[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UPJOHN CO., KALAMAZOO, MICH.]

Unsaturated Heterocyclic Systems. IX. Derivatives of 3H-Azepine[1-3]

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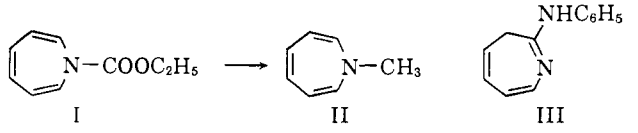
1,3-Dihydro-3,5,7-trimethyl-2H-azepin-2-one and its thio analog, 1,3-dihydro-3,5,7-trimethyl-2H-azepin-2-thione, reacted readily with triethyloxonium fluoroborate in methylene chloride solution to give rise to derivatives of 3H-azepine. The physical and spectral properties of these substances are discussed. 2-Ethoxy-3,5,7-trimethyl-3H-azepine has been shown to be rather stable under several sets of circumstances, but under forcing conditions has been found to be capable of nucleophilic substitution.

A number of reports dealing with the preparation of derivatives of various monocyclic azepines have recently appeared in the literature. Thus, generation of carbethoxynitrene, either by the photodecomposition[5] or thermolysis[6] of ethyl azidoformate or by the α-elimination of *p*-nitrobenzenesulfonic acid from its N-hydroxyurethane ester with triethylamine,[7] in the presence of benzene has been found to afford N-carbethoxyazepine (I). Lithium aluminum hydride reduction of I probably gives the unstable II.[8] Decomposition of phenyl azide in aniline is reported to result in the formation of 2-anilino-3H-azepine (III).[9] The present paper is concerned with the facile preparation of several new derivatives of 3H-azepine from 1,3-dihydro-2H-azepin-2-ones which are readily available by the chloramine ring expansion of appropriately substituted phenols.[10]

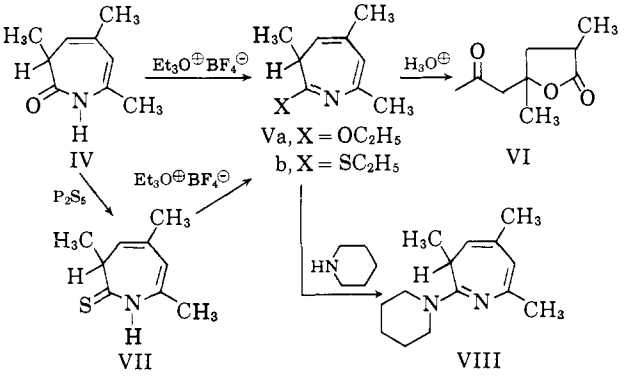


I II III

The ready conversion of an amide function to an imino derivative by a variety of reagents has been achieved. However, in the present instance, reaction of 1,3-dihydro-3,5,7-trimethyl-2H-azepin-2-one (IV) with dimethyl sulfate[11] or benzenesulfonyl chloride–pyridine[12] according to established directions gave tarry materials.

In another approach, addition of a slight excess of phosphorus pentachloride to a slurry of IV in dry benzene[13] resulted in a gentle exothermic reaction which continued for a short period and which terminated in a short reflux period. The oil which resulted on appropriate work-up proved to be quite unstable and was rapidly converted to dark tarry products. This was especially in evidence when the oil was treated with primary or secondary amines.

The failure of the above syntheses led us to examine the possibility of utilizing triethyloxonium fluoroborate[14] to achieve our goal. Reaction of the dihydroazepinone IV with this reagent was found to proceed readily at room temperature in methylene chloride solution. Decomposition of the reaction mixture with aqueous potassium carbonate solution gave rise to 2-ethoxy-3,5,7-trimethyl-3H-azepine (Va) in excellent yield. The infrared spectrum of Va displayed principal bands at 1613 (C=N) and 1551 cm.$^{-1}$ (C=C). Its ultraviolet absorption in ethanol at 257 mμ (6300) was unchanged in 0.1 *N* ethanolic sodium hydroxide, but broad ill-defined absorptions were obtained in 0.1 *N* ethanolic hydrogen chloride. Its n.m.r. spectrum (Fig. 1) was in full agreement with the proposed structure (see below).



