and eluted with 200 ml of dry benzene. Evaporation of the solvent gave 0.47 g of product.

An analytical sample was obtained by rechromatographing the above material on acid-washed alumina (38.0 g). Elution with 100 ml of dry hexane provided pure **19**: ir shows no absorptions above 3000 cm^{-1}; nmr (CCl_4) 3.69 ppm (s, 3, OCH_3).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.35. Found: C, 70.63; H, 9.48.

10-Carbethoxy-7,7-dimethyl-2-hydroxymethylene-*cis*-decal-1-one (20).—To a cold suspension of NaH (0.45 g of a 53% dispersion in mineral oil, 0.010 mol) in 4 ml of dry benzene was added dropwise, over a 10-min period, **19** (0.50 g, 0.0021 mol) and ethyl formate (0.75 g, 0.010 mol, distilled from P_2O_5) in 2 ml of dry benzene. After an initial induction period the reaction began spontaneously at room temperature with a rapid evolution of gas and was complete in 12 hr. Additional ethyl formate (15.0 g, 0.203 mol) was added to ensure the complete conversion to the ethyl ester. After stirring for a total of 24 hr at room temperature, 5 ml of water was added followed by 50 ml of ether. The organic material was extracted with three 25-ml portions of a 2% aqueous sodium hydroxide solution. The aqueous mixture was acidified with dilute HCl and extracted with three 25-ml portions of ether. Drying (Na_2SO_4) and evaporation of the solvent provided 0.37 g of a thick orange-red oil which was used directly in the following step without further purification: nmr (CCl_4) 8.52 (s, CHO), 7.40 ppm (s, vinyl). These two resonance peaks vary in intensity but not in position upon dilution. The integrated area of the two peaks is $^1/_{24}$ of the total resonance signal, equivalent to one proton.

Evaporation of the original ethereal solution led to the recovery of 0.12 g of **19**.

2-*n*-Butylthiomethylene-10-carbethoxy-7,7-dimethyl-*cis*-decal-1-one.—The hydroxymethylene derivative (**20**) prepared as above (0.37 g, 0.0010 mol) and *n*-butyl mercaptan (4.50 g, 0.0500 mol) were refluxed for 6 hr in 30 ml of dry benzene to which had been added 0.1 g of *p*-toluenesulfonic acid. The solution was washed with two 10-ml portions of a 2% sodium hydroxide solution and dried (Na_2SO_4), and the solvent was evaporated under dry air to yield 0.57 g of product: ir 1670 (C=O), 1550 cm^{-1} (C=C); nmr (CCl_4) 7.35 ppm (s, 1, vinyl).

10-Carbethoxy-2,7,7-trimethyl-*cis*-decal-1-one (2).—The unpurified thio compound was dissolved in 25 ml of 95% ethanol. Raney nickel (type W-2, *ca.* 1.0 g) was added, and the suspension was refluxed for 3 hr. Filtration and evaporation of the solvent under dry air yielded 0.28 g of **2**. This represents a 73% yield for the last three steps based on unrecovered **19**: ir and nmr are both very similar to those of **19**, but with nmr integration indicating the presence of three additional methyl protons.

An analytical sample was obtained by absorption of a portion of the material (0.13 g) on acid-washed alumina (5.0 g). Successive 30-ml portions of the following solvents were then run through the column: hexane, benzene, 30% ether–70% benzene, 30% ether–70% benzene, absolute methanol. The purest material was recovered upon evaporation of the first ether–benzene fraction. The sample weighed 0.0213 g.

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 71.84; H, 9.75.

Registry No.—**1**, 33122-28-0; **2**, 33065-73-5; **6**, 33065-74-6; **7**, 33065-75-7; **8**, 33065-76-8; **9**, 33065-77-9; **15**, 33122-29-1; **16**, 33065-78-0; **17**, 33065-79-1; **18**, 33065-80-4; **18** (keto acid), 33065-81-5; **19**, 33069-12-4; **20**, 33069-13-5; 10β-methyl-1α-carbomethoxy-5β-tetrahydropyranyloxy-*trans*-2-decalone, 7381-72-8; 10β-methyl-1α-carbomethoxy-5α-tetrahydropyranyloxy-*trans*-2-decalone, 33069-15-7; 2-*n*-butylthiomethylene-10-carbethoxy-7,7-dimethyl-*cis*-decal-1-one, 33069-16-8.

