at 25° to a solution of 0.80 g. of lithium borohydride in 50 cc. of tetrahydrofuran over a period of $^3/_4$ hr. The mixture was further stirred at room temperature for 4 hr. and then the excess lithium borohydride was decomposed under cooling with 40 cc. of 20% aqueous acetic acid. The resulting acidic solution was evaporated *in vacuo* to nearly dryness and after trituration with water the separated solid was filtered, washed with saturated sodium chloride solution and dried at 80° *in vacuo*. This crude product was acetylated with 10 cc. of pyridine and 10 cc. of acetic anhydride either at steam-bath temperature for 7 minutes or better at room temperature for 15 minutes. The excess of acetic anhydride was immediately decomposed by treatment with 10 cc. of water and the solvents were removed *in vacuo*. For the regeneration it was dissolved in 15 cc. of acetic acid. After addition of 4.6 cc. of water, 2.55 g. of anhydrous sodium acetate and 2.4 cc. of 90% pyruvic acid the mixture was heated at 75° under nitrogen for 4 hr. At the end of this period the solvents were removed *in vacuo* and the residue was extracted with ethyl acetate. The ethyl acetate solution was washed with 5% aqueous sodium bicarbonate solution and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the dry residue (0.832 g.) was dissolved in benzene–chloroform and chromatographed on acid-washed alumina. Fractional elution with benzene–chloroform afforded, as described previously,[1] 4-pregnene-17,20,21-triol-3,11-dione 20,21-diacetate (II) and 4-pregnene-11,17,20,21-tetrol-3-one 20,21-diacetate (III) melting first at 235–245° (about 60 mg.) and at 223–226° (about 100 mg.), respectively. Recrystallization from ethyl acetate gave the pure substances. Further elution with chloroform–methanol (1:1) gave the crude compound

(IV) melting at 219–230° (350–465 mg.). Recrystallization from acetone–ethyl acetate or from acetone raised the melting point to 235–237° depressed by admixture with (II) or (III), λ_{max} 2425, E% 399 (ethanol).

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 67.99; H, 8.38; $[\alpha]^{24}D$ +99 ± 1° (1% acetone).

Another run under essentially the same condition, but without the acetylation step, gave 4-pregnene-11,17,20,21-tetrol-3-one (V) as major product.

4-Pregnene-11,17,20,21-tetrol-3-one and Its Diacetate from (IV).—To a solution of 40.0 mg. of (IV) in 5 cc. of methanol was added at 40°, 1 cc. of water containing 30 mg. of potassium carbonate and 50 mg. of potassium bicarbonate. After standing at room temperature for 72 hr. the reaction mixture was acidified with acetic acid and concentrated *in vacuo* nearly to dryness. The residue was extracted with ethyl acetate and the ethyl acetate solution after washing with saturated sodium chloride solution and 5% sodium bicarbonate solution was dried over anhydrous sodium sulfate. Concentration of the filtrate and addition of ether afforded 4-pregnene-11,17,20,21-tetrol-3-one (V) melting at 126–127° not depressed by admixture with an authentic specimen. Infrared spectra confirm the identity in every respect.

Acetylation of (IV) by pyridine and acetic anhydride gave 4-pregnene-11,17,20,21-tetrol-3-one 20,21-diacetate melting at 228–230°. A mixed melting point of this material with an authentic specimen was not depressed.

11-Dihydroadrenosterone (VI) from (IV).—To a solution of 50 mg. of IV in 4 cc. of methanol was added a solution of 80 mg. of periodic acid in 0.6 cc. of water. After standing for 21 hr. at room temperature the reaction mixture was diluted with a few cc. of water, concentrated *in vacuo* to remove methanol and extracted with ethyl acetate–ether. The extract, after washing with 5% soda solution and then with water, was dried with anhydrous sodium sulfate and filtered. The filtrate was evaporated *in vacuo* yielding a brownish powder. On high vacuum sublimation at 170° (0.035 mm.), 26 mg. of crystalline sublimate was obtained; which after two recrystallizations from ether melted at 195.5–197° not depressed by admixture with an authentic sample of 11-dihydroadrenosterone prepared according to Reichstein[2] from 4-pregnene-11,17,20,21-tetrol-3-one (V). Infrared spectra confirm the identity in every respect.

RAHWAY, N. J.

