rangements.[5] The course of the reaction is not affected by the addition of the radical scavenger galvinoxyl and the decomposition shows no chemically induced dynamic nuclear polarization.[6] This makes free-radical or radical-pair intermediates seem unlikely. An intramolecular rearrangement of the alkoxysulfonium ion is suggested.

In contrast, when **1** is boiled for several days in ether in the presence of an aryl sulfide, such as phenyl trifluoromethyl sulfide, one observes reaction products reminiscent of the radical chain induced decompositions seen for peroxides in diethyl ether.[7]

$$\mathbf{1} + (C_2H_5)_2O \longrightarrow \underset{\mathbf{3}}{CH_3\overset{OR_F}{\overset{|}{C}}HOCH_2CH_3} + R_FOH + (C_6H_5)_2S$$

The acetal product, **3**, formed in yields up to 40%, gives characteristic ^1H and ^{19}F nmr spectra and is rapidly hydrolyzed to acetaldehyde, ethanol, and R_FOH. No **3** is formed in the presence of galvinoxyl nor in the absence of the added aryl sulfide. No evidence is seen for an exchange of the added aryl sulfide with **1** to give a new sulfurane. A radical initiation step involving a reaction of **1**, or its derivative alkoxysulfonium ion, with the aryl sulfide,[8] followed by more or less conventional chain propagation steps, is suggested as a possible mechanism for this reaction. (The second propagation step is more likely to involve an electron transfer step rather than a direct displacement by solvent radical on the highly hindered oxygen of **1** if this is, in fact, the mechanism.)

Initiation Steps

$$R_FO^- + (C_6H_5)_2\overset{OR_F}{\overset{|}{\overset{+}{S}}} + ArSR \longrightarrow \underset{\mathbf{4}}{(C_6H_5)_2\overset{R_FO}{\overset{|}{S}}-\overset{OR_F}{\overset{|}{S}}Ar}$$

$$\mathbf{4} \longrightarrow [(C_6H_5)_2\dot{S}OR_F + Ar\overset{R}{\overset{|}{\dot{S}}}OR_F] \longrightarrow (C_6H_5)_2S + ArSR + 2R_FO\cdot$$

Chain Propagation Steps

$$R_FO\cdot + (C_2H_5)_2O \longrightarrow R_FOH + CH_3\dot{C}HOC_2H_5$$

$$CH_3\dot{C}HOC_2H_5 + \mathbf{1} \longrightarrow R_FO\cdot + \mathbf{3} + (C_6H_5)_2S$$

The great reactivity of **1** toward active hydrogen compounds (O–H, N–H, S–H, etc.) combines with the unique pattern of reactivity which results from the absence in **1** of the halogen ligands present in other isolated sulfuranes[4] and an indefinite shelf life in the absence of moisture to make this compound very attractive as a reagent for dehydrations,[3] oxidations, and certain coupling reactions. These are under active investigation in our laboratory.

Acknowledgment. This work was supported in part by National Science Foundation Grant No. GP 13331. The National Science Foundation also assisted in the purchase of the 220-MHz nmr spectrometer used in this work.

(5) For a review see H. J. Shine, "Aromatic Rearrangements," Elsevier, Amsterdam, 1967.
(6) See G. L. Closs and D. R. Paulson, *J. Amer. Chem. Soc.*, **92**, 7229 (1970), and references therein.
(7) E. S. Huyser, "Free-Radical Chain Reactions," Wiley-Interscience, New York, N. Y., 1970, p 262.
(8) Evidence for bonding interactions between sulfide sulfur and sulfonium sulfur similar to that postulated for the initiation step has been reported in systems providing transannular juxtaposition of these groups. See N. J. Leonard, J. A. Klainer, and A. E. Yethon, manuscript to be published; S. M. Johnson, C. A. Maier, and I. C. Paul, *J. Chem. Soc. B*, 1603 (1970).
(9) Fellow, National Institutes of Health, 1967–1971.