Acid hydrolysis of Va readily yielded the ketolactone VI identical in all respects with the product arising from the acid treatment of IV.[15] A rearrangement of the carbon skeleton of IV can therefore be precluded in the triethyloxonium fluoroborate reaction. The 2-ethoxy-3H-azepine (Va) is remarkably stable substance under normal conditions and can be stored indefinitely at room temperature without change.

Although the reaction of 2-ethoxypyridine and 2-ethoxyquinoline with various alkyl halides readily gives

(1) Unsaturated Heterocyclic Systems. VIII: L. A. Paquette, *J. Am. Chem. Soc.*, **86**, 4092 (1964).

(2) For a preliminary account of this work, see L. A. Paquette, *ibid.*, **85**, 4053 (1963).

(3) Presented in part at the Gordon Research Conference on Heterocyclic Chemistry, New Hampton, N. H., Aug. 24–28, 1964.

(4) Correspondence should be addressed to the Department of Chemistry, The Ohio State University, Columbus 10, Ohio.

(5) K. Hafner and C. Kornig, *Angew. Chem.*, **75**, 89 (1963).

(6) R. J. Cotter and W. F. Beach, *J. Org. Chem.*, **29**, 751 (1964).

(7) W. Lwowski, T. J. Maricich, and T. W. Mattingly, Jr., *J. Am. Chem. Soc.*, **85**, 1200 (1963).

(8) K. Hafner, *Angew. Chem.*, **75**, 1041 (1963).

(9) (a) R. Huisgen, D. Vossius, and M. Appl, *Chem. Ber.*, **91**, 1 (1958); R. Huisgen and M. Appl, *ibid.*, **91**, 12 (1958); M. Appl and R. Huisgen, *ibid.*, **92**, 2961 (1959). (b) Prof. Huisgen has informed the author in a private communication that renewed investigations of the azepines resulting from this reaction have shown conclusively that the products are not 2-substituted 7H-azepines as originally formulated,[9a] but rather are derivatives of 3H-azepine such as III; see A. A. Bothner-By and E. Vogel, in press.

(10) L. A. Paquette, *J. Am. Chem. Soc.*, **84**, 4987 (1962); **85**, 3288 (1963).

(11) R. E. Benson and T. L. Cairns, *ibid.*, **70**, 2115 (1948); *Org. Syn.*, **31**, 72 (1951).

(12) P. Oxley, D. A. Peak, and W. F. Short, *J. Chem. Soc.*, 1618 (1948); H. Plieninger, H. Bauer, A. R. Katritzky, and U. Lerch, *Ann.*, **654**, 165 (1962).

(13) For the conversion of amides to iminochlorides with phosphorus pentachloride, see, for example, C. L. Stevens and J. C. French, *J. Am. Chem. Soc.*, **76**, 4398 (1954).

(14) H. Meerwein, W. Florian, N. Schön, and J. Stopp, *Ann.*, **641**, 1 (1961), and earlier references cited therein.

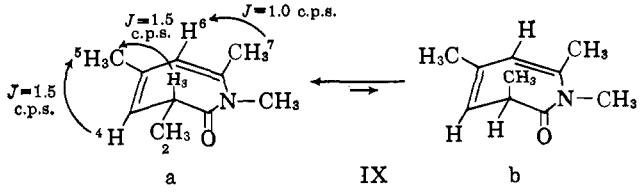
(15) It is important to note that the initial hydrolysis product of Va would be expected to be IV. However, the acid liability of the dihydroazepinone ring system has already been demonstrated[10] and therefore this intermediate is rapidly converted to VI under the conditions of the reaction.

