analyses, and Mr. C. Homnick for the Spinco Beckman amino acid analysis.

Registry No.—D-Penicillamine, 52-67-5; hydrogen fluoride, 7664-39-3; fluoroxytrifluoromethane, 373-91-1; 3-fluoro-D-valine hydrochloride, 59752-73-7; 3-fluoro-D-valine, 59752-74-8; (−)-ephedrine, 299-42-3; (+)-*threo*-1-phenyl-2-methylaminopropanethiol hydrochloride, 59752-75-9; bis(1-phenyl-2-methylaminopropyl) sulfide dihydrochloride, 59738-51-1; (+)-pseudoephedrine, 90-82-4; DL-*threo*-phenylserine, 2584-75-0; β-mercapto-DL-phenylalanine hydrochloride, 59779-79-2; *N*-chlorosuccinimide, 128-09-6; β-fluoro-DL-phenylalanine hydrochloride, 59729-21-4; β-fluoro-DL-phenylalanine, 57362-93-3; L-cysteine hydrochloride, 52-89-1; 3-fluoro-L-alanine hydrochloride, 59729-22-5; 3-fluoro-L-alanine, 35455-21-1; 3,3-difluoro-L-alanine, 59729-23-6; 2-diethylaminoethanethiol, 100-38-9; *N*,α-dimethyl-β-mercaptophenethylamine, 4389-42-8; homocysteine lactone, 2338-04-7; 3-mercapto-3-methylbutyric acid, 59729-24-7; 2-mercaptosuccinic acid, 70-49-5; 2,2-dibutyl-1,3-dithiolane, 59729-25-8; cysteinesulfinic acid, 1115-65-7; cystine 1,1-dioxide, 30452-69-8; 2-diethylaminoethyl fluoride, 369-60-8; 2-diethylamino-1,1-difluoroethane, 59729-26-9; *N*,α-dimethyl-β-fluorophenethylamine, 59729-27-0; homocystine 1,1-dioxide, 59729-28-1; 1,1-bis(ethylthio)-1-octene, 13880-01-8; 3,3-dimethylacrylic acid, 541-47-9; succinic acid, 110-15-6; 5,5-difluorononane, 59729-29-2.

