in vacuo (bath temperature 70 °C), and the residue was partitioned between Et_2O–ligroin (2:1) and H_2O. The organic layer was washed well with H_2O and then with NaCl–H_2O, dried ($MgSO_4$), and evaporated to give 0.25 g of nearly colorless, glassy material: one spot on TLC; NMR ($CDCl_3$) δ 6.10 (br t, J = 5.5 Hz, NH), 5.65 (1 H, br, olefinic), 3.79 (d, 2 H, J = 5.5 Hz, 11-H), 2.30 (s, 3 H, $COCH_3$), 1.98 (s, 3H, $-COCH_3$); IR (CCl_4) 1775, 1692 cm^{-1}; mass spectrum (70 ev) m/e 413.

11-Acetamido-Δ^8-tetrahydrocannabinol (4). To 0.23 g (0.00056 mol) of acetate **10** in 15 mL of MeOH under N_2 was added 3 drops of 10% NaOH. The mixture was stirred at room temperature for 1.5 h. Then, 3 drops of 10% HCl was added and the mixture partitioned between Et_2O and H_2O. The Et_2O was washed with H_2O and NaCl–H_2O, dried ($MgSO_4$), and evaporated to give 0.2 g of light-brown oil. Chromatography of this oil over silica gel using Me_2CO–ligroin (bp 30–60 °C) gave 0.11 g (53%) of **4** as a cream-colored glass: IR (CCl_4) 1669 cm^{-1}; MS m/e calcd for $C_{23}H_{33}NO_3$ 371.2460; found 371.2460.

9-Nor-9-oxohexahydrocannabinol Oxime (5). To 0.5 g (0.0016 mol) of ketone **11**[10] in 2.5 mL of dry pyridine and 2.5 mL of absolute EtOH was added 0.5 g of H_2NOH·HCl, and the mixture was heated to reflux for 2 h. Then the solvents were removed in vacuo and the residue was triturated in 2.5 mL of cold H_2O. After discarding the H_2O wash, the residue was taken up in a small amount of Et_2O and chromatographed over silica gel using Et_2O–ligroin (bp 30–60 °C). This gave 0.5 g (94%) of **5** as a white glass, mp 65–75 °C. On TLC (silica gel, ligroin–acetone–Et_2O, 7:2:1) this material gave two closely running spots; presumably syn and anti isomers. Recrystallization from ether–ligroin gave 0.3 g of cream-colored crystals, mp 114–117 °C; mass spectrum (70 ev) m/e 331. Anal. ($C_{20}H_{29}NO_3$) C, H, N.

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2′,3′-Bis(2-chloroethyl)aminophosphoryl-3′-amino-3′-deoxyadenosine: A Cyclic Nucleotide with Antitumor Activity

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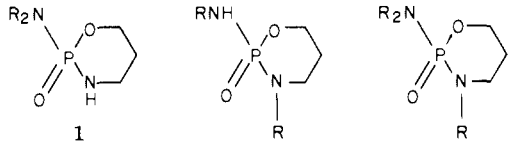
The synthesis of the title compound from 3′-amino-3′-deoxyadenosine in 40% yield is reported. 3′-Amino-3′-deoxyadenosine was made by an improved synthesis in 12 steps from inexpensive D-xylose in 15% overall yield. Both isomers of the title compound, separated by column chromatography, possess confirmed activity against KB tumor cell cultures.

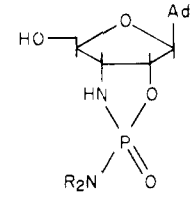
Cyclophosphamide (**1**) is effective against more varieties



1 2, R = $ClCH_2CH_2$ 3

of human cancer than any of the approximately 50 compounds shown to have clinically detectable antitumor activity.[2] It therefore becomes of interest to synthesize modifications of this drug and its highly promising analogues isophosphamide (**2**) and triphosphamide (**3**), which may enhance selectivity in tumor cell destruction.

