mg (31%); λ_{max} [in mμ ($\epsilon \times 10^{-3}$)] 0.1 *N* HCl 278 (15.4), 0.1 *N* NaOH 276 (11.5); ν (in cm^{-1}) 3410 (OH), 3070, 2930, 2810 (CH), 1690 (C=O), 1615, 1445 (C=C, C=N), 1055 (P-O-C); M_{In} (pH 4.4) 0.68, (pH 7.2) 0.41.

Anal. Calcd for $C_{18}H_{21}Br_2N_4O_{12}P$: C, 31.97; H, 3.13; N, 8.29; P, 4.58. Found: C, 31.89; H, 3.23; N, 8.13; P, 4.39.

2′-Deoxy-5-iodouridylyl-(5′→5′)-2′-deoxy-5-iodouridine (6c). —To 711 mg (1.80 mmoles) of **4c** in 10 ml of anhydrous dioxane was added 231 mg (0.90 mmole) of *p*-nitrophenylphosphorodichloridate followed by 1.95 ml of dry pyridine. The solution was worked up as described above for **6b**. The thin layer chromatography purification of the product was also run in the same way using 3:1 $CHCl_3$–MeOH as the developing solvent to give a white solid: 188 mg (27%); λ_{max} [in mμ ($\epsilon \times 10^{-3}$)] 0.1 *N* HCl 287 (12.9), 0.1 *N* NaOH 280 (10.1); ν (in cm^{-1}) 3410 (OH), 3070, 2940, 2810 (CH), 1680 (C=O), 1610, 1445 (C=C, C=N), 1055 (P-O-C); M_{In} (pH 4.4) 0.62, (pH 7.2) 0.33.

Anal. Calcd for $C_{18}H_{21}I_2N_4O_{12}P$: C, 28.07; H, 2.75; N, 7.28; P, 4.02. Found: C, 28.05; H, 2.89; N, 7.08; P, 3.91.

1-(2,3,-*O*-Isopropylidene-β-D-ribofuranosyl)-6-azauracil (7).[6]—To 13.5 ml of 2,2-dimethoxypropane in 500 ml of dry acetone was added 18.4 ml of 70% $HClO_4$.[12] After 5 min, 10.0 g (40.8 mmoles) of 6-azauridine was added. The resulting mixture was stirred for 50 min at room temperature, neutralized by the addition of 21 ml of pyridine, and evaporated to dryness *in vacuo*. The residue was shaken with a mixture of 100 ml of $CHCl_3$ and 30 ml of H_2O. The aqueous layer was again extracted with 100 ml of $CHCl_3$. The $CHCl_3$ solutions were combined, dried ($MgSO_4$), and evaporated to dryness *in vacuo*. An acetone solution of the residue was also evaporated to dryness. This residue was dissolved in 25 ml of acetone. The addition of 150 ml of cyclohexane produced an oil that crystallized upon seeding; yield 5.45 g. The aqueous layer from above was diluted with enough concentrated NH_4OH to give pH 2 and again extracted with $CHCl_3$ (two 100-ml portions). The $CHCl_3$ extracts were worked up as described above. A second crop of crystalline material weighing 2.30 g was obtained: total yield 7.75 g (66.5%); mp 141–142° (lit.[6] 141–142°); λ_{max} [in mμ ($\epsilon \times 10^{-3}$)] 0.1 *N* HCl 260 (6.48), 0.1 *N* NaOH 254 (7.25); ν (in cm^{-1}) 3540 (OH), 3140, 3100, 2990, 2820 (CH), 1725 (C=O), 1670 (NH), 1585 (sh) (C=N).

6-Azauridylyl-(5′→5′)-6-azauridine (10).—To 268 mg (0.94 mmole) of **7** in 5 ml of anhydrous dioxane was added 132 mg (0.52 mmole) of *p*-nitrophenylphosphorodichloridate followed by 1 ml of dry pyridine. The mixture was stirred at room temperature for 2 days. Examination of an aliquot by thin layer chromatography indicated incomplete reaction. Therefore, another 10 mg of *p*-nitrophenylphosphorodichloridate was added. After another 24 hr, the solution was diluted with 50 ml of H_2O and extracted with three 150-ml portions of $CHCl_3$. The $CHCl_3$ was dried ($MgSO_4$) and evaporated *in vacuo*. The *p*-nitrophenylbis(2,3-*O*-isopropylidene-6-azauridine) 5′,5‴-phosphate (**8**) was thus obtained as a white, powdery glass; yield 262 mg (74%).

