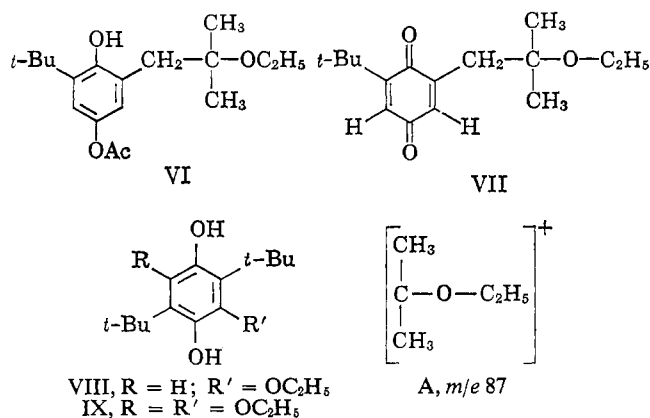


carbon to another, the two aromatic protons could not have been in a 1:3 position in the quinone VII.

The structure IIa is also supported by the mass spectrum of the rearranged product, which shows the base peak at  $m/e$  87 corresponding to a scission of the side chain to produce the fragment A.

Before the completion of our investigation a report<sup>8</sup> appeared in which structures VIII and IX were assigned to two of the products from the photolysis of Ib in ethanol. We have repeated this photolysis experiment and examined the n.m.r. spectra of the products of m.p. 167–167.5° and 209–210°. The spectral data indicate that the structures for these two compounds are IV and V, respectively.



There are a considerable number of naturally occurring compounds which possess the *p*-benzoquinone moiety.<sup>9</sup> An alkenylphenol has recently been shown to be a biosynthetic precursor of ubiquinone.<sup>10</sup> It would be of interest to ascertain the role, if any, of the photorearrangement of alkyl-*p*-benzoquinones to hydroquinones in the biogenesis of naturally occurring quinones. The scope and mechanism of the photorearrangement reported here is currently under investigation.

**Acknowledgment.** We thank Dr. M. S. Manhas for the mass spectrum, R. Tavares for the n.m.r. spectra, and Dr. E. R. Malinowski for the double resonance data.

(8) J. Petránek and O. Ryba, *Chem. Ind. (London)*, 225 (1965).

(9) L. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1961, p. 863.

(10) R. K. Olsen, J. L. Smith, G. D. Daves, H. W. Moore, K. Folkers, W. W. Parson, and H. Rudney, *J. Am. Chem. Soc.*, 87, 2298 (1965).

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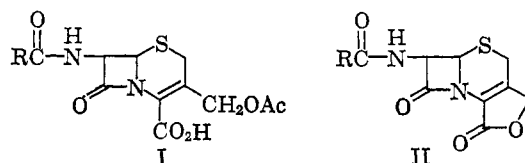
## Total Synthesis of the Cephalosporin Antibiotics.

### I. The Dihydrothiazine System of Cephalosporin C<sub>c</sub>.

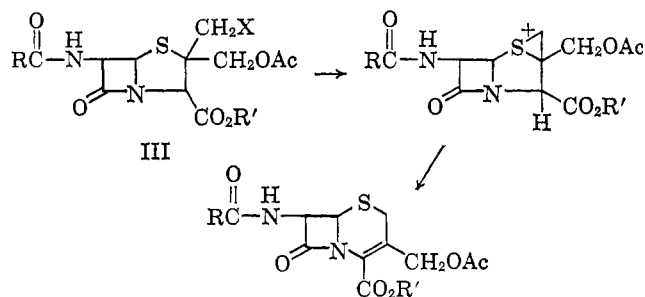
Sir:

The outstanding antibacterial properties of many of the antibiotics related to cephalosporin C (I, R = (CH<sub>2</sub>)<sub>3</sub>CH(NH<sub>2</sub>)CO<sub>2</sub>H),<sup>1</sup> together with their remarkable

lack of toxicity,<sup>2</sup> have established their importance in medicine. Of no less interest to the organic chemist has been the challenge presented by their molecular architecture which embodies within a single six-membered ring the features of an enamide, an  $\alpha,\beta$ -unsaturated carboxyl, an allylic alcohol, and an allylic sulfide. Although much progress has been made recently toward the construction of substituted 3,6-dihydro-2H-1,3-thiazines,<sup>3</sup> the synthesis of the actual dihydrothiazine system found in cephalosporin C, or in cephalosporin C<sub>c</sub> (II, R as in I), has not yet been successful.



We wish to report a solution to this problem which we believe to be a general one. It occurred to one of us some years ago that a suitably substituted penicillin derivative (*cf.* III) could be constructed which might be transformed into the cephalosporin C system. This scheme is



Since methods for the construction of the penicillin ring system are well worked out,<sup>4</sup> the crucial part of the synthesis is the postulated formation of the properly substituted dihydrothiazine by ring expansion of a thiazolidine.

We have now been able to put this synthetic scheme to the test and are able to report its success.