In this note, we describe the synthesis of the cyclic nucleotides **4a,b** which are isomeric at phosphorus and the



4a,b

0022-2623/79/1822-0882$01.00/0

Scheme I

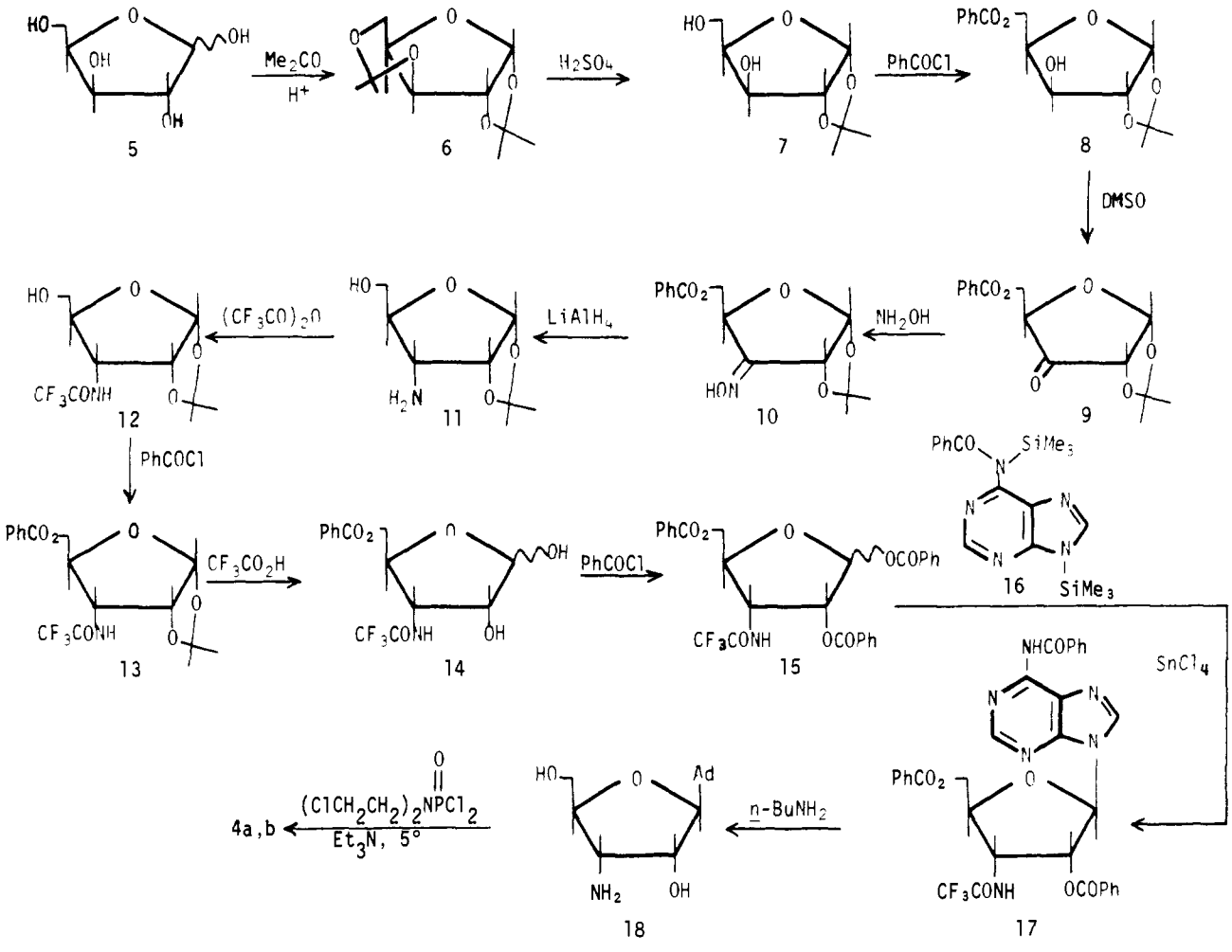


Table I. KB Cell Culture Data[a] for 4a and 4b

compd	slope[b]	ED_{50}, μg/mL
4a (NSC-295683)	−0.68	1.1
	−0.84	6.3×10^{-1}
	−0.83	1.7
4b (NSC-295763)	−0.51	1.2
	−0.00	6.3×10^{-1}
	−0.74	1.4×10^{-1}