Notes

Oxidation of Penicillin and Dihydrocephalosporin Derivatives with Ozone

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A recent publication revealed that ozone under certain conditions is an ideal reagent for converting penicillins into mixtures of *R* and *S* sulfoxides.[1] This communication details the reactions of ozone with various penicillin and cephalosporin derivatives. The results of the oxidation of various penicillin derivatives with ozone are shown in Table I. The determination of the *S* and *R* sulfoxide isomers was accomplished by a study of the nmr chemical shifts.[2,3]

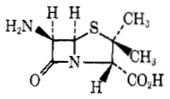
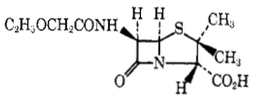
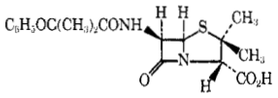
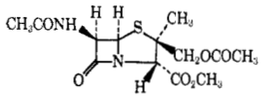
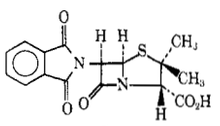
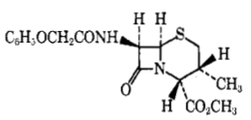
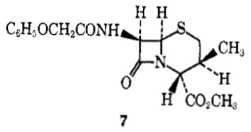
Of particular interest is the high-yielding conversion of 6-aminopenicillanic acid (6-APA) (**1**) into analytically pure, noncrystalline 6-APA sulfoxide having an *S*/*R* ratio of approximately 4/1 as determined from the products formed by acylation with phenoxyacetyl chloride.

Essery, *et al.*, have previously reported the synthesis of 6-APA sulfoxide in 8% yield by oxidation of 6-APA with sodium metaperiodate;[4] the stereochemistry from the latter synthesis, however, has been shown to be *S*, as is the case when various penicillins are oxidized with sodium metaperiodate.[2,5]

Further examination of Table I indicates that the various penicillin compounds exhibit a steric effect on the approach of the ozone molecule which consequently affects the stereochemistry of the resulting sulfoxide. Thus the sulfoxides of the nucleus (**1**) exhibit an *S*/*R* ratio of 4/1 as compared to those of compound **2** with a 1/1 ratio and to the 2-β-acyloxymethyl compound **4** with an *S*/*R* ratio of 1/2. Oxidation of the bulky β-phthalimidopenicillanic acid (**5**) resulted in only the *R* sulfoxide. However, this could possibly result from an *S* to *R* conversion *via* the olefin sulfenic acid, with the driving force being the release of strain between the

(1) D. O. Spry, *J. Amer. Chem. Soc.*, **92**, 5006 (1970).
(2) R. D. G. Copper, P. V. Demarco, J. C. Cheng, and N. D. Jones, *ibid.*, **91**, 1408 (1969).
(3) R. D. G. Cooper, P. V. Demarco, and D. O. Spry, *ibid.*, **91**, 1528 (1969).
(4) J. M. Essery, K. DaDabo, W. J. Gottstein, A. Hallstrand, and L. C. Cheney, *J. Org. Chem.*, **30**, 4388 (1965).
(5) D. H. R. Barton, F. Comer, and P. G. Sammes, *J. Amer. Chem. Soc.*, **91**, 1529 (1969).

TABLE I
OXIDATION OF PENICILLIN AND DIHYDRODEACETOXYCEPHALOSPORIN DERIVATIVES WITH OZONE

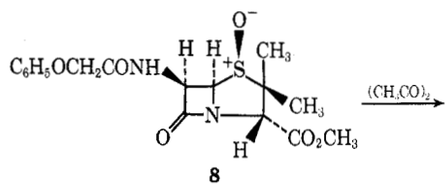
Derivative	Solvent	Yield of sulfoxide, %	S/R ratio
 1	H_2O	>95	4/1
 2	H_2O–acetone	>95	1/1
 3	H_2O–acetone	>95	1.4/1.0
 4	H_2O–acetone	70	1/2
 5	H_2O–acetone	>95	only R
 6	H_2O–acetone	91	1/7
 7	H_2O–acetone	>95	1/24