References and Notes

(1) (a) H. Kwart and L. J. Miller, *J. Am. Chem. Soc.*, **80**, 884 (1958), and following papers; (b) H. Baganz and G. Dransch, *Ber.*, **93**, 782 (1960); (c) B. E. Norcross and R. L. Martin, *J. Org. Chem.*, **34**, 3703 (1969).
(2) W. Hengstenberg and K. Wallenfels, *Carbohydr. Res.*, **11**, 85 (1969).
(3) (a) J. Kollonitsch, G. A. Doldouras, and V. F. Verdi, *J. Chem. Soc. B*, 1093 (1967). (b) J. Kollonitsch, L. Barash, and G. A. Doldouras, *J. Am. Chem. Soc.*, **92**, 7494 (1970). (c) The reaction of fluorine with amines often affords the *N,N*-difluoroamine. See, for example, C. M. Sharts, *J. Org. Chem.*, **33**, 1008 (1968); C. L. Coon, M. E. Hill, and D. L. Ross, *ibid.*, **33**, 1387 (1968).
(4) Cf. the attempted preparation of β-fluoro-DL-phenylalanine: E. D. Bergman and A. M. Cohen, *Isr. J. Chem.*, **8**, 925 (1970).
(5) To be published.
(6) The product was identified by NMR, electrophoretic migration to the positive electrode (10% acetic acid system, ninhydrin visualization), and a positive starch–iodide reaction.
(7) Identified by comparison with an authentic sample.
(8) R. Marshall, M. Winitz, S. M. Birnbaum, and J. P. Greenstein, *J. Am. Chem. Soc.*, **79**, 4538 (1957).
(9) Prepared in these laboratories by Dr. A. N. Scott following the procedure of G. Toennies and J. L. Kolb, *J. Biol. Chem.*, **128**, 399 (1939); cf. D. B. Reisner, *J. Am. Chem. Soc.*, **78**, 2132 (1956).
(10) Identified by its mass spectrum.
(11) Identified by comparison with an authentic sample (Calbiochem Corp., La Jolla, Calif.).
(12) Identified by comparison with a sample synthesized according to R. Emeleozzi and L. Pichat, *Bull. Soc. Chim. Fr.*, 1887 (1959).
(13) Identified by comparison with a sample obtained by photofluorination of L-alanine (J. Kollonitsch and L. Barash, to be published).
(14) Prepared in the usual way from 5-nonanone and 1,2-ethanedithiol. The compound, bp 135–138 °C (5 mm), was characterized by NMR and elemental analysis which afforded values within 0.30% of the calculated.
(15) L. C. Renzema, J. Stoffelsma, and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **78**, 354 (1959).
(16) H. Nashimura, *Yakugaku Zasshi*, **84**, 806 (1964).
(17) This compound was isolated as the hydrochloride, whose elemental analysis and mass spectrum were in accord with the proposed empirical formula. The absence of an SH stretching absorption in the ir (3.8–3.9 μ) supports the structural assignment.
(18) F. Seel, E. Heinrich, W. Gombler, and R. Budenz, *Chimia*, **23**, 73 (1969).
(19) M. Azeem, M. Brownstein, and R. J. Gillespie, *Can. J. Chem.*, **47**, 4159 (1969).
(20) (a) W. A. Sheppard, *J. Am. Chem. Soc.*, **84**, 3058 (1962); (b) K. R. Brower and I. B. Douglas, *ibid.*, **73**, 5787 (1951).
(21) A. Schoberl, J. Borchers, H. Grafje, and V. Grewe-Pape, *Angew. Chem., Int. Ed. Engl.*, **5**, 249 (1966).
(22) J. Kollonitsch, L. Barash, F. M. Kahan, and H. Kropp, *Nature (London)*, **243**, 346 (1973); J. Kollonitsch and L. Barash, *J. Am. Chem. Soc.*, **98**, 5591 (1976).
(23) A. J. Finkel, *Adv. Fluorine Chem.*, **7**, 199–203 (1973).

Effect of Hydrogen Bonding and Solvent on the Conformational Preferences of Some 4-Hydroxythioxanthene *S*-Oxides

Dwight W. Chasar

B. F. Goodrich Research and Development Center, Brecksville, Ohio 44141

Received April 9, 1976

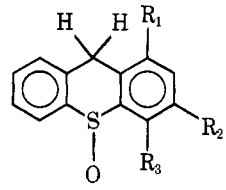
For a series of 4-hydroxythioxanthene *S*-oxides, it is shown by ^{1}H NMR spectroscopy that these molecules preferentially exist in conformations in which the sulfinyl oxygen is pseudoequatorial (e′) in chloroform but pseudoaxial (a′) in dimethyl sulfoxide solutions. Intra- vs. intermolecular hydrogen bonding is used to explain these observations. This is the first observation where the equilibrium between two possible conformations of a thioxanthene *S*-oxide type molecule has been altered such that either conformation can be preferred. The temperature dependence in the ^{1}H NMR spectrum was also examined.

The solution conformational preferences of thioxanthene *S*-oxide and its various substituted derivatives have been the subject of recent interest.[1-4] A number of conclusions have been made concerning the conformational dispositions of these molecules in solution.[5] The sulfinyl oxygen prefers to be in a pseudoequatorial position (10e′) (in a rapid conformational equilibrium) in thioxanthene *S*-oxide[3] (II, R = H). However, when a substituent (e.g., R = chloro, methyl) is placed in the 4 position peri to the sulfinyl moiety, the sulfinyl oxygen prefers the 10a′ position[3] (I). This is a result of steric repulsive interactions and demonstrates the larger steric requirement of sulfinyl oxygen vs. the sulfur lone pair. Thus, "the efficacy of peri substituents in altering the conformation of these (and related) systems"[3] was concluded.

