was identical with that of authentic allethrolone,[5] while those of the other two peaks exhibited similar fragmentation patterns. The bands at *m/e* 134 ($M^+ - H_2O$) and 121 ($M^+ - CH_2OH$) were much more intense in peak 3, structure **4**, than in the other two peaks.

Small amounts of the three pure components were separated by preparative glpc using the above column. Data for peak 1, structure **3**, follow: ir (neat) 2.92 (broad), 5.95, and 6.10 μ; nmr ($CDCl_3$, time averaged, 140 scans) δ 2.09 (s, 3, CH_3), 2.42 (m, 2, CH_2CH_2), 2.56 (m, 2, CH_2CH_2), 5.06 (m, 1, CHOH), 5.14 and 5.24 (m, 2, CH_2=), and 6.12 (m, 1, CH=). Peak 2 gave ir and nmr spectra identical with those of authentic allethrolone. Data for peak 3, structure **4**, follow: ir (neat) 2.92, 5.88, and 6.04 μ; nmr ($CDCl_3$) δ 2.36 (m, 2, CH_2CH_2), 2.61 (m, 2, CH_2CH_2), 2.94 (d, 2, J = 6 Hz, $-CH_2CH$=), 4.50 (s, 2, CH_2OH), 4.84 and 4.97 (m, 2, CH_2=), and 5.75 (m, 1, CH=).

Registry No.—**1**, 3569-36-6; **2**, 23680-22-0; **3**, 23680-23-1; **4**, 23680-24-2.

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Conversion of 2′,3′-*O*-Isopropylidene Adenosine into Its 5′,5′-Di-*C*-Methyl Derivative[1]

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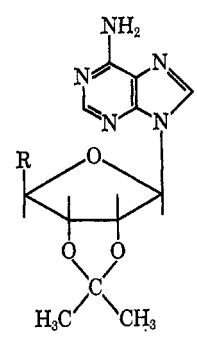
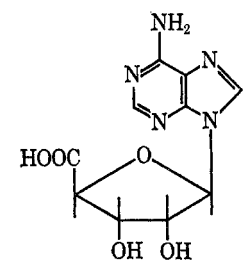
Direct chain extension and other carbon substitutions at the 5′ position of purine ribonucleosides have been restricted to oxidation of nucleosides to the 5′ aldehydes[2] followed by application of the Wittig reaction[3] or to conversion of a 5′-halogeno-5′-deoxy nucleoside into a 5′-cyano compound.[4] Syntheses of other 5′ carbon-substituted purine nucleosides, such as 5′-hydroxymethyl-5′-deoxyadenosine (homoadenosine)[5,6] and 5′,5′-di-*C*-methyladenosine,[7] have been effected by condensation of the respective blocked sugar derivatives with the adenine moiety. We now illustrate the practicability of a new approach which comprises conversion of a nucleoside, *via* its 5′-carboxylic acid, into the 5′-carbomethoxy derivative and application to the latter of the Grignard reaction.

Adenosine has been converted into the 5′-carboxylic acid **6** by oxidation with molecular oxygen in the presence of a platinum catalyst.[8] In our laboratory, this procedure, when applied to 2′,3′-*O*-isopropylidene adenosine (**1**), consistently gave low yields (2–5%) with reduced Adams catalyst from a variety of commerical preparations. Treatment of **1** with chromium trioxide in the presence of pyridine, acetic acid, or water yielded a complex mixture of products. Oxidation with potassium permanganate gave less complex mixtures, and after trials in the pH range of 2–12 and temperatures of 0–80°, a procedure was selected which employed 2 molar equiv of potassium permanganate at room temperature and pH 9–9.5. Although only *ca.* 30% conversion into the carboxylic acid **2** was obtained, the yield based on recovered isopropylidene adenosine was 90%. The product could be isolated directly in pure form and unreacted material could be readily recovered and recycled. When conversion of **1** into **2** was enhanced by the use of stronger oxidizing conditions, additional products were obtained and purification of **2** was rendered more tedious. The purification and properties of one such by-product (as yet of unassigned structure) is detailed in the Experimental Section. Two recently described alkaline potassium permanganate oxidations of **1**[9,10] were found to yield 50–60% homogeneous **2** and three by-products which amounted to 15% of the weight of **1** employed. Acidic treatment of **2** removed the isopropylidene group to furnish 9-(β-D-ribofuranosyluronic acid)adenine (**6**). Attempts to obtain **6** by direct oxidation of adenosine with potassium permanganate, chromium trioxide–acetic acid, or chromium trioxide–pyridine produced a complex mixture of products.



