of 1.12 g of **7a** in 25 ml of MeCN was added to the cell over a period of 60 min and reduction was continued for 100 min longer. Vpc (10% silicone rubber on Chromosorb W, 200°) of the $CHCl_3$-soluble product indicated the formation of ethyl β-phenylpropionate (**10**) (11%), identified by comparison with an authentic sample. Acidification of the aqueous layer to pH 1 and extraction with $CHCl_3$ gave 400 mg (43%) of phenylpropiolic acid.

Repetition of the procedure but with 2 equiv of anhydrous HBr added to the substrate solution raised the yield of **10** to 26%. With 4 equiv of HBr the yield of **10** was 55%.

Registry No.—**2a**, 31892-93-0; **2c**, 6258-32-8; **2d**, 31892-95-2; **3**, 31892-96-3; **5a**, 24393-65-5; **5b**, 31892-98-5; **6**, 31892-99-6; **7a**, 2216-94-6; **7b**, 29577-38-6; **7c**, 31893-02-4.

Nucleosides. XIV. Synthesis of 3′-Deoxyadenosine and 9-(3-Deoxy-α-L-*threo*-pentofuranosyl)adenine

K. L. NAGPAL AND JEROME P. HORWITZ*[1]

Detroit Institute of Cancer Research, Division of the Michigan Cancer Foundation, Detroit, Michigan 48201, and Department of Oncology, Wayne State University School of Medicine, Detroit, Michigan 48207

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Treatment of methyl 9-(2,3-*O*-isopropylideneribofuranosyluronate)adenine (**3**) with sodium isopropoxide at room temperature leads to isopropyl 3′-deoxy-3′-adenosinene 5′-carboxylate (**4**) in 70% yield. The latter on catalytic (Pd/C) hydrogenation affords a mixture of two (C-4′) epimeric esters **5** and **6**, one of which (**5**) on reduction with sodium bis(2-methoxyethoxy)aluminum hydride furnished 3′-deoxyadenosine (**7**, cordycepin). The other ester (**6**), subjected to the same conditions of reduction, gave 9-(3-deoxy-α-L-*threo*-pentofuranosyl)-adenine (**8**). Compounds **7** and **8** could also be obtained in a more efficacious manner by column chromatography (Dowex 1) of the mixture derived by performing the reductions consecutively without separation of the isomeric intermediates **5** and **6**.

Recent reports from this laboratory[2a-c] described the introduction of 3′,4′ unsaturation into both pyrimidine and purine 2′-deoxynucleosides *via* corresponding 2′-deoxy-β-D-*erythro*-pentofuranosyluronic acid derivatives. Concurrently, Jones and Moffatt[2d,e] and Howgate,[3] *et al.*, reported the facile conversion of 2′,3′-*O*-alkylidene ribonucleoside 5′-carboxaldehydes (**1**) into 3′,4′-unsaturated nucleosides (**2**) and derivatives thereof under relatively mild basic conditions. The present communication describes the application of the latter approach to methyl 9-(2,3-*O*-isopropylideneribofuranosyluronate)adenine (**3**) which led to a practical synthesis of the antibiotic 3′-deoxyadenosine (**7**, cordycepin) and its C-4′ epimer, 9-(3-deoxy-α-L-*threo*-pentofuranosyl)-adenine[4] (**8**). The fact that **7** is a strong inhibitor of RNA synthesis, which generally accounts for its cytostatic activity,[5] stimulated our interest in **8** (Scheme I).

