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Note

Synthesis of 9-(2,5-dideoxy-β-D-*glycero*-pent-4-enofuranosyl)adenine

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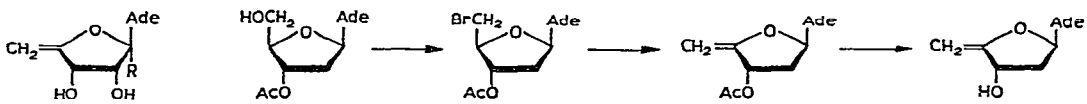
Decoyinine (angustmycin A) is a nucleoside antibiotic which has antibacterial and antitumor activity[1]. Its structure has been shown[2] to be 9-(6-deoxy-β-D-*erythro*-hex-5-enulofuranosyl)adenine (**1**). A related compound, 9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine (**2**), was prepared[3] from adenosine and inhibits *Streptococcus faecalis* with the same potency as **1**. It was of interest to explore further the biological effects of 4′,5′ unsaturation in pentofuranose nucleosides in order to understand better the structural requirements for biological activity and improve upon the observed biological effects of **1**. The preparation of 9-(2,5-dideoxy-β-D-*glycero*-pent-4-enofuranosyl)adenine (**6**), the 2′-deoxy analog of **2**, is described in this report. A similar study in the pyrimidine series has recently appeared[4].



1 R = CH_2OH
2 R = H
3 **4** **5** **6**

McCarthy *et al.*[3] utilized, in the preparation of **2**, the very acid-labile ethoxymethylidene blocking group and effected unsaturation by treatment of the 5-′toluenesulfonate with a strong base, potassium *tert*-butoxide. They had found that blocking with the base-labile acetyl group resulted in several unidentified products. 2′-Deoxyadenosine is even more acid-labile than adenosine, and the enol ether **6** would be expected to be extremely unstable to acidic conditions. Therefore, preparation of **6** starting from a 5′-bromide was considered. However, attempts to prepare 5′-bromo-2′,5′-dideoxyadenosine directly from 2′-deoxyadenosine by several recently developed procedures[5–7] for the preparation of 5′-halonucleosides failed to give the desired product.

A successful synthesis of **6** was performed starting from 3′-*O*-acetyl-2′-deoxyadenosine (**3**), which can be quite readily prepared from 2′-deoxyadenosine in four

steps[8]. Nucleoside **3** was treated with thionyl bromide in hexamethylphosphoramide to give 3′-*O*-acetyl-5′-bromo-2′,5′-dideoxyadenosine (**4**) in 29% yield. Treatment of **4** with silver fluoride in pyridine, a well-known dehydrohalogenating reagent in the sugar series[9], gave only an 18% yield of **5**. The preparation of **5** was greatly improved by the use of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in *N*,*N*-dimethylformamide, to afford a 53% yield. Attempts to remove the acetyl group with methanolic ammonia failed to give **6**, but the product was obtained in good yield by treatment of **5** with sodium methoxide in methanol–chloroform at low temperature. The n.m.r. and i.r. data of each of the new compounds, **4**, **5**, and **6**, were consistent with the proposed structures.

EXPERIMENTAL

General methods. — Melting points were determined with a Kofler hot-stage and correspond to corrected values. Infrared spectra were recorded with a Perkin–Elmer Model 21 spectrophotometer. N.m.r. spectra were recorded on di[^{2}H]methyl sulfoxide solutions with a Varian T-60A spectrometer. Elemental analyses were performed by the Baron Consulting Co., Orange, Conn. Thin-layer chromatography was performed on plates coated with Silica Gel HF (E. Merck AG, Darmstadt). The solvent system was 9:1 (v/v) chloroform–methanol and spots were located with a u.v. lamp.

3′-O-Acetyl-5′-bromo-2′,5′-dideoxyadenosine (**4**). — A mixture containing freshly distilled thionyl bromide (15 ml) and hexamethylphosphoramide (100 ml) was chilled in an ice-bath. To this mixture was added 3′-*O*-acetyl-2′-deoxyadenosine[8] (10 g, 34 mmol), and the mixture was stirred overnight at room temperature. It was then poured into a mixture of ice (600 g) and sodium hydrogencarbonate (36 g). After the ice had melted, the mixture was filtered to remove a solid material. The filtrate was extracted with chloroform (5 × 125 ml), and the extracts were combined and dried (magnesium sulfate). The chloroform was removed by evaporation on a rotary evaporator under reduced pressure at 30°. The resulting hexamethylphosphoramide solution was added dropwise to petroleum ether (1000 ml, b.p. 30–60°). The solid that precipitated was recrystallized from methanol to give 2.5 g, m.p. 175–176°. The compound revealed only one spot on t.l.c. and gave both positive Beilstein and alcoholic silver nitrate tests. The mother liquor was evaporated to a yellow syrup (5.5 g) that showed four components on t.l.c. The syrup was chromatographed on a silicic acid column (22 × 3 cm, Mallinckrodt, 100 mesh) with 19:1 (v/v) chloroform–methanol and an additional 1.0 g of **4**, m.p. 182° (total yield: 29%) was obtained as the second component to be eluted. Recrystallization of the combined crops from methanol gave pure **4**, m.p. 182°; u.v. data: λ_{max}^{EtOH} 260 nm; i.r. data: ν_{max}^{KBr} 1740 cm^{-1} ($CH_3C{=}O$); n.m.r. data: τ 1.69, 1.90 (both s, 1 proton each, H-8, H-2), 2.87 (s, 2, NH_2), 3.60 (t, 1, H-1′), 4.80 (m, 1, H-3′), 5.92 (m, 1, H-4′), 6.34 (m, 2, H-5′), 6.74 (m, 2, H-2′), and 7.97 (s, 3, CH_3 of acetyl).

