IIIb, R = CH_3CO- IVb, R = CH_3O-
IIIc, R = H

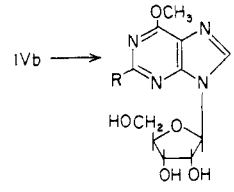
Again, the reaction was complex—at least four products were shown to be formed by an examination of a paper chromatogram of the reaction mixture. One of the spots had the same R_{ad} 1.00[5] as 6-amino-2-chloropurine riboside (IVa). Similar difficulties were observed by Fischer and Helferich[10] when they attempted to remove the acetyl blocking groups from 2,6,8-trichloro-9-(2′,3′,4′,6′-tetra-*O*-acetyl-D-glucopyranosyl)-purine.

Since one of the intermediates which we wished to prepare from IIIc was 6-amino-2-chloropurine riboside (IVa), we examined the reaction of IIIa with methanolic ammonia at higher temperatures. The results of these experiments will be described later in the paper.

We next turned our attention to the removal of the blocking groups of IIIa by means of sodium methoxide in methanol solution. An examination by means of paper chromatography of the effect of catalytic amounts of sodium methoxide revealed that, at room temperature or at 65°, practically no reaction occurred. However, when the blocked nucleoside IIIa was allowed to react with 1.1 equivalents of sodium methoxide at 65°, a reaction occurred with the formation of one major product as shown by the appearance of one spot (R_{ad} 1.61)[5] on a paper chromatogram. Repetition of this experiment on a larger scale resulted in the isolation of the crude product as a gel which was resistant to purification by the conventional means. Purification of the crude product was accomplished by partition chromatography on a Celite column using water as the immobile phase and butanol as the mobile phase. Elemental analysis of the purified product indicated that one of the chlorine atoms had been replaced by a methoxy group during the debenzoylation. In order to establish both the position of substitution and the stereochemistry of the nucleoside, the chloro group was removed by catalytic hydrogenolysis using a palladium-on-charcoal catalyst in the presence of magnesium oxide as the acid acceptor[11]; the resulting product was shown to be 6-methoxy-9-β-D-ribofuranosylpurine (V).[1] Therefore, the structure of the nucleoside produced from the reaction of IIIa with sodium methoxide is 2-chloro-6-methoxy-9-β-D-ribofuranosylpurine (IVb).

Because of the potential usefulness as anticancer agents of some 2-substituted-6-methoxypurine ribosides, we prepared several derivatives for biological evaluation. Treatment of 2-chloro-6-methoxypurine riboside (IVb) with a methanolic solution of sodium methyl mercaptide for two hours at 65° resulted in the formation of 6-methoxy-2-methylthiopurine riboside (VI). The progress of the reaction was followed by examining paper chromatograms prepared from aliquots removed from the reaction mixture at increasing time intervals and observing the disappearance of the spot corresponding to starting material (R_{ad}1.99)[12] and observing the formation of a new spot (R_{ad} 1.48).[12]

CHART II



V, R = H
VI, R = CH_3S-
VII, R = CH_3O-

The synthesis of 2,6-dimethoxypurine riboside (VII) was accomplished by allowing a solution of IVb to react with two equivalents of 1 *N* sodium methoxide for four hours at 65°. The dimethoxy analog VII also may be prepared by allowing IIIa to react with excess 1 *N* sodium methoxide.

An attempt was made to prepare 2-amino-6-methoxy-9-β-D-ribofuranosylpurine by allowing 2-chloro-6-methoxy-9-β-D-ribofuranosylpurine (IVb) to react with methanolic ammonia at 83° for 16 hours; however, the desired compound was not obtained. From the reaction mixture we isolated 6-amino-2-chloropurine riboside (IVa), whose formation arose from the nucleophilic displacement of the 6-methoxy group in preference to the displacement of the 2-chlorine atom.