Without further purification, the glass in 10 ml of 0.3 *N* NaOH was left 2 hr at room temperature. The solution was neutralized by stirring it with Rexyn RG 50 (H) ion-exchange resin. The resin was removed by filtration, and the filtrate was washed several times with ether to remove *p*-nitrophenol. Evaporation of the aqueous solution to dryness *in vacuo* gave a gummy residue which became a white solid upon trituration in EtOH. The EtOH was removed by evaporation. The process was repeated several times giving 167 mg of bis(2,3-*O*-isopropylidene-6-azauridine) 5′,5‴-phosphate (**9**) as a white solid which was dissolved in 50 ml of H_2O. The solution (pH 2) was refluxed for 1.5 hr, then evaporated to dryness *in vacuo*. The residue was triturated in EtOH, and the EtOH was removed by evaporation. The process was repeated several times. The white, powdery glass was dried for 18 hr at 100° (0.07 mm) over P_2O_5: yield 144 mg (49%); λ_{max} [in mμ ($\epsilon \times 10^{-3}$)] 0.1 *N* HCl 261 (12.6), 0.1 *N* NaOH 253 (14.2); ν (in cm^{-1}) 3430 (broad) (OH), 1740 (sh) and 1690 (C=O), 1025 (P-O-C); M_{In} (pH 4.4) 0.80, (pH 7.2) 1.07.

The analytical sample was obtained by chromatography on a Mallinckrodt silica gel no. SG7 plate using BuOH–AcOH–H_2O (5:2:3) as the eluent. The band obtained was removed from the silica gel with hot MeOH. The solid was dried at 100° (0.07 mm) over P_2O_5 for 18 hr.

(12) J. A. Zderic, J. G. Moffatt, D. Kau, K. Gerzon, and W. E. Fitzgibbon, *J. Med. Chem.*, **8**, 275 (1965).

Anal. Calcd for $C_{16}H_{21}N_6O_{14}P \cdot 0.6H_2O$: C, 34.12; H, 3.97; N, 14.92; P, 5.50. Found: C, 34.37; H, 4.31; N, 14.83; P, 5.41.

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3′-Deoxynucleosides. V. 3′-Deoxy-2-fluoroadenosine

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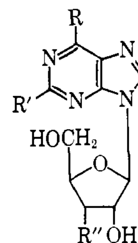
The effectiveness of 3′-deoxyadenosine (I) (cordycepin) as a cytotoxic agent is diminished by its rapid conversion into inactive 3′-deoxyinosine (II) through the action of adenosine deaminase.[1] On the other hand, 2-fluoroadenosine (III),[2] a potent cytotoxic



I, R = NH_2; R′ = H; R″ = H
II, R = OH; R′ = H; R″ = H
III, R = NH_2; R′ = F; R″ = OH
IV, R = NH_2; R′ = F; R″ = H
V, R = R′ = NH_2; R″ = H

agent,[2] is relatively inert to the action of adenosine deaminase.[3] It appeared that incorporation of a fluorine atom at the 2 position of 3′-deoxyadenosine would give a derivative, 3′-deoxy-2-fluoroadenosine (IV), which would be stable to adenosine deaminase and might retain the biological properties of I.[4] For the synthesis of IV, 2-amino-3′-deoxyadenosine (V)[5] was subjected to a modification of the procedure[2] used for the preparation of III, which involved the selective diazotization of the 2-amino group in the presence of fluoroboric acid. Crystalline 3′-deoxy-2-fluoroadenosine (IV) was obtained in 18% yield.

