Utilizing other ester groups, for example, the trichloroethyl or *p*-nitrobenzyl, in most cases resulted in inseparable mixtures. However, rearrangement of the penicillin sulfoxides **12** under milder conditions, followed by partial ozonization of the reaction mixture, resulted in selective oxidation of the cephem and dihydrocephem compounds. Subsequent silica gel chromatography gave pure **13**, thus providing a route to the various 2-β-acyloxymethylpenicillin derivatives (**14**).

Experimental Section

The ozone oxidations were run using a Welsbach model T-23 ozonizer with an output of 1.18 mm O_3/min or 3.4 g/hr. No attempt was made to monitor the uptake of ozone, excess ozone being employed, and in general on completion of the reaction the solvent was evaporated to give the oxidized product.

6-Aminopenicillanic Acid Sulfoxide.—Into a cooled (5°) slurry of 6-APA (2.16 g, 1.0 mmol) in 200 ml of water was bubbled ozone for 3.0 hr, complete solution being obtained after 2.5 hr. Lyophilization of the aqueous solution gave 2.26 g (98%) of pale yellow sulfoxide: ir (mull) 1790 (β-lactam) and 1025, 1007 cm^{-1} (S→O).

Anal. Calcd for $C_8H_{12}N_2O_4S$: C, 41.38; H, 5.21; N, 12.07. Found: C, 41.10; H, 5.34; N, 12.27.

Phenoxyacetamidopenicillanic Acid Sulfoxide.—Into a cooled (0–5°) solution of phenoxyacetamidopenicillanic acid (3.50 g, 0.01 mol) in 100 ml of 1/1 acetone–water was bubbled ozone for 2.5 hr. Evaporation of acetone from the slurry gave, after filtration, 1.80 g (49.18%) of crystalline β-sulfoxide: ir ($CHCl_3$) 1800 (β-lactam) and 1020, 1035, 1065, 1080 cm^{-1} (S→O); nmr (DMSO-d_6) δ 1.22 (s, 3, α-Me), 1.62 (s, 3, β-Me), 4.45 (s, 1, H_3), 5.47 (d, 1, J = 4 Hz, H_5), 5.95 (q, 1, J = 4, 9 Hz, H_6).

Anal. Calcd for $C_{16}H_{18}N_2O_6S$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.30; H, 5.02; N, 7.64.

Lyophilization of the aqueous solution gave 1.87 g (51.09%) of noncrystalline α-sulfoxide: ir ($CHCl_3$) 1796 (β-lactam) and 1040, 1065, 1080 cm^{-1} (S→O); nmr (DMSO-d_6) δ 1.25 (s, 3, α-Me), 1.62 (s, 3, β-Me), 4.35 (s, 1, H_3), 4.77 (d, 1, J = 4 Hz, H_5), 5.50 (q, 1, J = 4, 9 Hz, H_6).

Anal. Calcd for $C_{16}H_{18}N_2O_6S$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.25; H, 5.02; N, 7.48.

Registry No.—**1**, 551-16-6; **1** (*R* sulfoxide), 33069-17-9; **1** (*S* sulfoxide), 33069-18-0; **2**, 87-08-1; **2** (*R* sulfoxide), 33069-20-4; **2** (*S* sulfoxide), 33069-21-5; **3**, 4780-24-9; **4**, 33122-31-5; **5**, 20425-27-8; **6**, 32178-92-0; **7**, 33069-25-9.

Synthesis of 2′,3′-*O*-Isopropylidene-5′-keto-8,5′-cycloadenosine, a Novel Cyclonucleoside[1]

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Received August 16, 1971

Cyclonucleosides differ from simple nucleosides in that a nonanomeric carbon of the ribose moiety is linked to the purine or pyrimidine ring. They are useful synthetic intermediates[2–5] and have been valuable as reference compounds in ORD[4,6–9] and CD[10] studies of the disposition of the sugar and base moieties around the glycosidic linkage of nucleosides in aqueous solution.