The conversion of **1** to **2** has been effected with a relatively wide spectrum of bases[2d,e] ranging from sodium bicarbonate or sodium carbonate in DMF to alkali metal alkoxides in both protic and dipolar aprotic media. By contrast, **3** was recovered unchanged after prolonged treatment with sodium carbonate in DMF. Moreover, triethylamine in DMF, the system of choice for the conversion of ethyl 3′-*O*-methylsulfonylthymidine 5′-carboxylate[2b] into ethyl 3′-deoxy-3′-thymidinene 5′-carboxylate,[6] proved equally ineffective after 13 hr at 80°. The desired elimination was effected, along with transesterification, by the action of sodium isopropoxide[7] in 2-propanol to give isopropyl 3′-deoxy-3′-adenosinene 5′-carboxylate[6] (**4**) in 70% yield after 0.5 hr at ambient temperature. The structure of the olefinic ester **4** was readily deduced from its nmr spectrum which showed, *inter alia*, a doublet at τ 6.53 ppm characteristic of the C-3′ vinyl proton in the sugar moiety.[2b]

Jones and Moffatt[2d,e] reported the occurrence of epimerization at C-4′, along with elimination when nucleoside 5′-carboxaldehydes (**1**) were brought into contact with adsorbents such as silica gel. There was no evidence of epimerization in our experiments. However, a small amount of the corresponding 3′,4′-unsaturated acid was occasionally isolated along with the ester (**4**) which is apparently generated from **4** during the work-up of the reaction mixture.

It would appear that, with the exception of a need for a stronger base to effect the process of elimination in the case of **3** relative to the nucleoside 5′-carboxaldehyde, the two elimination reactions probably proceed *via* similar paths. However, the scope of the present study precludes any firm conclusion in regard to the exact mechanism(s).

Catalytic hydrogenation (Pd/C) of **4** yielded two saturated esters **5** and **6** in the ratio of 1.5:1 which were separated on preparative tlc. The faster moving component **5**, on reduction with sodium bis(2-methoxyethoxy)aluminum hydride in tetrahydrofuran, yielded 3′-deoxyadenosine (**7**) in 50% yield. The slower moving ester **6**, subjected to the same conditions of reduction, afforded the epimeric structure, 9-(3-deoxy-α-L-*threo*-pentofuranosyl)adenine (**8**), in virtually the same yield.

(1) To whom correspondence should be addressed: Detroit Institute of Cancer Research.

(2) (a) J. Zemlicka, R. Gasser, and J. P. Horwitz, Abstracts, 160th National Meeting of the American Chemical Society, Chicago, Ill., 1970, Abstract No. CARB 3; (b) *J. Amer. Chem. Soc.*, **92**, 4744 (1970); (c) Abstracts, Joint Conference Chemical Institute of Canada and American Chemical Society, Toronto, Canada, 1970, Abstract No. CARB 5; (d) G. H. Jones and J. G. Moffatt, Abstracts, 158th National Meeting of the American Chemical Society, New York, N. Y., 1969, Abstract No. CARB 15; (e) U. S. Patent 3,457,255 (1969); *Chem. Abstr.*, **72**, 3727 (1970).

(3) P. Howgate, A. S. Jones, and J. P. Tittensor, *Carbohyd. Res.*, **12**, 403 (1970).

(4) This compound has been described (*cf.* ref 2e), but corresponding physical constants have not been disclosed.

(5) For pertinent references, see R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley, New York, N. Y., 1970, p 50.

(6) See J. P. Horwitz, J. Chua, M. A. Da Rooge, M. Noel, and J. T. Donatti, *J. Org. Chem.*, **31**, 205 (1966), for the basis of this nomenclature.

(7) This base system was chosen because the ester **3** was relatively insoluble in both methanol and ethanol.

