TABLE I

ALKYLATION OF PHENOLS WITH *n*-OCTADECYL *p*-TOLUENESULFONATE

Phenol used	Mole of phenol	Mole of ester	Yield of ether, %	M. p. of ether, °C.	Molecular formula of ether	Analyses, % Calcd.	Analyses, % Found
Phenol	0.063	0.050	54.8	48–49	$C_{24}H_{42}O$	C, 83.3 H, 12.1	C, 83.1, 83.3 H, 12.4, 12.5
p-Cresol	.058	.050	50.5	49.5	$C_{25}H_{44}O$	C, 83.3 H, 12.2	C, 83.5 H, 12.1
p-Chlorophenol	.053	.050	61.1	54–54.5	$C_{24}H_{41}ClO$	Cl, 9.31	Cl, 9.31, 9.26
o-Nitrophenol	.057	.050	74.6	39–40	$C_{24}H_{41}NO_3$	N, 3.58	N, 3.44
α-Naphthol	.052	.050	66.0	42–43	$C_{28}H_{44}O$	C, 84.8 H, 11.2	C, 84.6, 84.6 H, 11.5, 11.6
β-Naphthol	.052	.050	55.3	64.5–65	$C_{28}H_{44}O$	C, 84.8 H, 11.2 Mol. wt., 396	C, 84.4, 84.9 H, 11.0, 11.0 Mol. wt., 396

phenyl *n*-octadecyl ether, 25 g. of stannous chloride dihydrate, and 150 ml. of glacial acetic acid. The mixture was heated at reflux temperature for about 4 hours. After cooling the solution was made basic by the addition of 6 *N* sodium hydroxide solution and filtered. The residue was then suspended in 200 ml. of 6 *N* hydrochloric acid and stirred for several minutes. The solid was then placed in 200 ml. of water (to which had been added 50 ml. of 6 *N* sodium hydroxide) and stirred. The mixture was again filtered with suction and washed several times with water and sucked as dry as possible. Recrystallization from petroleum ether gave a product melting at 64–66°. The solid was then dissolved in benzene and a small amount of decolorizing charcoal was added. The solution was heated and filtered and upon cooling in an ice-bath the *p*-aminophenyl *n*-octadecyl ether crystallized. It was collected and dried on a Buchner funnel. The 2.8 g. (melting point, 66–67°) obtained in this manner corresponded to a 61% yield.

Anal. Calcd. for $C_{24}H_{43}ON$: N, 3.87. Found: N, 3.86, 4.03.

Other Alkylation Reactions.—The phenols listed in Table I were all alkylated with *n*-octadecyl *p*-toluenesulfonate in general accordance with the procedure given above for *p*-nitrophenyl *n*-octadecyl ether.

NEW ORLEANS, LA. RECEIVED JULY 31, 1950

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF WALLACE & TIERNAN PRODUCTS, INC.]

The Reaction of Hydrazoic Acid with Thioether-sulfoxides: Synthesis of Sulfoximines

BY FERNANDA MISANI, T. W. FAIR AND L. REINER

The reaction of hydrazoic acid with thioether–sulfoxides in the presence of sulfuric acid as a catalyst yielded compounds which contained the characteristic configuration –S(O)(NH)–. The name sulfoximine is proposed for these compounds. The preparation and some of the properties of diamyl, diphenyl, methyl *p*-tolyl, methyl *p*-nitrophenyl and 4-aminophenyl methyl sulfoximines are described. In support of the assigned structure the results of the degradation of methionine sulfoximine previously isolated from nitrogen trichloride-treated prolamines are reviewed briefly and the formation of diphenyl N-acetylsulfoximine is described. The only sulfoximine which possessed convulsant properties was that derived from L-methionine.

