TABLE IV

PROPERTIES OF THE DEGRADATION PRODUCTS

Rf	*cis*-Glycol test[26]	Orcinol test[27]	Optical density at 288 mμ, *p*H 5.2[a]
0.084	+	+	0.78
.17	+	+	.75
.40	−	−	.16

[a] Determined on the material eluted from one lane with 4 ml. of water. Assuming an ϵ_{max} of 7250 for the products (ϵ_{max} at 289 = 7250 for the uncharged molecule of 4,5-diaminopyrimidine[52]), the two slow moving compounds each contained *ca.* one mole of ribose per mole of 4,5-diaminopyrimidine.

6-Methyl-D-ribofuranosylpurine.—A 402-mg. (3 mmoles) sample of IIa was converted to its chloromercuri derivative[41] giving 0.900 g. (2.44 mmoles, 81.5%) of product. The chloromercuri-6-methylpurine was condensed with 2,3,5-tri-*O*-acetyl-D-ribosyl chloride[53] prepared from 0.945 g. (3.0 mmoles) of tetraacetylribofuranose,[54] and the product was worked up as described below, except that the intermediate triacetyl compound was not obtained in crystalline form. Two recrystallizations of the crude 6-methyl-D-ribofuranosylpurine from ethyl alcohol gave 100 mg. (0.38 mmole, 12.5%) of product in the form of fine needles, m.p. 209–210°. In another preparation, from 2.6 g. of IIa, a yield of 21% was obtained.

Anal. Calcd. for $C_{11}H_{14}O_4N_4$ (266.3): C, 49.6; H, 5.29; N, 21.0. Found: C, 49.7; H, 5.50; N, 21.2.

The absorption maxima were: ϵ_{265} = 6340 at *p*H 1, ϵ_{261} = 7640 at *p*H 5.5 and 11 (when determined immediately).

9-D-Ribopyranosylpurine (IIIb).—A 1.00-g. (8.3 mmoles) sample of I was converted to its chloromercuri derivative (2.74 g., 7.8 mmoles),[3] and the dried, powdered chloromercuri salt was condensed with 2.8 g. (9.5 mmoles) of crystalline 2,3,4-tri-*O*-acetyl-D-ribosyl chloride[55] by refluxing in xylene for 4 hr. By previously described procedures,[41] 3.19 g. of crude crystalline 9-D-triacetylribopyranosylpurine (IIIa) was obtained, which, when recrystallized from ethyl alcohol, gave 1.1 g. of product (2.9 mmoles, 35%) melting at 169–171°.

Treatment of 570 mg. of IIIa (1.45 mmoles) for 16 hr. at 5° with methanolic ammonia gave 410 mg. of IIIb. After two recrystallizations from *n*-butyl alcohol, the product, 280 mg. (1.1 mmoles), melted at 250–252° (76% yield from the acetyl derivative, 13% over-all yield from I). A sample recrystallized from ethyl alcohol was analyzed.

Anal. Calcd. for $C_{10}H_{12}O_4N_4$ (252.2): C, 47.5; H, 4.80; N, 22.2. Found: C, 47.6; H, 4.73; N, 21.7; $[\alpha]^{20}_{546m\mu}$ −33.8°; $[\alpha]^{20}_{589m\mu}$ −28.7° (0.5% in water).

The absorption spectrum possessed a maximum at 262.5 mμ, the position of which did not change in acid or alkali (when determined immediately). The ϵ_{max} at *p*H 0.3 was 5.65 × 10³, at *p*H 7.7 was 6.91 × 10³ and at 12.3 was 7.06 × 10³. There were two isosbestic points: one at 231.5 mμ with ε 2.64 × 10³ and one at *ca.* 268 mμ with ε 4.67 × 10³. The apparent pK_a was found to be 1.80 ± 0.05 by the procedure outlined by Fox and Shugar.[56]

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[CONTRIBUTION FROM THE LABORATORIES OF THE SLOAN-KETTERING DIVISION OF CORNELL UNIVERSITY MEDICAL COLLEGE]

Synthesis of an Isopropylidene Derivative of an Alkali-labile Nucleoside: 2′,3′-O-Isopropylidene-9-β-D-ribofuranosylpurine[1]

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2′,3′-*O*-Isopropylidene-9-β-D-ribofuranosylpurine can be prepared in good yield by condensation of 9-β-D-ribofuranosylpurine with acetone in the presence of zinc chloride or in the presence of *p*-toluenesulfonic acid. The techniques should be useful for the preparation of isopropylidene derivatives of other alkali-labile purine nucleosides. With *p*-toluenesulfonic acid the conversion is rapid and quantitative at room temperature and the method may be applicable to nucleosides in general.

2′,3′-*O*-Isopropylidene-9-β-D-ribofuranosylpurine was desired for the synthesis of 9-β-D-ribofuranosylpurine-5′-phosphate,[2] and a number of procedures for its preparation have been examined.

The 2′,3′-*O*-isopropylidene derivatives of many nucleosides[3-6] have been prepared by condensations with acetone in the presence of zinc chloride. The resulting complex of the product with zinc chloride was in each case decomposed with warm barium hydroxide. 9-β-D-Ribofuranosylpurine[7] and its 2′,3′-*O*-isopropylidene derivative were found to be alkali-labile, and application of the usual work-up led to considerable losses. Milder conditions for breakdown of the zinc chloride complex were investigated. Ion-exchange chromatography of an aqueous solution of the reaction products using Dowex-50 resin (NH_4^+) effected the removal of the zinc ions without decomposition of the isopropylidene derivative, but a large excess of resin was required and 60% of the product was retained on the column. A more satisfactory procedure was treatment of the reaction mixture at 0° with aqueous sodium carbonate, whereupon the 2′,3′-*O*-isopro-

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pylidene compound could be isolated in 80% yield.

