Tetrahedron Letters No.11, pp. 849-852, 1969. Pergamon Press. Printed in Great Britain.

REARRANGEMENTS OF CYCLIC SULFOXIDES

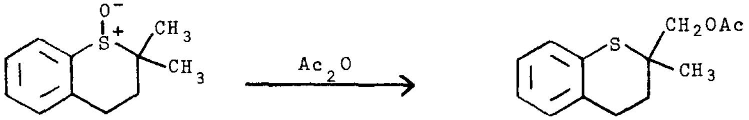
Robert B. Morin, Douglas O. Spry, and Richard A. Mueller

The Lilly Research Laboratories
Eli Lilly and Company
Indianapolis, Indiana

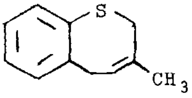
(Received in USA 25 November 1968; received in UK for publication 29 January 1969)

It has been found that phenoxymethyl penicillin sulfoxide methyl ester can undergo an internal oxidative-reductive reaction in which a carbon β to the sulfur becomes oxidized.[1] We have found in the work reported here that this appears to be a general reaction of cyclic sulfoxides which do not possess an α-hydrogen.

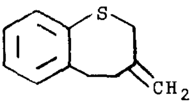
The 2,2-dimethylthiachroman 1-oxide 1, mp 60-61°, on treatment with



1 2



3

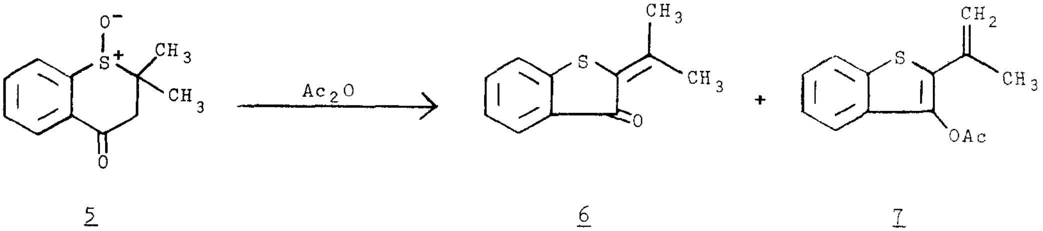


4

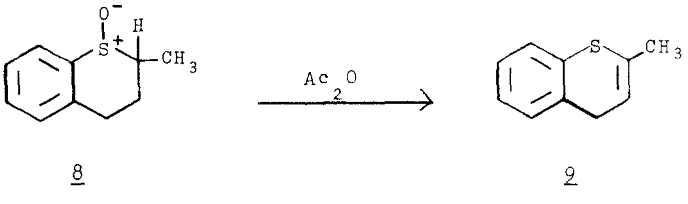
freshly distilled acetic anhydride at reflux temperature gave compound 2 in 80% yield. The structural assignment is based on physical data [ir ($CHCl_3$) 1733 cm^{-1}; nmr ($CHCl_3$) δ 1.40 (s, 3), 2.03 (s, 3), 1.93 (m, 2), 2.83 (m, 2), AB pattern 4.20 and 4.05 (m, 2, J = 11 Hz), 7.01 (s, 4)] and on further chemical transformations of the substance.[2] Addition of small quantities of water to the anhydride caused a decrease in yield of 2 with concomitant formation of olefinic compounds and the two products resulting from disproportionation. With addition of small quantities of conc HCl to Ac_2O only disproportionation was observed. Sodium acetate did not affect the nature of product of 1 with Ac_2O.

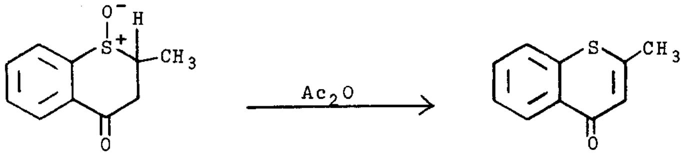
Two olefinic materials were isolated by VPC and shown to have structures 3 [nmr ($CHCl_3$) δ 1.68 (br. s, 3), 3.37 (br. s, 2), 3.58 (br. d, 2), 5.67 (m, 1), 7.2 (m, 4)] and 4 [nmr ($CHCl_3$) δ 2.4 (m, 2), 3.0 (m, 2), 3.28 (s, 2), 4.82 (br. s, 2), 7.2-7.5 (m, 4)]. The same olefins were produced in higher yield but in a different ratio by treatment of 1 with pTsOH in refluxing xylene.

The effect on the reaction of a carbonyl group β to the sulfoxide was studied with the keto-sulfoxide 5, mp 92.5-93.5°. In this case only the ring contracted products 6 [mp 103-5°; nmr ($CHCl_3$) δ 2.01 (s, 3), 2.50 (s, 3), 7.36 (m, 4)] and 7 [mp 38-40°; ir ($CHCl_3$) 1772 cm^{-1}; nmr ($CHCl_3$) δ 2.16 (br. s, 3), 2.35 (s, 3), 5.20 (br. s, 1), 5.45 (s, 1), 7.53 (m, 3), 8.50 (m, 1)], but not those arising from oxidation of the methyl groups, were obtained from Ac_2O treatment. As with the earlier sulfoxide, addition of acid caused disproportionation to occur.



In the Ac_2O treatment of the sulfoxides 8, mp 76-8°, and 10, mp 74-94°, which possess a hydrogen on the α-carbon and in which the carbon-sulfur bond





10

11

is not subject to steric constraints as in penicillin sulfoxide, a Pummerer reaction was observed.[3] The products 9 [nmr ($CHCl_3$) δ 1.98 (s, 3), 3.30 (m, 2), 5.63 (m, 1), 7.08 (s, 4)] and 11[4] are formed in nearly quantitative yields, and no substances resulting from oxidation of a carbon β to the sulfur were obtained. The sulfoxide 10 was a mixture of the two diastereomers; whereas, 8 was a single isomer, probably that in which the oxygen and methyl group are *cis*.[5]

The presently reported reactions of 1 and 5 can be described as an elimination followed by addition of the sulfenyl derivative to the generated double bond. A similar mechanism was suggested in the penicillin work. The different course between reaction of 1 and that of 5 can then be due to a difference in direction of the elimination. The results of the work on penicillin sulfoxide esters[1] and the sulfoxides of 2[2] indicate that the overall reaction can be stereospecific.

Some electrophilic reagent is needed as heating 1 at reflux in xylene did not cause a reaction. Sulfoxides 1 and 5 will undergo dehydrative rearrangements on photolysis[6] at room temperature to the same or similar products which were formed by heating with electrophilic agents.

REFERENCES

1. R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, *in press*.

2. D. O. Spry and R. B. Morin, unpublished results.

3. C. R. Johnson, J. C. Sharp, and W. G. Phillips, *Tetrahedron Letters*, 5299 (1967).

4. Farbenfabriken Bayer Akt.-Ges., British Patent 804,689; Chem. Abstr., 53, 11413d (1959).

5. This conclusion resulted from consideration of physical data, unpublished work from these laboratories and C. R. Johnson, personal communication.

6. R. A. Archer and B. S. Kitchell, J. Amer. Chem. Soc., 88, 3462 (1966), and R. A. Archer, personal communication.