Since 6-amino-2-chloropurine riboside (IVa) was an intermediate in which we were interested for the preparation of some 2-substituted adenosines, we have devised, as indicated earlier, a more convenient synthesis of IVa directly from the blocked nucleoside IIIa. Debenzoylation with concomitant substitution at the 6-position of 2,6-dichloro-9-β-D-(2′,3′,5′-tri-*O*-benzoyl)-ribofuranosylpurine(IIIa) with methanolic ammonia was studied under two reaction conditions: (a) 0° for 20 hours followed by 4 hours at 50° and (b) 18 hours at room temperature. Separate chromatograms of the reaction mixtures each showed three spots; one spot (R_{ad} 1.33)[12] was identified as 6-amino-2-chloropurine riboside (IVa), one spot (R_{ad} 2.04)[12] as benzamide, and the third spot has not been identified. The large scale synthesis of IVa was accomplished in a 20% yield by allowing the blocked nucleoside IIIa to react with methanolic ammonia at room temperature. The crude product was isolated as its picrate, and the free nucleoside was regenerated from its picrate with Dowex 1 (CO_3).[13a,b] The usefulness of 6-amino-2-chloropurine riboside (IVa) as an intermediate for the synthesis of 2-substituted-6-aminopurine ribosides is demonstrated by

(11) For a similar reaction, see ref. 9a.

(12) These chromatograms were developed with 0.1 *M* phosphate buffer (*p*H 6.9).

(13) (a) J. Davoll and B. A. Lowy, THIS JOURNAL, **73**, 1650 (1951); (b) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 959 (1957).

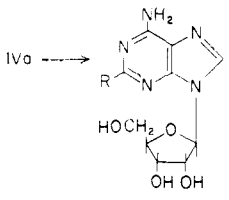
our preparation of six nucleosides from IVa as described below.

The preparation of 6-amino-2-methoxy-9-β-D-ribofuranosylpurine (VIII) was accomplished by treating IVa with 1 *N* sodium methoxide at 65°. The replacement of the chlorine atom was rather slow (16 hours), but the reaction proceeded without decomposition and a moderate yield of product was obtained. Bergmann and Stempien[14] recently reported the isolation of this riboside (spongosine) from natural sources and described its synthesis by a different procedure. The identity of the two products was established by the excellent agreement obtained upon comparison of their physical and optical properties.

Treatment of IVa with sodium methyl mercaptide in refluxing *n*-propyl alcohol for 2.5 hours resulted in the formation of a good yield of 6-amino-2-methylthiopurine riboside (IX). This compound has been prepared previously[15] in a 19% yield by the condensation of chloromercuri-6-acetamido-2-methylthiopurine and 2,3,5-tri-*O*-acetylribofuranosyl chloride.

6-Amino-2-dimethylaminopurine riboside (X) was prepared in good yield by allowing a methanolic solution of IVa to react with an aqueous solution of dimethylamine at 100° for 16 hours. However, when an attempt was made to prepare 6-amino-2-methylaminopurine riboside (XI) under similar reaction conditions, extensive decomposition occurred. A moderate yield of XI was obtained, however, when less strenuous reaction conditions were employed.

CHART III



VIII, R = CH_3O-
IX, R = CH_3S-
X, R = $(CH_3)_2N$-
XI, R = CH_3NH-
XII, R = H_2NNH-
XIII, R = N_3-

The preparation of 6-amino-2-hydrazinopurine riboside (XII) was accomplished by the usual procedure,[1,2] *i.e.*, treatment of IVa with anhydrous hydrazine at room temperature. This compound is rather unstable in the crude state, but if several rapid recrystallizations are performed a relatively stable analytical sample is obtained.

Treatment of 6-amino-2-hydrazinopurine riboside (XII) with nitrous acid at 0° resulted in the isolation of a product in good yield. The infrared spectrum of this product exhibited strong absorption at 2155 cm.$^{-1}$ which is characteristic of the azido group.[16,17] On this basis, in addition to the elemental analysis, the structure of this product has been established as 6-amino-2-azidopurine riboside (XIII).

Acknowledgment.—The authors are indebted to Mr. J. P. Holmquist and Mr. J. W. Murphy for the microanalytical results reported, to Mr. D. L. Norton and Mr. W. A. Rose for the ultraviolet and infrared spectral determinations, and especially to Dr. J. A. Montgomery for his helpful discussions on this research. Some of the analyses reported were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(14) W. Bergmann and M. F. Stempien, *J. Org. Chem.*, **22**, 1575 (1957), and earlier papers.

(15) J. Davoll and B. A. Lowy, *ibid.*, **74**, 1563 (1952).

(16) E. Lieber, D. R. Levering and L. J. Patterson, *Anal. Chem.*, **23**, 1594 (1951).

(17) J. H. Boyer, THIS JOURNAL, **73**, 5248 (1951).

