9-(2- and 3-Deoxy-β-D-*threo*-pentofuranosyl)adenine. The Epimers of 2′-Deoxyadenosine and 3′-Deoxyadenosine (Cordycepin)[1]

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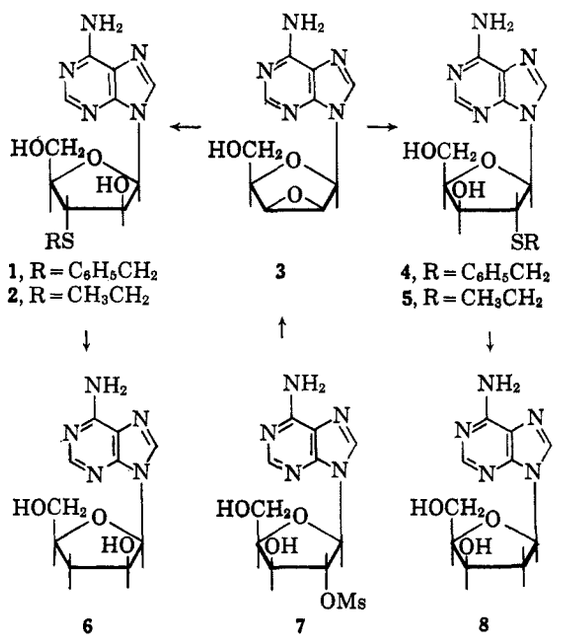
Ring opening of 9-(2,3-anhydro-β-D-lyxofuranosyl)adenine (**3**) with sodium benzyl mercaptide gave a mixture of the 3-benzylthio nucleoside (**1**) and the 2-benzylthio isomer (**4**) with **1** being the predominant product. Desulfurization of **1** and **4** gave good yields of 9-(3-deoxy-β-D-*threo*-pentofuranosyl)adenine (**6**) and 9-(2-deoxy-β-D-*threo*-pentofuranosyl)adenine (**8**), respectively. Attempts to isomerize the abundant 3-benzylthio nucleoside (**1**) to **4** were either impractical or completely unsuccessful, but they did illustrate some interesting aspects of episulfonium ion chemistry in the purine nucleoside area.

Subtle changes in the sugar portions of the nucleosides that occur in the nucleic acids have led to analogs that possess interesting and useful biological properties. Thus 9-(β-D-arabinofuranosyl)adenine[2] has antitumor properties[3] as does[4] 3′-deoxyadenosine (cordycepin).[5] We have been encouraged by these results to pursue the synthesis of other so-called "fraudulent" nucleosides; preparation of the epimer[6] of 2′-deoxyadenosine, 9-(2-deoxy-β-D-*threo*-pentofuranosyl)adenine (**8**) has been one of our main objectives. This manuscript reports the synthesis of **8** and of the companion 3′-deoxynucleoside (**6**) which is the epimer of cordycepin.

The first recorded synthesis of 2′-deoxyadenosine was accomplished by isomerization of a 3-ethylthio nucleoside to a 2-ethylthio nucleoside followed by desulfurization.[7] This same general route was visualized for the synthesis of **8**. Treatment of the 2,3-anhydrolyxoside (**3**)[2] with sodium ethyl mercaptide gave a fair yield of the crystalline 3-ethylthio nucleoside (**2**); there was paper chromatographic evidence for the presence of the 2-ethylthio isomer (**5**) in the mother liquors after isolation of **2**. Treatment of **3** (or more conveniently of **7**, the immediate precursor of **3**) with sodium benzylmercaptide gave a mixture of the 3-benzylthio (**1**) and 2-benzylthio (**4**) nucleosides in a ratio of about 5 to 1, respectively. The two isomers could be very conveniently separated by ion-exchange chromatography over Dowex 1 (OH), using the technique recently described by Dekker.[8] The reaction of **7** with sodium benzyl mercaptide was run at reflux for 15 min and at 0° for 2 hr. The total yield of **1** and **4** was essentially the same in both cases as was the ratio of **1** to **4**. The decided preponderances of ring opening at C-3 in the epoxide (**3**) stands in contrast to the situation with its glycosidic counterpart, methyl 2,3-anhydro-β-D-lyxofuranoside, where reaction with sodium benzyl mercaptide gave about 60% of the 2-benzylthio glycoside.[9]



The structures of **1**, **2**, and **4** were assigned on the basis of the nmr spectra of their acetates. The large difference in chemical shifts of the C-2′ protons between **1** and **2**, on the one hand, which have an acetate group at C-2′, and **4**, where there is an S-benzyl group is the significant spectral difference. Desulfurization of **1** and **2** gave the same product to afford additional evidence that they were related structurally. See Table I for the nmr data.

TABLE I

CHEMICAL SHIFTS[a] OF THE NUCLEOSIDE DI-O-ACETATES

Diacetyl derivative of	C-1′	C-2′	C-3′	C-4′	C-5′	Purine
1	3.64 d[b,c]	4.52 t	6.42 q	5.86 m	5.67 d	1.67 s, 2.06 s
2	3.47 d[c]	4.62 t	6.31 q	5.88 m	5.54 d	1.67 s, 2.02 s
4	3.90 d[d]	6.22 q	4.70 q	5.38 m	5.68 d	1.77 s, 2.09 s

[a] Given in τ units. The nmr spectra were run as solutions in deuteriochloroform using tetramethylsilane as an internal standard on the Varian HA-100 spectrometer. Decoupling experiments were used in the proton assignments. [b] s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. [c] $J_{1,2} \approx 5$ cps. [d] $J_{1,2} \approx 3$ cps.