Proton magnetic resonance (^{1}H NMR) spectroscopy has been the primary tool in making conformational assignments in these systems and several ^{1}H NMR parameters have become definitive in assigning preferred conformations in the thioxanthene *S*-oxide systems. When the 10e′ position (II) is preferred, the 9-H_a′ absorption appears upfield and broadened[2,3] relative to the 9-H_e′ absorption. It is broadened owing to long-range coupling to the peri (1,8) protons[2,3] as substantiated by decoupling experiments. Alternatively, when the 10a′ position (I) is preferred, the 9-H_a′ absorption appears downfield and broadened relative to the 9-H_e′ absorption. It appears downfield owing to the large deshielding effect of the 10a′ sulfinyl group. In addition, these criteria and the conformational preferences do not appear to depend significantly upon solvent, e.g., benzene, chloroform, or dimethyl sulfoxide (Me_2SO).[2,4]

In our search for new polymer additives, we began an investigation of some 4-hydroxythioxanthene *S*-oxide compounds. In the course of characterizing these compounds, we have shown (1) that a hydroxy group at C-4 does not necessarily drive the sulfinyl oxygen into the 10a′ position, (2) that solvent is sufficient for changing the conformational prefer-

Table I. Chemical Shifts of the C-9 Methylene Protons in Some Thioxanthene *S*-Oxides

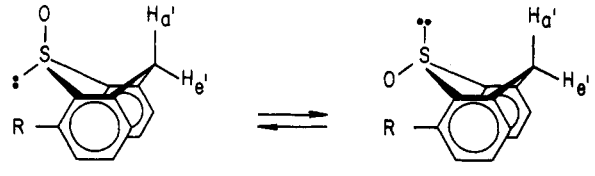


				Chemical shift[a-c]						
				$CDCl_3$			Me_2SO-d_6			
Compd	R_1	R_2	R_3	H_a'	H_e'	A^d	H_a'	H_e'	A^d	Ref
1	H	H	H	3.79 (b)	4.16	3.97				*e*
2	CH_3	H	CH_3	4.67 (b)	4.10	4.38				*f*
3	CH_3	H	OH	*g*	*g*		4.28[h]		4.28	This work
4	CH_3	CH_3	OH	3.29 (b)	4.17	3.73	4.38 (b)	4.02	4.20	This work
5	Cl	H	OH	3.48 (b)	4.63	4.05	4.47[h]		4.47	This work

[a] Chemical shifts are reported in parts per million downfield from internal tetramethylsilane. [b] This number represents the center of the doublet, calculated from $\delta_A - \delta_B = \sqrt{(\nu_4 - \nu_1)(\nu_3 - \nu_2)}$. The coupling constants are of the order of 17–18 Hz. [c] The letter b indicates that that absorption is broadened compared to the other. [d] This number represents the mathematical center of the AB quartet pattern and is included in the table to show the downfield shift of the methylene protons in the 10a′ conformer. [e] Reference 3. [f] J. L. Herrmann, Ph.D. Dissertation, Case Western Reserve University, 1970. [g] These values could not be determined due to poor solubility. [h] This number represents a broad singlet resulting from accidental equivalence of the H_a' and H_e' absorptions.

ences of these compounds, and (3) the first examples in which the same thioxanthene *S*-oxide molecule can be caused to exist preferentially in either of its two conformations.

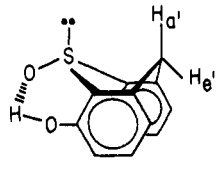
Compounds 1 and 2 (Table I) are representative of the 10e′ (II) and 10a′ (I) conformations, respectively. The H_a' ab-