Addition of hydrogen sulfide in methanol solution<sup>5</sup> to the known 2-phenyl-4-(2-acetoxy-1-acetoxymethylethylidene)-2-oxazolin-5-one,<sup>6</sup> followed by heating of the resulting thiazoline with a 1:2:4 mixture of hydrochloric acid, water, and acetic acid for 45 min. at 100°, gave the bicyclic thiazoline lactone V, obtained as its monohydrate, m.p. 52°, from aqueous ethanol. *Anal.* Found: C, 53.80; H, 4.72; N, 5.40. The substance had  $\lambda_{\text{max}}^{\text{MeOH}}$  246 m $\mu$  (log  $\epsilon$  4.28) and  $\nu_{\text{max}}^{\text{CHCl}_3}$  1780,

(1) E. P. Abraham and G. G. F. Newton, *Biochem. J.*, 79, 377 (1961); D. C. Hodgkin and E. N. Maslen, *ibid.*, 79, 393 (1961).

(2) *Cf.*, *inter alia*, W. E. Wick and W. S. Boniece, *Appl. Microbiol.*, 13, 248 (1965); E. V. Heyniger, *J. Med. Chem.*, 8, 22 (1965).

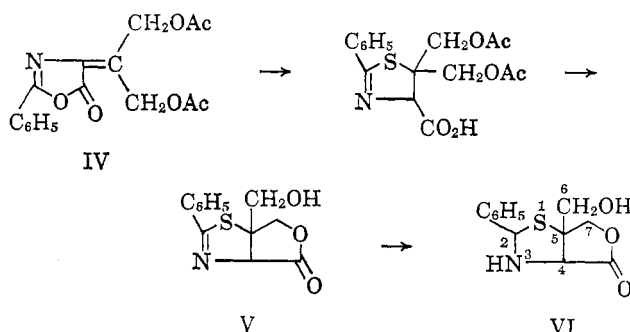
(3) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Am. Chem. Soc.*, 85, 1896 (1963); D. M. Green, A. G. Long, P. J. May, and A. T. Turner, *J. Chem. Soc.*, 766 (1964); G. C. Barrett, V. V. Kane, and G. Lowe, *ibid.*, 783 (1964); G. C. Barrett, S. H. Eggers, T. R. Emerson, and G. Lowe, *ibid.*, 788 (1964); E. Galantay, H. Engel, A. Szabo, and J. Fried, *J. Org. Chem.*, 29, 3560 (1964); S. H. Eggers, V. V. Kane, and G. Lowe, *J. Chem. Soc.*, 1262 (1965).

(4) *Cf.* J. C. Sheehan and K. R. Henery-Logan, *J. Am. Chem. Soc.*, 84, 2983 (1962), and earlier references therein.

(5) *Cf.* J. W. Cornforth in H. T. Clarke, *et al.*, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 737.

(6) E. Galantay, A. Szabo, and J. Fried, *J. Org. Chem.*, 28, 98 (1963).

1600, 1580, 960, and 905  $\text{cm}^{-1}$ . The mass spectrum showed, in addition to the molecular ion at 249, important peaks at 205, 174 (base peak), 121, 104, and 77. The n.m.r. spectrum in chloroform showed resonance at  $\tau$  4.55 (singlet, 1 H; C-4), 5.3 (2 H; C-7), and 6.05 (singlet, 2 H; C-6). The lactone ring of V is



undoubtedly *cis*-fused to the thiazoline as shown.

Reduction of V with aluminum amalgam in moist ether<sup>7</sup> for 45 min. at room temperature gave the hydroxymethylthiazolidine lactone VI as prisms melting at 159.5–160° from aqueous methanol. *Anal.* Found: C, 57.40; H, 5.15. The substance had end absorption at 215  $\text{m}\mu$  ( $\epsilon$  5,250) and  $\nu_{\text{max}}^{\text{Nujol}}$  3400, 3300, and 1770  $\text{cm}^{-1}$ . The important features of the n.m.r. spectrum of VI (in acetone), compared to that of V, were the appearance of a singlet at  $\tau$  4.4 due to the hydrogen at C-2, while the C-4 hydrogen was moved upfield to  $\tau$  5.4 because of the increased shielding resulting from the saturation of the 2,3-double bond.

Acetylation of VI with acetic anhydride in benzene at room temperature gave large prisms of the N-acetyl derivative VII, m.p. 201–203°. *Anal.* Found: C, 57.08; H, 5.13. The ultraviolet spectrum showed only end absorption due to the benzene ring ( $\epsilon$  4650 at 220  $\text{m}\mu$ ). The substance had  $\nu_{\text{max}}^{\text{Nujol}}$  3300, 1790, and 1630  $\text{cm}^{-1}$ , and its mass spectrum showed, in addition to the molecular ion at  $m/e$  293, peaks at 250, 220, 218, 179 (base peak), 146, 122, and 121. The n.m.r. spectrum (in acetonitrile or acetone) showed the anticipated deshielding of the C-2 and C-4 hydrogens resulting from acetylation of the nitrogen; they now gave rise to resonance at  $\tau$  3.9 and 4.7, respectively.