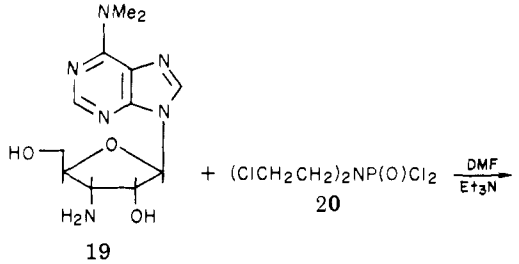
[a] From National Cancer Institute screening results. [b] Change of response for each 1-log change of dose.

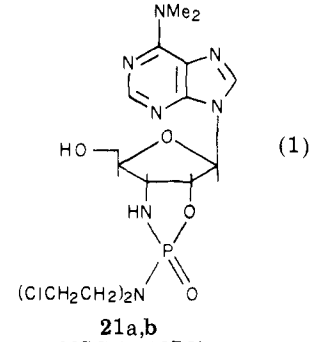
preliminary results of antitumor screening by the National Cancer Institute.

The first objective in achieving the target molecule 4 in Scheme I was to devise a more efficient synthesis of the key intermediate 3′-amino-3′-deoxyadenosine (18). An older route described in the literature[3] produces 18 from D-xylose in 20 steps and in 3% overall yield. A more recent disclosure[4] reveals a 12-step synthesis which provides a 5% yield of 18, but the relatively expensive adenosine is utilized as a starting material. Compound 18 has also been isolated from the action of Helminthosporium sp. 215 in a sucrose-containing medium,[5] but yields are low (65 mg/L of original broth) and the purification of the product is arduous.

Although only a 6% overall yield of 18 could be expected from the literature data pertaining to the intermediates given in Scheme I, modification of some of the procedures as detailed under the Experimental Section allowed us to more than double the projected yield to 15%.

Earlier there appeared a report in which 19, an *N,N*-dimethyl analogue of 18, was found to form an isomeric mixture of **21a,b** in 51% yield according to reaction 1.[6]





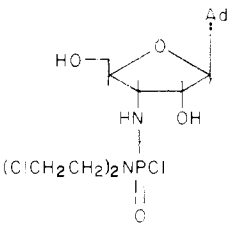
(1)

Somewhat unexpectedly, application of this technique to the phosphorylation of 18 failed to produce spectroscopic or chromatographic evidence for more than traces of **4a,b**,

although 80% of the expected Et_3N·HCl precipitated. No reaction was observed to occur using CH_2Cl_2 as a solvent.

Since $(EtO)_3PO$ has been successfully used as a solvent in nucleotide synthesis[7] and in phosphorylations of aminonucleosides,[8] we sought to carry out the last step in Scheme I in this solvent. With this technique a 20% yield for each isomer **4a** and **4b** was achieved. These yields represent an overall yield for **4a,b** of 6%. Both isomers gave satisfactory analyses, but neither gave a parent ion in their mass spectra. Although both spectra were nearly identical, the highest m/e peak value which could be observed was 281, which may correspond to loss of a chlorine atom and an adenine moiety. The similarities of the IR, UV, and ^1H, ^{13}C, and ^{31}P NMR spectra are also consistent with compounds isomeric at phosphorus. The relatively low-field ^{31}P chemical shifts (**4a**, 30.0; **4b**, 33.2 ppm) suggests that **4a** and **4b** contain five- rather than six-membered rings. Thus, cyclophosphamide (1), for example, has a δ ^{31}P value of 12.6 ppm.[9] Furthermore, cyclic organophosphorus compounds containing five-membered rings typically absorb 10–20-ppm downfield from their six-membered ring analogues.[10] Further support for five-membered rings in **4a** and **4b** stems from the presence of the ca. 3-Hz splitting of the 1′ hydrogen in their ^1H NMR spectra. Such spectra of five-membered ring amidonucleosides display this splitting, whereas their six-membered ring analogues do not.[8b]