Weakly basic ribonucleosides, *e.g.*, uridine,[8] or ones that form acetone-soluble sulfates[9] have given 2′,3′-*O*-isopropylidene derivatives when treated with acetone in the presence of sulfuric acid and anhydrous copper sulfate, but 9-β-D-ribofuranosylpurine did not react under these conditions. It has been shown in the case of 2-methylmercapto-6-dimethylamino-9-β-D-xylofuranosylpurine that the yield of the 3′,5′-*O*-isopropylidene derivative can be improved by replacing the sulfuric acid with ethanesulfonic acid, thereby forming a more acetone-soluble salt.[10] In the present work, when *p*-toluenesulfonic acid was substituted for sulfuric acid, 50% of the 9-β-D-ribofuranosylpurine was converted to the isopropylidene derivative, with dissolution of some copper (presumably as copper *p*-toluenesulfonate) and concomitant production of sulfuric acid, and prolonging the reaction yielded no more isopropylidene compound. The effect of omitting copper sulfate from the mixture was accordingly examined. In the presence of a sufficient quantity (10 equivalents) of *p*-toluenesulfonic acid monohydrate, 9-β-D-ribofuranosylpurine formed a salt which was readily soluble in acetone, and in 30 minutes quantitative conversion to the isopropylidene derivative occurred.

Conversions to isopropylidene derivatives by the acetone–sulfuric acid–copper sulfate method are either slow[8] or incomplete[9,10] and the use of acetone and *p*-toluenesulfonic acid monohydrate (or anhydrous) may prove generally useful.

Experimental

Paper chromatograms were run by the ascending method using Schleicher and Schuell No. 597 paper and were inspected in ultraviolet light.

Zinc Chloride Method.—A solution of zinc chloride (43 g.) in acetone (450 cc., distilled from a slight excess of potassium permanganate, then dried over sodium sulfate) was filtered into a dry flask containing 9-β-D-ribofuranosylpurine (13.7 g., dried over phosphorus pentoxide for 3 hr., 110°, 0.4 mm.). The cloudy solution was refluxed for 30 hr.[11] with exclusion of moisture. About half the acetone was removed under vacuum and the pale yellow solution poured into a solution of anhydrous sodium carbonate (43 g., 30% excess) in water (450 cc.) containing ice (50 g.). The mixture was stirred for 10 minutes and the zinc carbonate collected, washed with water and then with acetone. A solution of barium chloride dihydrate (33 g., 50% excess) in water (100 cc.) was added to the combined filtrate and washings and the barium carbonate collected. The filtrate was evaporated to dryness *in vacuo* and the residue dried azeotropically with benzene, then triturated with hot benzene (2 × 100 cc.). The benzene extract was concentrated *in vacuo* to *ca.* 80 cc., treated with charcoal (0.5 g.) and evaporated to dryness *in vacuo*. A solution of the yellow gum (14.6 g.) in methanol (25 cc., concentrated to *ca.* 15 cc.) furnished white hygroscopic needles (dried over phosphorus pentoxide at 0.1 mm.; 12.8 g., 80% yield), m.p. 44–45° (uncor.); light absorption in water, maximum 262.5 mμ; R_f 0.80 and 0.87 for paper chromatography in 1-butanol–water and in 1-butanol–water–acetic acid (5:3:2), respectively.

Anal.[12] Calcd. for $C_{13}H_{16}N_4O_4$: C, 53.40; H, 5.52; N, 19.17. Found: C, 53.03; H, 5.75; N, 19.03.

***p*-Toluenesulfonic Acid Method.**—*p*-Toluenesulfonic acid monohydrate[13] (7.5 g., 10 equivalents; dried over NaOH) was added to a magnetically-stirred suspension of dry 9-β-D-ribofuranosylpurine (1.0 g.) in acetone (150 cc., dried with Drierite and distilled). The pale yellow solution was kept at 25° and protected from moisture. At intervals, portions were withdrawn, treated with a small excess of 0.5 *N* sodium bicarbonate and examined by paper chromatography, using ethanol (85%)–water(15%) as the solvent system. After 30 minutes, conversion of the ribosylpurine (R_f 0.53) to the isopropylidene derivative (R_f 0.79) was complete. The solution was then added to 0.5 *N* aqueous sodium bicarbonate (170 cc.) and the mixture evaporated to dryness *in vacuo*. The residue was extracted with benzene and the product purified as described above, giving white needles, m.p. 44–45°, of the isopropylidene derivative (1.05 g., 90%).

When a solution of the product in 0.2 *N* NaOH was allowed to stand at room temperature for 24 hr., the initial single-peak ultraviolet spectrum (262.5 mμ) was replaced by a spectrum showing two well-defined maxima at 249 and 288 mμ, respectively (ratio of ϵ_{249} to ϵ_{288} = 0.92). This is similar to the spectrum[2,14] of 4,5-diaminopyrimidine in alkaline solution and to the ratio of ϵ_{246} to ϵ_{289} of 0.93[14] for that pyrimidine.

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(11) With shorter periods of reaction conversion was incomplete.

(12) Analysis by J. F. Alicino, Metuchen, N. J.

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