A methionine derivative was isolated recently from nitrogen trichloride-treated prolamines[1,2,3] and it was shown by degradation studies that it differed from methionine in having an NH group and an oxygen atom directly attached to the sulfur atom.[2,4] This conclusion was reached on the basis of the following evidence: The elementary composition differed from that of methionine by one additional atom of each, hydrogen, nitrogen and oxygen. Hydrolysis of the compound with 57% hydriodic acid yielded one mole of methyl iodide and the thiolactone of homocysteine. Reduction with Raney nickel gave α-aminobutyric acid. Oxidation with hydrogen peroxide converted the compound into methionine sulfone and nitric acid. There was no appreciable decomposition when the compound was refluxed with 1 *N* hydrochloric acid for 1 hour but it was hydrolyzed by refluxing with 5 *N* sulfuric acid for 24 hours liberating one mole of ammonia and a number of ninhydrin-positive compounds the presence of which was demonstrated by paper chromatography. Thus the compound, just as methionine, contained an unsubstituted methyl group and an unsubstituted α-amino-γ-butyryl group attached to the sulfur atom. Consequently, the remaining three atoms (H, N and O) must be attached to the sulfur atom. Since ammonia was formed by hydrolysis and nitrate by oxidation, it was most likely that these atoms formed with the sulfur the configuration $=\mathrm{S}\begin{smallmatrix}\rightarrow\mathrm{NH}\\ \rightarrow\mathrm{O}\end{smallmatrix}$. We further confirmed the existence of this hitherto unknown configuration, for which we propose the name "sulfoximine," by the synthesis of methionine sulfoximine from racemic methionine sulfoxide and hydrazoic acid.[5] The resulting compound was identical with that isolated from nitrogen trichloride-treated zein with respect to its analytical characteristics. It was, however, only half as toxic, presumably because it was prepared from D,L-methionine whereas the isolated compound was derived from L-methionine. In this paper we

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[1] L. Reiner, F. Misani, T. W. Fair, P. Weiss and M. G. Cordasco, THIS JOURNAL, **72**, 2297 (1950).

[2] H. R. Bentley, E. E. McDermott, J. Pace, J. K. Whitehead and T. Moran, *Nature*, **165**, 150 (1950).

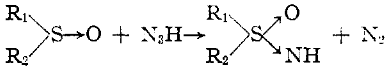
[3] R. H. Campbell, T. S. Work and E. Mellanby, *ibid.*, **165**, 345 (1950).

[4] L. Reiner, F. Misani, M. G. Cordasco and T. W. Fair, *Federation Proc.*, **9**, 218 (1950).

[5] F. Misani and L. Reiner, *Arch. Biochem.*, **27**, 234 (1950).

are reporting the synthesis of various sulfoximines illustrating the rather general applicability of this reaction. Quite recently Bentley, *et al.*,[6] announced the synthesis of dimethyl and methionine sulfoximines but did not report their physical and chemical characteristics.

The reaction involved is akin to the Schmidt reaction except that the addition of the NH group is not followed by rearrangement.



$$R_1R_2S{\rightarrow}O + N_3H \rightarrow R_1R_2S(\rightarrow O)(\rightarrow NH) + N_2$$

As in the Schmidt reaction, sulfuric acid was found to be the most efficient catalyst. The optimal temperature range is 35–50°. Diamyl, diphenyl, methyl *p*-tolyl, methyl *p*-nitrophenyl and methionine sulfoximines were prepared by this reaction.

The physical properties of sulfoximines resemble those of the corresponding sulfoxides. This makes the separation of the sulfoximine from the unreacted sulfoxide often difficult and the yields are often low. The sulfoximines, especially the aromatic ones, tend to be more basic than the corresponding sulfoxides. Thus, for example, after dilution of the reaction mixture with ice-water the unreacted diphenyl sulfoxide was mainly in the chloroform layer, whereas the diphenyl sulfoximine was in the acid aqueous layer and could be extracted from it with chloroform only after neutralization. Most of the diamyl sulfoximine was, however, found in the chloroform layer even before neutralization.