J. C. Martin,* R. J. Arhart[9]
Department of Chemistry, University of Illinois
Urbana, Illinois 61801
Received February 10, 1971

Stereospecific Alkylation of a Penicillin at C-6 Using a Nitrogen Ylide. Methyl 6-α-Allyl-6-β-*N*,*N*-dimethylaminopenicillanate

Sir:

As part of our continuing program of modification of β-lactam antibiotics, we have developed a procedure which allows us to alkylate the C-6 position of the penicillin nucleus without cleaving the β-lactam or inverting the 6-β-amino group. Reiner and Zeller[1] have also pursued this goal following a suggestion that introducing an α-methyl group at C-6 could enhance antibiotic activity.[2]

Several investigators have demonstrated the lability of the C-6 proton in N-protected penicillin derivatives.[3–6] However, base-catalyzed proton removal is usually accompanied by irreversible epimerization to the unnatural (6-α) isomer. Thus, even if alkylation at C-6 did occur, some of the unnatural epimer might be expected. We have used an intramolecular rearrangement of a nitrogen ylide to overcome this problem.

N,*N*-Dimethylaminopenicillanic acid hydrochloride[7] (**1**) was treated with excess diazomethane in ether to give the methyl ester **2** as an oil. Compound **2**, isolated in nearly quantitative yield, reacted with phenoxyacetyl chloride in acetone at room temperature to give the hydrochloride **3**: mp 145–146°; γ_{max} ($CHCl_3$) 1780, 1745 cm^{-1}.

Quaternization of **2** with allyl bromide in acetone at room temperature gave crystalline **4** in 80% yield: mp 126–127°; γ_{max} ($CHCl_3$) 1780, 1740 cm^{-1}. When **4** was treated with 1.5 equiv of sodium hydride in 2:5 DMF–benzene at room temperature for 30 min, it rearranged to **5**. The amine, **5**, was isolated as an oil in 75% yield and then converted with phenoxyacetyl chloride in acetone to its hydrochloride **6**: mp 159–160°; γ_{max} ($CHCl_3$) 1785, 1750 cm^{-1}. Quaternization of **5** with methyl iodide gave the methiodide **7**: mp 180–181°; γ_{max} (mull) 1775, 1740 cm^{-1}.

Quaternization of **2** with methyl iodide in acetone gave **8**: mp 157–158°; γ_{max} (mull) 1785, 1750 cm^{-1}. Compound **8**, when stirred in $NaHCO_3$ solution at pH 8.0 at room temperature followed by acidification with aqueous HI, was converted quantitatively to **9**, isolated as an amorphous solid: γ_{max} (mull) 1780, 1740 cm^{-1}. The allyldimethylammonium salt **4** was similarly converted to its C-6 epimer **10** when stirred in $NaHCO_3$ solution followed by acidification with

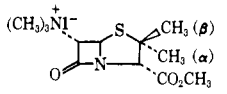
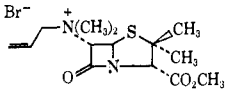
(1) R. Reiner and P. Zeller, *Helv. Chim. Acta*, **51**, 1905 (1968).
(2) J. L. Strominger and D. J. Tipper, *Amer. J. Med.*, **39**, 708 (1965).
(3) D. A. Johnson, D. Mania, C. A. Panetta, and H. H. Silvestri, *Tetrahedron Lett.*, 1903 (1968).
(4) S. Wolfe and W. S. Lee, *Chem. Commun.*, 242 (1968).
(5) J. P. Clayton, J. H. C. Naylor, R. Southgate, and E. R. Stove, *ibid.*, 129 (1969).
(6) S. Wolfe, W. S. Lee, and R. Misra, *ibid.*, 1067 (1970).
(7) T. Leigh, *J. Chem. Soc.*, 3616 (1965).