1, R = CH_2OH
2, R = COOH
3, R = $COOCH_3$
4, R = CH_2NH_2
5, R = $C(CH_3)_2OH$



6

Treatment of the carboxylic acid **2** with diazomethane produced the methyl ester **3** in 90% yield. The only other product detected was trace amounts of the amine **4**, the structure of which was deduced from nmr data and elemental analysis and confirmed by comparison with a specimen prepared by reduction of 5′-azido-5′-deoxy-2′,3′-*O*-isopropylidene adenosine.[11]

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Addition of a large excess of methylmagnesium iodide to a solution of **3** in dioxane–tetrahydrofuran resulted in the immediate precipitation of an intermediate product, which presumably resulted from reaction of the Grignard reagent with the 6-amino group of **3**. However, reaction at the 5′ position of **3** slowly proceeded to completion in the essentially heterogenous mixture and yielded 30% tertiary alcohol **5**. The yield of **5** was not enhanced by prior N-benzoylation of **3**. Reaction of a Grignard reagent with a nucleoside derivative has not hitherto been demonstrated to be a feasible synthetic procedure. Methyl Grignard reagents did not react with 2′,5′-di-*O*-trityl-3′-ketouridine,[12] owing possibly to steric interference by the 2′-*O*-trityl group.

The nmr spectrum of **5** showed nonequivalence of the protons of the two 5′-methyl groups, and a Corey–Pauling–Koltun molecular model indicated that restricted rotation about the 4′–5′ bond could result from a concerted steric interaction of the 3′ and 4′ hydrogens with the 5′ methyls.

Experimental Section

Melting points (uncorrected) were determined by the capillary method. Ultraviolet spectra were obtained in buffered aqueous solutions with a Cary Model 15 spectrophotometer and infrared spectra (in KBr disks) with a Perkin-Elmer 137 spectrophotometer. The nmr spectra were run in deuterated dimethyl sulfoxide with a Varian HA-100 instrument. Thin layer chromatograms were run on Eastman cellulose sheets in (A) 5% aqueous K_2HPO_4 overlaid with isoamyl alcohol and (B) 1-butanol saturated with water and on Eastman silica gel in (C) methanol–chloroform (6:94). Preparative tlc was carried out with Merck 2-mm silica gel plates in system C. Elemental analyses were by Spang Microanalytical Laboratories, Ann Arbor, Mich.

9-(2′,3′-*O*-Isopropylidene-β-D-ribofuranosyluronic acid)adenine (2).—2′,3′-*O*-Isopropylidene adenosine (**1**, 0.8 g) was dissolved in boiling water (200 ml), and potassium permanganate (1.2 g) and ammonia (30 ml, 15 *N*) were added to the cooled (25°) solution. After 12–15 hr at 25° the permanganate color had disappeared and ammonia (50 ml) was added to convert the colloidal manganese oxides into a readily filterable form. The filtrate was evaporated at 40° to *ca.* 15 ml and stored for 1 hr at 10°, when unreacted starting material (0.5–0.6 g) crystallized and was removed by filtration. The filtrate was evaporated to 15 ml, adjusted to pH 3–4 with acetic acid, and cooled to 10°. The precipitate which formed was filtered off, dried, and crystallized from methanol to give **2** (0.18–0.28 g, 90–95% yield based on unrecovered starting material) as fine needles: mp 300–305° dec; ir 3050, 1718, 1640, and 1520 cm^{-1}; uv max (pH 3) 256 mμ (ε 14,400), (pH >7) 259 (14,700); R_f 0.75 (system A) and 0.47 (system B).

