141.5–143° with decomposition. The literature reports a melting point of 145° with decomposition.[16]

Bromine Oxidation of 1,1-Dibenzylhydrazine.—A well stirred solution of 12 g. (0.057 mole) of 1,1-dibenzylhydrazine in 60 ml. of 48% hydrobromic acid at 0° was treated dropwise with bromine (9.1 g.) (0.057 mole). The resulting solution was heated at 100° for 2 hr., cooled, and extracted with ether. Removal of the ether gave 5 g. of benzaldehyde.

The acid layer, upon cooling to 0°, gave 5 g. of benzylhydrazine hydrobromide melting at 165° with decomposition. The product was characterized by liberating the free hydrazine with base and forming the benzaldehyde benzylhydrazone m.p. 64–65° (lit. m.p. 63°).[17] A mixture with an authentic sample melted at the same point.

The Reaction of Benzyl Chloride with 1,1-Dimethyl-2-*p*-tolylsulfonylhydrazine.—A solution of 50 g. (0.23 mole) of 1,1-dimethyl-2-*p*-tolylsulfonylhydrazine and 30 g. (0.23 mole) of benzyl chloride in 90 ml. of benzene was refluxed for 2 hr. Evolution of methyl chloride and nitrogen occurred at the start of the refluxing. During the reaction, ammonium chloride (1.5 g.) precipitated on the sides of the flask.

The resulting solution was poured into ice water and the benzene layer was separated. Removal of the solvent gave 38 g. (67%) of benzyl *p*-tolyl sulfone melting at 143°. The literature reports a melting point of 144°.[11]

The aqueous layer was concentrated to a sirup and added to a hot solution of potassium hydroxide. The distillate boiling below 100° was dried over sodium hydroxide and analyzed by gas chromatography on a tetraethylene glycol dimethyl ether column. The products identified with their relative percentages were methylamine 2%, dimethylamine 54%, trimethylamine 1.5%, 1,1-dimethylhydrazine 31%, and trimethylhydrazine 10%.

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Potential Anticancer Agents.[1] LXXXI. 2′-Deoxyribofuranosides of 6-Mercaptopurine and Related Purines

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Condensation of a protected 2-deoxyribofuranosyl chloride (II) with chloromercuri-6-chloropurine (I) afforded the anomeric protected 6-chloropurine-2′-deoxyribofuranosyl nucleosides, which were separated by alumina chromatography. These anomers were converted to the corresponding α- and β-2-deoxyribofuranosides of several 6-substituted purines. The thiol (VI) in the β-series, especially, is of interest for possible antitumor properties.

The useful anticancer drug, 6-mercaptopurine (6-MP), is believed[2,3] to exert its activity as the corresponding nucleotide. The riboside of 6-MP, a possible precursor to the ribotide, was prepared[4] in a search for improved activity and was found[5] to have a much greater therapeutic index in mice with a transplanted tumor, although this was not borne out in human testing; cross resistance with 6-MP was also found. The effectiveness of 6-MP and its derivatives and analogs prepared to date is severely limited by the development of resistance to the drugs. Among possible mechanisms of resistance, deletion of the enzymatic process for converting the purine to the nucleotide[2,6] or cleavage of the active nucleotide back to the purine base[7] seems to be important. The 2-deoxyriboside of 6-MP (β-VI) is desirable as a possible nucleotide precursor which might be less susceptible to the mechanisms of resistance or might circumvent them entirely. So far, only an enzymatic synthesis[8] of β-VI, in low yield and with incomplete purification and characterization, has been reported. The chemical synthesis of 2′-deoxyribonucleosides, compared to that of ribonucleosides, presents special difficulties related to increased lability of the glycosidic linkage[9] and lack of steric control[10] in its formation. Recently, nucleosides of adenine[11] and of some pyrimidines[12,13] have been prepared directly from protected 2-