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. PH-43-64-500. The opinions expressed in this paper are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center.

(2) W. W. Lee, A. Benitez, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **82**, 2648 (1960).

(3) J. J. Brink and G. A. LePage, *Cancer Res.*, **24**, 312 (1964).

(4) D. V. Jagger, N. M. Kredich, and A. J. Guarino, *ibid.*, **21**, 216 (1961).

(5) (a) W. W. Lee, A. Benitez, C. D. Anderson, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **83**, 1906 (1961); (b) E. A. Kaczka, N. R. Trenner, B. Arison, R. W. Walker, and K. Folkers, *Biochem. Biophys. Res. Commun.*, **14**, 456 (1964).

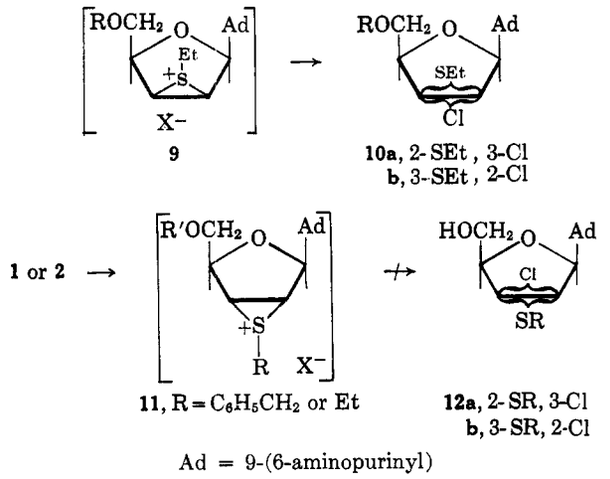
(6) In this manuscript the definition of epimer is that given in L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1961, p 91.

(7) C. D. Anderson, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **81**, 3967 (1959).

(8) C. A. Dekker, *ibid.*, **87**, 4027 (1965).

(9) G. Casini and L. Goodman, *ibid.*, **86**, 1427 (1964).

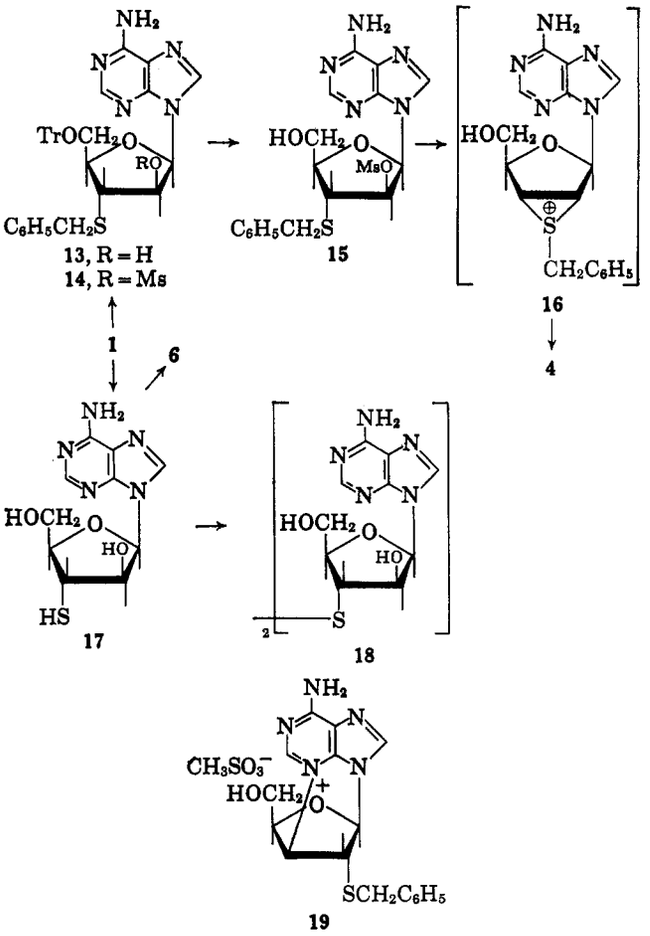
Isomerization of 9-(3-S-ethyl-3-thio-β-D-xylofuranosyl)adenine *via* the episulfonium ion intermediate **9** to the 2-ethylthio nucleoside **10a** had proceeded in good yield.[7] Similar thionyl chloride treatment of **2** or **1** was expected to proceed *via* the analogous episulfonium ion **11** to the 2-alkylthio nucleoside **12a**, but afforded intractable mixtures instead. Ethyl mercaptan was one of the products easily identified in the reaction of thionyl chloride with **2**, and dibenzyl disulfide was a major product from **1**. In one reaction 50% of the potential dibenzyl disulfide was isolated in addition to some recovered **1**.



Ad = 9-(6-aminopurinyl)

That inversion of the stereochemistry of the intermediate episulfonium ion from *lyxo* **9** to *ribo* **11** should so drastically affect the course of the isomerization reaction is surprising. One can speculate that the intermediate ion **11** eliminates the alkylthio moiety easily[10] because anchimeric assistance from the purine base is possible; on the other hand, the configuration of **9** does not favor such assistance.