rise to 1-alkyl-2-pyridones and -quinolones,[16] 2-ethoxy-3,5,7-trimethyl-3H-azepine (Va) is completely unreactive to methyl iodide. For example, Va was recovered in excellent yield after heating in a sealed tube at 100° with excess methyl iodide for 7 hr. No 1,3-dihydro-1,3,5,7-tetramethyl-2H-azepin-2-one[10] was found on careful examination of the reaction mixture. The failure of this reaction can be ascribed to the reduced basicity of the azepine nitrogen atom relative to that in pyridine or quinoline, thereby resulting in a greatly diminished capability to enter into nucleophilic displacement reactions.

With the removal of possible reactions at the azepine nitrogen, our attention was directed to a study of reactions at the imino carbon atom. Reaction of Va with secondary amines was very sluggish and generally required prolonged heating at elevated temperatures.[17] For example, when Va was heated in excess refluxing piperidine for 5 days, there was obtained a 58% recovery of the ethoxyazepine and a 72% yield (based on recovered azepine) of 2-piperidino-3,5,7-trimethyl-3H-azepine (VIII), identified as its perchlorate salt. The structure of VIII follows from its elemental analysis, n.m.r. and ultraviolet spectra [λ_{max}^{EtOH} 225 (13,450) and 276 mμ (8850)]. Similar reactions with morpholine and pyrrolidine afforded only tarry products.[17] Attempts to condense Va with ammonium chloride or amino acids were likewise unsuccessful.

The dihydroazepinone IV could also be converted to its thio analog VII with phosphorus pentasulfide in pyridine.[18] This dihydroazepinethione likewise smoothly reacted with triethyloxonium fluoroborate[19] and gave 2-ethyl-thio-3,5,7-trimethyl-3H-azepine (Vb). Assignment of structure was confirmed by analytical and spectral data. The absence of any gross structural change in this conversion was attested to by the close similarity of the n.m.r. spectra of Va and Vb (see figures).

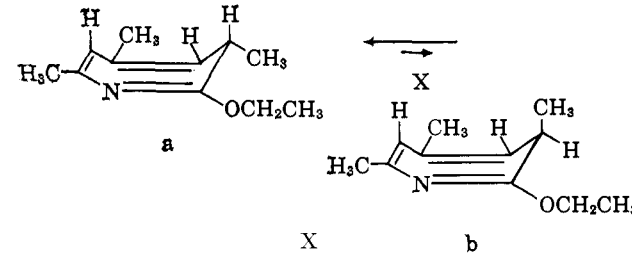
N.m.r. Spectra.—The published n.m.r. spectra of IV[10] and its N-methyl homolog[20] demonstrate that such systems display long-range coupling. Thus, normal *allylic coupling*[21] exists between the 7-methyl and H-6 on the one hand (J = 1.0 c.p.s.), and between the 5-methyl and H-4 on the other hand (J = 1.5 c.p.s.), as illustrated in structure IXa. The differing electronic environments of H-6 and H-4, because of their relative proximities to nitrogen, are undoubtedly



a IX b

responsible for the difference in the magnitude of the allylic coupling. The 5-methyl group is seen as a triplet (J = 1.5 c.p.s.) because of the superimposed *homoallylic coupling*[22] (of equal magnitude to the allylic coupling) of this substituent with the axially oriented 3-proton. This finding is in agreement with the observations of other workers[23] that axial allylic protons are ideally positioned to transmit spin information *via* the π-electron system to the vinyl substituent three carbons removed and substantiates the greater population of conformer IXa (with the axial H-3). Similar patterns for these substituents were also found in 1,3-dihydro-3,5,7-trimethyl-2H-azepine-2-thione (VII).