[CONTRIBUTION FROM THE LABORATORIES OF THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

# Some Synthetic Analogs of the Natural Purine Nucleosides[1]

BY JOHN DAVOLL[2] AND BERTRAM A. LOWY

The synthesis of a number of 9-glycosylpurines is reported. These include the pyranosyl analogs of the natural purine nucleosides, and the 2-methyl, 2-methylthio and 2-chloro derivatives of adenosine. The structure of Fischer and Helferich's "trichloropurine tetraacetyl glucoside"[8] has been determined.

The chloromercuri derivatives of purines form convenient starting materials for the synthesis of the 9-β-D-ribofuranosyl derivatives of adenine, 2,6-diaminopurine, guanine[3] and isoguanine.[4] These methods have now been applied to the preparation of various analogous glycosylpurines of possible biological interest.

9-β-D-Ribopyranosyladenine, 9-β-D-ribopyranosylguanine and 2,6-diamino-9-β-D-ribopyranosylpurine were prepared by replacing the triacetyl D-ribofuranosyl chloride used in the synthesis of the

ribofuranosylpurines[8] by its pyranose isomer. Treatment of 2,6-diamino-9-β-D-ribopyranosylpurine with nitrous acid under the conditions used for the synthesis of crotonoside[4] appeared to give 9-β-D-ribopyranosylisoguanine, though this compound could not be obtained in a pure condition. 2,6-Diamino-9-β-D-xylofuranosylpurine was prepared by deacetylation of the condensation product of chloromercuri-2,6-diacetamidopurine and triacetyl D-xylofuranosyl chloride.
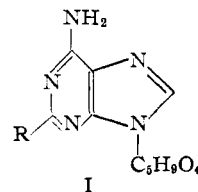
$C_5H_9O_4$

I

(2) Fellow of the United States Public Health Service.
(3) J. Davoll and B. A. Lowy, THIS JOURNAL, 73, 1650 (1951).
(4) J. Davoll, ibid., 73, 3174 (1951).

Several derivatives of adenosine, substituted in position 2 of the purine ring, were synthesized. 2-Methylthio-9-β-D-ribofuranosyladenine (I, R = CH_3S) was prepared by condensation of the chloromercuri derivative of acetylated 2-methylthioadenine with triacetyl D-ribofuranosyl chloride, followed by deacetylation of the product. The structure of this compound was demonstrated by desulfurization to adenosine. 2-Methyl-9-β-D-ribofuranosyladenine (I, R = CH_3) (obtained as the picrate) was prepared in a similar manner from 2-methyladenine; it is assigned the structure of a 9- rather than a 7-glycosylpurine on the basis of a comparison of its ultraviolet absorption spectrum with those of other derivatives of 2-methyladenine[5] (Table I).

TABLE I

| | λ_{max}, mμ | |
	0.1 N HCl	0.1 N NaOH
2,7-Dimethyladenine	273	277
2,9-Dimethyladenine	264	264
2-Methyl-9-D-xylosyladenine	260.5	262.5
2-Methyl-9-β-D-ribofuranosyladenine	258	262.5

2-Chloroadenine was prepared by partial reduction of 2,8-dichloroadenine; deacetylation of the condensation product of its chloromercuri derivative with triacetyl D-ribofuranosyl chloride gave 2-chloro-9-β-D-ribofuranosyladenine (I, R = Cl), identical with an authentic sample obtained by partial reduction of 2,8-dichloro-9-β-D-ribofuranosyladenine.[6]

9-α-L-Arabofuranosyladenine was prepared by the method previously reported for the preparation of its enantiomorph.[7]

2,6,8-Trichloro-9-triacetyl-β-D-ribofuranosylpurine was prepared from silver trichloropurine and triacetyl D-ribofuranosyl chloride. The structure assigned to it is based on analogy with the similarly prepared glucosyl derivative[8]; the position of the tetraacetyl glucosyl residue in the latter compound has now been demonstrated by its conversion to 2,8 - dichloro - 9 - tetraacetyl - β - D - glucopyranosyladenine, identical with an authentic sample.

Results of biological testing of the above compounds will be published elsewhere.

Experimental

Melting points were determined on a heated microscope stage, and are uncorrected. Evaporations were carried out at 10-20 mm. pressure. Ultraviolet absorption spectra were determined on a Beckman spectrophotometer, Model DU, or on a Cary recording spectrophotometer.