Experimental[18]

Bis-(2,6-dichloropurinyl)-mercury.—To a stirred suspension of 1.60 g. (8.45 mmoles) of 2,6-dichloropurine and 2.40 g. of Celite in 210 ml. of 50% aqueous ethanol containing 1.14 g. (4.12 mmoles) of mercuric chloride was added slowly 3.04 ml. of 10% sodium hydroxide solution (8.45 mmoles). After cooling the suspension overnight, the product was collected by filtration, washed with cold water, ethanol, and finally with ether, and dried at 61° (3 mm.) for 8 hours over phosphorus pentoxide; yield 4.80 g. (includes 2.40 g. of Celite) (100%). From a pilot run in which Celite was not added, the analytical sample of the mercury derivative was obtained in a 97% yield.

Anal. Calcd. for $C_{10}H_2N_8Cl_4Hg$: N, 19.43. Found: N, 19.12.

2-Chloro-6-methoxy-9-β-D-ribofuranosylpurine (IVb).—A solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride, which was prepared[3] from 7.67 g. (15.2 mmoles) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose, in 50 ml. of xylene was added to an azeotropically dried suspension of 4.38 g. (7.60 mmoles) of bis-(2,6-dichloropurinyl)-mercury and 4.60 g. of Celite in 400 ml. of xylene. The mixture was refluxed with stirring for two hours and then filtered; the filter cake was washed with hot chloroform (3 × 50 ml.). The xylene filtrate was evaporated *in vacuo;* the residue was dissolved in hot chloroform, and the solution was combined with the chloroform washings. The combined chloroform solution was washed with 30% aqueous potassium iodide (2 × 100 ml.) and water (2 × 100 ml.), then dried with magnesium sulfate, clarified with decolorizing carbon, and filtered. Concentration of the filtrate gave the crude, blocked nucleoside IIIa as a tan glass; yield 9.93 g. (103%); $\tilde{\nu}$ in cm.$^{-1}$: 1720 (C=O, ester); 1595, 1555 and 1495 (C=N, C=C); 1265 and 1100 (C-O-, benzoate); 760 and 705 (monosubstituted benzene).

To a solution of 2.11 g. (3.33 mmoles) of the crude blocked nucleoside IIIa in 100 ml. of absolute methanol was added 3.7 ml. of 1 *N* sodium methoxide in methanol. The mixture was refluxed for one hour, neutralized with acetic acid, and evaporated *in vacuo*. The residue was dissolved in water (30 ml.) and extracted with chloroform (2 × 10 ml.); evaporation of the aqueous solution gave the crude nucleoside (800 mg.) as a gel, which could not be purified by recrystallization. Therefore, 200 mg. of the crude product was purified by partition chromatography on a column of acid-washed Celite 545 (35 cm. × 2.1 cm.). The column was developed with water-saturated butanol. The first 60 ml. of eluate was discarded; the main fraction came off the column over the next 60 ml. of eluate. Evaporation of this solution gave 140 mg. of white crystals, m.p. 140°. Two recrystallizations from isopropyl alcohol–ethyl acetate gave the analytical material, m.p. 140°, $[\alpha]^{26}D$ −30.4 ± 2.3° (0.612% in methanol); λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 259 (10.8); *p*H 7, 258 (11.0); *p*H 13, 259 (11.2); ν in cm.$^{-1}$: 3370 (broad OH); 1600 and 1580 (C=N, C=C); 1120, 1085 and 1055 (C-O-).

Anal. Calcd. for $C_{11}H_{13}N_4O_5Cl$: C, 41.74; H, 4.14; N, 17.65. Found: C, 42.16; H, 4.72; N, 17.46.

After the seed crystals were obtained, the pure product could be obtained directly from the crude reaction mixture by recrystallization from isopropyl alcohol–ethyl acetate. In a different experiment, the pure nucleoside, m.p. 140°, was obtained in a yield of 61% by direct crystallization of the crude reaction mixture.

(18) The ultraviolet spectra were determined in aqueous solution with a Beckman model DK-2 spectrophotometer, the infrared spectra with a Perkin-Elmer model 21 spectrophotometer, and the optical rotations with a standard polarimeter model D attachment to the Beckman DU spectrophotometer calibrated with standard sucrose solutions.[19] Melting points were determined on a Kofler Heizbank.

(19) A. Keston, Abst. 127th Meeting, Am. Chem. Soc., p. 18-C (1955).