The possibility existed that the acidic conditions of the thionyl chloride reaction were responsible for the instability of the episulfonium ion intermediate. A second route to such an intermediate ion was sought that would utilize a sulfonate ester as the leaving group. The 3-benzylthio nucleoside (**1**) was treated with trityl chloride in pyridine to give a mixture of three nucleosides, two of which were N-trityl derivatives and from which the desired 5-O-trityl compound (**13**) could be easily separated. Reaction of **13** with methanesulfonyl chloride in pyridine afforded **14** as a foam that was obtained in analytical purity. Treatment of **14** with dry hydrogen chloride in chloroform cleaved the trityl group (compound **14** proved not to be suitable for the isomerization experiments) and provided crystalline **15**. Reaction of **15** with sodium acetate in refluxing 95% aqueous 2-methoxyethanol, the conditions that had been useful in the 2′-deoxyadenosine work,[7] gave a very poor material balance of products containing the adenine moiety. A low yield of the desired 2-benzylthio nucleoside (**4**) was isolated, thus demonstrating the intervention of the episulfonium ion intermediate (**16**). Some adenine was present in the



reaction product. A small amount of a very water-soluble solid that had an ultraviolet maximum at 293 mμ at pH 1 was isolated by ion-exchange chromatography. This ultraviolet shift from the characteristic adenine spectrum resembles that seen in the formation of purine 3,5′-cyclonucleosides[11,12] and is in complete accord with assignment of the 3,3′-cyclonucleoside structure (**19**) to this solid; elemental analyses also were those predicted for **19**. A similar ultraviolet spectrum was noted recently for the reaction products from 9-(2,3-anhydro-5-deoxy-β-D-ribofuranosyl)adenine where a similar 3,3′-cyclonucleoside might be anticipated.[13]

Clearly the isomerization of **1** or **2** or **4** or **5** *via* an episulfonium ion intermediate like **11** or **16** is not practical and it seems logical to ascribe this difficulty to instability of the episulfonium ion intermediates. The isolation of **19** lends credence to the idea that neighboring-group participation by the purine base is largely responsible for this instability. In the episulfonium ions that have the lyxose configuration,[7] the purine base is not disposed to form a cyclonucleoside, and the isomerizations from C-3 to C-2 proceed smoothly.

The best source of the 2-benzylthio nucleoside (**4**) was that recovered from the opening of **3**. Desulfurization of **4** with commercial sponge nickel catalyst[14] was accomplished in N,N-dimethylformamide at 90–

(10) If one can assume an analogy between episulfonium ions and episulfides, then the ready elimination of the alkylthio moiety can be explained. The elimination of the sulfur atom in reactions where episulfides are assumed intermediates is well documented: (a) C. C. J. Culvenor, W. Davies, and N. S. Heath, *J. Chem. Soc.*, 278 (1949); (b) T. C. Owen, C. L. Gladys, and L. Field, *ibid.*, 656 (1962).

(11) V. M. Clark, A. R. Todd, and J. Zussman, *ibid.*, 2952 (1951).

(12) B. R. Baker and J. P. Joseph, *J. Am. Chem. Soc.*, **77**, 15 (1955).

(13) E. J. Reist, V. J. Bartuska, D. F. Calkins, and L. Goodman, *J. Org. Chem.*, **30**, 3401 (1965).

(14) Sponge nickel catalyst, W. R. Grace and Co., Davison Chemical Division, Baltimore, Md.

100° to give a good yield of **8**. The desulfurization was much more rapid and gave better yields when heat was supplied by an infrared lamp rather than by an oil bath. We can only suggest that the infrared light was better absorbed by the black surface of the catalyst to give a higher effective temperature than in the case of heating with the oil bath. It is also possible that a higher surface temperature may assist in desorbing the product **8**. The 3-substituted nucleosides (**1** and **2**) were desulfurized similarly to give **6**; the benzylthio compound (**1**) was more easily reduced than was the ethylthio nucleoside (**2**).

Treatment of **1** with sodium and liquid ammonia yielded the 3-mercaptoarabinoside (**17**). Compound **17** was easily oxidized to the disulfide (**18**) which was the directly isolated product of cleavage of **2** unless special precautions were taken during the isolation of **17**. Reaction of **17** with trimethyl phosphite using azobisisobutyronitrile[15] gave the 3′-deoxy nucleoside (**6**) according to paper chromatography; this represents another technique of desulfurization that may have advantages in nucleoside work.