Formation of **4a,b** in the phosphorylation of **18** implies that **22** may be the intermediate. A similar intermediate



22

has been proposed for the phosphorylation of **18** by $P(S)Cl_3$.[8b] In contrast, $P(O)Cl_3$ attacks **18** preponderantly at the 5′-hydroxyl group.[8]

While **21a,b** is inactive against KB cell cultures (derived from a human epidermoid carcinoma of the mouth), both **4a** (NSC-295683) and **4b** (NSC-295763) show preliminary activity in this NCI screening procedure (Table I). The average ED_{50} of three tests with ranges are 1.1 (0.6–1.7) and 0.66 (0.14–1.2) μg/mL, respectively. Isomers **4a** and **4b**, as well as the isomeric mixture **21a,b**, are inactive against LE 1210 mouse tumors, however, each showing T/C values of 101% upon ip injection at the highest dose tested (0.625 mg/kg).

Experimental Section

All solvents were reagent grade and were dried over molecular sieves before use. Melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H NMR spectra were taken with Varian A-60 or HA-100 spectrometers with Me_4Si as an internal reference. ^{31}P and ^{13}C NMR spectra were obtained with a Bruker HX-90 spectrometer using external H_3PO_4 and internal Me_4Si as references, respectively. Thin-layer chromatography was carried out using Mallinkrodt Chromar 7 GF precoated plates. Spots were visualized by UV light and/or exposure to iodine vapors. Column chromatography was done with Baker 60–200 mesh silica gel and was followed by TLC. Optical rotations were measured with a Perkin-Elmer 141 polarimeter at 589 nm. Infrared and UV spectra were recorded with a Beckman IR 4250 and a Cary 14 spectrophotometer, respectively.

Compounds **6–8** were made following literature reports.[11–13] In some preparations a partial decomposition occurred during the distillation of **7**. It was found, however, that crude **7** may be used in the next step after stirring under vacuum for 24 h at 60 °C.

5-*O*-Benzoyl-1,2-isopropylidene-α-D-erythropentofuranos-3-ulose (9). Into a 1-L distillation flask containing a mixture of Me_2SO (300 mL) and acetic anhydride (200 mL) was dissolved 50.5 g (0.171 mol) of crude **8**. The flask was connected to a condenser and a 1-L ice-cooled receiver. After the pressure was adjusted to about 250 mmHg with an aspirator, the reaction flask, equipped with a distillation capillary, was heated at 110 °C in an oil bath. After a few minutes, an exothermic reaction took place and a mixture of Me_2S, AcOH, and Ac_2O began to distill. At this point, the heating bath was removed for ca. 15 min. The mixture was then heated for 30 min at 130 °C, after which the pressure was adjusted to 15 mmHg while most of the volatiles evaporated. Higher boiling fractions were removed at 0.5 mmHg, leaving a dark-red, thick residue. The residue was dissolved in 150 mL of boiling ether and filtered. Refrigeration gave **9** in the form of white crystals (27.6 g, 55%; mp 93–95 °C, lit.[13] 98–99 °C) after working up the mother liquors.

Compounds **10–12** were prepared following a literature preparation.[6]

3-Deoxy-1,2-*O*-isopropylidene-5-*O*-benzoyl-3-(trifluoroacetamido)-α-D-ribofuranose (13). Because the conversion of **12** into **18** was outlined only briefly in two communications,[14] our procedure is given in detail. To a solution of 74.5 g (0.261 mol) of **12** in pyridine (400 mL) was added dropwise, with stirring and ice cooling, a solution of 42.0 g of benzoyl chloride. After stirring the mixture overnight at room temperature, 10 mL of water was added followed by evaporation to a volume of 200 mL. The residue was poured into 1000 mL of ice–water and extracted with CH_2Cl_2 (1 × 300 mL and 2 × 200 mL). The combined extracts were washed with 5% H_2SO_4 solution (3 × 100 mL) and with water (100 mL). After drying with anhydrous Na_2SO_4, the solution was evaporated, leaving crude **13** (104 g) as a white crystalline mass. The product was used for the next step without further purification.