10a′ 10e′

I II

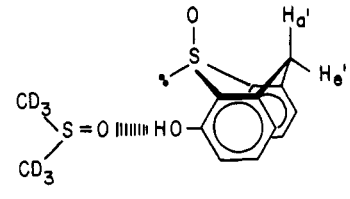
sorption is upfield and broadened in 1 and downfield and broadened in 2 compared to their respective H_e' absorptions (vide infra). Compounds 4 and 5 (and presumably 3) follow the same pattern in $CDCl_3$ as 1, which establishes their conformations as 10e′ (II). Apparently, strong intramolecular hydrogen bonding[6] between the sulfinyl and hydroxyl groups overpowers a steric or dipolar repulsive interaction, stabilizing the 10e′ conformer (III). However, in Me_2SO-d_6 solutions 4



10e′

III

exhibits a pattern similar to that of 2 (10a′) in $CDCl_3$, indicating that a conformational shift has occurred in changing solvents. Indeed, while the C-9 proton absorptions of 3 and 5 are accidentally equivalent in Me_2SO-d_6, there is a net downfield shift in the absorptions (compare *A* values in Table I). Thus, compounds 3, 4, and 5 exist in the 10a′ conformation (I) in Me_2SO-d_6. Presumably, the sulfinyl group of Me_2SO competes better for the hydroxyl group in 3, 4, and 5 than does the sulfinyl group of the molecule itself, breaking the intramolecular hydrogen bond. When this occurs, the steric bulk of the solvated hydroxyl group forces the 10e′ sulfinyl group into the 10a′ position (IV). This results in a deshielding of the



10a′

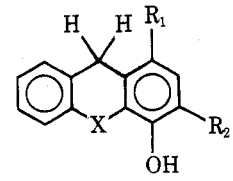
IV

H_a' absorption.[3] Thus, solvent can be important in determining the conformations of these types of heterocycles.

To lend credence to these conclusions, the effect of solvent on the hydroxyl proton absorptions in the sulfoxides and their corresponding sulfides was examined. The exact position of hydroxyl protons is dependent upon temperature and concentration, as well as solvent.[7] The chemical shifts of the hydroxyl protons shown in Table II were determined at approximately the same temperature (35 °C) and concentration (20% w/v) in each solvent. Therefore, any gross changes in position (in a particular solvent) should reflect changes in structure, i.e., hydrogen bonding. It is seen that the hydroxyl proton absorptions of the sulfoxides are shifted downfield by ~3 ppm compared to their corresponding sulfides in $CDCl_3$. This suggests that strong intramolecular hydrogen bonds exist between the 10e′ sulfinyl oxygen and the hydroxyl proton in the sulfoxides but at best only weak ones (between sulfur lone pair and hydroxyl) in the sulfides. However, in Me_2SO-d_6, all the hydroxy protons are shifted into the 9.5–11-ppm region, suggesting that all are bound strongly to solvent. This is certainly in tune with the deductions reached above.

Since the strength of hydrogen bonding is dependent upon temperature,[8] an examination of the ^1H NMR spectrum of the C-9 protons of the sulfoxides vs. temperature might prove revealing. An increase in temperature should weaken and break the hydrogen bond between the sulfinyl and hydroxyl groups (in a nonpolar solvent), resulting in a conformational shift from II to I. We examined the ^1H NMR spectrum of 4 in *o*-dichlorobenzene from 60 to 170 °C. The only alteration in

Table II. Chemical Shifts of the Hydroxyl Proton in Some 4-Hydroxythioxanthenes and Their S-Oxides



Compd		Registry no.		Chemical shift (OH) [a]			
				$CDCl_3$		Me_2SO-d_6	
R_1	R_2	X = S	X = SO	X = S	X = SO	X = S	X = SO
CH_3	H	59803-16-6	59803-19-9	5.17	*b*	9.74	10.42
CH_3	CH_3	59803-17-7	59803-20-2	5.20	9.42	*c*	9.47
Cl	H	59803-18-8	59803-21-3	5.39	8.7[d]	10.38	11.06

[a] Chemical shifts are reported in parts per million downfield from internal Me_4Si. [b] Insoluble. [c] Was not determined. [d] Extremely broad absorption.

the C-9 proton absorptions was a continual downfield shift of these absorptions (H_e', 9 Hz; H_a', 14 Hz). The upfield absorption remained broadened while the downfield one remained narrow indicating the H_a' and H_e' protons, respectively. Thus, even at 170 °C, the hydrogen bond is sufficiently strong to hold **4** in the $10_e'$ conformation.