Experimental Section[16]

9-(3-S-Benzyl-3-thio-β-D-arabinofuranosyl)adenine (1).—To a solution of 2.27 g (42 mmoles) of sodium methoxide in 150 ml of methanol was added 7.0 g (18.2 mmoles) of the 2-O-mesyl nucleoside **7**. The reaction mixture was protected from moisture and heated at reflux for 10 min. To this hot solution was added 8.4 g (0.16 mole) of sodium methoxide and 24.5 ml (26 g, 0.21 moles) of benzyl mercaptan in 165 ml of methanol. The mixture was heated for 10 min more, allowed to cool with stirring for 2 hr, then treated with 105 g of Amberlite IR 50 (H) resin (prewashed with methanol), and stirred until pH 7 was attained. The resin was collected by filtration and washed with 280 ml of methanol, and then 150 ml of warm DMF. The combined filtrate and washes were evaporated at 50°. The residue was stirred in a mixture of 175 ml of water and 400 ml of ether. The crystalline material at the interface was collected and dried to afford 4.48 g (66%) of **1**, mp 196–197°, homogeneous by thin layer chromatography (TF). An additional 3% of **1** (total yield, 69%) was recovered during the isolation of the 2-benzylthio nucleoside **4**, described below. A sample from an earlier run was recrystallized from ethanol to afford the analytical sample of **1**: mp 199–199.5°; $\lambda_{max}^{pH\ 1}$ 258 mμ (ε 15,300), $\lambda_{max}^{pH\ 7}$ 260 (ε 15,700), $\lambda_{max}^{pH\ 13}$ 260 mμ (ε 16,200); it moved as a single spot in solvents A, B, and D, with R_{Ad} 1.66, 0.82, and 1.37, respectively.

Anal. Calcd for $C_{17}H_{19}N_5O_3S$: C, 54.7; H, 5.13; N, 18.8. Found: C, 54.4; H, 5.38; N, 18.7.

The rotation was determined on another similarly recrystallized sample of **1**, mp 197.5–198.0, $[\alpha]_{589}^{22}$ +27° (*c* 1, DMF).

Anal. Found: N, 18.7.

The ether and water washes from above were evaporated to dryness and the 1.43 g of residue was used below to obtain the 2-benzylthio isomer **4**.

9-(2-S-Benzyl-2-thio-β-D-xylofuranosyl)adenine (4).—The 1.43-g residue from the ether and water washes above were redissolved in water, washed with 200 ml of toluene (this removed dibenzyl disulfide, but not any nucleoside according to chromatography results). The aqueous phase was chromatographed on a column of Dowex 1-2 (OH) (35 g/100 mg of mixture).[8] Elution with 60% aqueous methanol afforded 861 mg (12.7%) of **4** as an amorphous, hydroscopic solid, homogeneous by chromatography. Elution with absolute methanol afforded the additional 3% of **1**.

Some of the amorphous **4** was dissolved in methanol and precipitated with ether to afford the analytical sample of **4**: $[\alpha]^{22}D$ +20° (*c* 0.50, DMF); $\lambda_{max}^{pH\ 1}$ 258 mμ (ε 12,600), $\lambda_{max}^{pH\ 7}$ 261 mμ (ε 12,800), $\lambda_{max}^{pH\ 13}$ 261 mμ (ε 13,200). (The low ε values result from hydration during handling.) It moved as a single spot in solvents B and E with R_{Ad} 1.34 and 1.30, respectively.

Anal. Calcd for $C_{17}H_{19}N_5O_3S$: C, 54.7; H, 5.13; N, 18.8. Found: C, 54.8; H, 5.12; N, 18.4.

9-(3-S-Ethyl-3-thio-β-D-arabinofuranosyl)adenine (2).—A solution of 2.75 g (7.95 mmoles) of the mesylate **7** was treated with sodium methoxide and ethanethiol by the procedure used to prepare **1** to afford, at the water–ether interface, 1.44 g (59%) of crystalline **2**, mp 207–208°, containing only a trace contaminant: R_{Ad} 1.22 in solvent A, R_{Ad} 1.12 and 1.40 (trace) in solvent B. The aqueous phase apparently contained some **2** (R_{Ad} 1.12) and some **5** (R_{Ad} 1.33) for it exhibited these two spots of almost equal intensity in solvents B. Two recrystallizations from ethanol afforded the analytical sample of **2** as white crystals: mp 209.5–210.0°; $[\alpha]_{589}^{24}$ −11° (*c* 1, DMF); $\lambda_{max}^{pH\ 1}$ 257 mμ (ε 14,900), $\lambda_{max}^{pH\ 7}$ 260 mμ (ε 15,000), $\lambda_{max}^{pH\ 13}$ 260 mμ (ε 14,900); it moved as one spot in solvents A, B, and E with R_{Ad} 1.34, 1.23, and 1.23, respectively.

Anal. Calcd for $C_{12}H_{17}N_5O_3S$: C, 46.3; H, 5.50; N, 22.5; S, 10.3. Found: C, 46.2; H, 5.60; N, 22.3; S, 10.2.

9-(3-Thio-β-D-arabinofuranosyl)adenine (17).—To a solution of 0.95 g (41 mg-atoms) of sodium in 50 ml of ammonia at about −70° was added 2.37 g (6.4 mmoles) of the 3-benzylthio nucleoside **1**. The reaction mixture was stirred for 45 min at −70° and evaporated to dryness with a stream of nitrogen. The residue was treated with a solution of 55 ml of methanol and 5 ml of acetic acid and to this was added 5 g of mercuric acetate in 60 ml of water. The precipitate was collected, triturated with about 150 ml of water, washed with methanol, and dried to afford 1.52 g of mercuric salt. The salt was suspended in 150 ml of methanol containing 2% mercaptoethanol, treated with a stream of hydrogen sulfide for 30 min, then filtered. The filtrate and methanol washes were combined, concentrated to about 50 ml, and stored in a refrigerator overnight. The white crystals were collected and dried to afford 0.49 g (56%) of **17** as a solvate: mp 228.5–229.5°; SH found by iodine titration,[17] 97% of theory.