In the presence of calf intestine adenosine deaminase, IV was not measurably deaminated under conditions which accomplished complete deamination of adenosine. 3′-Deoxy-2-fluoroadenosine did not inhibit the deamina-

(1) H. Klenow, *Biochim. Biophys. Acta*, **76**, 347 (1963).
(2) (a) J. A. Montgomery and K. Hewson, *J. Am. Chem. Soc.*, **79**, 4559 (1957); (b) *ibid.*, **82**, 463 (1960).
(3) (a) O. P. Chilson and J. R. Fisher, *Arch. Biochem. Biophys.*, **102**, 77 (1963); H. P. Barr and G. I. Drummond, *Biochem. Biophys. Res. Commun.*, **24**, 584 (1966).
(4) S. Fredericksen, *Biochim. Biophys. Acta*, **76**, 366 (1963), has reported that cordycepin 1-oxide is resistant to enzymic deamination and that enzymic reduction provides for *in situ* release of cordycepin.
(5) E. Walton, F. W. Holly, G. E. Boxer, R. F. Nutt, and S. R. Jenkins, *J. Med. Chem.*, **8**, 659 (1965).

tion of adenosine at equimolar concentrations. The rate of deamination of 3′-deoxyadenosine was the same as that for adenosine.

Experimental Section

3′-Deoxy-2-fluoroadenosine.—A solution of 600 mg (2.26 mmoles) of 3′-deoxy-2-aminoadenosine (V)[5] in 6.8 ml of 48% aqueous HBF_4 at 0° was cooled to −10°, vigorously stirred, and 0.6 ml of a solution containing 300 mg of KNO_2 was added in 0.05-ml portions. The temperature was lowered to −30 to −40° and stirring was continued for 15 min. The pH of the reaction mixture was adjusted to 4 by adding 3.1 *N* KOH dropwise at −5 to −10°. The neutralization was continued to pH 6 at 0°. During the neutralization a total of 17 ml of BuOH-saturated water was added to facilitate stirring. After being stirred at 25° for 1 hr, the reaction solution was extracted with four 35-ml portions of BuOH-saturated water. The combined extracts were washed with four 15-ml portions of water-saturated BuOH. Concentration of the BuOH layer gave a residue (250 mg) which was purified by chromatography on 25 g of silica gel in Me_2CO–EtOH (99:1). Fractions containing only the desired product [R_f 0.5, tlc on silica in Me_2CO–EtOH (99:1)] were combined and concentrated. The residue (130 mg) was dissoved in 100 ml of EtOH, concentrated to 7 ml, and cooled. The crystalline 3′-deoxy-2-fluoroadenosine, mp 259–260°, so obtained amounted to 100 mg (17%). For analysis, a sample was washed (cold H_2O, EtOH, Et_2O) and dried at 50° for 4 hr at reduced pressure.

Anal. Calcd for $C_{10}H_{12}FN_5O_3$: C, 44.61; H, 4.49; N, 26.01; F, 7.06. Found: C, 44.93; H, 4.51; N, 26.08; F, 7.11.

3′-Deoxy-2-fluoroadenosine shows $[\alpha]_D$ −65°, $[\alpha]_{578}$ −67° (*c* 0.165, ethanol); $\lambda_{max}^{H_2O}$ [mμ ($\epsilon \times 10^{-3}$)] pH 1 262.5 (13.5), 267.5 (12.5); pH 7 262 (14.9), 268 (12.0); pH 13 261 (14.5), 267.5 (11.9).

In a larger preparation, starting with 5.1 g (19.2 mmoles) of V, the yield of IV was 900 mg (18%).

Action of Adenosine Deaminase on IV.—Individual solutions of IV and adenosine (8×10^{-4} *M*) in 3 ml of 0.05 *M* phosphate buffer (pH 7.5) were treated with equal amounts of calf intestine adenosine deaminase. The rate of deamination of the nucleosides was determined by the rate of the decrease in optical absorption at 265 mμ in a Cary spectrophotometer. At an enzyme concentration which brought about a change in optical density of 1.38 (equivalent to complete conversion to inosine) in 1 min with the adenosine sample, there was no measurable change in optical density with the solution containing 3′-deoxy-2-fluoroadenosine (IV) after 5 min. At this time the solution of IV was treated with an equimolar amount of adenosine. The latter was deaminated at the same rate (in 1 min) as was the adenosine in the absence of IV which indicated that IV is neither a substrate nor an inhibitor of the deaminase. In a separate experiment it was determined that 3′-deoxyadenosine was deaminated in about the same period of time as that required for adenosine.