In conclusion, these experiments have demonstrated the first examples wherein the two limiting conformations (in a rapid conformational equilibrium) of the same thioxanthene S-oxide molecule have been observed and that hydrogen bonding and solvent play the crucial role in establishing these conformations.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are not corrected. The ir spectra were taken as KBr pellets (except where indicated) on a Perkin-Elmer Model 467. All ^1H NMR spectra were obtained on a Varian Model A-60 spectrometer. Microanalyses were performed by Avon Lake Technical Center, B. F. Goodrich Co., Avon Lake, Ohio, and Huffman Labs, Inc., Wheatridge, Colo. All TLC analyses were performed on Analtech, Inc. precoated glass plates of silica gel using benzene or chloroform as eluent and uv light or iodine vapor for visualization. The silica gel used in column chromatography was Woelm silica gel, 70–230 mesh.

1-Methyl-4-hydroxythioxanthene (6). Diborane (40 ml of a 1.0 M solution in THF, 0.04 mol) was added by syringe to a stirred solution of 1-methyl-4-hydroxythioxanthone[9] (5.0 g, 0.02 mol) in 100 ml of THF at 0–5 °C under nitrogen. This mixture was stirred at 0–5 °C for 2 h, at ambient temperature overnight, and at reflux for 2 h. Ice and then water were added, the THF was evaporated, and the resulting mixture was extracted with chloroform. The extracts were dried ($MgSO_4$) and evaporated to afford a dark oil. Column chromatography on silica gel (100 g) using chloroform as eluent yielded 2.92 g (62%) of an oil which slowly crystallized to a tan solid: mp 99–101 °C; ir (neat) 3430, 1475, 1205, 810, 750 cm^{-1}; NMR ($CDCl_3$) δ 2.32 (3 H, s), 3.77 (2 H, s), 5.17 (1 H, s), 6.65 (1 H, d, J = 8 Hz), 6.95 (1 H, d, J = 8 Hz), 6.98–7.52 (4 H, m). Anal. Calcd for $C_{14}H_{12}OS$: C, 73.64; H, 5.31; S, 14.04. Found: C, 73.61; H, 5.41; S, 14.16.

1-Methyl-4-hydroxythioxanthene S-Oxide (3). A solution of *m*-chloroperbenzoic acid (6.68 g, 0.034 mol) in CH_2Cl_2 (120 ml) was added dropwise to a cold (0–5 °C) solution of **6** (7.72 g, 0.034 mol) in CH_2Cl_2 (35 ml). After stirring overnight, the mixture was warmed to room temperature and washed with a saturated solution of $NaHCO_3$ (2 × 100 ml) and water (100 ml). Drying ($MgSO_4$) and evaporation of the solvent led to 6.2 g (75%) of a white solid, mp 192–196 °C. Recrystallization from ethanol afforded TLC pure **3**: mp 205–206 °C dec; ir 3040 (OH), 970 cm^{-1} (S–O); NMR (Me_2SO-d_6) δ 2.35 (3 H, s), 4.28 (2 H, s), 6.86 (1 H, d, J = 8.5 Hz), 7.22 (1 H, d, J = 8.5 Hz), 7.35–7.92 (4, H, m), 10.42 (1 H, s). Anal. Calcd for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95; S, 13.12. Found: C, 68.79; H, 4.78; S, 12.98.

1-Chloro-4-hydroxythioxanthene (8). 1-Chloro-4-hydroxythioxanthone[10] was reduced as in the preparation of **6** to give a 92% yield of an off-white solid, mp 122–124 °C. Recrystallization from benzene afforded TLC pure **8**: mp 125–126 °C; ir 3400, 800, 735 cm^{-1}; NMR ($CDCl_3$) δ 3.99 (2 H, s), 5.39 (1 H, s), 6.67 (1 H, d, J = 8.5 Hz), 7.10 (1 H, d, J = 8.5 Hz), 7.0–7.5 (4 H, m). Anal. Calcd for $C_{13}H_9ClOS$: C, 62.78; H, 3.65; Cl, 14.25; S, 12.89. Found: C, 62.94; H, 3.40; Cl, 14.43; S, 12.99.