Table I. Chemical Shift Values (D_2O)

Compd[a]	2-CH_3	$\overset{+}{N}(CH_3)_n$	CO_2CH_3	H_3	H_5	H_6	$-CH_2CH{=}CH_2$
3	1.53, 1.71	3.07	3.83	4.80	5.20 (d, J = 4)	5.77 (d, J = 4)	
4	1.53, 1.74	3.45	3.86	4.88	5.58 (d, J = 4)	5.86 (d, J = 4)	δ 4.15–4.35 (m, 2 H) δ 5.65–6.35 (m, 3 H)
6	1.52, 1.70	3.03	3.83	4.82	5.61		δ 2.95–3.10 (m, 2 H) δ 5.30–6.00 (m, 3 H)
7	1.52, 1.74	3.51	3.85	4.92	5.70		δ 3.15–3.35 (m, 2 H) δ 5.35–6.05 (m, 3 H)
8	1.54, 1.74	3.47	3.86	4.91	5.54 (d, J = 4.5)	5.86 (d, J = 4.5)	
9	1.51, 1.64	3.41	3.86	4.95	6.02 (d, J = 2)	5.35 (d, J = 2)	
10	1.50, 1.63	3.36	3.86	4.92	6.06 (d, J = 2)	5.35 (d, J = 2)	δ 4.15–4.30 (m, 2 H) δ 5.70–6.20 (m, 3 H)

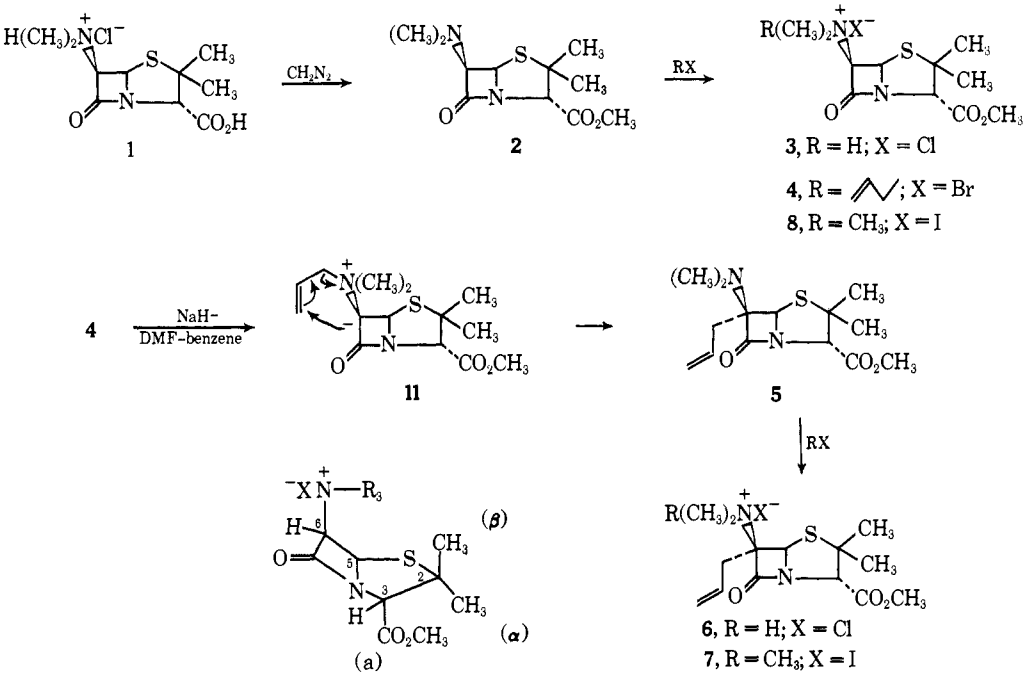
[a] Satisfactory elemental analyses were obtained for all crystalline compounds. J values in hertz.

Table II. Nmr Data Used to Assign Stereochemistry at C-6

Compd	Chemical shift, δ, ppm β-Me	α-Me	Nuclear Overhauser effects, % Δ(β-α), Hz	β-Me-H_3	α-Me-H_3	β-Me-H_5	α-Me-H_5
8	1.74	1.54	20	18	*a*	Nil	Nil
 (9)	1.64	1.51	13	18	*a*	Nil	Nil
4	1.74	1.53	21	22	*a*	Nil	Nil
 (10)	1.63	1.50	13	23	*a*	Nil	Nil
7	1.74	1.52	22	28	*a*	Nil	Nil

[a] Small, but reproducible interaction of 2–5%.