In cyclonucleosides described hitherto a nonanomeric ribose carbon is bonded either directly to a purine nitrogen or indirectly to a purine or pyrimidine carbon *via* an oxygen, sulfur, or nitrogen. The cyclonucleoside described in this communication is possibly unique in that it contains a bond from a ribose carbon to a purine carbon, although a photolysis product of coenzyme B_{12} has been tentatively identified as 5′-deoxy-8,5′-cycloadenosine.[11] The present cyclonucleoside contains a keto function at the 5′ carbon and reduction to the corresponding secondary alcohol furnishes a 2′,3′-*O*-isopropylidene derivative of the first cyclonucleoside in which all three ribofuranose hydroxyls are retained.

Treatment of 2′,3′-*O*-isopropylidene adenosine 5′-carboxylic acid (**1**)[12] with methyllithium in tetrahydrofuran yielded a complex mixture of products under a variety of reaction conditions. From this, a pale yellow component which fluoresced in ultraviolet light was isolated in *ca.* 5% yield and obtained crystalline and homogeneous. The product was identified as 2′,3′-*O*-isopropylidene-5′-keto-8,5′-cycloadenosine (**3**) on the basis of evidence presented below. Elemental analysis and the pmr spectrum showed that the crystals contained 0.5 mol of tetrahydrofuran. In the mass spectrum the most prominent peak (relative intensity 53) with *m/e* higher than adenine corresponded to the molecular ion of nonsolvated **3**. In accord with the cyclic structure of **3**, the amount of molecular ion relative to adenine ion was *ca.* 50-fold greater than in the case of noncyclic adenine nucleosides.[13,14]

Retention of an adenine ring system in **3** was indicated by uv and ir spectra, by pmr signals assignable to the 6-amino group and to either H-2 or H-8 (but not to both), and by the substantial mass spectral peak of *m/e* 135 corresponding to adenine.

The presence of a keto group in **3** was shown by the formation of an oxime, and by an ir absorption at 1720 cm^{-1} which disappeared upon reduction of **3** with sodium borohydride; furthermore, oxidation of the reduction product **5** with chromic acid regenerated **3**. The product of reduction of **3** showed nmr signals corresponding to the single 5′ proton and one exchangeable proton expected in the secondary alcohol **5**. In addition, large shifts of H-2′, H-3′, and H-4′ signals suggested the removal of the diamagnetically anisotropic

(1) This work was supported by U. S. P. H. S. Grant CA-11196, American Cancer Society Grant T-490, an award from the Pennsylvania Science and Engineering Fund, grants to The Institute for Cancer Research, U. S. P. H. S. Grants CA-06927 and RR-05539 from the National Institutes of Health, and an appropriation from the Commonwealth of Pennsylvania.

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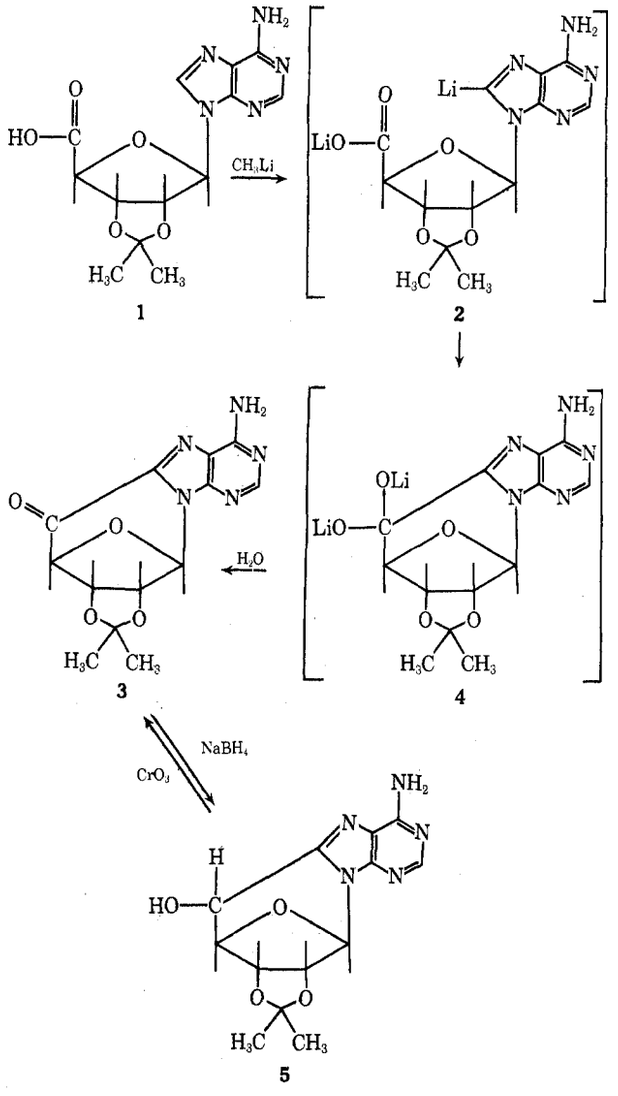
carbonyl group upon conversion of **3** to **5**. The spectrum of **5** showed poorly resolved absorptions for H-4′ and H-5′, as expected, since the product is almost certainly a mixture of stereoisomers at C-5′.