Another compound could be isolated in small amounts (2–5%) from the mother liquors by evaporation and preparative tlc. It was also produced in larger amounts by using more forcing conditions in the oxidation. Crystallization from chloroform–petroleum ether (bp 30–60°) gave the compound as prisms: mp 250–255° dec; ir 3050, 1695, 1602, 1555, 1125, and 1080 cm^{-1}; uv max (pH 3) 256 mμ (ε 14,500), (pH >7) 259 (14,800); nmr δ 8.27 (s, 1, H-8), 8.10 (s, 1, H-2), 7.23 (s, 2, exchanges with D_2O, NH_2), 6.09 (d, 1, J = 3 Hz, H-1′), 5.30 (d of d, 1, J = 3 and 7 Hz, H-2′), 4.94 (d of d, 1, J = 2.5 and 7.0 Hz, H-3′), 4.20 (m, 1, H-4′), 3.50 (apparent d), 3.41 (exchanges with D_2O), and 1.52 and 1.30 (s, 3, isopropylidene methyls); R_f 0.68 (system C).

Anal. Calcd for $C_{13}H_{17}N_5O_4$: C, 50.76; H, 5.57; N, 22.77. Found: C, 51.03; H, 5.55; N, 22.87.

Oxidation of **1** according to Schmidt, *et al.*,[9] or Harmon, *et al.*,[10] gave 50–60% pure **2**, mp 300–305° dec (lit. mp 276° dec,[9] 277–279° [10]), after crystallization of the crude product from water. Preparative tlc of the mother liquors of crude **2** in solvents B and C gave the by-product described above together with two additional ultraviolet-absorbing solids in amounts of 6, 6, and 3%, respectively, of the weight of the starting material. All three by-products had higher R_f values than **2** in systems B and C.

9-(β-D-Ribofuranosyluronic acid)adenine (6).—Compound **2** (0.2 g) was dissolved in the minimum amount of boiling water, and acetic acid was added to give pH 2.3–2.4. The solution was heated on a steam bath until tlc (system B) showed that the reaction was complete (1–1.5 hr), then cooled and evaporated under vacuum to *ca.* 20 ml. The crystalline solid was filtered off and recrystallized twice from water to give **6** (0.19 g, 95%) as small plates: mp 285–295° dec; ir 3210, 1720, 1640, and 1525 cm^{-1}; uv max (pH 3) 256 mμ (ε 14,300), (pH ≥7) 259 (14,600); R_f 0.08 (system A) and 0.12 (system B). A melting point of >320° has been reported[9,10] for **6**. Repetition of these procedures gave material, mp 288–297° dec and 290–296° dec, respectively.

Anal. Calcd for $C_{10}H_{11}N_5O_5$: C, 42.70; H, 3.97; N, 24.90. Found: C, 42.96; H, 4.06; N, 24.78.

9-(2′,3′-*O*-Isopropylidene-β-D-riburonic acid methyl ester)-adenine (3).—Compound **2** (1 g) was dissolved in dioxane–methanol (1:1, 1600 ml) and cooled to 0°. Diazomethane (3 g) in diethyl ether (200 ml) was added and the mixture was held at 0° for 1 hr and then evaporated to dryness under vacuum. Recrystallization from methanol afforded **3** (0.9 g, 90%) as fine needles: mp 245–248° dec; ir 3120, 2950, 1728, 1670, 1600, 1080, and 840 cm^{-1}; uv max (pH 3) 256 mμ (ε 14,800), (pH >7), 259 (15,000); nmr δ 8.15 (s, 1, H-8), 7.97 (s, 1, H-2), 7.38 (s, 2, exchanges with D_2O, NH_2), 6.31 (s, 1, H-1′), 5.55 (d of d, 1, J = 6.0 and 1.5 Hz, H-3′), 5.34 (d, 1, J = 6.0 Hz, H-2′), 4.75 (d, 1, J = 1.5 Hz, H-4′), 3.23 (s, 3, $CH_3OC{=}O$), and 1.51 and 1.26 (s, 3, isopropylidene methyls); R_f 0.72 (system C).