Anal. Calc. for $C_{12}H_{14}BrN_5O_3$: C, 40.46; H, 3.96; N, 19.66; Br, 22.43. Found: C, 40.21; H, 4.05; N, 19.93; Br, 21.69.

*9-(3-O-Acetyl-2,5-dideoxy-β-*D*-glycero-pent-4-enofuranosyl)adenine* (**5**). *Method A.* — To a solution of **4** (1.45 g, 4.08 mmol) in *N,N*-dimethylformamide (7 ml) was added 1,5-diazabicyclo[5.4.0]undec-5-ene (620 mg, 4.08 mmol) and the mixture was kept for 8 days at room temperature. The solution was evaporated (30°, 1 torr) and the yellow oil was chromatographed on a small silicic acid column (3 × 1 cm) with chloroform. The oily product solidified upon addition of ethyl ether. Recrystallization from methanol afforded white crystals (616 mg, 53%), m.p. 169–170°; i.r. data: ν_{max}^{KBr} 1745 ($CH_3C{=}O$) and 820 cm^{-1} ($H_2C{=}C\langle^{O-}$); n.m.r. data: τ 1.64, 1.84 (both s, 1 proton each, H-8, H-2), 2.67 (s, 2, NH_2), 3.34 (t, 1, H-1′), 3.97 (m, 1, H-3′), 5.60 (AB pattern, 2, 5′ $CH_2{=}$), 6.74 (broad peak, 2, H-2′), and 7.92 (s, 3, $CH_3C{=}O$).

Anal. Calc. for $C_{12}H_{13}N_5O_3 \cdot 0.5H_2O$: C, 50.70; H, 4.96; N, 24.63. Found: C, 50.71; H, 4.78; N, 24.45.

Method B. — To a solution of **4** (356 mg, 1 mmol) in pyridine (10 ml) was added silver fluoride* (300 mg, 2.36 mmol), and the mixture was kept for 4 days at room temperature. The dark mixture was filtered and partitioned between water and ethyl acetate. The aqueous layer was further extracted with ethyl acetate several times, and the organic extracts were combined and dried (magnesium sulfate). Evaporation under reduced pressure gave a yellow, oily residue that was dissolved in chloroform and chromatographed through a small silicic acid column. Evaporation gave an oil that solidified when ethyl ether was added to afford **5** (50 mg, 18%), m.p. 169–170°. Recrystallization from methanol did not alter the melting point. This material was identical with the substance **5** prepared in Method A, as determined by m.p., i.r., and t.l.c. data.

*9-(2,5-Dideoxy-β-*D*-glycero-pent-4-enofuranosyl)adenine* (**6**). — Compound **5** (300 mg) was added to a mixture of sodium methoxide (1.2 ml of a M solution in methanol) and chloroform (8 ml). The mixture was stirred at −20° until complete dissolution occurred (about 20 min), whereupon the mixture was diluted with methanol (10 ml), treated with Amberlite IRC-50 (H^+) ion-exchange resin, and stirred until neutral. The resin was removed by filtration and washed with methanol. The solvents were evaporated, leaving an oil that was triturated with ethyl ether. The solid formed was dissolved in water and chromatographed on a column (16 × 1 cm, 200–400 mesh) of Bio-Rad AG1-X2 (OH^-) ion-exchange resin. Elution with water afforded 125 mg (50%) after evaporation of the solvent and crystallization from acetone, m.p. 165–166°; i.r. data: ν_{max}^{KBr} 821 cm^{-1} ($CH_2{=}C\langle^{O-}$); n.m.r. data: τ 1.64, 1.77 (both s, 1 proton each, H-8, H-2), 2.64 (s, 2, NH_2), 3.30 (t, 1, H-1′), 4.27 (m, 1, 3′ OH), 4.84 (m, 1, H-3′), 5.67 (AB pattern, 2, $CH_2{=}$), and 6.57 (broad peak, 2, H-2′).

Anal. Calc. for $C_{10}H_{11}N_5O_2$: C, 51.50; H, 4.75; N, 30.03. Found: C, 51.60; H, 4.95; N, 29.75.

*Ventron Corp., Alfa Products, Beverly, MA 01915.

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REFERENCES

1 R. J. SUHADOLNIK, *Nucleoside Antibiotics*, Wiley–Interscience, New York, 1970, pp. 115–119.
2 H. HOEKSEMA, G. SLOMP, AND E. E. VAN TAMELEN, *Tetrahedron Lett.*, (1964) 1787–1795.
3 J. R. MCCARTHY, JR., R. K. ROBINS, AND M. J. ROBINS, *J. Amer. Chem. Soc.*, 90 (1968) 4993–4999.
4 J. P. H. VERHEYDEN AND J. G. MOFFATT, *J. Org. Chem.*, 39 (1974) 3573–3579.
5 K. KIKUGAWA AND M. ICHINO, *Tetrahedron Lett.*, (1971) 87–90.
6 K. HAGA, M. YOSHIKAWA, AND T. KATO, *Bull. Chem. Soc. Jap.*, 43 (1970) 3922–3924.
7 S. HANESSIAN, M. M. PONPIPOM, AND P. LAVALLEE, *Carbohydr. Res.*, 24 (1972) 45–56.
8 A. HOLÝ, in W. W. ZORBACH AND R. S. TIPSON (Eds.), *Synthetic Procedures in Nucleic Acid Chemistry*, Vol. 1, Wiley–Interscience. New York, 1968, pp. 172–175.
9 L. HOUGH AND B. OTTER, *Chem. Commun.*, (1966) 173–174.