The direct link of the carbonyl group of **3** to the purine ring was indicated by the appearance of an additional absorption peak at 337 nm attendant upon conversion of **1** to **3**. This corresponds to the excitation absorption for the blue fluorescence of **3** and suggests conjugation of another chromophore with the purine ring. In confirmation of this, the borohydride reduction product of **3** lacked both the blue fluorescence and the 337-nm absorption maximum. On the other hand, the oxime of **3** retained the blue fluorescence.

With Corey–Pauling–Koltun space-filling molecular models the 8–5′ bond of **3** could be readily assembled whereas a 2–5′ bond was not possible. Furthermore, the single pmr signal from the purine ring of **3** did not exchange with D_2O under conditions in which H-8 of adenosine did exchange; it is known that H-8 of adenosine exchanges with tritium far more rapidly than does H-2.[15] In addition, the absorption maximum of **5** (264 nm at pH 11 and 268 nm at pH 1) is similar to that of 8-methyladenine (266 nm at pH 11 and 269 nm at pH 1)[16] but different from that of 2-methyladenine (271 nm at pH 11 and 265.5 nm at pH 1).[17]

Conversion of **1** to **3** probably proceeds *via* lithium 2′,3′-*O*-isopropylidene-8-lithioadenosine 5′-carboxylate (**2**). Nucleophilic attack of C-8 on the carbonyl carbon would then give a dilithio intermediate **4** of the type considered to mediate the conversion of carboxylic acids to ketones with organolithium reagents.[18]

Experimental Section

Melting points (uncorrected) were determined by the capillary method. Ultraviolet spectra were obtained in buffered aqueous solutions with a Cary Model 15 spectrophotometer and infrared spectra with a Perkin-Elmer 137 spectrophotometer. The pmr spectra were run with Varian XL-100-15 and Jeolco MH60 instruments. Thin layer chromatograms were run on Merck F-254 silica gel plates in (A) methanol–chloroform (1:9), (B) ethanol–ethyl acetate (1:9), and (C) acetone–diethyl ether (1:4). Elemental analyses were by the Spang Microanalytical Laboratories, Ann Arbor, Mich.