Chart I



aqueous HBr. Compound **10** was an amorphous solid: γ_{max} ($CHCl_3$) 1785, 1750 cm^{-1}. The unsubstituted C-6-α epimers **9** and **10** are quite readily distinguished from the epimers with the natural β configuration, **4** and **8**, by examination of the J values for the β-lactam protons.[8] Green and coworkers[9] have generalized that for penicillin $J_{cis} \simeq 4$ Hz and $J_{tran} \simeq 2$ Hz. J_{cis} is always larger than J_{trans} (Table I).

(8) I. McMillan and R. J. Stoodley, *Tetrahedron Lett.*, 1205 (1966), and references therein.

(9) G. F. H. Green, J. E. Page, and S. E. Staniforth, *Chem. Commun.*, 597 (1966).

Assignment of the stereochemistry at C-6 for the allyl rearrangement product **7** was based on nmr data[10] (Table II). Examination of 6-β-ammoniumpenicillanates showed that the resonance for the β-methyl group at C-2 was shifted significantly downfield from the α-methyl resonance. This deshielding phenomenon is probably a result of the proximity of the positively charged transannular ammonium function. Epimerization of the natural 6-β isomer to the 6-α-ammonium derivative results in a pronounced upfield shift of the C-2 β-methyl resonance. Nuclear Overhauser effects (NOE) of the C-2 methyl groups with the protons at C-3 and C-5 were determined on the ammonium compounds to show that they had the normal penicillin conformation (a) and that the downfield resonance was indeed due to the β-methyl.[11] The methiodide **7** clearly fits the pattern of the compounds with the natural β-ammonium stereochemistry.

Formation of **5** probably involves a [2,3]-sigmatropic rearrangement of the derived nitrogen ylide **11**.[12] Similar allylic migration of nitrogen ylides under mild temperature conditions are well documented[13] but to our knowledge it has not been previously established that the carbanionic center retains its configuration.[14] The present results may be rationalized in the following way. In the aprotic benzene–DMF system the ylide **11** is converted by a [2,3]-sigmatropic rearrangement to **5**, the stereochemistry at C-6 being determined by more ready alignment of the allylic terminus from the α face of the β-lactam. The driving force for rearrangement is provided by the relief of the charge separation inherent in the betaine **11**. However, in the aqueous case epimerization could be achieved *via* an enol, a species with the same geometry as the betaine but lacking the driving force of charge separation. Thus although our system does proceed with retention of configuration at C-6, the result may not be a general stereochemical phenomenon, but is rather a consequence of the adjacent geometry in this molecule.

Acknowledgments. We wish to acknowledge our many helpful discussions with Drs. R. D. G. Cooper and M. Gorman of the Lilly Research Laboratories.

(10) We wish to thank Dr. P. V. Demarco and T. Elzey of the Lilly Research Laboratories for determination and interpretation of the nmr data.

(11) R. D. G. Cooper, P. V. Demarco, J. C. Cheng, and N. D. Jones, *J. Amer. Chem. Soc.*, **91**, 1408 (1969).

(12) This is an example of a widely occurring general process in allylically substituted ylides, *cf.* J. E. Baldwin, J. E. Brown, and R. W. Cordell, *Chem. Commun.*, 31 (1970).

(13) R. W. Jemison and W. D. Ollis, *ibid.*, 294 (1969); B. J. Millard and T. S. Stevens, *J. Chem. Soc.*, 3397 (1963).

(14) There are, however, several examples of stereochemical induction at the terminus of Stevens 1,2 rearrangements: R. K. Hill and T. H. Chan, *J. Amer. Chem. Soc.*, **88**, 866 (1966); H. Joshua, R. Gans, and K. Mislow, *ibid.*, 90, 4884 (1968).