9-β-D-Ribopyranosyladenine.—A suspension of 1.54 g. of chloromercuri-6-acetamidopurine[3] in 150 ml. of xylene was dried by slow distillation of one-third of the xylene and treated with 1.25 g. of triacetyl D-ribopyranosyl chloride.[9] The mixture was refluxed, with stirring, for 4 hours, then evaporated under reduced pressure and the residue extracted with chloroform. The extract was washed with 30% aqueous potassium iodide and with water, dried over sodium sulfate, and evaporated to a sirup. A solution of this material in 20 ml. of methanol was treated with 40 ml. of methanolic ammonia (saturated at 0°), kept overnight at 0°, and evaporated to dryness. Crystallization of the

(5) J. Baddiley, B. Lythgoe and A. R. Todd, J. Chem. Soc., 318 (1944).

(6) J. Davoll, B. Lythgoe and A. R. Todd, ibid., 1685 (1948).

(7) N. W. Bristow and B. Lythgoe, ibid., 2306 (1949).

(8) E. Fischer and B. Helferich, Ber., 47, 210 (1914)

(9) H. Zinner, ibid., 83, 153 (1950).

residue from water gave 0.164 g. (16%) of 9-β-D-ribopyranosyladenine, m.p. 254°; $[\alpha]^{26}D$ $-37°$ (c 0.6% in water) (reported,[10] m.p. 254° with sintering at 234-235°; $[\alpha]^{20}D$ $-38°$ (c 0.28% in water)).

Anal. Calcd. for $C_{10}H_{13}O_4N_5$: N, 26.2. Found: N, 26.3.

2,6-Diacetamido-9-triacetyl-β-D-ribopyranosylpurine.—Chloromercuri-2,6-diacetamidopurine[3] (6.3 g.) and 4.2 g. of triacetyl D-ribopyranosyl chloride were condensed together in 300 ml. of xylene and the product isolated as described in the foregoing experiment. Crystallized from a large volume of ethanol the compound formed colorless leaflets, m.p. 254-260°; yield 2.61 g. (40%).

Anal. Calcd. for $C_{20}H_{24}O_9N_6$: C, 48.9; H, 4.9; N, 17.1. Found: C, 49.1; H, 4.9; N, 16.9.

2,6-Diamino-9-β-D-ribopyranosylpurine.—A solution of 1.7 g. of the above pentaacetate in 50 ml. of boiling methanol was treated with a solution of 0.3 g. of sodium in 20 ml. of methanol. The mixture was kept 1.5 hours at 25°, then refluxed for 30 minutes, neutralized with acetic acid and evaporated to dryness. Crystallization of the residue from 10 ml. of water, using Norit, gave 0.83 g. (85%) of colorless needles. After two recrystallizations the compound had m.p. 188-190°; $[\alpha]^{25}D$ $-21°$ (c 0.68% in water).

Anal. Calcd. for $C_{10}H_{14}O_4N_6$: N, 29.8. Found: N, 29.6.

2-Acetamido-6-amino-9-β-D-ribopyranosylpurine.—A solution of 2.71 g. of 2,6-diacetamido-9-triacetyl-β-D-ribopyranosylpurine in 75 ml. of hot methanol was cooled rapidly and treated with 150 ml. of methanolic ammonia (saturated at 0°). The mixture was kept overnight at 0°, then evaporated to dryness and the residue crystallized from 15 ml. of water, to give 1.2 g. (67%) of the monoacetyl compound as leaflets, m.p. 227-230°.

Anal. Calcd. for $C_{12}H_{16}O_5N_6$: C, 44.5; H, 5.0; N, 25.9. Found: C, 44.4; H, 4.8; N, 25.8.