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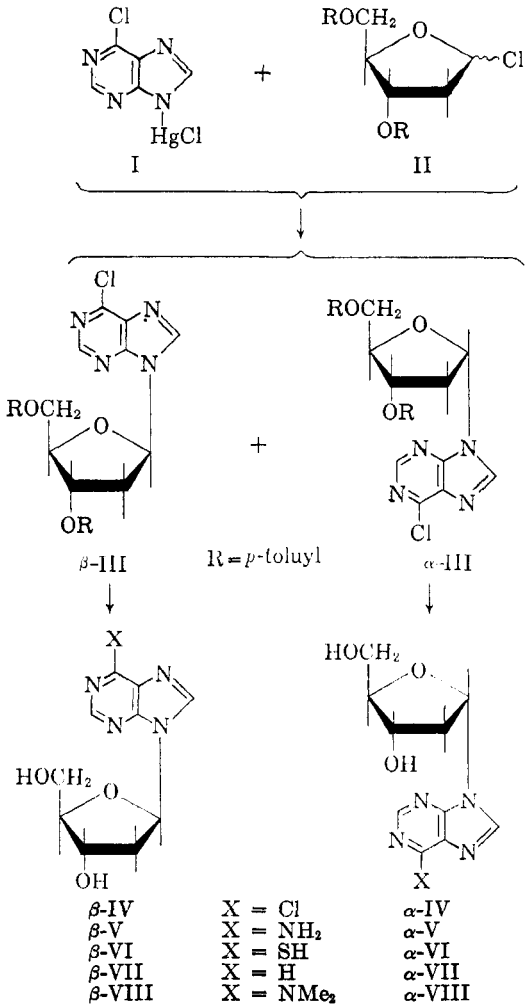
deoxy-D-ribofuranosyl chlorides by the mercuri procedure[14]; successful use of a silver purine[15] has also been reported, and, in preliminary form, the direct condensation of adenine and deoxyribose.[16] This paper reports the first chemical synthesis of fraudulent purine deoxyribonucleosides.

Condensation of crystalline 3,5-di-O-*p*-toluyl-2-deoxy-D-ribofuranosyl chloride (II)[12] with chloromercuri-6-chloropurine (I)[17] in refluxing benzene afforded 6-chloro-9-(3′,5′-di-O-*p*-toluyl-2′-deoxy-α,β-D-ribofuranosyl)purine (α,β-III) as a glass. The proportion of anomers was studied by simultaneous[18] deacylation and amination with hot methanolic ammonia to a mixture, obtained in high yield, of 2′-deoxyadenosine (β-V) and its alpha anomer, α-V. The product was chromatographically homogeneous and possessed a ratio α-V/β-V = 49/51 based on (as in methods A and B, see Experimental) the optical rotation and ultraviolet extinction coefficient; a similar α/β ratio is assumed for crude III. The anomers of III could be separated by alumina chromatography when the eluent was gradually changed from benzene to 35% ethyl acetate in benzene. The pure β-anomer of III was obtained in a 14% yield (based on II) from the later chromatographic fractions. Its purity was ascertained by conversion in high yield to 2′-deoxyadenosine (β-V), the physical properties of which were compared with those of an authentic sample.



Deacylation with methanolic ammonia at 0°[17] afforded 35–40% of 6-chloro-9-(2′-deoxy-β-D-ribofuranosyl)purine (β-IV). The modest yields of β-IV could best be explained by losses suffered on removal by recrystallization of a contaminant which may have been the 6-methoxylnucleoside, but which was not detected in the infrared or resolved by paper chromatography; alternative deacylations attempted with anhydrous ammonia in isopropanol and with aqueous ammonia in dioxane[19] were unsuccessful. The configuration of β-IV was verified by amination (method B) to 2′-deoxyadenosine (β-V). The desired 9-(2′-deoxy-β-D-ribofuranosyl)purine-6-thiol (β-VI) was obtained from β-IV in 40–50% yield on treatment with methanolic sodium hydrogen sulfide.[4a] Better yields of the 6-substituted 2′-deoxyribofuranosyl nucleosides (based on β-III) were obtained by first replacing the chlorine in β-III, then deacylating. Thus, reaction of β-III with methanolic sodium hydrogen sulfide, followed, without isolation, by a further treatment with additional sodium methoxide, gave a better yield of β-VI than was obtained from β-IV. Dehalogenation of β-III by catalytic hydrogenation[20] furnished the analytically pure blocked nucleoside as a glass, which was deacylated with hot methanolic ammonia to yield the crystalline 9-(2′-deoxy-β-D-ribofuranosyl)purine (β-VII). The reaction of β-III with methanolic dimethylamine at 100° was the best method of preparation of the crystalline 6-dimethylamino analog (β-VIII).