1-Chloro-4-hydroxythioxanthene S-Oxide (5). **8** was oxidized as in the preparation of **3** to afford an 89% yield of a light brown solid, mp 161–174 °C. Recrystallization from ethyl acetate gave TLC pure tan **5**: mp 191–193 °C dec; ir ~3000 (OH), 1432, 1308, 970 (S–O), 818, 755 cm^{-1}; NMR ($CDCl_3$) δ 3.48 (1 H, d, J = 17.6 Hz), 4.63 (1 H, d, J = 17.6 Hz), 6.78 (1 H, d, J = 9 Hz), 7.31 (1 H, d, J = 9 Hz), 7.49–7.97 (4 H, m), 8.67 (1 H, broad). Anal. Calcd for $C_{13}H_9ClO_2S$: C, 58.98; H, 3.43; Cl, 13.39; S, 12.11. Found: C, 59.21; H, 3.26; Cl, 13.58; S, 11.79.

1,3-Dimethyl-4-hydroxythioxanthene (7). A. 1,3-Dimethyl-4-hydroxythioxanthone. This compound was made from 2,4-dimethylphenol and thiosalicyclic acid by a procedure similar to that used to make 1-methyl-4-hydroxythioxanthone.[9] After recrystallization of the crude material from acetic acid, there was obtained a 32% yield of green product:[11] mp 252–255 °C; ir 3230, 1593, 1583, 1175, 860, 745 cm^{-1}; NMR (Me_2SO-d_6, 100 °C)[13] δ 2.35 (3 H, s), 2.75 (3 H, s), 7.03 (1 H, s), 7.3–7.7 (3 H, m), 8.2–8.5 (1 H, m).

B. 1,3-Dimethyl-4-hydroxythioxanthene (7). The product from **A** was reduced as in the preparation of **6** to give, after column chromatography (100 g of silica gel, $CHCl_3$ eluent), a 53% yield of amber oil: ir (neat) 3490, 1468, 1195, 1075, 752 cm^{-1}; NMR ($CDCl_3$) δ 2.20 (3 H, s), 2.32 (3 H, s), 3.75 (2 H, s), 5.20 (1 H, s), 6.83 (1 H, s), 7.02–7.54 (4 H, m). This material was relatively unstable, turning green in light and air. A good elemental analysis could not be obtained.

1,3-Dimethyl-4-hydroxythioxanthene S-Oxide (4). **7** was oxidized as in the preparation of **3** to afford a 96% of yellow crude product, mp 136–157 °C. Two recrystallizations from ethanol gave a white solid: mp 158–163 °C; ir ~3020 (OH), 1278, 960 cm^{-1} (S–O); NMR ($CDCl_3$) δ 2.17 (3 H, s), 2.31 (3 H, s), 3.29 (1 H, d, J = 17 Hz), 4.17 (1 H, d, J = 17 Hz), 6.95 (1 H, s), 7.3–7.90 (4 H, m), 9.42 (1 H, broad). Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46; S, 12.41. Found: C, 69.39; H, 5.24; S, 12.44.

Acknowledgment. We would like to thank the B. F. Goodrich Co. for allowing this paper to be published. Special gratitude goes to Mr. Timothy Pratt, who performed many of the syntheses, and Dr. Jerry Westfahl, who obtained all the ^1H NMR spectra.

Registry No.—1-Methyl-4-hydroxythioxanthone, 21896-76-4; *m*-chloroperbenzoic acid, 5106-10-5; 1-chloro-4-hydroxythioxanthone, 59803-22-4; 1,3-dimethyl-4-hydroxythioxanthone, 59803-23-5.