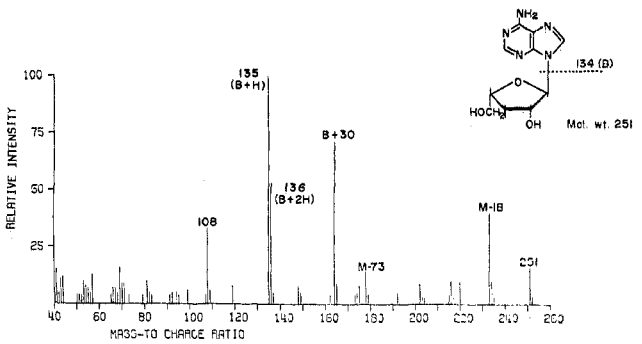
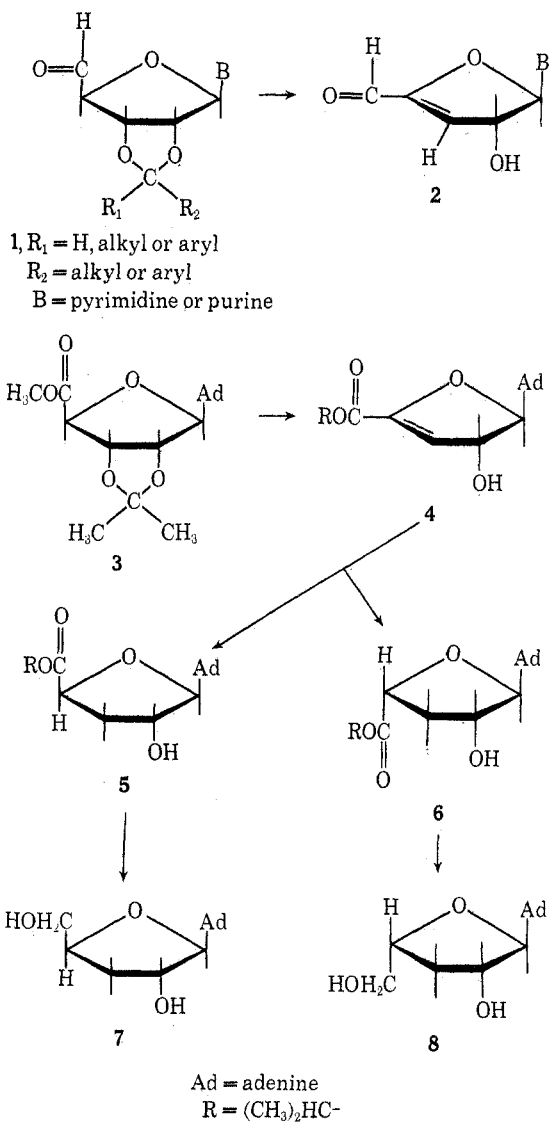


Figure 1.—Mass spectrum of 9-(3-deoxy-α-L-*threo*-pentofuranosyl)adenine.

SCHEME I



A more convenient route to **7** and **8** consisted of performing consecutively the catalytic and chemical reductions of **4** and then resolving the mixture of β-D and α-L isomers on column chromatography (Dowex-1).[8] The ratio of yields of products **7** and **8** obtained in the two procedures is essentially the same.

The formation of two products (**5** and **6**) from the hydrogenation of **4** differs from the course of reduction of ethyl 3′-deoxy-3′-thymidinene 5′-carboxylate which gave ethyl 3′deoxythymidine 5′-carboxylate as the sole product.[9] This difference probably can be ascribed in part to the presence of the 2′-OH in **4** coupled with the relative influence of the purine moiety vis-à-vis a thymine residue.

The nmr spectrum of **7** has been reported by two groups of workers.[10,11] As the compounds **7** and **8** differ in their configuration at C-4′, an attempt was made to assign the signal of this proton in the nmr spectra of the two isomers. Unfortunately, this signal is obliterated in both compounds by strong HDO absorption at τ 5.30 ppm. Moreover, efforts to resolve the C-4′ proton in solvents such as methyl sulfoxide and pyridine were equally unsuccessful. The spectra of **7** and **8** were generally similar and the anomeric proton in both structures shows essentially identical chemical shifts. However, the coupling constant of the anomeric proton of **8** (J = 3.5 Hz) is significantly larger than that of **7** (J = 2.0 Hz). A comparable difference prevailed as well in the precursory esters (**5** and **6**).