By the same procedures, a series of corresponding α-anomers was obtained from the protected chloronucleoside α-III; this was isolated in pure, crystalline form (8% yield from II) by further chromatography of crystalline mixtures (α- and β-III) which remained after removal of most of the β-III. The anomeric configuration of α-III was established by nearly quantitative conversion to crude α-V, whose optical rotation, after correction by the use of the ultraviolet extinction value, did not permit the presence of any appreciable quantity of 2′-deoxyadenosine (β-V). In the crystalline state, the anomers α- and β-III could be distinguished by characteristic infrared absorption bands. The α-nucleosides (α-IV, α-VI, α-VII, and α-VIII) obtained from α-III, when

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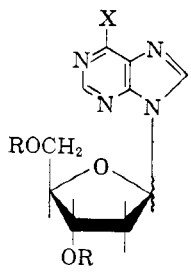
compared to the β-anomers, were chromatographically identical and exhibited identical ultraviolet maxima, with only minor differences in molar extinction. The dimethylaminonucleoside α-VIII was a hygroscopic gum, whether prepared directly from α-III or from α-IV; though chromatographically homogeneous, it could not be obtained in a state of analytical purity. The purinedeoxyriboside α-VIII, which was obtained by dehalogenation and deacylation of α-III, was identical chromatographically and in ultraviolet absorption to a sample obtained in low yield by Raney nickel desulfurization of crystalline α-VI in refluxing methanol.

The optical rotations of these compounds and the differences in molecular rotations for the anomeric pairs are listed in Table I. In that the β-anomers are the more *levo*-rotatory in the solvents used, the anomeric pairs follow Hudson's rules, unlike certain pyrimidine deoxynucleosides recently reported.[21]

TABLE I

6-SUBSTITUTED PURINE-α- AND -β-DEOXYRIBOSIDES



No.	X	R	[α]D, deg. α	[α]D, deg. β	Δ[M]D (α-β)
III	Cl	*p*-Toluyl	−12.4	−56.1	222
IV	Cl	H	+60.0	−11.0	192
VI	SH	H	+66.2	−23.5	239
VII	H	H	+70.6	−28.0	233
VIII	$N(CH_3)_2$	H	+50.2[a]	−21.2	199
V	NH_2	H	+71[11]	−27[11]	246

[a] Of a hygroscopic gum.

Experimental[22]

Paper chromatography was run by the descending technique with Whatman No. 1 paper in solvent systems A: water-saturated *n*-butyl alcohol; or B: 5% aqueous Na_2HPO_4. Spots were detected visually under ultraviolet light. The deacylated nucleosides gave positive deoxysugar tests with vanillin–perchloric acid reagent[23] in system A. All compounds described were homogeneous when purified. Adenine was the standard of comparison.

6-Chloro-9-(2′-deoxy-3′,5′-di-O-*p*-toluyl-α,β-D-ribofuranosyl)purine (α,β-III).—An azeotropically dried suspension of 34.4 g. (0.0884 mole) of chloromercuri-6-chloropurine (II)[17] in 650 ml. of benzene was treated, at reflux, with 33.1 g. (0.0853 mole) of powdered, crystalline 2-deoxy-3,5-di-O-*p*-toluyl-D-ribofuranosyl chloride (I)[12] (the transfer was completed with 50 ml. of dry benzene). After 20 min. at reflux, the pale yellow mixture was cooled and filtered, and by an established procedure[13,18] the product was precipitated with petroleum ether and washed in methylene chloride solution with aqueous potassium iodide. Upon removal of solvent, the product (25.0 g., 58%) was obtained as a nearly white, foamed glass, $\lambda_{max}^{CHCl_3}$ 265 mμ (ε 10,140).