The n.m.r. spectrum of 2-ethoxy-3,5,7-trimethyl-3H-azepine (Va) is illustrated in Fig. 1. One of the interesting aspects of this spectrum was the appearance of the methylene portion of the ethoxy group as an AB system, indicating restricted rotation of this grouping. Of even greater interest was the observation that the 3-methyl substituent[24] is again seen as a triplet (J = 1.5 c.p.s.). This fact can only be congruent with the conclusion that at the temperature of the spectral determination (*ca.* 41°) Va exists predominantly in the form Xa which possesses the axial allylic H-6 and equatorial



a X b

5-methyl, with a low concentration of Xb in the equilibrium mixture. Examination of conformer Xa renders abundantly clear the source of steric bulk (the equatorial 3-methyl) which restricts the free rotation of the ethoxy group.

A similar conformational situation exists in the case of 2-ethylthio-3,5,7-trimethyl-3H-azepine (Vb) as evidenced by its n.m.r. spectrum (Fig. 2). The replacement of the oxygen atom by sulfur has resulted, however, in the appearance of the methylene portion of the ethyl thio grouping as a simple quartet centered at 173 c.p.s. (J = 8 c.p.s.). The increased van der Waals radius of the sulfur atom is obviously of the proper order of magnitude to permit free rotation of this grouping.

Experimental[25]

2-Ethoxy-3,5,7-trimethyl-3H-azepine (Va).—Into a dry 1-l. three-neck flask protected from atmospheric moisture was placed a solution of 91 g. (0.64 mole) of freshly redistilled boron trifluoride etherate in 300 ml. of anhydrous ether. Epichlorohydrin (44.4 g., 0.48 mole) was added dropwise at such a rate that the stirred solution remained in a state of constant gentle reflux. When the

(16) L. A. Paquette and G. Slomp, *J. Am. Chem. Soc.*, **85**, 765 (1963); L. A. Paquette and N. A. Nelson, *J. Org. Chem.*, **27**, 1085 (1962); E. C. Taylor, Jr., and A. J. Grovetti, *J. Am. Chem. Soc.*, **78**, 214 (1956); E. Späth and G. Koller, *Ber.*, **56**, 2454 (1923); L. Knorr and P. Rabe, *ibid.*, **30**, 927 (1892).

(17) Concomitant decomposition of the resulting amidines unfortunately also occurred in the useful temperature range.

(18) E. Klingsberg and D. Papa, *J. Am. Chem. Soc.*, **73**, 4988 (1951); E. C. Taylor, Jr., and A. E. Martin, *ibid.*, **74**, 6295 (1952).

(19) See S. Petersen and E. Tietze, *Ann.*, **623**, 166 (1959).

(20) L. A. Paquette, *J. Org. Chem.*, **28**, 3590 (1963).

(21) Proton spin–spin coupling between nuclei separated by one double and three single bonds, termed *allylic coupling*, has been extensively investigated. For a comprehensive listing of the references in this area, see J. T. Pinhey and S. Sternhell, *Tetrahedron Letters*, **No. 4**, 275 (1963).

(22) The term homoallylic coupling to describe coupling across symmetrically disposed four single and one double bonds was initially proposed by Pinhey and Sternhell,[21] and has apparently been accepted: M. Palmade, P. Pasnelle, J. Streith, and G. Ourisson, *Bull. soc. chim. France*, 1950 (1963); K. Takeda and M. Ikuta, *Tetrahedron Letters*, 277 (1964).

(23) D. J. Collins, J. J. Hobbs, and S. Sternhell, *ibid.*, 197 (1963); *Australian J. Chem.*, **16**, 1030 (1963); T. A. Wittstruck, S. K. Malhotra, and H. J. Ringold, *J. Am. Chem. Soc.*, **85**, 1699 (1963).

(24) The 3-methyl group in Va and Vb corresponds to the 5-methyl substituent in IX.

(25) Melting points are corrected while boiling points are uncorrected. All n.m.r. spectra were obtained on dilute solutions in deuteriochloroform with a Varian A-60 spectrometer (TMS = 0 c.p.s.).