2′,3′-*O*-Isopropylidene-5′-keto-8,5′-cycloadenosine (3).—2′,3′-*O*-isopropylidene adenosine 5′-carboxylic acid[12] (3.2 g, 10^{-2} mol) was suspended in dry THF (100 ml), and methyllithium (30 ml of a 1 *M* solution in ether) was added over 2 hr. The suspension was stirred overnight and ammonium chloride (200 ml of a 20% aqueous solution) was added. The upper layer was removed, washed with saturated sodium bicarbonate (two 100-ml portions), dried (Na_2SO_4), and evaporated to dryness. The residue (0.85 g) was chromatographed on silica (Merck, 85 g) using a linear gradient of chloroform to 20% methanol–chloroform in 1 l. Fractions containing **3** were yellow and exhibited a strong blue fluorescence when irradiated at 360 nm. Removal of volatiles and crystallization of the residue from methanol gave **3** (0.075 g) as flat yellow plates, mp 232–234°, homogeneous upon tlc in systems A, B, and C (R_f 0.78, 0.40, and 0.35, respectively): ir (Nujol mull) 3200, 3100 (NH_2), 1720 (C=O), 1648, 1582 cm^{-1} (C=C, C=N); uv max (pH 2.5) 263 nm (ϵ 19,100), (pH 7.0) 337 (4800) and 267 (16,000), (pH 11.5) 337 (4500) and 267 (16,000); nmr ($CDCl_3$, 100 MHz) δ 8.75 (s, 1, H-2), 8.45 (broad, 2, NH_2), 6.97 (s, 1, H-1′), 5.47 (d of d, 2, J = 5 Hz, H-2′ and -3′), 5.42 (s, 1, H-4′), 3.72 (m, ~2, THF of crystallization), 1.95 and 1.72 (s, 3, isopropylidene methyls), 1.62 (m, ~2, THF of crystallization); mass spectrum (70 eV) *m/e* (rel intensity) 303 (53), 288 (20), 274 (17), 246 (20), 218 (20), 188 (50), 135 (22), 57 (100).

Anal. Calcd for $C_{13}H_{13}N_5O_4 \cdot 0.5C_4H_8O$: C, 53.42; H, 5.06; N, 20.66. Found (for material dried at 78°): C, 53.79; H, 5.02; N, 20.86.

The yield of **3** was essentially constant among reactions run for the optimum periods of time at temperatures between −40 and 50°. Substitution of dioxane or ether for THF at room temperature reduced the yield by *ca.* 50%.

A solution of compound **3** in methanol was treated with hydroxylamine hydrochloride (2 mg) and sodium acetate (5 mg). After 16 hr a single product was observed on tlc with R_f 0.55 (system A) and an intense dark blue fluorescence at 360 nm.

2′,3′-*O*-Isopropylidene-8,5′-cycloadenosine (5).—Compound **3** (75 mg) was dissolved in methanol (20 ml), and 0.1 *M* aqueous sodium borohydride (2.5 ml) was added. After 5 min, tlc in system A showed complete conversion to material of R_f 0.5 which no longer fluoresced. The material was purified by preparative tlc on silica gel in chloroform–methanol (8:1) and crystallized from methanol. The purified material showed uv max (pH 1) 268 nm (ϵ 13,900), (pH 11), 264 (14,500); the ir spectrum (KBr disc) showed absorption at 3300, 3200, 1651, 1585, 1085, and 1040 cm^{-1} but no carbonyl absorption near 1700 cm^{-1}; nmr (DMSO-d_6, 60 MHz) δ 8.62 (s, 1, H-2), 7.70 (broad, 2, exchanges with D_2O, NH_2), 6.56 (s, 1, H-1′), 5.46 (d, 1, J = 6 Hz, H-2′), 4.98 (d, 1, J = 6 Hz, H-3′), 4.32 (broad, 1, H-4′), 3.74 (broad, 2, exchanges 1 H with D_2O, H-5′ and OH), 1.77 (s, 3, CH_3), 1.58 (broad, 3, CH_3).

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Anal. Calcd for $C_{13}H_{16}N_5O_4$: C, 51.14; H, 5.00; N, 22.61. Found [sample dried to constant weight at 100° (0.1 mm) over P_2O_5]: C, 50.80; H, 5.09; N, 22.78.

A portion of the material was dissolved in acetone and treated with Jones reagent[19] until an orange color persisted for 2 min. Tlc of this material in systems A, B, and C showed it to be identical with **3** in R_f and fluorescence color, and the ultraviolet absorption characteristics at acid, neutral, and alkaline pH values were likewise indistinguishable from those of **3**.