6-Chloro-9-(2′-deoxy-3′,5′-di-O-*p*-toluyl-β-D-ribofuranosyl)purine (β-III).—A solution of 23.0 g. of α,β-III in 100 ml. of benzene was added to a column (31 × 6.4 cm.) of 1 kg. of neutral alumina[24] in benzene. The column was washed with 2 l. of benzene and the washings discarded. Elution was started with 2% ethyl acetate in benzene (600 ml.) and the ethyl acetate was gradually increased to 35% as follows: 5% (600 ml.), 10% (600 ml.), 15% (1.50 l.), 20% (4.20 l.), 25% (2.40 l.), 30% (1.80 l.), 35% (2.40 l.); 300-ml. fractions were collected and were concentrated *in vacuo*. No material appeared in the eluate until one third of the 20% ethyl acetate was used. Optical rotations of the residual sirups began at +35° (in $CHCl_3$), fell rapidly to −20° while the rest of the 20% ethyl acetate was used, and then fell gradually to −40°. The total weight recovered was 19.3 g.

All sirups of $[\alpha]_D$ −25° or more negative (12.7 g., eluted with 25–35% ethyl acetate) were combined and dissolved in 200 ml. of boiling methanol, and the solution was cooled slowly to room temperature. After 15 hr., 4.1 g. of crystals were collected, m.p. 106–108°, $[\alpha]^{23}_D$ −51 ± 3.4° ($CHCl_3$), $\lambda_{max}^{C_2H_5OH}$ 242 mμ (ε 30,700). Recrystallization from 50 ml. of boiling methanol with slow cooling afforded 3.23 g., m.p. 112–116°, $[\alpha]^{26}_D$ −53.0 ± 3.4° ($CHCl_3$). Further recrystallization afforded an analytical sample, m.p. 114–116°; $[\alpha]^{30}_D$ −56.1 ± 0.4° ($CHCl_3$); $\lambda_{max}^{C_2H_5OH}$ 242 mμ (ε 32,200), 264 mμ (shouder, ε 9940); R_{Ad} 3.2 in system A and 0.0 in system B. A strong infrared band at 10.82 μ was characteristic of β-III and absent from α-III.

Anal. Calcd. for $C_{26}H_{23}ClN_4O_5$: C, 61.6; H, 4.57; Cl, 6.99; N, 11.0. Found: C, 61.9; H, 4.47; Cl, 6.90; N, 10.9.

The combined mother liquors from these recrystallizations were concentrated. The residual sirup and the sirups from the initial fractions (2.8 g., $[\alpha]^{25}_D$ from +35 to 0°) and intermediate fractions (3.8 g., $[\alpha]^{25}_D$ *ca.* −20°, eluted from the chromatogram with 20% ethyl acetate) were all combined. A second pass through alumina as before afforded an additional 0.86 g. of β-III; a third pass afforded only 0.25 g. The yield was 4.34 g. (11% based on II); an additional 3% (total yield 14%) was obtained after the isolation of α-III, below.

6-Chloro-9-(2′-deoxy-3′,5′-di-O-*p*-toluyl-α-D-ribofuranosyl)purine (α-III).—After crystallization of β-III from the later chromatographic fractions with methanol the second crops obtained consisted of crystalline mixtures of the anomers (α- and β-III) in nearly 1:1 proportions. Similar mixtures were obtained by crystallization of intermediate chromatographic fractions from methanol. Melting points ranged between 93 and 99° and rotations from −19 to −28°. Repeated recrystallization did not permit any separation of the anomers. When combined, all such solids generally amounted to *ca.* 43% of crude, glassy α,β-III. Typically, 6.9 g., m.p. 94–99°, $[\alpha]^{26}_D$ −28.0 ± 2.8° ($CHCl_3$), were subjected to further alumina chromatography. No material was eluted until the ethyl acetate in the benzene eluent was increased to 10%. Fractions eluted with 10 to 20% ethyl acetate could, after evaporation and treatment with methanol, be induced to crystallize and the solids ($[\alpha]_D$ −10 to −19° in $CHCl_3$) were predominantly α-III according to the infrared spectra. Bands at 10.63 (s) and 9.84 μ (m) were characteristic of α-III; absorption at 10.82 μ

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(22) Melting points were observed on a Fisher-Johns apparatus and are uncorrected. Optical rotations were determined in 1% solutions and at 1-dm. path length. Only infrared bands which permitted differentiation of an anomeric pair are recorded; bands of medium or strong intensity are labeled m or s; the spectra were obtained in Nujol mulls.