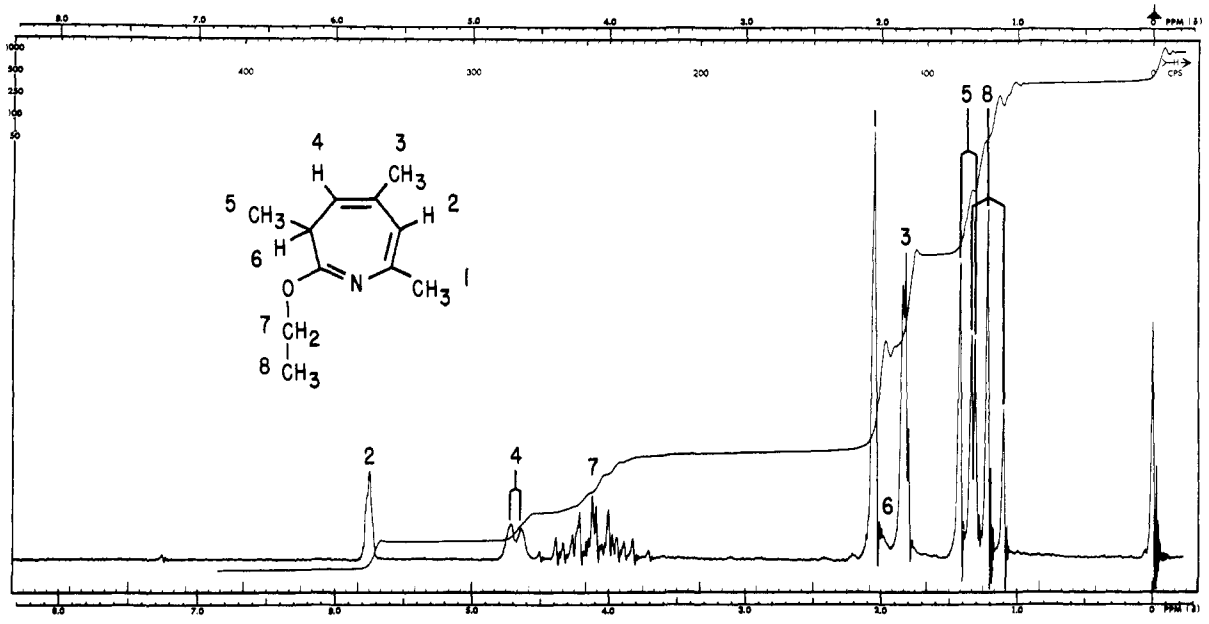


Fig. 1.—N.m.r. spectrum of 2-ethoxy-3,5,7-trimethyl-3H-azepine (Va).