6-Methoxy-9-β-D-ribofuranosylpurine from 2-Chloro-6-methoxy-9-β-D-ribofuranosylpurine (IVb).—To a solution of 308 mg. (0.970 mmole) of 2-chloro-6-methoxy-9-β-D-ribofuranosylpurine in 50 ml. of 50% aqueous methanol were added 100 mg. of 5% palladium-on-charcoal catalyst and 40 mg. of magnesium oxide. The mixture was hydrogenated at room temperature and atmospheric pressure; the theoretical amount of hydrogen was absorbed in 39 minutes. The catalyst was removed by filtration, and the filtrate was evaporated *in vacuo* to dryness. The residue was crystallized from a mixture of methanol and ethyl acetate; the white solid was collected by filtration; yield 203 mg. (74.0%), m.p. 140°; mixed m.p. with an authentic sample of 6-methoxy-9-β-D-ribofuranosylpurine[1] was 140°. The ultraviolet and infrared spectra of this sample were identical to those of a sample prepared by a different procedure.[1]

Reaction of 2-Chloro-6-methoxy-9-β-D-ribofuranosylpurine with Methanolic Ammonia.—A solution of 176 mg. (0.555 mmole) of 2-chloro-6-methoxy-9-β-D-ribofuranosylpurine in 15 ml. of methanol saturated with ammonia at 0° was heated in a stainless steel bomb at 83° for 16 hours. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to dryness. The residue was dissolved in water, and 10 ml. of a 14% aqueous solution of picric acid was added. The resulting picrate was collected by filtration and then dissolved in water. The aqueous solution was stirred with 0.3 g. of Dowex 1 (CO_3) ion exchange resin. The resin was removed by filtration; concentration of the filtrate caused the precipitation of a white solid; yield 61 mg. (37%), m.p. 145–146° dec. This compound was shown to be identical with 6-amino-2-chloro-9-β-D-ribofuranosylpurine by comparison of its infrared and ultraviolet spectra with those of an authentic sample.

6-Methoxy-2-methylthio-9-β-D-ribofuranosylpurine (VI).—To a solution of 500 mg. (1.58 mmoles) of 2-chloro-6-methoxy-9-β-D-ribofuranosylpurine in 75 ml. of methanol was added 3.16 ml. of 1 *N* sodium methyl mercaptide in methanol, which was prepared by saturating a 1 *N* solution of sodium methoxide in methanol with methyl mercaptan. The mixture was heated under reflux for two hours; the cooled solution was neutralized with 1 *N* hydrochloric acid and evaporated *in vacuo*. The solid residue was dissolved in hot water; the non-crystalline solid that separated was collected by filtration; yield 203 mg. (39.2%), m.p. 159–160° (softening at 116°). A second crop (140 mg.) of material that was obtained from the mother liquor was shown by ultraviolet analysis to be 84% pure.

The crude material was recrystallized from water and dried at 110° (0.08 mm.) over phosphorus pentoxide for 48 hours; m.p. 160–161° (softening at 116°), $[\alpha]^{26}D$ −16.9 ± 2.1° (0.649% in methanol); λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 262 (9.90), 283 (shoulder) (7.20); *p*H 7, 263 (10.3); *p*H 13, 223 (10.7), 264 (10.2); $\bar{\nu}$ in cm.$^{-1}$: 3420–3400 (broad OH); 1600 and 1580 (shoulder) (C=N, C=C); 1125, 1085 and 1055 (C–O–).

Anal. Calcd. for $C_{12}H_{16}N_4O_5S$: C, 44.00; H, 4.92; N, 17.08. Found: C, 44.52; H, 4.91; N, 17.18.

2,6-Dimethoxy-9-β-D-ribofuranosylpurine (VII).—To a solution of 500 mg. (1.58 mmoles) of 2-chloro-6-methoxy-9-β-D-ribofuranosylpurine in 75 ml. of methanol was added 3.16 ml. of 1 *N* sodium methoxide. The solution was heated under reflux for four hours, neutralized with 1 *N* hydrochloric acid, and evaporated *in vacuo*. The residue was recrystallized from water, and the pure product was dried at 110° (0.08 mm.) over phosphorus pentoxide for 24 hours; yield 155 mg., m.p. 163° (softening at 120°), $[\alpha]^{32}D$ −33.6 ± 2.2° (0.648% in methanol); λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 235 (5.33), 267 (10.2); *p*H 7, 243 (7.50), 264 (10.4); *p*H 13, 244 (7.45), 264 (10.7); $\bar{\nu}$ in cm.$^{-1}$: 3320 (broad OH); 1600 and 1560 (shoulder) (C=N, C=C); 1085, 1070 and 1045 (C–O–).