Organic Disulfides and Related Substances. XXIV. Unsymmetrical *n*-Decylaminoethyl Disulfides as Antiradiation Drugs[1]

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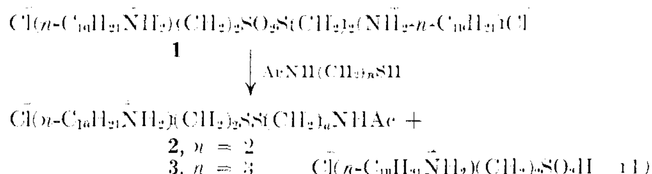
We reported earlier that 2-(*n*-decylamino)ethyl 2-(*n*-decylamino)ethanethiolsulfonate dihydrochloride (1) was rated "good" as an antiradiation drug at a dose level of 50 mg/kg or less.[2] This result has prompted us to examine the *n*-decylaminoethyl system further by preparing two model unsymmetrical disulfides for evaluation (**2** and **3**). Disulfides **2** and **3** were prepared as shown by eq 1.



3-Acetamidopropanethiol, not previously readily available, was prepared by the reaction of 3-aminopropanethiol with acetyl chloride as described for 2-acetamidoethanethiol.[3] Usually in reactions like that shown in eq 1 we have isolated the unsymmetrical disulfide by making the reaction mixture basic, quickly extracting with organic solvent, and then acidifying the extract. This procedure unfortunately was impossible with the *n*-decylaminoethyl derivatives because of the formation of emulsions. However, good results were obtained by simply chromatographing the crude reaction mixture on acid-washed alumina.

The results from testing of **2** and **3** as antiradiation drugs are shown in Table I.[4] The marked difference between the radioprotective activities of the ethyl compound **2** and its propyl homolog **3** appears to be real, since both were checked. This strongly suggests that differences which might be thought trivial may be quite significant. Extensive differences of this kind have often been observed in other series of medicinal agents.

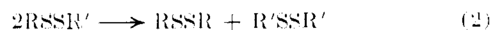
Table I

Protective Activities of Disulfides **2** and **3** in Mice against Ionizing Radiation[a]

Compd	Approx LD_{50}, mg/kg	Drug dose, mg/kg[b]	pH of prepn	Admind preirradiation, min	Survival (30 days), %	Act. rating
2	<50	<50	5.4	30	Insig	None to sl[c]
3	100	28	6	15	33	Good[c]
	100	56	6	15	67	

[a] 825 r (X-rays) or 1000 r (cobalt-60, γ rays). [b] Suspended in physiological saline solution containing 0.3% carboxymethylcellulose and 0.1% Tween 80. [c] On the basis of per cent survival: >45%, good; 25–44%, fair; 1–24%, slight; 0%, none.

It was also of interest to determine the resistance of **2** and **3** toward thermally induced disproportionation, as formulated in eq 2, since such values have been



$$2RSSR' \longrightarrow RSSR + R'SSR' \quad (2)$$

reported in earlier papers of this series for other classes of disulfides; possibly as such results continue to be obtained, correlations with antiradiation activity will emerge. Disulfide **2** disproportionated to the extent of 6% in 22 hr and of 22% in 72 hr (95% ethanol, 100°).

(1) (a) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DA-49-193-MD-2030. (b) Paper XXIII: L. Field and J. D. Buckman, *J. Org. Chem.*, in press.

(2) L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964).

(3) R. B. Martin, S. Lowey, E. L. Elson, and J. T. Edsall, *J. Am. Chem. Soc.*, **81**, 5089 (1959).

(4) Results were kindly provided by Drs. D. P. Jacobus, T. R. Sweeney, B. Alexander, and E. A. Steck of the Walter Reed Army Institute of Research. General procedures are described in ref 2. Both compounds, with the pH unadjusted, were administered intraperitoneally. The radiation was at a lethal level.