Gary V. Kaiser,* Charles W. Ashbrook

The Lilly Research Laboratories, Eli Lilly and Company
Indianapolis, Indiana 46206

J. E. Baldwin

Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

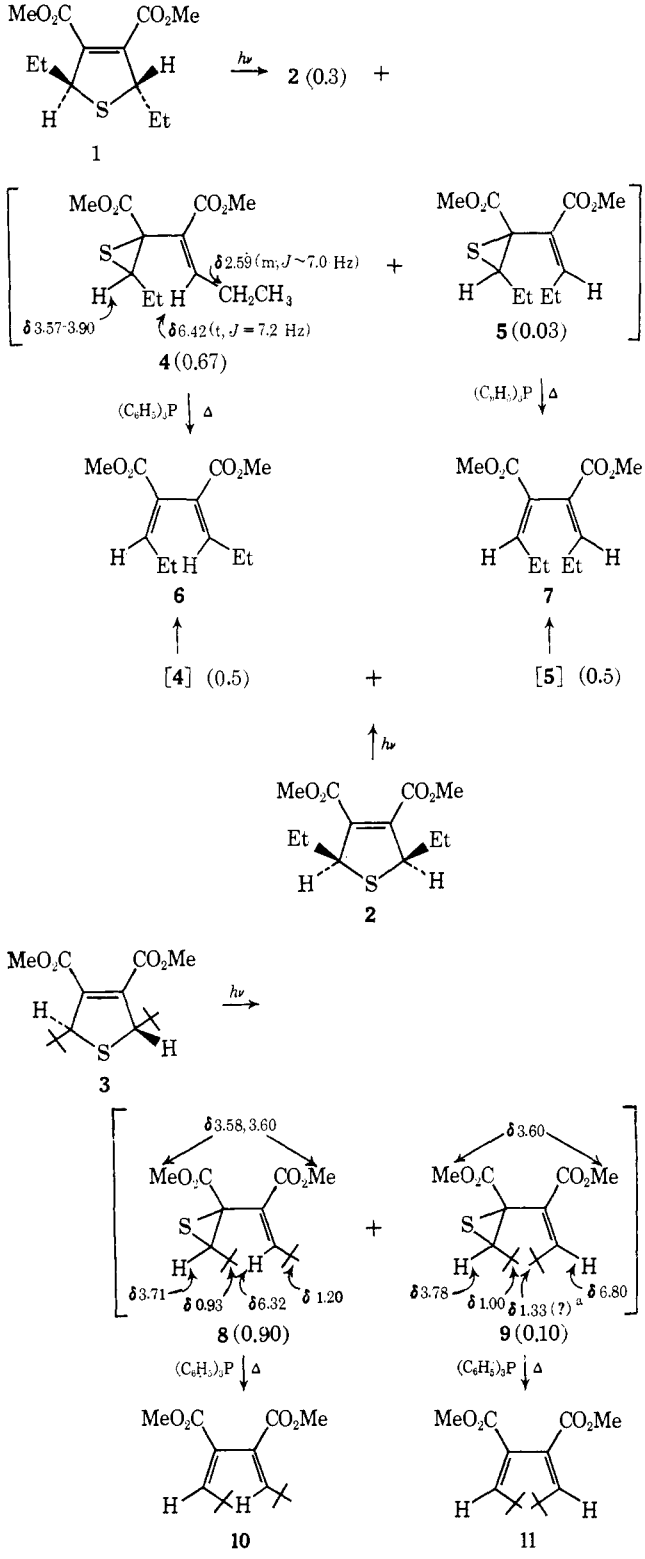
Received January 21, 1971

Photochemistry of 2,5-Dihydrothiophenes. A Facile, Stereoselective Ring Contraction

Sir:

The 2,5-dihydrothiophenes **1–3** recently became available through the stereospecific thermal addition of thiocarbonyl ylides[1] to dimethyl acetylenedicarboxylate.

Chart I



[a] Overlap with adsorptions from **11** makes assignment difficult in the CAT spectrum.

(1) R. M. Kellogg, S. Wassenaar, and J. Buter, *Tetrahedron Lett.*, 4689 (1970).