Anal. Calcd. for $C_{12}H_{16}N_4O_6$: C, 46.15; H, 5.17; N, 17.95. Found: C, 45.76; H, 5.01; N, 17.87.

6-Amino-2-chloro-9-β-D-ribofuranosylpurine (IVa).—A mixture of 6.00 g. (9.48 mmoles) of crude 2,6-dichloro-9-(2′,3′,5′-tri-*O*-benzoyl)-β-D-ribofuranosylpurine (IIIa) and 420 ml. of methanol saturated with ammonia at 0° was stirred in an ice-bath until solution was complete. The solution was allowed to stand overnight at room temperature and then evaporated *in vacuo* to dryness. The residue was dissolved in water (40 ml.) and extracted with chloroform (2 × 20 ml.). To the aqueous solution was added 25 ml. of an 11% aqueous picric acid solution; the resulting picrate was collected by filtration and then dissolved in water. The aqueous solution of the picrate was stirred with 9 g. of Dowex 1 (CO_3) ion exchange resin. The resin was removed by filtration; concentration of the filtrate to 20 ml. caused the precipitation of the product; yield 670 mg. (23%), m.p. 142° dec.; λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 264 (14.0); *p*H 7, 264 (14.9); *p*H 13, 265 (14.9); $\bar{\nu}$ in cm.$^{-1}$: 3320 (broad OH and NH); 1650 (NH); 1600 and 1580 (C=N, C=C); 1095 and 1050 (C–O–).

Davoll and Lowy[15] have prepared this compound in a 13% yield by a different procedure; they reported m.p. 135° and λ_{max} in mμ ($\epsilon \times 10^{-3}$): 0.1 *N* HCl, 265 (13.9); 0.1 *N* NaOH, 265 (15.0).

6-Amino-2-methoxy-9-β-D-ribofuranosylpurine (VIII).—To a solution of 302 mg. (1.00 mmole) of 6-amino-2-chloro-9-β-D-ribofuranosylpurine in 50 ml. of methanol was added 2 ml. of 1 *N* sodium methoxide. The mixture was heated under reflux for 16 hours; the cooled reaction mixture was neutralized with 1 *N* hydrochloric acid and evaporated *in vacuo*. Two recrystallizations of the residue from water gave the pure material, which was dried at 130° (0.07 mm.) over phosphorus pentoxide for 48 hours before analysis; yield 104 mg. (35%), m.p. 190–192° dec. (reported[14] m.p. 192–193°), $[\alpha]^{26}D$ −43.3 ± 2.3° (0.610% in methanol); λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 249 (8.35), 274 (11.9); *p*H 7, 267 (12.5); *p*H 13, 268 (12.7); $\bar{\nu}$ in cm.$^{-1}$: 3370 and 3220 (broad OH and NH); 1645 (NH); 1610 and 1520 (C=N, C=C); 1080, 1060 and 1030 (C–O–).

Anal. Calcd. for $C_{11}H_{15}N_5O_5 \cdot {}^1/_2H_2O$: C, 43.13; H, 5.26; N, 22.87. Found: C, 43.32; H, 4.93; N, 23.30, 23.11.

6-Amino-2-methylthio-9-β-D-ribofuranosylpurine (IX).—To a solution of 300 mg. (1.00 mmole) of 6-amino-2-chloro-9-β-D-ribofuranosylpurine in 50 ml. of *n*-propyl alcohol was added 2.0 ml. of 1 *N* sodium methyl mercaptide, which was prepared by saturating a 1 *N* solution of sodium methoxide in *n*-propyl alcohol with methyl mercaptan. The mixture was heated under reflux for 2.5 hours, neutralized with 1 *N* hydrochloric acid, and filtered to remove the insoluble sodium chloride. The filtrate was evaporated *in vacuo* to dryness, and the residue was crystallized from water; yield 172 mg., m.p. 163–164°. Two recrystallizations from water gave the pure material, which was dried at 132° (0.08 mm.) over phosphorus pentoxide for 48 hours; yield 119 mg. (38%), m.p. 153°, resolidified at 185–190° and remelted with decomposition at 220°; λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 270 (15.2); *p*H 7, 235 (17.7), 274 (13.5); *p*H 13, 235 (17.8), 274 (13.5); $\bar{\nu}$ in cm.$^{-1}$ 3340 (broad OH and NH); 1640 (NH); 1600 and 1510 (C=N, C=C); 1080, 1050 and 1025 (C–O–). This compound has been prepared[15] by a different procedure. The reported[15] m.p. is 227°.