Anal. Calcd for $C_{10}H_{13}N_5O_3S \cdot CH_3OH$: N, 22.2. Found: N, 22.0.

A sample from another run appeared to be a different crystal form. It had mp 232–233°, λ_{max}^{Nujol} 3.6–4.3 (SH), free of absorption at 13.6 and 14.3 (phenyl). It moved as one spot in solvent D with R_{Ad} 1.05 and in F R_{Ad} 0.86 (elongated); SH found by iodine titration was 105% of theory for **17** as a methanol solvate.

Anal. Calcd for $C_{10}H_{13}N_5O_3S \cdot 0.5CH_3OH$: C, 42.20; H, 5.05; N, 23.4; S, 10.7. Found: C, 42.3; H, 4.65; N, 23.2; S, 10.9.

Disulfide of 9-(3-Thio-β-D-arabinofuranosyl)adenine (18).—The 3-benzylthio nucleoside **1** (1.00 g) was treated with sodium and ammonia as in the preparation of **17**. After removal of the ammonia, the residue and 3.0 g of Amberlite IRC 50 resin in 50 ml of methanol was stirred for 3 hr, the resin was removed, and the filtrate was treated with charcoal, partially evaporated, and chilled to afford 0.41 g (54%) of the disulfide **13**, mp 173–174°; it moved as two spots in solvents A (R_{Ad} 0.45 and 0.73), B (R_{Ad} 0.21 and 0.57), D (R_{Ad} 0.94 and 1.07), and F (R_{Ad} 0.40 and 0.75). By iodine titration, it was devoid of mercaptan. The slower moving spots suggest some contamination with **17** that apparently was below the limit of detection of the titration.

Anal. Calcd for $C_{20}H_{24}N_{10}O_6S_2 \cdot CH_3OH$: C, 42.3; H, 4.74; N, 23.6; S, 10.8. Found: C, 41.3, 41.8; H, 4.56, 5.30; N, 23.4; S, 10.5.

(15) C. Walling and R. Rabinowitz, *J. Am. Chem. Soc.*, **81**, 1243 (1959).

(16) Melting points are determined on a Fisher-Johns apparatus and are uncorrected. Paper chromatography was done by the descending technique on Whatman No. 1 paper. Adenine was used as a standard; the spots were located relative to R_{Ad} 1.00. The solvent systems follow: (A) 1-butanol saturated with water; (B) 5% aqueous disodium hydrogen phosphate, pH 8.9; (C) 1-butanol–acetic acid–water (4:1:5); (D) 1-butanol–acetic acid–water (5:2:3); (E) water; (F) t-butyl alcohol–2-butanone–formic acid–water (4:3:1.5:1.5); (G) benzene–water–methanol (2:1:6) on Schleicher and Schuell No. 2496 acetylated paper; (H) same as G except on Whatman No. 1 paper. Thin layer chromatography was done on silica gel HF plates with these solvents: (TA) ethyl acetate, (TB) chloroform, (TD) methanol–ethyl acetate (1:10), (TE) methanol–ethyl acetate (1:4), (TF) methanol. In the one case where alumina plates were used the solvent system (TC) was ethyl acetate. The spots are located relative to the front, R_f 1.00. The spots were detected in all systems by ultraviolet light. Anhydrous magnesium sulfate was used as drying agent. All evaporations were performed under reduced pressure, either water aspirator or vacuum pump, with the bath temperature generally under 50°. N,N-Dimethylformamide is designated as DMF. Skellysolve B is a petroleum fraction, essentially *n*-hexane, bp 62–70°.

(17) S. Siggia, "Quantitative Organic Analysis by Functional Groups," 3rd ed, John Wiley and Sons, Inc., New York, N. Y., 1963, p 578.

9-(2,5-Di-O-acetyl-3-S-benzyl-3-thio-β-D-arabinofuranosyl)-adenine.—A solution of 0.20 g (0.54 mmole) of the 3-benzylthio nucleoside **1**, 5 ml of pyridine, and 0.20 ml (2 mmoles) of acetic anhydride was left overnight at room temperature, then evaporated to dryness. The residue was dissolved in methylene chloride, and the solution was washed with water, saturated sodium bicarbonate solution, and water, dried, and evaporated to dryness to leave 0.23 g (94%) of the di-O-acetyl derivative of **1**: mp 50–60°; $[\alpha]_{589}^{22}$ +23° (*c* 1, DMF); λ_{max}^{Nujol} 5.72 (C=O), 8.15 μ (broad, COC of acetate); λ_{589}^{MeOH} 259 mμ (ε 14,600); it moved as a single spot in solvents G, A, and B with R_{Ad} 0.49, 1.80, and 0.81 (broad), respectively.

Anal. Calcd for $C_{21}H_{23}N_5O_5S$: C, 55.1; H, 5.06. Found: C, 54.8; H, 5.19.

The di-O-acetate of **2** was prepared as above; it had mp 82–84° and $[\alpha]^{21}D$ −23° (*c* 0.5, DMF).

Anal. Calcd for $C_{16}H_{21}N_5O_5S$: C, 48.5; H, 5.35. Found: C, 48.3; H, 5.25.