Registry No.—**3**, 33066-26-1; **5**, 33189-80-9.

Acknowledgment.—The authors are pleased to thank Dr. M. J. Mitchell, University of Pennsylvania, for determination of the mass spectrum.

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Stereochemistry of the Reduction of Homobenzyl Halides[1]

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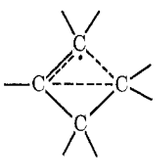
The existence of homoallylic participation in carbonium ion chemistry is well established.[3] The search for analogous participation in free-radical reactions has proven fruitless.[4] The chemical reactivities[5] and physical properties[6] of these radicals are also consistent only with that of equilibrating radicals rather than a single delocalized species such as **1**.



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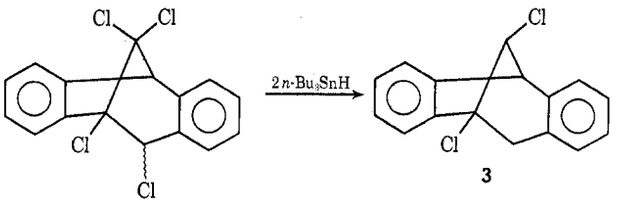
Results and Discussion

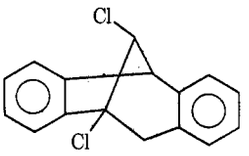
Our interest in this problem arose from the observation that treatment of the tetrachlorides **2**[7] with 2 equiv of tributyltin hydride gave only the dichloride **3** with no observable amount of the epimer **4** formed.

Subsequently it was shown that under these conditions the trichloride **5** reacts with tributyltin hydride to give only **3**; no **4** is formed.[1] The structural assignment for **3** is based on elemental analysis and the proton magnetic resonance (pmr) spectrum of **3**: a pair of



2a, *exo*-Cl
b, *endo*-Cl

3



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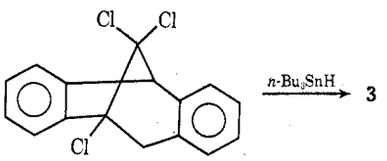
doublets (1 H each) at τ 5.97 and 5.33 (J_{18} = 2.5 Hz), a pair of doublets (1 H each) at τ 6.95 and 6.33 ($J_{\text{gem-4}}$ = 17 Hz), and aromatic protons (8 H) at τ 2.5–3.0. The value of the coupling constant J_{18} is consistent only with structure **3**.[8] Since it is the ring anti to the C-4 position that has the highest capability for delocalization of a charge or unpaired electron at C-8,[9] the nonclassical radical intermediate (if one were to exist) should be represented by **6**. The dichloride **4**



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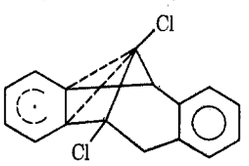

6

should be the product formed[10] from such an intermediate.

Just what effect the C-5 and C-8 chlorine atoms in **5** have on the stereochemical course of this reaction was not clear. It would be preferable to deal with a radical intermediate that lacked any complicating substituents. For this purpose, the two alkyl bromides **7** and **8** were prepared as shown in Scheme I.

The starting dibromides **9**[13] and **10**[14] have been reported previously. The conversion of **10** to the acetate **11** is analogous to the acetolysis of the corresponding trans dichloride.[15] Treatment of the bromides **7**

(1) For a preliminary communication of a portion of this work, see B. B. Jarvis and J. B. Yount, III, *Chem. Commun.*, 1405 (1969).

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(10) This assumes that the three-membered ring is opened with inversion. Previous workers who have postulated the existence of bridged radicals (bromine and sulfur atom bridging)[11] have observed products consistent with opening of the ring with inversion. However, serious doubts exist as to whether there is such a phenomenon as free radical bridging involving bromine atoms.[12]

(11) For example, see W. Thaler, *J. Amer. Chem. Soc.*, **85**, 2607 (1963).

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(15) S. J. Cristol, F. P. Parungo, and D. E. Plorde, *ibid.*, **87**, 2870 (1965).