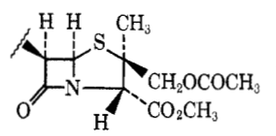
two bulky β groups.[1,6] Attempts to prepare the cis-β compound by acylation of 6-APA β-sulfoxide with *N*-carboethoxyphthalimide gave 6-epiphthalimido β-sulfoxide due to base-catalyzed epimerization of 6-β-phthalimidopenicillanic acid β-sulfoxide.[3]

Oxidation of the penicillin sulfoxide to sulfone did not occur under these conditions even with a large excess of ozone. Although monosulfides are generally oxidized to sulfones by excess ozone,[7] Bernard has reported that the ease of such ozone oxidations is a function of the electron density on sulfur and that sterically hindered sulfoxides, for example, diphenyl sulfoxide, are resistant to further oxidation by ozone.[8]

Treatment of 3-cephems,[9] for example, 7-aminodeacetoxycephalosporanic acid (7-ADCA) or 7-aminocephalosporanic acid (7-ACA), under these conditions failed to give the corresponding sulfoxides, as a result of the double bond being more reactive toward ozone than the sulfide.[8] Hydrogenation of the double bond, however, followed by ozonization of the dihydrodeacetoxycephalosporins, for example, compounds **6** and **7**, led to mixtures of the *S* and *R* sulfoxides with a predominance of the *R* isomer (see Table I).

Further use of ozone in penicillin–cephalosporin chemistry is illustrated by the isolation of pure 2-β-acyloxymethylpenicillin derivatives. Morin, *et al.*, in their elegant conversion of the penam to the cephem system, described the rearrangement of the penicillin sulfoxide **8** in refluxing acetic anhydride to give **9**, **10**, and **11**.[10] Separation of the rearrangement products


8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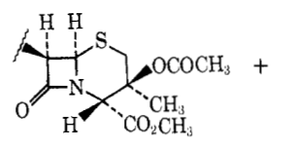
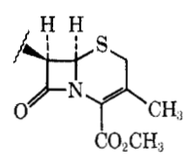
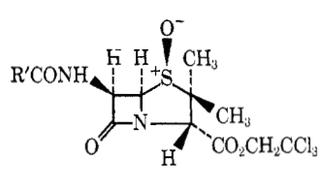
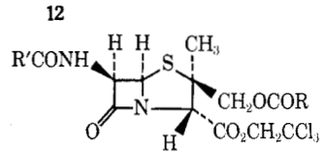
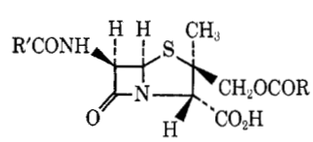

10


11


12


13
15-20%


14
60-80%

R′	R
$C_6H_5OCH_2$	CH_3
$C_6H_5OCH_2$	$CH(CH_3)_2$
$C_6H_5CH_2$	CH_3

could be accomplished by silica gel chromatography; however, basic hydrolysis of the 2-substituted penicillin methyl ester **9** to the salt led to extensive degradation.

(6) Since submission of this manuscript we have found that the ozonization of 2-α-trideuteriomethyl phthalimidopenicillin sulfide methyl ester leads predominately to the α-sulfoxide-α-trideuteriomethyl compound.
(7) H. Bohme and H. Fischer, *Chem. Ber.*, **75**, 1310 (1942).
(8) D. Barnard, *J. Chem. Soc.*, 4547 (1957).
(9) R. B. Morin, B. G. Jackson, E. FH.lynn, and R. W. Roeske, *J. Amer. Chem. Soc.*, **84**, 3400 (1962).
(10) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *ibid.*, **91**, 1401 (1969).

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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(3) A. M. Michelson, "The Chemistry of Nucleosides and Nucleotides, Academic Press, New York, N. Y., 1963, p 15.
(4) M. Ikehara, *Accounts Chem. Res.*, **2**, 47 (1969).
(5) J. Nagyvary, *Biochemistry*, **5**, 1316 (1966), and references cited therein.
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(13) K. Biemann and J. A. McCloskey, *J. Amer. Chem. Soc.*, **84**, 2005 (1962).
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