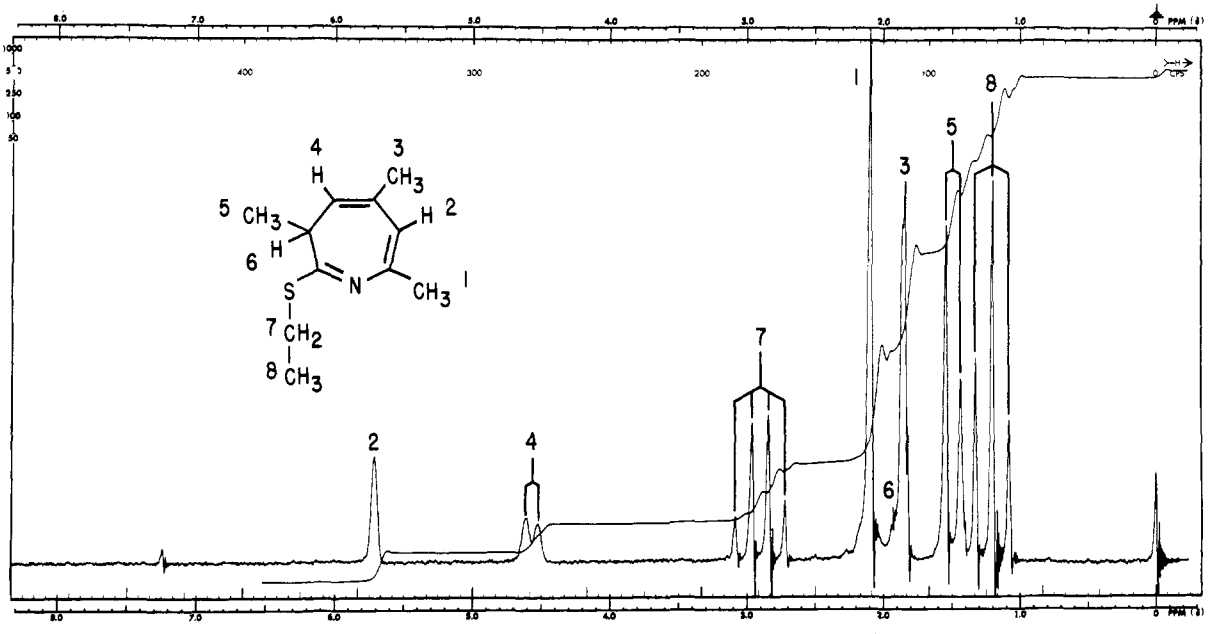


Fig. 2.—N.m.r. spectrum of 2-ethylthio-3,5,7-trimethyl-3H-azepine (Vb).

epichlorohydrin had been added, the oil which initially formed began to solidify. The mixture was stirred at room temperature for 2 hr. and the solvent was decanted. The triethyloxonium fluoroborate was washed well with anhydrous ether and dissolved in 50 ml. of dry methylene chloride. This solution was stirred at 10–15° while a solution of 60.4 g. (0.40 mole) of IV[10] in 200 ml. of dry methylene chloride was added dropwise. The resulting solution was stirred at room temperature for 2 hr. and allowed to stand overnight. To the stirred solution was cautiously added 76 g. of a 50% aqueous potassium carbonate solution. The precipitated solid was removed by filtration and the filtrate was dried, filtered, and evaporated. The residual oil was distilled to give 59.8 g. (83.5%) of a colorless liquid, b.p. 86–91° (13 mm.), n^{24}D 1.4940. A redistilled sample, b.p. 57° (1.1 mm.), n^{25}D 1.4946, was submitted for analysis.

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.73; H, 9.58; N, 7.79.

Acid Hydrolysis of Va.—A mixture of 5.4 g. (0.03 mole) of Va and 30 ml. of 4 *N* hydrochloric acid was refluxed for 1 hr. The resulting solution was cooled and twice extracted with 25-ml. portions of methylene chloride. The combined organic layers were dried, filtered, and evaporated to give a pale yellow oil. Distillation of this material afforded 4.6 g. (90.3%) of 5-acetonyl-dihydro-3,5-dimethyl-2(3H)-furanone (VI) as a colorless liquid, b.p. 99–102° (0.25 mm.), n^{25}D 1.4538. The infrared spectrum of this material was superimposable on that of an authentic sample.[10]

3,5,7-Trimethyl-2-piperidino-3H-azepine Perchlorate (VIII·HClO$_4$).—A mixture of 14.0 g. (0.076 mole) of Va and 17 g. (0.2 mole) of piperidine was heated under reflux in an oil bath (140–150°) for 5 days. The resulting dark liquid was directly distilled to give 8.2 g. (58%) of recovered Va, b.p. 59–62° (1.3 mm.), and 5.1 g. (72.2% based on recovered starting material) of a pale yellow oil, b.p. 105–112° (1.3 mm.). This material was converted to its perchlorate salt by dissolving the base in ether and adding a 50% solution of 70% perchloric acid in ethanol dropwise to pH 3; white platelets, m.p. 156–157° after several recrystallizations from ethanol–ether.