9-β-D-Ribopyranosylguanine.—A solution of 0.535 g. of the above monoacetyl compound and 1.4 g. of sodium nitrite in 15 ml. of hot water was cooled rapidly to room temperature and treated with 1.3 ml. of glacial acetic acid. After 30 minutes an equal volume of water was added and the mixture kept overnight at room temperature. Excess aqueous lead acetate and ammonia was added, and the precipitate collected, washed and dissolved in cold 20% acetic acid. After treatment with hydrogen sulfide and filtration through Celite, the filtrate was evaporated to dryness and the residue treated with a solution of 0.3 g. of sodium in 50 ml. of methanol. The mixture was refluxed 45 minutes, treated with 10 ml. of water and refluxed a further 45 minutes. The solution was neutralized with acetic acid and evaporated to dryness, and a solution of the residue in 75 ml. of hot water allowed to cool slowly with stirring. The separated material was collected and washed, and after drying formed a white amorphous powder, decomposing above 240°; yield 0.238 g. (51%). The ultraviolet absorption spectrum, 22 mg. per liter, showed maxima as follows: In 0.1 N hydrochloric acid, 255 mμ (ϵ_m 12,400), and in 0.1 N sodium hydroxide, 265 mμ (ϵ_m 11,400). The corresponding values for guanosine were 255 mμ (ϵ_m 12,000) and 265 mμ (ϵ_m 11,400), respectively.

Anal. Calcd. for $C_{10}H_{13}O_5N_5$: C, 42.4; H, 4.6; N, 24.7. Found: C, 42.7; H, 4.8; N, 24.7.

Action of Nitrous Acid on 2,6-Diamino-9-β-D-ribopyranosylpurine.—A solution of 0.8 g. of 2,6-diamino-9-β-D-ribopyranosylpurine and 1.2 g. of sodium nitrite in 15 ml. of hot water was cooled to 50° and treated with 1.2 ml. of glacial acetic acid. The solution was kept at 50° for 5 minutes, and the product isolated through the lead salt in the usual way. The ultraviolet absorption spectra of solutions of the material obtained closely resembled those of crotonoside,[4] but concentrated solutions formed clear gels from which no solid material could be isolated.

2,6-Diamino-9-β-D-xylofuranosylpurine.—Chloromercuri-2,6-diacetamidopurine (6 g.) and triacetyl D-xylofuranosyl chloride[11] (prepared from 4 g. of the tetraacetate) were condensed together and the sirupy product isolated and deacetylated as described for the corresponding ribopyranosyl derivative. Purified by conversion to the picrate and regeneration by treatment with an anion-exchange resin,[3]

(10) J. Baddiley, G. W. Kenner, B. Lythgoe and A. R. Todd, J. Chem. Soc., 657 (1944).

(11) P. Chang and B. Lythgoe, ibid., 1992 (1950).

2,6-diamino-9-β-D-xylofuranosylpurine separated from water as colorless, irregular crystals, m.p. 160–163°; yield 0.33 g. (9%).

Anal. Calcd. for $C_{10}H_{14}O_4N_6 \cdot 0.5H_2O$: C, 41.2; H, 5.2; N, 28.9. Found: C, 40.8; H, 4.9; N, 29.0.

Picrate.—The picrate crystallized from aqueous ethanol in fine yellow needles, m.p. 226° (dec.).

Anal. Calcd. for $C_{16}H_{17}O_{11}N_9$: N, 24.7. Found: N, 24.8.

2-Methylthio-9-β-D-ribofuranosyladenine.—A mixture of 1.8 g. of 2-methylthioadenine and 12 ml. of acetic anhydride was refluxed gently for 2.5 hours, cooled, and diluted with 12 ml. of ether. The product appeared to consist mainly of a diacetyl compound (*Anal.* Calcd. for $C_{10}H_{11}O_2N_5S$: N, 26.4; COCH$_3$, 32.4. Found: N, 27.0; COCH$_3$, 32.5); yield 1.8 g. (68%).

A suspension of 1.24 g. of the above material in 60 ml. of hot 50% ethanol was treated with 9.4 ml. (2 equivalents) of N sodium hydroxide, followed by a solution of 1.28 g. of mercuric chloride in 15 ml. of ethanol. The precipitate, assumed to be chloromercuri-2-methylthio-6-acetamido-purine, was collected and dried; yield 1.73 g. (80%).