The absorption due to 3′-CH_2 in the L-threo compound **8** appears as a series of ten lines centered at 2.67 ppm and spread from 2.10 to 3.25 ppm. The corresponding multiplet for the isomer **7** consists of four lines that are poorly resolved and spread over a narrower range (2.52–2.69 ppm).[10,11]

Mass spectrometric evidence in support of the structure of cordycepin was provided by Hanessian, *et al.*[12] Interpretation of the mass spectrum of **8** lends additional support to the assigned structure. Thus the molecular ion m/e 251, which corresponds to a deoxyriboside of adenine, is common (Figure 1) to both spectra. Moreover, the structural identities of the most significant peaks in **8**, namely m/e 135, 136 (B + H and 2 H, respectively, where B = adenine residue) and 164 (B + 30) follow the previous interpretation of **7**. Thus the ion at 164 (B + 30) agrees with the presence of 2′-OH group and the one at 178 as in **7** indicates the absence of this group at C-3′.

Unlike **7**, its C-4′ epimer, **8** shows a prominent peak at m/e 233 (M − 18) due to the loss of water, but there is an absence of the peak at 221 (M − 30) characteristic of the loss of the elements of formaldehyde from the 5′-hydroxy group. The appearance of the peak (M − 30) requires that the labile hydrogen of the 5′-hydroxyl function be in relatively close proximity to the aglycon.[13] Since the 5′-OH in **8** is oriented trans to the base across the furanose ring, the labile hydrogen in this group becomes sterically inaccessible to the base which would explain the absence of a peak at m/e 221. A similar situation exists in 9-α-xylofuranosyladenine and 2′-deoxy-9-α-adenosine[13] which have the same geometrical relationship between the 5′-OH and the base as exists in **8**. The former does not exhibit the loss of the elements of formaldehyde, whereas the peak in the latter due to this loss (M − 30) is of low abundance as compared to its β isomer, 2′-deoxyadenosine. Biological

(8) C. A. Dekker, *J. Amer. Chem. Soc.*, **87**, 4027 (1965).

(9) J. Zemlicka and J. P. Horwitz, unpublished results.

(10) W. W. Lee, A. Benitez, C. D. Anderson, L. Goodman, and B. R. Baker, *J. Amer. Chem. Soc.*, **83**, 1906 (1961).

(11) E. A. Kaczka, E. L. Dulaney, C. O. Gitterman, H. B. Woodruff, and K. Folkers, *Biochem. Biophys. Res. Commun.*, **14**, 452 (1964).

(12) S. Hanessian, D. C. DeJongh, and J. A. McCloskey, *Biochim. Biophys. Acta*, **117**, 480 (1966).

(13) S. J. Shaw, D. M. Desiderio, K. Tsuboyama, and J. A. McCloskey, *J. Amer. Chem. Soc.*, **92**, 2510 (1970).

and biochemical studies with **8** are currently in progress and the results will be reported elsewhere.

Experimental Section

General Procedures.—Evaporations were carried out *in vacuo* at a bath temperature below 45°. Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. Thin layer chromatography (tlc) was performed on silica gel GF (Merck); preparative tlc was carried out on 20 × 20 cm glass plates coated with 1-mm layers of the same absorbent. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter. The ir spectra were measured in a Perkin-Elmer Model 21 spectrophotometer. Nuclear magnetic resonance spectra were obtained using a Varian A-60A spectrometer and mass spectra using an AEI MS-902 instrument with a direct inlet system and an ionizing voltage of 70 eV. Ultraviolet spectra were obtained by using a Cary recording spectrometer.