(23) A. P. MacLennan, H. M. Randall, and D. W. Smith, *Anal. Chem.*, **31**, 2020 (1959).

(24) Bio-Rad Laboratories, Richmond, California: pH 6.9–7.1 Brockmann activity I.

that would have been due to β-III was weak or missing. Recrystallization of the solids from methanol afforded 1.66 g. of α-III, m.p. 95–96°, $[\alpha]^{26}D$ −12.4 ± 0.2° ($CHCl_3$); $\lambda_{max}^{C_2H_5OH}$ 241 mμ (ε 36,200), 265 mμ (shoulder, ε 11,800); R_{Ad} 3.2 in system A and 0.0 in system B.

Anal. Found: C, 61.8; H, 4.74; Cl, 7.11; N, 10.8.

After the crystallization of α-III from appropriate fractions, the mother liquors and the later chromatographic fractions were seeded separately with β-III, and 0.53 g. of β-III (recrystallized once, m.p. 114–116°) was recovered. All material then remaining was passed through another chromatogram, for further separation. The final yield of α-III was 2.19 g. (14% of crude α,β-III, or 8% yield from II); the β-III amounted to 0.93 g. (6% of α,β-III, 3% from II) and supplemented that from the original chromatograms.

2′-Deoxyadenosine (β-V). (1) **Method A.**—Concurrent deacylation and amination of 0.242 g. (0.480 mmole) of 6-chloro-9-(2′-deoxy-3′,5′-di-O-*p*-toluyl-β-D-ribofuranosyl)purine (β-III) was carried out with methanolic ammonia.[18] Concentration of an extracted water solution of the crude product afforded 0.168 g. (140% yield but quantitative when corrected with the ultraviolet data) of a white solid, which was homogeneous to paper chromatography, R_{Ad} 0.7 in system A and 1.4 in system B, $\lambda_{max}^{H_2O}$ 259 mμ (ε 10,300, or 72% pure compared to ε of the analytical sample), $[\alpha]^{30}D$ −17.0 ± 3.0° (H_2O). Presumably the impurities here were ammonium chloride and water of hydration; on extrapolation to 100% purity, the rotation was −24 ± 4.0° (lit. values,[11,15,25] range from 24 to 27°). Recrystallization from water afforded 0.092 g. (77%), $[\alpha]D$ −24.0 ± 3.0° (H_2O); melting point behavior[11,15] (192–196° with softening at 165°) and elemental analysis suggested the material was a hydrate. After further drying at 0.2 mm. and 110° for 48 hr., the m.p. was 194–197° (no prior softening), $\lambda_{max}^{H_2O}$ 259 mμ (ε 14,300; lit., 14,800–14,900[15,25] and 15,900–16,600[11]), and the elemental analysis indicated no hydration.

Anal. Calcd. for $C_{10}H_{13}N_5O_3$: C, 47.8; H, 5.22; N, 27.9. Found: C, 47.6; H, 5.45; N, 27.8.

(2) Nearly identical material (ε 14,600) was obtained from β-IV by method B, below.

6-Amino-9-(2′-deoxy-α-D-ribofuranosyl)purine (α-V). (1) **Method B.**—6-Chloro-9-(2′-deoxy-α-D-ribofuranosyl)-purine (α-IV, see below) (175 mg., 0.650 mmole) was aminated with 10 ml. of methanolic ammonia[18] as in method A. Concentration of the reaction mixture afforded 188 mg. (116% of theory but quantitative yield of α-V when corrected with the ultraviolet data) of white solid, chromatographically homogeneous, R_{Ad} same as β-V, $\lambda_{max}^{H_2O}$ 260 mμ (ε 13,060, or 88% pure), $[\alpha]D$ +63.8 ± 3.6°(H_2O). Assuming the impurites were water or ammonium chloride, the rotation extrapolated as in method A to 100% purity was 74 ± 4.0° (lit.,[11] 69°, 71°). Methanol recrystallization afforded 105 mg. of α-V (65% yield), m.p. 210–212° (lit.,[11] 209–211°), which was dried at 65° and 0.3 mm.; $\lambda_{max}^{H_2O}$ 260 mμ (ε 14,810; lit.,[11] 15,900–16,290), $[\alpha]^{29}D$ +68.2 ± 3.7°(H_2O).