An azeotropically dried suspension of 1.73 g. of the chloromercuri compound in 120 ml. of xylene was treated with the triacetyl D-ribofuranosyl chloride[12] prepared from 1.5 g. of the tetraacetate, and refluxed for 2 hours. After cooling, 250 ml. of petroleum ether (b.p. 30–60°) was added, and the solid material collected, dried and extracted with cold chloroform. The extract was washed, dried and evaporated in the usual way to give the tetraacetyl derivative as a sirup; yield 0.85 g. (47%). This was deacetylated with methanolic ammonia at 0° and the product crystallized from 50 ml. of water, using Norit, to give 0.41 g. (19% from 2-methylthioadenine) of 2-methylthio-9-β-D-ribofuranosyladenine as colorless, hydrated needles, m.p. 227° after drying *in vacuo* at 130°, unchanged by further recrystallization; $[\alpha]^{29}D$ +4° (c 1% in 0.1 N hydrochloric acid). The ultraviolet absorption spectrum, 17.5 mg. per liter, showed maxima as follows: In 0.05 N hydrochloric acid, 270 mμ (ϵ_m 16,000); and in 0.05 N sodium hydroxide, 235 mμ (ϵ_m 21,200) and 277 mμ (ϵ_m 14,700).

Anal. Calcd. for $C_{11}H_{15}O_4N_5S$: C, 42.2; H, 4.8; N, 22.4. Found: C, 42.1; H, 5.1; N, 22.6.

Adenosine from 2-Methylthio-9-β-D-ribofuranosyladenine.—2-Methylthio-9-β-D-ribofuranosyladenine (90 mg.) was heated on a steam-bath for 1.5 hours with 1 ml. of pyridine and 0.6 ml. of acetic anhydride. Excess acetic anhydride was destroyed by addition of ethanol, and solvents were removed under reduced pressure. A solution of the sirupy residue in 25 ml. of ethanol was boiled under reflux for 2 hours with *ca.* 3 g. of Raney nickel containing adsorbed hydrogen. The nickel was collected and thoroughly extracted with ethanol (soxhlet). The combined filtrates were evaporated and the residue deacetylated with methanolic ammonia. Addition of ethanolic picric acid to an aqueous solution of the material thus obtained gave 70 mg. (50%) of adenosine picrate, which, after recrystallization, was treated with an anion-exchange resin[3] to give 23 mg. of adenosine, m.p. 235–236°, which did not depress the melting point of a sample of natural adenosine of m.p. 234–235°.

Anal. Calcd. for $C_{10}H_{13}O_4N_5$: N, 26.2. Found: N, 26.7.

2-Methyladenine.—The following method is more convenient than that previously described.[13] A solution of 1.0 g. of 4,6-diamino-5-benzeneazo-2-methylpyrimidine[14] in 25 ml. of 90% formic acid was hydrogenated at room temperature and pressure, using a 5% palladized charcoal catalyst. After 45 minutes reduction was complete and the catalyst was removed by filtration. The filtrate was kept overnight at room temperature, then evaporated to small volume and diluted with ethanol, giving the 5-formamido compound as fine needles; yield 0.68 g. (93%). A suspension of this material in 7 ml. of formamide was heated in a sealed tube at 165° for 2.5 hours. After cooling, the contents of the tube were diluted with 80 ml. of water, heated to boiling, and treated with dilute hydrochloric acid to give a clear

solution which was treated with Norit and filtered. The filtrate was made just alkaline with ammonia and the 2-methyladenine collected after cooling; yield 0.43 g. (71%).

2-Methyl-9-β-D-ribofuranosyladenine Picrate.—2-Methyladenine was converted to its ribofuranosyl derivative exactly as described for the 2-methylthio compound. The product could not be crystallized, but gave a crystalline picrate, decomposing above 200°; yield 11% from 2-methyladenine.

Anal. Calcd. for $C_{17}H_{18}O_{11}N_8$: C, 40.0; H, 3.5; N, 22.0. Found: C, 40.1; H, 3.3; N, 22.0.

After removal of picric acid with an anion-exchange resin a solution of this material showed an ultraviolet absorption maximum at 258 mμ in 0.1 N hydrochloric acid and 262.5 mμ in 0.1 N sodium hydroxide.

2-Chloroadenine.—A solution of 3.7 g. of 2,8-dichloroadenine in 300 ml. of 0.2 N sodium hydroxide was hydrogenated at room temperature and pressure, using 4 g. of 5% palladized barium sulfate as catalyst. After 5 hours 441 ml. of hydrogen (1 mole per mole of substance) had been absorbed. The catalyst was collected, and the filtrate acidified with acetic acid, giving 2.7 g. of material which was contaminated with adenine and 2,8-dichloroadenine. A solution of this material in 75 ml. of N sodium hydroxide was treated with 75 ml. of N sodium hydrogen carbonate. 2,8-Dichloroadenine remains dissolved at the pH of the mixture, and the precipitated 2-chloroadenine was collected and washed by resuspension in 100 ml. of hot water to remove adenine. The dried material formed an amorphous powder; yield 1.55 g. (51%). The analytical figures indicate slight contamination with adenine, and this was confirmed by paper chromatography. The ultraviolet absorption spectrum in 0.1 N hydrochloric acid, 14.5 mg. per liter, showed a maximum at 265 mμ (ϵ_m 12,500); and in 0.1 N sodium hydroxide, 16 mg. per liter, at 272 mμ (ϵ_m 12,500).