6-Amino-2-dimethylamino-9-β-D-ribofuranosylpurine (X).—A solution of 302 mg. (1.00 mmole) of 6-amino-2-chloro-9-β-D-ribofuranosylpurine in 10 ml. of a 25% aqueous solution of dimethylamine was diluted with 35 ml. of methyl alcohol and heated in a stainless steel bomb at 100° for 16 hours. The resulting light yellow reaction solution was evaporated *in vacuo* to dryness. Crystallization of the residue from 40 ml. of water gave a light orange crystalline solid; yield 221 mg. (72%), m.p. 213° dec.

The analytical sample was prepared by recrystallization from water and was dried over phosphorus pentoxide at 140° (0.07 mm.); yield 174 mg. of a white crystalline material, m.p. 213° dec., $[\alpha]^{26}D$ −12.5 ± 1.5° (0.603% in methanol); λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 261 (16.2), 305 (8.76); *p*H 7, 227 (20.9), 262 (12.6), 294 (8.05); *p*H 13, 262 (12.5), 295 (8.32); $\bar{\nu}$ in cm.$^{-1}$: 3440 and 3350 (broad OH, NH); 1640 (shoulder) (NH); 1620, 1600 and 1560 (C=C, C=N); 1135, 1080 and 1045 (C–O–).

Anal. Calcd. for $C_{12}H_{18}N_6O_4$: C, 46.44; H, 5.85; N, 27.08. Found: C, 46.10; H, 5.56; N, 26.99.

6-Amino-2-methylamino-9-β-D-ribofuranosylpurine (XI).—A solution of 302 mg. (1.00 mmole) of 6-amino-2-chloro-9-β-D-ribofuranosylpurine in 10 ml. of a 40% aqueous solution of methylamine was diluted with 35 ml. of methyl alcohol and heated in a stainless steel bomb at 100° for 4 hours.

The resulting light yellow reaction solution was evaporated to dryness *in vacuo*. Crystallization of the residue from a methanol–ethyl acetate solution gave a white solid; yield 116 mg., m.p. 192° dec. The crude product was re-

crystallized from methanol–ethyl acetate and dried over phosphorus pentoxide for 48 hours at 110° (0.07 mm.); yield 93 mg. (32%), m.p. 198° dec., $[\alpha]^{26}D$ −42.8 ± 3.3° (0.416% in methanol); λ_{max} in mμ (ε × 10^{-3}): *p*H 1, 254 (13.7), 299 (9.30); *p*H 7, 258 (11.0), 287 (8.75); *p*H 13, 257 (10.7), 288 (8.99); $\bar{\nu}$ in $cm.^{-1}$: 3350 and 3150 (broad, OH, NH); 1660 (NH); 1600, 1540 and 1510 (C=C, C=N); 1125, 1080 and 1055 (C–O–).

Anal. Calcd. for $C_{11}H_{16}N_6O_4$: C, 44.59; H, 5.44; N, 28.37. Found: C, 44.48; H, 5.73; N, 28.00.

6-Amino-2-hydrazino-9-β-D-ribofuranosylpurine (XII).—To 30 ml. of anhydrous hydrazine was added portionwise 602 mg. (2.00 mmoles) of 6-amino-2-chloro-9-β-D-ribofuranosylpurine. The reaction mixture was kept at room temperature for 16 hours in a nitrogen atmosphere, and then the volatile materials were removed *in vacuo* (bath 30°). The last traces of hydrazine were removed by evaporating the residue with isopropyl alcohol (3 × 15 ml.). The residue was crystallized from a mixture of water and ethanol; yield 225 mg. (38%), m.p. 143°, resolidified at 150–155° and melted with decomposition at 200°. A second crop (51 mg.) of material which had the same melting point, was obtained from the mother liquor. Two recrystallizations of the crude product from water and ethanol gave the pure material; m.p. 143°. Since this compound was sensitive to heat, it was dried at room temperature at 0.07 mm. for 24 hours before analysis, $[\alpha]^{26}D$ −33.0 ± 1.8° (0.763% in water); λ_{max} in mμ (ε × 10^{-3}): *p*H 1, 256 (9.48), 277 (10.2); *p*H 7, 257 (11.0), 278 (9.30); *p*H 13, 250 (10.2), 282 (9.05); $\bar{\nu}$ in $cm.^{-1}$: 3380 (broad OH, NH); 1645 (NH); 1605, 1600 and 1525 (C=N, C=C); 1130, 1080 and 1045 (C–O–).