Anal. Calcd for $C_{14}H_{17}N_5O_5$: C, 50.26; H, 5.11; N, 20.89. Found: C, 50.49; H, 5.09; N, 20.96.

In some cases 3–6% yields of another compound (**4**) could be isolated by preparative tlc (system C) of the mother liquors. Recrystallization from methanol afforded needles: mp 215–217° (under vacuum); with authentic amine, mmp 214–217°; ir 3300 (sh), 3230, 3120, 3025, 1670, 1545, 1499, 1200, 1090, 1055, and 865 cm^{-1}; uv max (pH 3) 256 mμ (ε 14,800), (pH >7) 259 (14,900); nmr δ 8.17 (s, 1, H-8), 8.00 (s, 1, H-2), 7.17 (s, 2, NH_2), 7.04 (s, 2, NH_2), 6.18 (d, 1, J = 1.5 Hz, H-1′), 5.23 (m, 2, H-2′ and H-3′), 4.42 (d, 1, J = 1.8 Hz, H-4′), 3.10 (d, 1, J = 4.0 Hz, CH_2NH_2), and 1.50 and 1.24 (s, 3, isopropylidene methyls); R_f 0.16 (system C).

Anal. Calcd for $C_{13}H_{18}N_6O_3$: C, 50.92; H, 5.91; N, 27.40. Found: C, 51.20; H, 5.80; N, 27.34.

5′,5′-Di-*C*-methyl-2′,3′-*O*-isopropylidene Adenosine (5).—Compound **3** (1.0 g) was dissolved in dioxane–tetrahydrofuran (1:1, 150 ml) and added with stirring to a solution of methylmagnesium iodide (prepared from 6.2 ml of methyl iodide and 2.4 g of magnesium in 50 ml of ether) at 20° in an atmosphere of nitrogen. A dense white precipitate formed immediately and stirring was continued for 7 days, at which time the ir spectrum of the product showed no absorption near 1728 cm^{-1}. The solution was treated with water dropwise until excess reagent was destroyed, and the precipitate of magnesium salts was removed by filtration. The filtrate was evaporated to dryness and the product was purified by preparative tlc (system C). The major component (R_f 0.82) was eluted with methanol and recrystallized from acetone and then from methanol to give **5** (0.24–0.35 g, 24–35%) as large prisms: mp 225–227°; ir 3380 (sh), 3140, 2980, 1685, 1601, 1225, and 1085 cm^{-1}; uv max (pH 3) 256 mμ (ε 14,300), (pH >7) 259 (14,600); nmr δ 8.31 (s, 1, H-8), 8.09 (s, 1, H-2), 7.24 (s, 2, exchanges with D_2O, NH_2), 6.03 (d, 1, J = 4.2 Hz, H-1′), 5.09 (d of d, J = 4.2 and 6.3 Hz, H-2′), 4.91 (d of d, J = 2.7 and 6.3 Hz, H-3′), 3.90 (d, 1, J = 2.7 Hz, H-4′), 3.30 (s, *ca.* 2, exchanges with D_2O, H_2O, and OH), 1.53 and 1.28 (s, 3, isopropylidene methyls), and 1.1 [two peaks partly resolved, 6, $CH_3C(CH_3)O$–]; R_f 0.82 (system C).

Anal. Calcd for $C_{15}H_{21}N_5O_4 \cdot {}^1/_2H_2O$: C, 52.35; H, 6.43; N, 20.38. Found: C, 52.79; H, 5.95; H, 20.68.

Registry No.—**1**, 362-75-4; **2**, 19234-66-3; **3**, 23754-29-2; **4**, 21950-58-3; **5**, 23680-27-5; **6**, 3415-09-6.

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