Anal. Found: C, 48.0; H, 5.30; N, 27.7.

(2) A nearly identical sample (ε 14,310 and $[\alpha]^{25}D$ +67.7 ± 1.6° in H_2O) of analytical purity was obtained from α-III by method A.

6-Chloro-9-(2′-deoxy-β-D-ribofuranosyl)purine (β-IV).—6-Chloro-9-(2′-deoxy-3′,5′-di-O-*p*-toluyl-β-D-ribofuranosyl)purine (β-III) (1.90 g., 3.75 mmoles) was deacylated in cold methanolic ammonia[17] and the crude product was partitioned between water and ether (instead of chloroform). The residual product (934 mg., 92%) from concentration of the aqueous layer was dissolved in 2.5 ml. of hot methanol; on chilling slowly and storing at 3° overnight, 442 mg. (44%) deposited, m.p. 130–144°. Recrystallization afforded 393 mg. (39%), m.p. 142–145°, $[\alpha]^{26}D$ −11.0 ± 0.5° (CH_3OH), $\lambda_{max}^{H_2O}$ 264 mμ (ε 8930), R_{Ad} 1.9 in system A and 2.0 in system B. Characteristic infrared bands were at 8.77 (s) and 10.75 μ (s). Methanol solubility was several times that of α-IV.

Anal. Calcd. for $C_{10}H_{11}ClN_4O_3$: C, 44.4; H, 4.10; Cl, 13.1; N, 20.7. Found: C, 44.3; H, 4.20; Cl, 12.9; N, 20.7.

6-Chloro-9-(2′-deoxy-α-D-ribofuranosyl)purine (α-IV) was obtained in the same manner from 130 mg. of α-III. The yield of α-IV after recrystallization from methanol was 31.4 mg. (46%), m.p. 150–152°, $[\alpha]^{26}D$ +60.0 ± 0.8° (H_2O), $\lambda_{max}^{H_2O}$ 264 mμ (ε 8860), R_{Ad} same as β-IV. Characteristic infrared bands were at 9.22 (s) and 12.25 μ (m).

Anal. Found: C, 44.6; H, 4.02; Cl, 13.0; N, 21.0.

9-(2′-Deoxy-β-D-ribofuranosyl)purine-6-thiol (β-VI)—(1) Treatment of β-IV (0.350 g., 1.40 mmoles) with anhydrous methanolic NaHS[4] afforded a crystalline solid (0.214 g., 63%), $[\alpha]^{26}D$ −22.9 ± 1.0° (1 *M* NaOH), which slowly decomposed on heating above 178°. Use of boiling water for recrystallization caused some decomposition to 6-MP, which precipitated from the hot solution. Recrystallization from 50% aqueous methanol at 60° afforded a sample (53% yield) for analysis, m.p. 180–185°; $[\alpha]^{26}D$ −23.5 ± 1.0° (1 *M* NaOH); $\lambda_{max}^{0.1\ M\ NaOH}$ 233 mμ (ε 13,960), 311 mμ (ε 22,540); R_{Ad} 0.6 in system A and 1.8 in system B. Infrared absorption at 10.8 μ (m) was characteristic of β-VI.

Anal. Calcd. for $C_{10}H_{12}N_4O_3S$: C, 44.8; H, 4.51; N, 20.9; S, 12.0. Found: C, 44.9; H, 4.71; N, 21.1; S, 12.0.

(2) **Method C.**—A solution of 1.01 g. (2.00 mmoles) of β-III in 30 ml. of anhydrous methanol saturated with a gentle stream of hydrogen sulfide was treated with 6.0 ml. of 1 *M* methanolic sodium methoxide previously saturated with hydrogen sulfide. As in (1), the solution was refluxed for 10 min., then the hydrogen sulfide source was removed, 2.0 ml. of 1 *M* methanolic sodium methoxide added, and reflux continued for 4 hr. Concentration *in vacuo* of the cooled solution afforded a sirup, which was partitioned between 10 ml. of water and 20 ml. of ether. The water layer was extracted further with two 20-ml. portions of ether, clarified by filtration, neutralized (pH 6–8) with dilute acetic acid, and chilled at 5° overnight. The crystalline product when collected, washed, and dried weighed 0.301 g. (58%), m.p. 193–197°. The physical constants, before and after recrystallization (45% yield), were essentially the same as in (1).