Anal. Calcd. for $C_{10}H_{15}N_4O_4 \cdot {}^1/_2C_2H_5OH$: C, 41.30; H, 5.68; N, 30.70. Found: C, 41.21; H, 5.84; N, 31.27.

6-Amino-2-azido-9-β-D-ribofuranosylpurine (XIII).—To a solution of 297 mg. (1.00 mmole) of 6-amino-2-hydrazino-9-β-D-ribofuranosylpurine in 7 ml. of 5% aqueous acetic acid which was cooled in an ice-bath, was added a cooled solution of 83 mg. (1.20 mmoles) of sodium nitrite in 17 ml. of water. After ten minutes, crystals began to separate; the reaction mixture was kept cold for one hour, and the solid was collected by filtration; yield 218 mg. (71%), m.p. 157–160° dec. One recrystallization from water gave the pure material, which was dried at 100° (0.07 mm.) over phosphorus pentoxide for 48 hours before analysis; yield 142 mg. (46.3%), m.p. 159–160° dec., $[\alpha]^{26}D$ −27.6 ± 5.8° (0.232% in methanol); λ_{max} in mμ (ε × 10^{-3}): *p*H 1, 273 (14.6); *p*H 7, 230 (20.8), 271 (11.9), 309 (4.75); *p*H 13, 230 (16.2), 271 (12.7); $\bar{\nu}$ in $cm.^{-1}$: 3370 (OH, NH); 2155 ($-N_3$); 1645 (NH); 1605, 1600 and 1520 (C=N, C=C); 1140, 1080 and 1055 (C–O–).

Anal. Calcd. for $C_{10}H_{12}N_8O_4$: C, 38.96; H, 3.92; N, 36.35. Found: C, 39.20; H, 4.47; N, 36.27.

BIRMINGHAM, ALABAMA

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Near Ultraviolet Absorption of Hindered Biphenyls[1]

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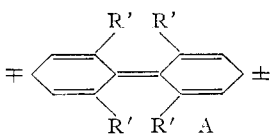
RECEIVED FEBRUARY 8, 1958

Several biphenyls (Ar–Ar) with alkyl substituents in the four *o*-positions have been synthesized. A study of their spectra in the near ultraviolet region indicates that a comparison of the extinction coefficients of a biphenyl derivative with its monophenyl analog (Ar–H) at corresponding peaks, for the purpose of determining differences in steric effects is not unequivocal.

The broad, relatively intense absorption bands which characterize biphenyl derivatives in the 250–300 mμ region usually are attributed to resonance interactions involving the two benzenoid rings as shown in A.



A

It is now well established[3-5] that the position and intensity of these absorption bands are determined by the nature and size of the substituents present.

The insertion of *o*-substituents into biphenyl brings about dramatic changes in its spectrum. This effect is usually attributed[4] to non-bonded repulsions which inhibit coplanarity and thus reduce resonance interactions between the benzenoid rings. Although the characteristic "K-band" in these derivatives is shifted to shorter wave lengths and diminished in intensity,[5] its influence on the "B-band," which is the object of this study, is still quite evident.

The present investigation was initiated in the hope that an examination of the spectra of carefully selected biphenyl derivatives related to hydrindene and tetralin would permit a more quantitative evaluation of the difference in the steric effect of methylene groups in five- and six-membered rings. Such a difference has been observed repeatedly in earlier studies reported from this Laboratory.[6]

For this purpose, the following compounds (I–V) were prepared and their spectra in the near ultraviolet region examined.

It has been common practice[3,4,7] in studies of this kind to compare the spectra of symmetrical biphenyls (Ar–Ar) with their corresponding monophenyl analogs (Ar–H) and we, at first, followed this procedure (see Figs. 1 and 2).

Such comparisons seem to imply that it should be possible to "insulate" the two halves of a biphenyl molecule by rotating the two benzenoid rings sufficiently with respect to each other and thus reduce the resonance interaction to an insignificant value. If this were true, the spectrum of a

(1) Taken from the Ph.D. Thesis of Erich Marcus, June, 1956.

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