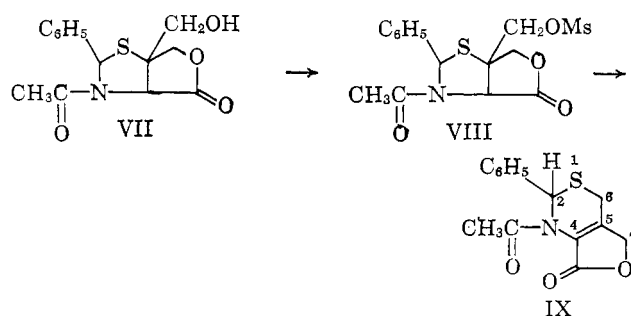
Treatment of VII with methanesulfonyl chloride in pyridine overnight at 5° gave an almost quantitative yield of the methanesulfonate VIII, m.p. 177–178° dec. The infrared spectrum showed  $\nu_{\text{max}}^{\text{Nujol}}$  1790, 1650, 1340, 1330, and 1170  $\text{cm}^{-1}$ , while the n.m.r. spectrum (in dimethylformamide) showed the deshielding caused by the methanesulfonyl group on the hydrogens at C-4 and C-6 which now appear at  $\tau$  4.2 and 5.2 (compared with  $\tau$  4.7 and 6.2 for VII).

The stage was now set for the crucial step in the construction of the dihydrothiazine ring of cephalosporin C<sub>6</sub>; when the mesylate VIII was refluxed for 5 hr. in dioxane with anhydrous sodium acetate, the desired substance IX appeared to be the only product formed, since the spectral properties of the crude reaction product were identical with those of pure IX. The latter was isolated in good yield on crystallization from petroleum ether–carbon tetrachloride as large prisms which melted at 77–78°<sup>8</sup> after chromatography on alumina.

(7) A. H. Cook and I. M. Heilbron in ref. 5, p. 922.

(8) The dihydrothiazine IX crystallized well only as a carbon tetra-

The structure of the dihydrothiazine IX was confirmed by analytical and spectral data<sup>8</sup>: molecular weight (mass spectrum) 275 (other peaks at 233 (base peak), 215, 200, 122, 121, and 105). The presence of the unsaturated lactone and of the N-acetyl group was confirmed by the infrared spectrum ( $\nu_{\text{max}}^{\text{CHCl}_3}$  1775, 1690, and 1660  $\text{cm}^{-1}$ ),<sup>9</sup> while the n.m.r. spectrum in carbon tetrachloride was entirely in agreement with structure IX:  $\tau$  2.6–2.9 (5 H; phenyl), 3.05 (singlet, 1 H; C-2), 5.4 (quartet,  $J = 17$  c.p.s., 2 H; C-7), 6.7 (singlet, broad, 2 H; C-6), and 7.7 (singlet, 3 H; N-acetyl). The absence of resonance corresponding to a hydrogen at C-4 and the characteristic position of the maximum in the ultraviolet ( $\lambda_{\text{max}}^{\text{MeOH}}$  268  $\text{m}\mu$  (3.65)<sup>10</sup>) were further evidence of the correctness of structure IX.<sup>11</sup>



chloride solvate which seemed to contain 4 molecules of  $\text{CCl}_4$  for 9 molecules of IX. *Anal.* Calcd. for  $\text{C}_{14}\text{H}_{13}\text{O}_3\text{NS} \cdot 0.44\text{CCl}_4$ : C, 50.55; H, 3.82; S, 9.35; Cl, 18.20. Found: C, 50.73; H, 3.79; S, 9.29; Cl, 18.39. Correct analytical figures for solvent-free IX were obtained after heating under reduced pressure for 2 hr. at 100°. *Anal.* Found: C, 61.27; H, 4.79.

(9) Cf. infrared spectrum of 4-benzylthiomethyl-3-aminofuran-2 (5H)-one: Green *et al.*, ref. 3.

(10) Cf. the spectrum of cephalosporin C<sub>6</sub> (II), ref. 1.

(11) We wish to thank the National Institutes of Health for their support of this work.

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## Transannular Participation of Ether Oxygen in the Hydrolysis of a Mesocyclic Dienamine<sup>1</sup>

Sir:

Leonard's extensive study<sup>2,3</sup> of transannular interactions between heteroatoms and ketone carbonyls in mesocycles<sup>4</sup> has demonstrated the existence of transannular bonding of the N–C=O and S–C=O type, but the absence of O–C=O interactions. This effective electron-donating ability was found, however, to be restricted only to those molecules in which the interacting groups were diametrically opposed.

We wish to present evidence that ether oxygen, despite its low order of nucleophilicity, can indeed profoundly affect the course of a reaction by transannular bonding and that the participating groups need not be diametrically opposed.

(1) Unsaturated Heterocyclic Systems, part XIX. For part XVIII, see L. A. Paquette, J. H. Barrett, R. P. Spitz, and R. Pitcher, *J. Am. Chem. Soc.*, **87**, 3417 (1965).

(2) N. J. Leonard, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.) **17**, 243 (1956).

(3) N. J. Leonard, T. W. Milligan, and T. L. Brown, *J. Am. Chem. Soc.*, **82**, 4075 (1960).

(4) "Mesocycle" is herein employed as an alternative to "medium-sized ring," as suggested in footnote 4 of ref. 3.