9-(2′-Deoxy-α-D-ribofuranosyl)purine-6-thiol (α-VI) was obtained from α-III by method C in 46% yield; $[\alpha]^{26}D$ +66.2 ± 1.0° (0.1 *M* NaOH); $\lambda_{max}^{0.1\ M\ NaOH}$ 311 mμ (ε 22,510), 233 mμ (ε 13,670); R_{Ad} same as β-VI. The solid slowly decomposed on heating above 150°; an infrared band at 11.56 μ (m) was characteristic of α-VI.

Anal. Found: C, 45.2; H, 4.69; N, 21.1; S, 12.0.

9-(2′-Deoxy-β-D-ribofuranosyl)purine (β-VII).—The procedure for the preparation of 9-α-L-rhamnopyranosylpurine[20] was used in the conversion of β-III to β-VII, with the substitution of 2-methoxyethanol as the solvent. The residue after removal of solvent was washed in ether solution, with three portions of water. Concentration of the ether layer (dried with magnesium sulfate and filtered) afforded 9-(2′-deoxy-3′,5′-di-O-*p*-toluyl-β-D-ribofuranosyl)purine as a fluffed glass (94%), free of chlorine.

Anal. Calcd. for $C_{26}H_{24}N_4O_5$: C, 66.1; H, 5.12; N, 11.9. Found: C, 66.1; H, 5.30; N, 11.8.

Deacylation with methanolic ammonia at 95° for 5.5 hr.[18] afforded a gum (90% yield from β-III), that crystallized (66%) from a hot methanol solution on slow cooling to 5°, m.p. 169–176° with softening at 160°. The compound melted at 192–194° after drying (110°, 0.03 mm.) for analysis, $[\alpha]^{26}D$ −28.0 ± 0.4° (H_2O), $\lambda_{max}^{H_2O}$ 263 mμ (ε 6850), R_{Ad} 1.3 in system A and 2.1 in system B. Characteristic

(25) C. D. Anderson, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **81**, 3967 (1959).

infrared bands were at 10.59 (s), 11.53 (m), and 13.18 μ(s).

Anal. Calcd. for $C_{10}H_{12}N_4O_3$: C, 50.8; H, 5.12; N, 23.7. Found: C, 50.9; H, 5.14; N, 23.7.

9-(2′-Deoxy-α-D-ribofuranosyl)purine (**α-VII**) was prepared from crystalline α-III by the same procedure as for β-VII. The intermediate glass (93% yield) was again free of chlorine. After deacylation, and recrystallization of α-VII from acetonitrile, a 52% yield was obtained, m.p. 138–139°, $[\alpha]^{25}D$ +70.6 ± 1.0° (H_2O), $\lambda_{max}^{H_2O}$ 263 mμ (ε 7000), R_{Ad} same as β-VII. Characteristic infrared bands were at 10.2 (m) and 11.62 μ (m).

Anal. Found: C, 51.0; H, 5.03; N, 23.6.

6-Dimethylamino-9-(2′-deoxy-β-D-ribofuranosyl)purine (**β-VIII**).—Concurrent deacylation and amination of 0.250 g. (0.495 mmole) of β-III with 1.25 ml. of anhydrous dimethylamine in 10 ml. of methanol was performed by the procedure[18] for using methanolic ammonia. The reaction mixture was evaporated *in vacuo* and the residue was dissolved in water, then extracted with chloroform. The aqueous phase containing the product and dimethylamine hydrochloride was stirred for 20 min. with 0.115 g. (0.495 mmole) of silver oxide, and the resulting silver chloride was removed by filtration. The filtrate was concentrated *in vacuo* to a sirup, ethanol was added and removed *in vacuo*, and the semisolid residue was crystallized from acetonitrile solution to form 74 mg. (54%) of β-VIII, m.p. 177.5–179.0°, $[\alpha]^{26}D$ −21.2 ± 0.3° (H_2O), $\lambda_{max}^{H_2O}$ 276 mμ (ε 17,950), R_{Ad} 2.2 in system A and 1.6 in system B.