Isopropyl 3′-Deoxy-3′-adenosinene 5′-Carboxylate (4).—To a solution of 0.335 g (1 mmol) of methyl 9-(2,3-*O*-isopropylideneribofuranosyluronate)adenine (**3**),[14] dissolved by heating in 150 ml of dry 2-propanol, was added at room temperature 20 ml of 2-propanol containing 0.04 g of sodium (1.73 g-atoms) and the clear solution, protected from moisture, was stirred magnetically for 0.5 hr. The pH of the reaction mixture was adjusted to *ca.* 7 by dropwise addition of glacial acetic acid and the solution was evaporated to dryness. The residue was triturated with water and collected. The air-dried product crystallized from aqueous methanol as colorless needles: wt 0.215 g (70% yield); mp *ca.* 200° with prior softening *ca.* 115°; ir (KBr) 1733 cm^{-1} (ester C=O); uv max (95% EtOH) 256 nm (ϵ 15,800); nmr (acetone-d_6) δ 8.19 (s, 1, H-8) 8.10 (s, 1, H-2), 6.82 (s, 2, exchanges with D_2O, NH_2) 6.25 (d, 1, $J_{1',2'}$ = 2.5 Hz, H-1′), 6.53 (d, 1, $J_{2',3'}$ = 3.3 Hz, H-3′), 5.71 (t, 1, H-2′), 5.07 (m, 1, isopropyl hydrogen), 1.18 and 1.28 (s, isopropyl methyls); $[\alpha]^{24}D$ −145°; $[\alpha]^{24}_{578}$ −151° (*c* 0.5, methanol).

Anal. Calcd for $C_{13}H_{15}N_5O_4$: C, 51.14; H, 4.91; N, 22.95. Found: C, 50.97; H, 5.00; N, 23.01.

Isopropyl 9-(3-Deoxy-β-D-ribofuranosyluronate)adenine (5) and Isopropyl 9-(3-Deoxy-α-L-*threo*-ribofuranosyluronate)adenine (6).—A solution of **4** (0.305 g, 1 mmol) in 95% alcohol (40 ml) containing 0.3 g of 10% palladium/charcoal catalyst was shaken for 2 hr under 1 atm of hydrogen at 25°. The catalyst was filtered through Celite and the Celite was washed with alcohol. The combined filtrate and washings were evaporated to dryness and the residue (0.261 g), dissolved in methanol, was applied to five silica gel (20 × 20) plates ($CHCl_3$:CH_3OH, 4:1). Elution of the faster moving component with 95% ethanol gave **5** (148 mg, 49% yield), whereas the slower moving band furnished **6** (96 mg, 31% yield). Compound **5** was recrystallized from a mixture of ethanol and water: mp *ca.* 210° with a prior softening at *ca.* 105°; ir (KBr) 1753 cm^{-1} (ester C=O); uv max (95% EtOH) 260 nm (ϵ 16,300); nmr (acetone-d_6, TMS internal standard) δ 8.38 (s, 1, H-8), 8.18 (s, 1, H-2), 6.64 (s, 2, exchanges with D_2O, NH_2), 6.10 (d, 1, $J_{1',2'}$ = 1.5 Hz, H-1′), 2.40 (m, 2, 3′-CH_2), 1.15 and 1.25 (isopropyl methyls); $[\alpha]^{23}D$ −11.6°; $[\alpha]^{23}_{578}$ −13° (*c* 0.5, methanol).

Anal. Calcd for $C_{13}H_{17}N_5O_4 \cdot 0.5H_2O$: C, 49.36; H, 5.68; N, 22.19. Found: C, 49.03; H, 5.28; N, 21.89.

Compound **6** was recrystallized from isopropyl alcohol: mp *ca.* 235° with prior softening *ca.* 180°; ir (KBr) 1750 cm^{-1} (ester C=O); uv max (95% EtOH) 259 nm (ϵ 16,100); nmr (acetone-d_6, TMS internal standard) δ 8.19 (s, 1, H-8), 8.08 (s, 1, H-2), 6.57 (s, 2, exchanges with D_2O, NH_2), 6.15 (d, 1, $J_{1',2'}$ = 3.0 Hz, H-1′), 2.83 (m, 2, 3′-CH_2), 1.18 and 1.28 (s, isopropyl methyls); $[\alpha]^{24}D$ −17.5°; $[\alpha]^{24}_{578}$ −18.8° (*c* 0.5, methanol).

Anal. Calcd for $C_{13}H_{17}N_5O_4$: C, 50.81; H, 5.53; N, 22.80. Found: C, 50.60; H, 5.57; N, 22.96.