The di-O-acetate of **4** was prepared as above and was a chromatographically homogeneous material; no other analytical data were obtained.

9-(3-S-Benzyl-3-thio-5-O-trityl-β-D-arabinofuranosyl)adenine (13).—A mixture of 0.47 g (1.26 mmoles) of the 3-benzylthio nucleoside **1**, 6 ml of pyridine, 6 ml of DMF, and 25 ml of benzene was distilled at 50° (15 mm) to remove most of the benzene. The mixture was treated with 0.53 g (1.9 mmoles) of trityl chloride, then heated at 40° for 20 hr while protected from moisture. The mixture was evaporated to dryness at 45–50°, toluene was added and removed by evaporation several times to remove traces of DMF. The residue was partitioned between 75 ml of chloroform and 100 ml of water. The chloroform solution was dried and evaporated to leave 1.0 g of crude product. This was dissolved in 40 ml of ether. The addition of 120 ml of Skellysolve B precipitated 0.47 g (61%) of **13**: mp 108–110°; $[\alpha]_{509}^{22}$ +21° (*c* 1.1, DMF); λ_{max}^{MeOH} 266 mμ (ε 14,900); it moved as one spot in solvents H, A, and D with R_{Ad} 1.26 (long), 1.84, and 1.47, respectively. Product of the same melting point from an earlier run was analyzed.

Anal. Calcd for $C_{36}H_{33}N_5O_3S$: C, 70.2; H, 5.40; N, 11.4. Found: C, 70.5; H, 5.42; N, 11.3.

The mother liquors from several runs, from which **13** had been removed, were evaporated to afford 1.0 g of gum. This was dissolved in chloroform and chromatographed on two thick layer (1.25 mm) silica gel plates, 20 × 20 cm, developing with ethyl acetate. The band with R_f 0.20 was extracted with acetone to afford 280 mg of 5′-O-trityl nucleoside **13**. The material beyond R_f 0.20 was extracted with acetone to afford 540 mg of material. A 400-mg portion of this was again chromatographed, developing with 15% ethyl acetate in chloroform. The band of R_f 0.57 was extracted to afford 180 mg of an amorphous ditrityl nucleoside, probably the N^6-5′-O-ditrityl derivative of **1**.

Anal. Calcd for $C_{55}H_{47}N_5O_3S$: C, 77.0; H, 5.57; N, 8.16. Found: C, 77.2; H, 5.46; N, 7.80.

The slower moving band of R_f 0.19 was extracted with acetone to afford 90 mg of white, amorphous material that is assumed to be the N^6-trityl derivative of **1**.

Anal. Calcd for $C_{36}H_{33}N_5O_3S$: C, 70.2; H, 5.40; N, 11.4. Found: C, 70.4; H, 5.13; N, 10.1.

9-(3-S-Benzyl-2-O-methylsulfonyl-3-thio-5-O-trityl-β-D-arabinofuranosyl)adenine (14).—A solution of 0.50 g (0.8 mmole) of crude 5-O-trityl nucleoside **13**, 0.22 ml (2.9 mmoles) of methanesulfonyl chloride, and 7.0 ml of pyridine was stirred at room temperature for 40 hr, treated with 0.3 ml of water, stirred for another 60 min, then diluted with 100 ml of water and extracted with two 125-ml portions of chloroform. The chloroform solution was dried and evaporated, and evaporated with toluene several times to remove all traces of pyridine, leaving as a tan foam 0.54 g (96%) of **14** containing some minor contaminants.

For analysis, 100 mg of the above was chromatographed on a thick layer silica gel plate, developing with ethyl acetate. The band with R_f 0.65 was eluted with acetone to afford 56 mg of **14** as a white foam: R_f 0.65, 0.09, and 0.22 in solvents TA, TB, and TC, respectively.

Anal. Calcd for $C_{37}H_{35}N_5O_5S_2$: C, 64.3; H, 5.09; S, 9.27. Found: C, 64.0; H, 5.15; S, 9.01.

In later experiments it was found that the use of chromatographed **13** afforded much purer **14** that could be used directly in the next step.

9-(3-S-Benzyl-2-O-methylsulfonyl-3-thio-β-D-arabinofuranosyl)adenine (15).—A solution of 37 ml of dry chloroform saturated with dry hydrogen chloride was added to a stirred solution of 0.75 g (1.08 mmoles) of the trityl nucleoside **14** in 37 ml of dry chloroform. A precipitate formed immediately. The mixture was stirred for 1 min, then evaporated at 40°. The residue was evaporated with several portions of chloroform to remove all traces of hydrogen chloride. The residue was triturated with toluene to afford 0.45 g (94%) of amorphous **15**, R_f 0.51 in solvent TD; it was suitable for use in the next step.

Product from an earlier run was crystallized from methanol to afford 19% yield of **15**: mp 165–166°; $[\alpha]_{589}^{22}$ +12° (*c* 0.7, DMF); $\lambda_{max}^{pH\ 1}$ 257 mμ (ε 15,400), $\lambda_{max}^{pH\ 7}$ 258 mμ (ε 15,300), $\lambda_{max}^{pH\ 13}$ 258 mμ (ε 15,300); it moved as one spot R_f 0.64 in solvent TD and R_{Ad} 1.70 and 0.98 in solvents A and B, respectively.