References and Notes

(1) W. Michaelis, O. Schindler, and R. Signer, *Helv. Chim. Acta*, **49**, 42 (1966).
(2) A. L. Ternay, Jr. and D. W. Chasar, *J. Org. Chem.*, **33**, 2237 (1968).
(3) A. L. Ternay, Jr., L. Ens, J. Herrmann, and S. Evans, *J. Org. Chem.*, **34**, 940 (1969).
(4) S. A. Evans and A. L. Ternay, Jr., *J. Org. Chem.*, **40**, 2993 (1975).
(5) Some of these conformational assignments have been substantiated in the solid phase; see, for example, A. L. Ternay, Jr., D. W. Chasar, and M. Sax, *J. Org. Chem.*, **32**, 2465 (1967); M. Sundaralingam and J. Jackobs, *Acta Crystallogr., Sect. B*, **25**, 2487 (1969); S. S. C. Chu and B. Chung, *Ibid.*, **30**, 235 (1974); S. S. C. Chu, *Ibid.*, **31**, 1082 (1975).
(6) Owing to the relative insolubility of these compounds in nonpolar solvents (e.g., CCl_4), solution ir investigations could not be performed.
(7) L.M. Jackson and S. Sternhell, "Nuclear Magnetic Resonance Spectroscopy

in Organic Chemistry", 2d ed, Pergamon Press, Oxford, 1969, p 215. A referee has pointed out that OH chemical shifts will respond to difference in phenolic acidity also. This is reflected in some of our data.
(8) L. Pauling, "The Nature of the Chemical Bond", 3d ed, Cornell University Press, Ithaca, N.Y., 1960, p 449.
(9) A. A. Levi and S. Smiles, *J. Chem. Soc.*, 520 (1931).
(10) E. G. Marsden and S. Smiles, *J. Chem. Soc.*, **99**, 1353 (1911).
(11) The isomer, 1-hydroxy-2,4-dimethylthioxanthone, mp 170–172 °C, has been reported.[12]
(12) G. Kunesh and F. Wessely, *Monatsh. Chem.*, **96**, 1547 (1965).
(13) The ^{1}H NMR spectrum had to be obtained at 100 °C for solubility purposes. The hydroxyl absorption could not be observed.

The SN1 Hydrolysis of Isothioureas. 1

D. R. Flanagan* and A. P. Simonelli

School of Pharmacy, University of Connecticut, Storrs, Connecticut 06268

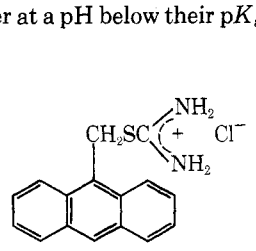
Received December 2, 1975

The hydrolysis of certain arylmethylisothioureas in water was studied. Evidence is presented which indicates that 9-anthrylmethylisothiourea (1), 10-methyl-9-anthrylmethylisothiourea (2), and 7(10)-benzanthrylmethylisothiourea (3) hydrolyze under acidic conditions by an SN1 mechanism. Support for this mechanism arises from a significant thiourea ("common ion") effect and from differences in the reactivity of 1–3, which can only be rationalized on the basis of a carbonium ion mediated mechanism.

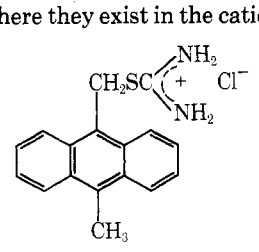
Recently there has been much interest in investigating the mechanistic details of hydrolysis reactions in pure water.[1] The development of sensitive conductance methods has allowed the accurate determination of hydrolysis rates for organic halides and sulfonates in water, which otherwise would have been difficult to study by conventional titrimetric methods. Most hydrolytic investigations have been conducted in mixed solvent systems, which avoided the analytical difficulties associated with the low aqueous solubilities of organic nonelectrolytes and moderated the high reactivity of many organic halides. Despite the development of more sensitive analytical techniques, low solubility remains as a major barrier to the systematic study of the hydrolysis of many compounds in water. Thus, correlations of reactivity with structure have been conducted in partially aqueous solvent systems, and comparison of results from different investigators is difficult because of the wide variety of solvent systems employed.