Anal. Calcd. for $C_{14}H_{23}ClN_2O_4$: C, 52.74; H, 7.27; N, 8.79. Found: C, 52.54; H, 7.25; N, 9.14.

1,3-Dihydro-3,5,7-trimethyl-2H-azepine-2-thione (VII).—A solution of 45.3 g. (0.30 mole) of IV and 78.0 g. (0.35 mole) of phosphorus pentasulfide in 450 ml. of pyridine was refluxed with stirring for 3 hr. The warm solution was poured into 1500 ml. of warm water. After cooling the mixture, the precipitated solid was filtered, washed with water, and dried. The crude product was chromatographed on Florisil. Elution with hexane–acetone

(9:1) gave a pale yellow solid which was recrystallized from ethyl acetate–hexane to give 22.1 g. (44.2%) of VII, m.p. 136.5–137°. Three recrystallizations of this material from ethyl acetate–hexane gave pure dihydroazepinethione as pale yellow needles, m.p. 136.5–137°; λ_{max}^{EtOH} 244 (8150), 310 (13,450), and 364 sh mμ (1050). The n.m.r. spectrum of VII is very similar to that of IV[10]: 3-methyl (94 c.p.s., doublet, J = 6.5 c.p.s.), 3-proton (153 c.p.s., quintuplet, J = 5.5 c.p.s.), 4-proton (294 c.p.s., doublet, J = 5.5 c.p.s.), 5-methyl (109 c.p.s., triplet, J = 1.5 c.p.s.), 6-proton (350 c.p.s., singlet), and 7-methyl (224.5 c.p.s., singlet).

Anal. Calcd. for $C_9H_{13}NS$: C, 64.62; H, 7.83; N, 8.37; S, 19.17. Found: C, 65.00; H, 7.79; N, 8.24; S, 19.37.

2-Ethylthio-3,5,7-trimethyl-3H-azepine (Vb).—Triethyloxonium fluoroborate, prepared in the usual manner (see above) from 11.1 g. (0.12 mole) of epichlorohydrin, 22.8 g. (0.16 mole) of boron trifluoride etherate, and 75 ml. of anhydrous ether, was dissolved in 50 ml. of dry methylene chloride. This solution was stirred while a solution of 16.7 g. (0.10 mole) of VII in 100 ml. of dry methylene chloride was added dropwise. The resulting solution was stirred at room temperature for 2 hr. and allowed to stand overnight. To the stirred solution was cautiously added 19 g. of a 50% aqueous potassium carbonate solution. The precipitated solid was removed by filtration and the filtrate was dried, filtered, and evaporated. The residual oil was distilled to give 9.2 g. (47.2%) of colorless liquid, b.p. 72–74° (0.2 mm.), $n^{26}D$ 1.5462. A redistilled sample, b.p. 76° (0.25 mm.), $n^{26}D$ 1.5498, was submitted for analysis; λ_{max}^{EtOH} 225 (12,900) and 284 mμ (6800).

Anal. Calcd. for $C_{11}H_{17}NS$: C, 67.63; H, 8.77; N, 7.17; S, 16.42. Found: C, 67.73; H, 8.66; N, 6.63; S, 16.05.

Acknowledgment.—The author is indebted to P. E. Marlatt for the preparation of substantial quantities of IV and to Dr. D. R. Myers and staff of our Physical and Analytical Chemistry Department for the analytical and spectral data.

[CONTRIBUTION FROM THE ESSO RESEARCH AND ENGINEERING CO., PROCESS RESEARCH DIVISION, EXPLORATORY RESEARCH SECTION, LINDEN, N. J.]