Anal. Calcd. for $C_5H_4N_5Cl$: N, 41.3; Cl, 20.9. Found: N, 41.9; Cl, 19.6.

Isoguanine from 2-Chloroadenine.[15]—The above compound (0.1 g.) and 2 ml. of 20% hydrochloric acid were refluxed together for 45 minutes. The mixture was cooled, made alkaline with ammonia, and the solid collected, washed, and heated with 3 ml. of 2 N sulfuric acid, giving 57 mg. (46%) of isoguanine sulfate, identified by its ultraviolet absorption spectrum and by paper chromatography.

2-Chloro-9-β-D-ribofuranosyladenine.—A solution of 0.17 g. of 2-chloroadenine in 10 ml. of hot water containing 1 ml. of N sodium hyroxide was treated with 0.27 g. of mercuric chloride in 5 ml. of ethanol. The chloromercuri compound was collected after cooling as a white powder; yield 0.31 g. (77%). This material was refluxed for 2.5 hours in 10 ml. of xylene with the triacetyl D-ribofuranosyl chloride prepared from 0.35 g. of tetraacetate, and the product, isolated in the usual way, was deacetylated with methanolic ammonia. Crystallization of the material thus obtained from water gave 30 mg. (13%) of 2-chloro-9-β-D-ribofuranosyladenine, m.p. 135° after recrystallization from water. The ultraviolet absorption spectrum in 0.1 N hydrochloric acid and 0.1 N sodium hydroxide was indistinguishable from that of an authentic sample (next experiment) under similar conditions.

Anal. Calcd. for $C_{10}H_{12}O_4N_5Cl$: N, 23.2. Found: N, 23.2.

2-Chloro-9-β-D-ribofuranosyladenine from 2,8-Dichloro-9-β-D-ribofuranosyladenine.—The solution obtained by partial reduction[6] of 1.0 g. of the dichloro compound was neutralized and evaporated to 4 ml. Crude 2-chloro-9-β-D-ribofuranosyladenine separated slowly as an amorphous or microcrystalline powder; yield 0.53 g. (59%). Recrystallization from water gave, with considerable loss, the pure compound as tiny needles, m.p. 135° alone or in admixture with the material prepared from 2-chloroadenine. The ultraviolet absorption spectrum, 18 mg. per liter, showed maxima as follows: In 0.1 N hydrochloric acid, 265 mμ (ϵ_m 13,900); and in 0.1 N sodium hydroxide, 265 mμ (ϵ_m 15,000).

Anal. Calcd. for $C_{10}H_{12}O_4N_5Cl$: C, 39.8; H, 4.0; N, 23.2. Found: C, 40.0; H, 4.0; N, 23.1.

9-α-L-Arabofuranosyladenine.—Prepared by the method previously described for its enantiomorph,[7] the compound had m.p. 211–212°; $[\alpha]^{23}D$ −68° (c 0.74% in water); (re-

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

(13) J. Baddiley, B. Lythgoe, D. McNeil and A. R. Todd, *ibid.*, 383 (1943).

(14) B. Lythgoe, A. R. Todd and A. Topham, *ibid.*, 315 (1944).

(15) *Cf.* E. Fischer, *Ber.*, **30**, 2242 (1897), for a similar reaction.

ported for 9-α-D-arabofuranosyladenine[7]: m.p. 208°; [α][17]D +69° (c 1.1% in water)).