3-Deoxy-3-(trifluoroacetamido)-5-*O*-benzoyl-α-D-ribofuranose (14). A mixture of 30.0 g (0.0771 mol) of **13** and excess 90% trifluoroacetic acid was stirred at room temperature for 3 h. After removal of most of the CF_3CO_2H in vacuo, the residue was evaporated twice with CH_2Cl_2 (100 mL) and with benzene (200 mL) to remove the rest of the acid. Crude **14** was obtained as a white crystalline mass (27.0 g) and was used for the next step without further purification.

3-Deoxy-3-(trifluoroacetamido)-1,2,5-*O*-benzoyl-D-ribofuranose (15). Into a solution of 92.0 g (0.274 mol) of the crude **14** in pyridine (800 mL) was added, with stirring, a solution of 84.0 g (0.598 mol) of benzoyl chloride in 200 mL of pyridine at 0 °C. After the mixture was left overnight at room temperature, 20 mL of water was added. The mixture was evaporated to a volume of 300 mL and poured into 1000 mL of cold water. This mixture was extracted with CH_2Cl_2 (500 mL and then 3 × 100 mL), and the combined extracts were washed with cold 15% H_2SO_4 (6 × 100 mL) and water (100 mL). The solution was dried with anhydrous Na_2SO_4 and evaporated, leaving an oily dark-red residue. The residue was then dissolved in 100 mL of benzene and cooled. White crystals (12 g) were deposited, which were identified as benzoic acid (mp 118–120 °C). The filtrate was evaporated, dissolved in a small amount of $CHCl_3$, and partially purified by filtration through 150 g of silica gel (benzene–$CHCl_3$–methanol, 21:10:1, eluent). Evaporation of the solvent left 121.0 g of **15** as white crystals in 86% yield from **12**. Thin-layer chromatography of this product showed two spots at R_f 0.40 and 0.55 (benzene–$CHCl_3$–methanol, 20:10:1). A sample of 16.0 g was chromatographed on a column packed with 250 g of silica gel using the same solvent mixture as eluent. Compound **15a** was isolated as white crystals: yield 6.9 g; mp 163–164 °C following recrystallization from $CHCl_3$–CCl_4; $[\alpha]^{25}_D$ +46.3° ($CHCl_3$). Compound **15b** appeared as a white solid: yield 6.6 g; $[\alpha]^{25}_D$ +129.8° ($CHCl_3$). The earlier report[14a] indicated that **15** was obtained as a single anomer in 48% yield from **12**. In our hands, **12** produces an 86% overall yield of the anomers in a 1:1 ratio. Our compound **15a** appears to be identical with the single anomer reported earlier:[14a] mp 164 °C; $[\alpha]^{21}_D$ +43° ($CHCl_3$).

6-*N*-Benzoyladenine[15] and 6-*N*-benzoyl-6,9-*N*,*N*-bis(trimethylsilyl)adenine (**16**)[16] were prepared as reported previously.

3′-Amino-3′-deoxyadenosine (18). Into 300 mL of dry 1,2-dichloroethane was dissolved 34.0 g (0.0569 mol) of **15** which had been partially purified by filtration through silica gel. A solution of 28.0 g (0.0726 mol) of **16** in 50 mL of 1,2-dichloroethane was added with stirring, followed by the addition of 22.5 g (0.0979 mol) of $SnCl_4$, whereupon an exothermic reaction ensued. The mixture was stirred at 70 °C for 30 h, cooled, and cautiously washed with 400 mL of saturated aqueous $NaHCO_3$ solution. The organic solution was dried with anhydrous Na_2SO_4 and evaporated. The residue, containing crude **17**, was dissolved in 400 mL of methanol. To this mixture was added 60 mL of *n*-butylamine, and then the solution was refluxed for 48 h. After 48 h, the dark solution, containing a white precipitate, was refrigerated overnight. The white crystalline aminonucleoside **18** was filtered off and washed with hot methanol: yield 16.2 g, 79%; mp 270–272 °C dec; $[\alpha]^{25}_D$ −35.0° (0.1 N HCl); R_f 0.46 (MeOH) [lit.[5] mp 271–273 °C dec; $[\alpha]^{25}_D$ −37.0° (0.1 N HCl)]. The identity and purity of **18** were confirmed by comparing its physical, spectroscopic, and chromatographic characteristics with those of an authentic sample kindly provided by Dr. H. A. Lechevalier. Essentially the same results were obtained using the separated isomers **15a** or **15b**.