Anal. Calcd for $C_{18}H_{21}N_5O_5S_2$: C, 47.9; H, 4.81; N, 15.5; S, 14.2. Found: C, 47.7; H, 4.65; N, 15.6; S, 14.3.

A second crop (21% yield) of **15** was obtained, mp 174–175°, which was identical with the first crop in ultraviolet spectrum, rotation, chromatographic behavior, nitrogen analysis, and nmr spectrum.

Reaction of 15 with Sodium Acetate in Aqueous 2-Methoxyethanol.—A mixture of 250 mg of **15**, 400 mg of anhydrous sodium acetate, and 5 ml of 2-methoxyethanol containing 5% water was heated at reflux for 3.25 hr, then the mixture was evaporated to dryness. The residue was dissolved in 30 ml of water and extracted with three 100-ml portions of ethyl acetate which were dried and evaporated to afford 71 mg of amber gum, R_{Ad} 0.98 and 1.30 in solvent E (R_{Ad} 0.98, 1.34, and 0.42 for **15**, **4**, and **1**, respectively). A 56-mg portion of the 71 mg was chromatographed on a 16 × 280 mm column containing 25 g of Dowex 1 (OH) to afford 7.1 mg of the 2-benzylthio nucleoside **4** (eluted with 30% aqueous methanol) and 0.1 mg of the 3-benzylthio nucleoside **1** (eluted with methanol). The remainder of the material was not elutable. In another run, a gum similar to the above 71 mg was purified by thick layer chromatography on silica gel. The plate was developed with ethyl acetate containing 5% methanol to afford a 12% yield of the 2-benzylthio nucleoside **4**, containing a small amount of the 3-benzylthio nucleoside **1**, according to paper chromatography data.

The 30 ml of water solution from the above described experiment was made up to 100 ml and an aliquot was taken for ultraviolet spectral analysis. The water solution was then charged on a 1.8 × 35 cm column of 100 g of Dowex 1 (Cl) resin, 200–400 mesh (thoroughly prewashed with water) and eluted with water to afford a fast fraction of 300 mg containing salts and the material absorbing at 293 mμ, several trace contaminants, and the slow fraction of 8.0 mg of adenine.[18] The 300-mg fast fraction was triturated with 20 ml of methanol to afford some insoluble inorganic salts with no ultraviolet absorption. The methanol solution was diluted with ethyl acetate to precipitate some more inorganic salts without ultraviolet absorption. Evaporation of the organic solution afforded 15 mg of **19**: λ_{max}^{Nujol} 8.5 (RSO_3) 9.44, 9.68 μ (shoulder) (OH, RSO_3);[19] $\lambda_{max}^{pH\ 1}$ 293 mμ (ε 13,300); $\lambda_{max}^{pH\ 7}$ 293 (ε 13,100); $\lambda_{max}^{pH\ 13}$ 275 (ε 9000) and 334 (ε 3200). It moved as a single spot in solvent B with R_{Ad} 1.75.

Anal. Calcd for $(C_{17}H_{18}N_5O_2S)^+(CH_3SO_3^-)$: C, 47.9; H, 4.69; N, 15.5. Found: C, 47.3; H, 4.90; N, 15.6.

9-(2-Deoxy-β-D-*threo*-pentofuranosyl)adenine (8).—A mixture of 200 mg (0.73 mmole) of the 2-benzylthio nucleoside **4**, 3.0 g of sponge nickel catalyst[14] (prewashed with DMF) and 50 ml of DMF was stirred under a hydrogen atmosphere and heated at 100–102° with an infrared lamp for 3 hr, at which time the desulfurization was complete according to thin layer chromatography. The sponge nickel was collected and washed with 250 ml of hot DMF. The filtrate and wash were combined and evaporated to afford 99.5 mg (74%) of **8**, mp 210–212°, homogeneous by chromatography. Two recrystallizations from methanol afforded the analytical sample: mp 218.9–219.5°; $[\alpha]_{589}^{24}$ −76° (*c* 1, DMF); $\lambda_{max}^{pH\ 1}$ 258 mμ (ε 14,200), $\lambda_{max}^{pH\ 7}$ 259 mμ (ε 15,000),

(18) Trial experiments had demonstrated that the Dowex 1 (chloride form) column gave good separation and high recovery with a known mixture of the 3,5′-cyclonucleoside of adenosine (97% recovery) and adenine (93% recovery).

(19) Sulfonic acids and salts are suggested as absorbing in the ranges 1260–1150 (7.94–8.70 μ) and 1060–1040 cm^{-1} (9.40–9.61 μ) according to L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958, p 364.

$\lambda_{max}^{pH\ 13}$ 259 mμ (ε 15,700); it moved as a single spot with R_f 0.21 in solvent TE (R_f 0.80 for **4**).

Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.8; H, 5.22; N, 27.9. Found: C, 48.0; H, 5.28; N, 28.1.