2,8-Dichloro-9-tetraacetyl-β-D-glucopyranosyladenine from 2,6,8-Trichloro-9-tetraacetyl-β-D-glucopyranosylpurine.—The tetraacetyl glucosyltrichloropurine[8] (0.8 g.) was heated in a sealed tube with 15 ml. of ethanolic ammonia (saturated at 0°) for one hour at 100°. The cooled solution was evaporated to dryness and the residue dissolved in 5 ml. of pyridine and 2 ml. of acetic anhydride and kept overnight at room temperature. Ethanol was added, solvents removed under reduced pressure, and the residue crystallized from 4 ml. of glacial acetic acid, giving 0.11 g. (14%) of 2,8-dichloro-9-tetraacetyl-β-D-glucopyranosyladenine as colorless needles, m.p. 213–216°, alone or in admixture with an authentic specimen.[8]

Anal. Calcd. for $C_{19}H_{21}O_9N_5Cl_2$: N, 13.1. Found: N, 13.2.

2,6,8-Trichloro-9-triacetyl-β-D-ribofuranosylpurine.—A suspension of 4.5 g. of silver 2,6,8-trichloropurine in 120 ml. of xylene was treated with triacetyl D-ribofuranosyl chloride prepared from 4 g. of tetraacetate. The mixture

was refluxed for 1.5 hours, then filtered hot and the filtrate evaporated to dryness. Crystallization of the residue from 75 ml. of ethanol gave 3.9 g. (60%) of fine needles, m.p. 164–165°, raised to 166–168° by recrystallization from ethanol.

Anal. Calcd. for $C_{16}H_{15}O_7N_4Cl_3$: C, 39.9; H, 3.1; N, 11.6. Found: C, 40.4; H, 3.5; N, 11.5.

[Contribution from the Department of Chemistry, Brooklyn College]

Tertiary Amines Derived from N-(2-Pyridyl, 2-Thiazolyl and 2-Lepidyl)-1,2-diphenylethylamine

By Irving Allan Kaye and Chester L. Parris

N-(2-Pyridyl)-1,2-diphenylethylamine was prepared by the reductive alkylation of 2-benzylideneaminopyridine with benzylmagnesium chloride. The 2-thiazolyl isostere was formed similarly, as well as by total synthesis, and the 2-lepidyl analog by condensing 2-chlorolepidine with 1,2-diphenylethylamine. Although these secondary amines could be alkylated in the presence of lithium amide with several diverse alkyl halides and with styrene oxide to yield products desired for testing as potential antimitotic agents, reaction between 1,2-diphenylethyl chloride and either 2-aminopyridine or N,N-dimethyl-N',-(2-pyridyl)-ethylenediamine under the same conditions yielded *trans*-stilbene as the only isolable product.

Interest in the preparation of compounds related to 1,2-diphenylethylamine has been whetted by the observation that some of these substances show promise as tumor growth-inhibitors[1–7] or as analgesics.[8–13] Since a heterocyclic nucleus frequently enhances or is essential for pharmacological activity, some 1,2-diphenylethylamines, having an amino hydrogen replaced by either a 2-pyridyl, 2-thiazolyl or a 2-lepidyl group, were prepared for evaluation as tumor-necrotizing agents.[14]

The tertiary amines (II Aa-g, II Ba, II Ca)

were prepared by alkylating an N-(2-pyridyl, 2-thiazolyl or 2-lepidyl)-1,2-diphenylethylamine (IA, B or C) with a β- or γ-substituted alkyl chloride in the presence of lithium amide[15a] (Method D). A similar reaction, wherein the alkyl halide was replaced by styrene oxide, yielded the tertiary aminoalcohol, II Ai (Method E).[16]

Although this procedure has yielded the homologous 2-pyridyl and 2-lepidyl benzohydrylamines,[15] the only product isolated from the reaction of 1,2-diphenylethyl chloride with either 2-aminopyridine or N,N-dimethyl-N'-(2-pyridyl)-ethylenediamine, in the presence of lithium amide, was *trans*-stilbene. This hydrocarbon has been obtained by others as the major product formed in the reaction between piperidine and 1,2-diphenylethyl bromide; the desired tertiary amine was isolated in only 10% yield.[4] The pyridine and thiazole secondary amines (IA, B) were obtained in good yield by treatment of either 2-benzylideneaminopyridine or 2-benzylideneaminothiazole with benzylmagnesium chloride[11,15b] (Method A). The thiazole amine (I B) was also prepared in excellent yield by total

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(16) The reaction of epoxides with the lithium derivatives of heterocyclic amines has been studied in this Laboratory. A report of this investigation is in preparation and will substantiate the structure assigned the aminoalcohol, II Ai.