The $(ClCH_2CH_2)_2NP(O)Cl_2$ for the next step was made according to a literature preparation.[17]

2′,3′-Bis(2-chloroethyl)aminophosphoryl-3′-amino-3′-deoxyadenosine (4a,b). To a suspension of **18** (1.33 g, 0.00500 mol) in dry $(EtO)_3PO$ (70 mL, freshly distilled from NaH) was added dropwise at 5 °C, with stirring, a solution of 1.3 g (0.00500 mol) of $(ClCH_2CH_2)_2NP(O)Cl_2$ in 15 mL of $(EtO)_3PO$. After stirring the mixture for 18 h at 5 °C and overnight at room temperature, triethylamine (1.1 g, 0.0011 mol) was added and the mixture stirred for 8 h at room temperature. The white precipitate which was filtered off and washed with $(EtO)_3PO$ was identified by its ^1H NMR spectrum (D_2O) as triethylamine hydrochloride. The filtrate was evaporated under vacuum at 50 °C to a glassy mass. A sample dissolved in Me_2SO-d_6 showed absorptions in the ^{31}P NMR spectrum at 30.0 and 33.2 ppm. Thin-layer chromatography ($CHCl_3$–MeOH, 4:1) showed two spots at R_f 0.45 and 0.55. The mixture was dissolved in a small amount of MeOH, diluted with chloroform, and chromatographed on a column packed with 150 g of silica gel. Elution with $CHCl_3$–MeOH (4:1) gave **4a** [20%; R_f 0.55; ^{31}P NMR (Me_2SO-d_6) δ 30.0] which was recrystallized as white crystals from MeOH–CH_2Cl_2: mp 218–220 °C dec; IR ($CHCl_3$) 1225 cm^{-1} (P=O); UV (MeOH) λ_{max} 259 nm (ε 1.4 × 10^4); ^1H NMR (Me_2SO-d_6) δ 8.47 (s 1 H), 8.23 (s, 1 H adenine ring protons), 7.43 (s, 2 H, NH_2), 6.27 (d, J = 3 Hz, 1 H, 1′-H), 3.9–6.1 (m, ribose protons), 3.1–3.8 (CH_2CH_2Cl); ^{13}C NMR (Me_2SO-d_6) δ 118.9, 139.6, 148.9, 152.7, and 156.2 (adenine carbons), 57.2, 61.3, 82.5, 87.9, and 88.5 (ribose carbons), 42.2 and 48.4 (CH_2CH_2Cl), no $^{31}P^{13}C$ couplings could be resolved. Compound **4b** was then eluted [20%, R_f 0.45; ^{31}P NMR (Me_2SO-d_6) δ 33.2], which was recrystallized from MeOH–Et_2O as white crystals: mp 231–233 °C dec; IR ($CHCl_3$) 1238, 1222 (P=O) cm^{-1}; UV (MeOH) λ_{max} 260 nm (ε 1.4 × 10^4); ^1H NMR (Me_2SO-d_6) δ 8.44 (s), 8.24 (s, adenine ring protons), 7.40 (s, 2 H NH_2), 6.24 (d, J = 3 Hz, 1 H, 1′-H), 3.9–6.1 (m, ribose protons), 3.2–3.9 (CH_2CH_2Cl); ^{13}C NMR (Me_2SO-d_6) 118.9, 139.7, 148.9, 152.7, and 155.9 (adenine carbons), 56.0, 61.4, 81.1, and 88.6 (ribose carbons), 42.2 and 48.1 (CH_2CH_2Cl), no $^{31}P^{13}C$ couplings could be resolved. Both isomers gave satisfactory elemental analyses.

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