This report describes our investigations into the hydrolysis of certain arylmethylisothioureas in water. The isothiouronium moiety represents a new type of leaving group for an SN1 reaction. The proposed SN1 mechanism for these isothioureas is shown in Scheme I.

The compounds studied as their hydrochloride salts are 9-anthrylmethylisothiourea (1), 10-methyl-9-anthrylmethylisothiourea (2), and 7(10)-benzanthrylmethylisothiourea (3). These isothioureas are moderately soluble in water at a pH below their pK_a where they exist in the cationic isothiouronium form. Isothioureas normally decompose to thiols in alkaline media,[2] but no information is available on their stability in acidic media.



1



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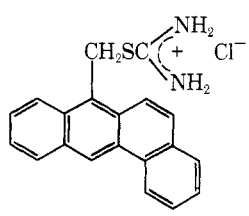
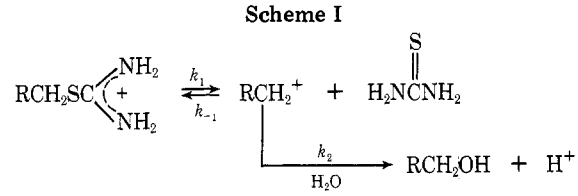


3

Scheme I



Experimental Section

9-Anthrylmethylisothiourea Hydrochloride (1). 9-Anthraldehyde was synthesized by the Vilsmeier method.[3] Reduction of 9-anthraldehyde with sodium borohydride in refluxing methanol gave 9-hydroxymethylanthracene.[4] The 9-hydroxymethylanthracene was dissolved in benzene and chlorinated by passing hydrogen chloride gas into the solution. The 9-chloromethylanthracene was not isolated because direct addition of excess thiourea in ethanol to this solution with refluxing gave 1 as a yellow precipitate. The isolated solid 1 was mixed with a small amount of water and ultrasonified to dissolve any excess thiourea which may have contaminated the product. The slurry was filtered and, after drying, 1 melted with decomposition at 213–215 °C. Anal. Calcd for $C_{16}H_{17}ClN_2OS$ (monohydrate): C, 59.9; H, 5.34; H_2O, 5.61. Found: C, 60.13; H, 5.25; H_2O, 5.20.

10-Methyl-9-anthrylmethylisothiourea Hydrochloride (2). 10-Methyl-9-chloromethylanthracene was synthesized by chloromethylation of 9-methylanthracene.[5] The resulting chloromethyl compound, after recrystallization, was refluxed with a slight excess of thiourea in benzene. A yellow precipitate of 2 formed, which was isolated and washed with water in a manner similar to 1. After drying, 2 melted with decomposition at 208–210 °C. Anal. Calcd for $C_{17}H_{17}ClN_2S$: C, 64.44; H, 5.41. Found: C, 64.31; H, 5.50.

7(10)-Benzanthrylmethylisothiourea Hydrochloride (3). The procedure of Wood and Fieser[6] was followed in synthesizing 3. Chloromethylation of benzanthracene produced 7(10)-chloromethylbenzanthracene,[7] which was reacted with thiourea to give 3, which melted with decomposition at 212–215 °C (reported 213–214 °C).

Other Isothioureas. Benzylisothiourea hydrochloride (4) was available commercially and was used as received. 1-Naphthylmethylisothiourea hydrochloride (5) was synthesized by reacting 1-chloromethylnaphthalene with thiourea.[8] 9-Phenanthrylmethylisothiourea hydrochloride (6) was obtained similarly by reacting 9-chloromethylphenanthrene with thiourea.

Kinetic Methods. Two methods were used to follow the hydrolysis of isothioureas. One method depended on hydrogen ion production, while the other depended on a change in the uv–visible absorption spectrum as hydrolysis proceeded.