Anal. Calcd. for $C_{12}H_{17}N_5O_3$: C, 51.6; H, 6.13; N, 25.1. Found: C, 51.7; H, 6.39; N, 25.2.

6-Dimethylamino-9-(2′-deoxy-α-D-ribofuranosyl)purine (**α-VIII**) was obtained from α-III as a hygroscopic glass (87% yield), which was chromatographically homogeneous, by the same procedure as for β-VIII; R_{Ad} same as for β-VIII, $\lambda_{max}^{H_2O}$ 276 mμ (ε 17,150), $[\alpha]^{25}D$ +50.2 ± 0.7° (H_2O).

Anal. Found: C, 51.5; H, 6.89; N, 23.6.

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The Cyclization of Dinitriles by Anhydrous Halogen Acids. A New Synthesis of Isoquinolines[1]

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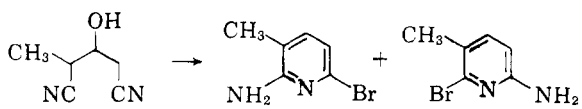
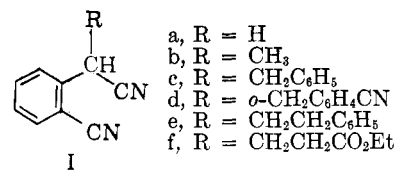
The action of anhydrous hydrogen chloride, bromide, and iodide, on a number of *o*-cyanobenzyl cyanides has been examined. While hydrogen chloride effects no cyclization, the other two acids afford 1-halo-3-aminoisoquinolines in excellent yield. Using this method, several polycyclic heterocycles were synthesized. In addition, a number of reactions of 1-bromo-3-aminoisoquinoline itself were studied.

In a recent study[2] of the action of hydrogen halides on 3-hydroxyglutaronitriles, we described a method for the facile preparation of simple 2-amino-6-halopyridines. In all but one case the dinitrile starting materials were symmetrical, and, in this instance, an equimolar mixture of the expected pyridines was obtained, *viz.*



We have continued these studies with an examination of other unsymmetrical dinitrile systems and an investigation of the applicability of this method of cyclization to the synthesis of isoquinoline derivatives. For these purposes, a series of α-substituted 2-cyanobenzyl cyanides were synthesized. 2-Cyanobenzyl cyanide (Ia, R = H) itself was prepared according to Gabriel and Otto,[3] while the simple alkyl derivatives Ib–d were made by the alkylation of Ia using the appropriate alkyl halide and sodium ethoxide in ethanol.[4–6] Besides these, alkylations were carried out with β-phenethyl iodide (β-phenethyl chloride caused no alkylation under the conditions used) and ethyl 3-bromopropionate to give the corresponding products, Ie and If, respectively.



a, R = H
b, R = CH_3
c, R = $CH_2C_6H_5$
d, R = *o*-$CH_2C_6H_4CN$
e, R = $CH_2CH_2C_6H_5$
f, R = $CH_2CH_2CO_2Et$

I

All attempts to alkylate Ia with ethyl chloroacetate failed. Of the catalyst systems used, sodium ethoxide in ethanol, triethylamine in tetrahydrofuran, sodamide in benzene, and potassium *t*-butoxide in *t*-butyl alcohol, none led to the desired product.

In all of these reactions, concomitant addition of the reacting components to the sodium ethoxide solution was necessary for optimum yields. Attempts to preform the anion of 2-cyanobenzyl cyanide led to self-condensation. This had already

(1) This paper is to be regarded as Part III of the series, Polyfunctional Aliphatic Compounds.

(2) Francis Johnson, J. P. Panella, A. A. Carlson, and D. H. Hunneman, *J. Org. Chem.*, in press.

(3) S. Gabriel and R. Otto, *Ber.*, **20**, 2222 (1887).

(4) S. Gabriel, *ibid.*, **20**, 2499 (1887).

(5) S. Gabriel and T. Posner, *ibid.*, **27**, 2492 (1894).

(6) G. Eichelbaum, *ibid.*, **21**, 2679 (1888).