9-(3-Deoxy-α-L-*threo*-pentofuranosyl)adenine (8).—To a solution of **6** (0.1 g, 0.32 mmol) in dry THF (5 ml), cooled externally by an ice bath, was added 0.64 ml (0.128 g, 2 equiv) of a 21% benzene–THF solution of sodium bis(methoxyethoxy)aluminum hydride. The turbid mixture was stirred at room temperature for 1.25 hr after which additional (2 equiv) reducing agent was introduced and the stirring was continued for 3 hr. The reaction mixture was cooled by an ice bath and treated with 15 ml of ethanol and excess Dowex-50 (NH_4^+). The mixture was stirred at room temperature for 1.5 hr and the resin was removed by filtration. The filtrate and combined alcohol washings were evaporated to dryness. The residue, dissolved in methanol, was applied to a nonadhering (loose layer) silica gel (70–235 mesh) glass plate (20 × 20 cm) and the preparative tlc was developed in $CHCl_3$–CH_3OH, 4:1 (v/v). The principal and slower moving band was eluted with ethanol and the filtered solution, on evaporation, left a residue which crystallized from water: wt 0.039 g (48% yield); $[\alpha]^{25}D$ − 52°; $[\alpha]^{25}_{578}$ −54° (*c* 0.5, H_2O); uv max (95% EtOH) 260 nm (ϵ 13,100); nmr (D_2O, external standard TMS) δ 8.58 (s, 1, H-8), 8.53 (s, 1, H-2), 6.43 (d, 1, $J_{1',2'}$ = 3.5 Hz, H-1′), 4.18 (m, 2, 5′-CH_2), 2.67 (m, 2, 3′-CH_2).

Anal. Calcd for $C_{10}H_{13}N_5O_3 \cdot 0.75H_2O$: C, 45.36; H, 5.48; N, 26.46. Found: 45.25; H, 5.37; N, 26.65.

3-Deoxyadenosine (7).—The reduction of **5** (0.1 g, 0.32 mmol) with sodium bis(methoxyethoxy)aluminum hydride (0.64 ml diluted to 10 ml in THF) was effected in exactly the same manner described above for the corresponding reductions of **5**. Preparative tlc afforded 0.042 g of a solid (52% yield), after crystallization from water: mp 222–224°; $[\alpha]^{25}D$ −44°; $[\alpha]^{25}_{578}$ −46° (*c* 0.5, H_2O);[15] uv max (95% EtOH) 260 nm (ϵ 13,500); nmr[10,11] (D_2O, external standard TMS) δ 8.63 (s, 1, H-8), 8.51 (s, 1, H-2), 6.40 (d, 1, $J_{1',2'}$ = 2.0 Hz, H-1′), 4.25 (m, 2, 5′-CH_2), 2.66 (m, 2, 3′-CH_2).

An Alternate Route to 7 and 8.—A mixture of **5** and **6** (307 mg, 1 mmol) as obtained from the (Pd/C) hydrogenation of **4** was reduced with 4 equiv of sodium bis(2-methoxyethoxy)aluminum hydride in THF, as described above, to give 148 mg of a mixture of **7** and **8**. A sample (0.1 g) of the mixture, dissolved in 30% methanol (20 ml), was put on a column (2.5 × 38 cm) of Dowex-1 (OH-, 200–400 mesh), and the column was eluted with 1.6 l. of 30% methanol. Removal of the solvent from the faster moving product contained in fractions 48–65 (each fraction was of 15 ml) furnished **7** (53 mg), and the slower moving component (fractions 85–100) yielded **8** (34 mg). Both **7** and **8** were recrystallized from water and were found to be identical with the compounds obtained according to the method described above.

Registry No.—**4**, 31735-23-6; **5**, 31735-24-7; **6**, 31735-25-8; **7**, 73-03-0; **8**, 26302-05-6.

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(14) P. J. Harper and A. Hampton, *J. Org. Chem.*, **35**, 1988 (1970).

(15) The following physical constants have been recorded (see ref 5, 10, and 11) for this compound: mp 230–231°; $[\alpha]^{26}D$ −35° (*c* 9.452, H_2O); uv max (pH 4) 259 nm (ϵ 13,100).