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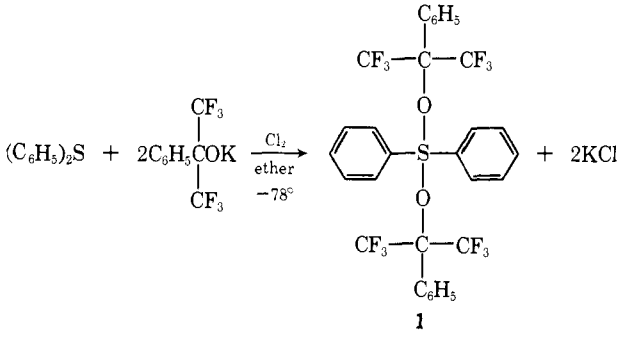
Sulfuranes. II. The Isolation and Characterization of a Crystalline Dialkoxydiarylsulfurane

Sir:

In the preceding paper[1] spectroscopic evidence was advanced for the covalent nature of the S–O bonds of an unsymmetrical dialkoxydiarylsulfurane in solution. We now describe the isolation and characterization of a crystalline symmetrical dialkoxydiarylsulfurane (**1**) of surprising stability.



1

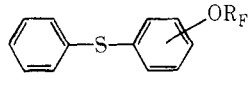
Sulfurane **1** was prepared in solution by both of the routes described in the preceding communication.[1] It is most conveniently prepared by the illustrated route involving treatment of an ether solution of the potassium salt of hexafluoro-2-phenyl-2-propanol (R_FOH), prepared by reaction of the alcohol with potassium metal, and diphenyl sulfide with chlorine at −78°. Filtration removes the potassium chloride and removal of the ether from the filtrate *in vacuo* leaves white, crystalline **1** in nearly quantitative yield. Moisture must be avoided at all stages since the sulfurane is hydrolyzed very rapidly to give diphenyl sulfoxide and R_FOH. The synthesis can easily be carried out on a large scale. The product is purified by grinding the crystals and removing volatile impurities (excess diphenyl sulfide or R_FOH) at high vacuum ($<10^{-4}$ Torr) at room temperature or by recrystallization from pentane; mp 107–109°. *Anal.* Calcd for $C_{30}H_{20}O_2F_{12}S$: C, 53.57; H, 3.00; S, 4.77. Found: C, 54.11; H, 3.20; S, 4.65. The crystalline material is stable indefinitely at room temperature.

The mass spectrum shows a sizable (1.8% of the base peak at low ionizing voltage) molecular ion peak at *m/e* 672 and a prominent fragmentation peak at *m/e* 429 corresponding to loss of one alkoxy ligand to give an alkoxysulfonium ion. High-resolution peak matching techniques show the molecular ion at *m/e* 672.0987 (calcd for **1**, 672.0992): ir (CCl_4) 1258 (s), 1208 (s), 1168 (s), 1060 (s), 962 (m), 945 (m), 710 (m), and 675 cm^{-1} (m). The 220-MHz proton nmr (CCl_4) shows peaks at δ 8.1 (m, 4, ortho protons of SC_6H_5), 7.5 (m, 10, meta and para protons of SC_6H_5 and ortho protons of the alkoxy phenyl), and 7.3 ppm (m, 6, meta and para protons of the alkoxy phenyl). The ^{19}F spectrum (ether, −43°) shows a single peak at 69.3 ppm (upfield from $CFCl_3$) together with an ubiquitous R_FOH impurity peak at 74.6 ppm resulting from hydrolysis of **1**. At high temperature both peaks begin to show exchange broadening.

The exchange of alkoxy ligands with R_FOH is much faster in solvents $CDCl_3$ and CCl_4, which are less able than is ether to serve as hydrogen bond acceptors toward R_FOH. To one sample in CCl_4, showing marked broadening of sulfurane and R_FOH ^{19}F nmr peaks at room temperature, was added enough potassium hydride to convert the alcohol to R_FOK. The resulting solution showed sharp peaks for sulfurane and alkoxide in a dramatic demonstration that ligand exchange is more rapid with R_FOH than with R_FOK. A mechanistic interpretation has been given.[1]

Ligand exchange of **1** with other alcohols is also rapid. Alcohols lacking β protons, such as perfluoro-*tert*-butyl alcohol[2] or neopentyl alcohol, show rapid exchange in an equilibrium mixture of relatively stable dialkoxydiarylsulfuranes. Exchange with other alcohols, acids, and other active hydrogen compounds appears also to be rapid, with subsequent reaction of the sulfurane providing a basis for several synthetic applications, some of which are described in another paper.[3]

Compounds analogous to **1**, but bearing halogen ligands, are very unstable,[4] decomposing in the range −40 to 10°. These compounds decompose by a route involving chloride as a nucleophile or by routes involving the generation of a chlorinating agent. In contrast to this, **1**, lacking halogen ligands, decomposes only slowly in solution at room temperature. Upon boiling an ether solution of **1** for several days, or heating molten **1** at 120° a few hours, 1 equiv of R_FOH and 1 equiv of a mixture of nuclear alkoxylation products, **2a**, **b**, and **c**, are generated.



2a (ortho)
b (meta)
c (para)

These compounds were identified by elemental analyses, mass spectrometry, and nmr. The ortho:meta:para ratios in the product mixture (49:18:33 in the melt at 120°, 61:14:25 at 77° in ether in a sealed tube) favor ortho substitution in a pattern similar to that seen for several intramolecular aromatic rear-

(1) I: J. C. Martin and R. J. Arhart, *J. Amer. Chem. Soc.*, **93**, 2339 (1971).

(2) D. E. Young, L. R. Anderson, D. E. Gould, and W. B. Fox, *ibid.*, **92**, 2313 (1970). We are grateful to Dr. Anderson for the gift of a sample of this compound.

(3) J. C. Martin and R. J. Arhart, to be submitted for publication.

(4) R. J. Maner, Ph.D. Thesis, University of Iowa, 1968; N. C. Baenziger, R. E. Buckles, R. J. Maner, and T. D. Simpson. *J. Amer. Chem. Soc.*, **91**, 5749 (1969); I. B. Douglass, K. R. Brower, and F. T. Martin, *ibid.*, **74**, 5770 (1952); D. C. Owsley, G. K. Helmkamp, and M. F. Rettig, *ibid.*, **91**, 5239 (1969); see also C. Walling and M. J. Mintz, *J. Org. Chem.*, **32**, 1286 (1967).

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

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

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

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).
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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

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(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).
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(6) S. Wolfe, W. S. Lee, and R. Misra, *ibid.*, 1067 (1970).
(7) T. Leigh, *J. Chem. Soc.*, 3616 (1965).