9-(3-Deoxy-β-D-*threo*-pentofuranosyl)adenine (6).—By the procedure used for preparing **8**, 1.00 g of the 3-benzylthio nucleoside **1** was converted, after 8 hr reaction time, to afford 0.45 g (67%) of **6**, mp 190–194°, homogeneous by chromatography. One recrystallization from methanol afforded 0.30 (50%) of **6**, mp 195–196°, identical with the analytical sample, obtained by another recrystallization from methanol of **6**: mp 195–196°; $[\alpha]_{589}^{22}$ −27° (*c* 1, DMF); $\lambda_{max}^{pH\ 1}$ 258 mμ (ε 14,600), $\lambda_{max}^{pH\ 7}$ 260 mμ (ε 15,800), $\lambda_{max}^{pH\ 13}$ 260 mμ (ε 15,100); it moved as one spot in solvents G, A, and B, with R_{Ad} 0.62, 0.71, and 1.15, respectively. It had R_f 0.68 in solvent TF (**1** had R_f 0.81).

Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.8; H, 5.22; N, 27.9. Found: C, 47.9; H, 4.94; N, 27.9.

The ratio of sponge nickel catalyst to substrate used above was 15. Satisfactory results were obtained with the ratio of 10. Reduction of the ratio to 5 resulted in incomplete desulfurization under identical conditions. In a later run using 0.20 g of **1** with a catalyst ratio of 10, aliquots were removed at intervals and examined by chromatography. Desulfurization was complete in about 2 hr. When an oil bath was used as the heat source, the desulfurization was not complete after 8 hr. When an oil bath was the heat source, and 2,2′-azobisisobutyronitrile was added as a free-radical source, the reaction was only one-third complete after 3.5 hr.

Two desulfurizations at 50–75° for 2.5 hr, comparing the effect of an infrared lamp and an ultraviolet lamp (using quartz apparatus), showed that the infrared lamp reaction was about 50% complete; the other one was about 25% complete, according to qualitative results by thin layer chromatography.

Two desulfurizations at 100° using an infrared lamp for heat and a catalyst–substrate ratio of 20 demonstrated that the 3-benzylthio nucleoside **1** was completely desulfurized after 2 hr, but the 3-ethylthio nucleoside **2** was only about 67% reduced after 8 hr.

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Cleavage of β-Ketonic Esters by the Action of Metal Iodides. I. The Reactions with Acetoacetic Ester and Its Mono- and Dimethyl Derivatives

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Acetoacetic ester and its α-methylated derivatives were found to undergo decomposition under the influence of metal iodides, notably iodides of sodium and calcium, at temperatures ranging from 130 to 170°. The key products with acetoacetic ester and its mono- and dimethylated derivatives so far identified were carbon dioxide, acetone and its homologs, ethyl iodide, ethyl alcohol, and the ethyl ester of acetic acid and its homologs. The production of a ketone and ethyl acetate or its homolog from a β-ketonic ester revealed that ketonic cleavage and acid cleavage had taken place simultaneously, although the former pathway predominated. With the use of calcium iodide and in the presence of a hydroxylic solvent, the reaction of an α-substituted β-ketonic ester afforded the corresponding ketone in a yield as high as 65%. The reaction is useful for the production of ketones from β-ketonic esters, particularly those that are resistant to ketonic cleavage by ordinary means. The action of sodium iodide and that of calcium iodide differed from each other in several respects. Mechanisms are formulated that account for the difference. The effects of hydroxylic solvents are discussed.

In a series of investigations on the reaction between disodiosuccinosuccinic ester and ethyl iodoacetate[1,2] the senior author and his collaborators found that evolution of carbon dioxide and production of volatile substances comprising ethyl alcohol and ethyl iodide took place when the reaction mixture was held at a temperature slightly above 150°. The main products consisted of two geometric isomers of diethyl 1,4-dicarbethoxycyclohexane-2,5-dione-1,4-bis(acetate). These latter substances, when heated with sodium iodide at 150–160°, decomposed with evolution of carbon dioxide. With sodium bromide in place of sodium iodide, the reaction took place only with difficulty. With sodium chloride, the reaction did not occur at all.

To test whether the decomposition under the influence of sodium iodide might be specific for β-ketonic esters with a carbalkoxy group joined to a tertiary α-carbon atom, a number of β-ketonic esters, including acetoacetic ester and its mono- and dimethyl derivatives, were investigated. The reaction with unsubstituted acetoacetic ester took place more readily than that with its mono- and dimethyl derivatives.

More extensive investigations have since been undertaken on the reactions of these β-ketonic esters toward sodium iodide under varying conditions. In one set of experiments acetoacetic ester was heated with an equimolar amount of sodium iodide. At 150°, there was a copious evolution of carbon dioxide and the distillate proved to be mainly acetone (24% yield), ethyl alcohol, ethyl acetate, and ethyl iodide. Water, ethyl ether, methyl *n*-propyl ketone, and mesityl oxide were found in minor amounts.

The production of acetone and carbon dioxide from acetoacetic ester showed that ketonic cleavage had taken place, and the formation of ethyl iodide was suggestive of mechanisms 1–3. The decarboxylation

$$CH_3COCH_2COOEt + I^- \longrightarrow \underset{\text{I}}{CH_3COCH_2COO^-} + EtI \quad (1)$$

$$\underset{\text{I}}{CH_3COCH_2COO^-} \longrightarrow \underset{\text{II}}{(CH_3COCH_2)^-} + CO_2 \quad (2)$$

$$\underset{\text{II}}{(CH_3COCH_2)^-} + CH_3COCH_2COOEt \longrightarrow CH_3COCH_3 + \underset{\text{III}}{(CH_3COCHCOOEt)^-} \quad (3)$$

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