Reactions of Thiols with Sulfoxides. II. Kinetics and Mechanistic Implications[1]

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A detailed kinetic study on various thiol–sulfoxide reactions has been carried out. The reactions investigated gave good pseudo-first-order kinetics for thiol and sulfoxide disappearance in the presence of excess sulfoxide and thiol, respectively. When equimolar quantities of thiol and sulfoxide were employed, good second-order behavior was observed. Thus it is concluded that these reactions are over-all second order in nature. Rates of reaction were markedly dependent on the acidity of the thiol. The ease of oxidation for a series of thiols by TMSO was benzene- > 2-methylbenzene- > α-toluene- > 1-dodecanethiol. A linear relationship between the pK_a of each thiol and the activation energy for reaction with TMSO was observed. It is concluded that these reactions proceed by a rate-determining step involving formation of an unstable sulfoxide–thiol adduct which is rapidly consumed by reaction with another molecule of thiol. This conclusion was substantiated by n.m.r. studies.

Introduction

In a previous paper,[2] the scope, synthetic applications, and limitations for the oxidation of thiols and dithiols by aliphatic sulfoxides in a nitrogen atmosphere were presented. Of the sulfoxides investigated, tetramethylene sulfoxide (TMSO) and dimethyl sulfoxide (DMSO) were found to be the most efficient oxidizing agents. Stoichiometrically, it was established that 2 moles of thiol react with 1 mole of sulfoxide to produce 1 mole of disulfide (oxidized thiol), 1 mole of sulfide (reduced sulfoxide), and 1 mole of water. In these initial studies,[1,2] a variation of the reaction temperature established that the ease of thiol oxidation was markedly dependent on the acidity of the thiol. In the presence of TMSO and DMSO at room temperature the order of thiol reactivity based on the yield of disulfide was ArSH > $ArCH_2SH$ >> RSH. On the basis of this finding, it was suggested that the mechanism of thiol–sulfoxide reactions was analogous to the oxidation of halogen acids by DMSO.[3] Such reactions are believed to proceed by formation of a protonated sulfoxide adduct which is formed in an equilibrium reaction (eq. 1). It has been suggested that the protonated intermediate is then destroyed by reaction with another molecule of acid (eq. 2 and 3). The stoichiometry previously observed for the thiol–sulfoxide reactions is also consistent with a reaction sequence of this general type. However, the results in the previous paper did not allow any definite conclusions on the rate-determining step and over-all reaction mechanism to be made. Conclusions of this type must be substantiated by detailed kinetic analyses. Such kinetic studies are the subject matter of the present paper.

$$R_2SO + HX \rightleftharpoons \left[R\text{–}\overset{\oplus}{S}(OH)\text{–}R \right] X^{\ominus} \quad (1)$$

$$\left[R\text{–}\overset{\oplus}{S}(OH)\text{–}R \right] X^{\ominus} + HX \rightleftharpoons \left[R_2\overset{\oplus}{S}X \right] X^{\ominus} + H_2O \quad (2)$$

$$\left[R_2\overset{\oplus}{S}X \right] X^{\ominus} \rightleftharpoons R_2S + X_2 \quad (3)$$

Results

A detailed kinetic study on the oxidation of various thiols by TMSO and DMSO has been carried out. All reactions were conducted under nitrogen in sealed vials. Rate measurements were obtained by sampling the reaction mixture with a syringe and subsequently analyzing the aliquot by gas chromatography using the procedure outlined in the Experimental section. Quantitative data were obtained with the aid of an internal hydrocarbon standard. Initially, the effect of thiol acidity on the rate of oxidation was examined with four thiols and TMSO at 100°. In all cases, 6.25 mmoles of thiol was added to a four molar excess of sulfoxide which contained 6.25 mmoles of an internal standard. Pseudo-first-order rate constants for the

(1) T. J. Wallace, *Chem. Ind.* (London), 501 (1964), contains a preliminary account of a portion of this work.

(2) T. J. Wallace, *J. Am. Chem. Soc.*, **86**, 2018 (1964).

(3) For a summary see: W. O. Ranky and D. C. Nelson, "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed. Pergamon Press, Inc., New York, N. Y., 1961, Chapter 17.