Sulfoximines are relatively stable compounds. They are decomposed at high temperatures and by prolonged hydrolysis in strong acid or alkali at reflux temperature. They are readily oxidized to the sulfones but less readily reduced than the sulfoxides, as will be reported in greater detail in connection with the degradation studies of methionine sulfoximine. Aliphatic sulfoxides liberate iodine from hydriodic acid solutions but sulfoximines do not. They do not react appreciably with nitrous acid at near 0° temperatures so that a diazonium salt could be prepared from *p*-aminophenyl methyl sulfoximine which was coupled with β-naphthol yielding a bright red dye. They form N-acyl derivatives quite readily. Diphenyl sulfoximine treated with a mixture of acetic anhydride and acetic acid gave diphenyl N-acetylsulfoximine.

The diastereoisomeric properties of sulfoximines and their absorption spectra in the ultraviolet and infrared are being investigated.

Pharmacology.—Since methionine sulfoximine is a powerful convulsant, it was of interest to investigate the role of the sulfoximine group in this toxicity. Diphenyl, methyl *p*-tolyl and 4-aminophenyl methyl sulfoximines did not produce symptoms in mice at a dose of 400 mg./kg. intraperitoneally. Diamyl sulfoximine produced spastic tremors but no convulsions in mice at a dose of 100/mg./kg. intraperitoneally. At this dose methionine sulfoximine prepared from L-methionine produced violent convulsions and death. Thus it seems that in general, compounds containing the sulfoximine group are not convulsants and that the L-methionine sulfoximine is a convulsant only because it is in an antagonist of the natural enantiomorph of methionine in some unknown phase of brain metabolism.

Experimental

Diamyl Sulfoximine.—Diamyl sulfoxide[7] (0.044 mole) dissolved in 50 cc. of chloroform was placed in a three-necked flask equipped with thermometer, mercury-sealed stirrer, dropping funnel and gas exit tube. Concentrated sulfuric acid (11.5 cc.) was added, the temperature raised to 43° and 0.085 mole of hydrazoic acid in chloroform (31 cc.) added dropwise over a period of 3 hours. Stirring was continued for 2 additional hours at the same temperature. The mixture was then poured into ice-water, the chloroform layer removed, the aqueous layer neutralized with aqueous sodium hydroxide, concentrated and again extracted with chloroform. The combined chloroform solutions were dried with anhydrous sodium sulfate and the solvent removed *in vacuo*. The crude product weighing 4.5 g. was recrystallized from low-boiling petroleum ether yielding white needles; m.p. 56–57°,[8] soluble in water and most organic solvents.

Anal. Calcd. for $C_{10}H_{23}NOS$: C, 58.48; H, 11.28; N, 6.82; S, 15.61. Found: C, 58.31; H, 11.16; N, 6.95; S, 15.50.

Diphenyl Sulfoximine.—Diphenyl sulfoxide[9] (0.033 mole) reacted with 0.52 mole of hydrazoic acid under the conditions described above. The chloroform layer containing mostly unreacted sulfoxide was discarded. The aqueous layer was then neutralized and again extracted with chloroform. The product was isolated from the dried chloroform solution in the same manner as the diamyl sulfoximine. White needles were obtained which were sparingly soluble in water, soluble in most organic solvents; m.p. 97–98°.

Anal. Calcd. for $C_{12}H_{11}NOS$: C, 66.33; H, 5.09; N, 6.44; S, 14.76. Found: C, 66.22; H, 4.89; N, 6.61; S, 14.53.

Diphenyl N-Acetylsulfoximine.—Diphenyl sulfoximine (1.2 millimoles) and acetic anhydride (2.5 millimoles) were dissolved in 1 cc. of glacial acetic acid and kept at 50° for 1 hour. The excess anhydride and the acetic acid were then removed *in vacuo* and the residue was dissolved in chloroform. After addition of low-boiling petroleum ether the product crystallized rapidly in rectangular prisms; m.p. 127–130°; yield 205 mg. (79%).

Anal. Calcd. for $C_{14}H_{13}NO_2S$: N, 5.41. Found: N, 5.39.

Methyl *p*-tolyl sulfoximine was prepared in the same manner as the diphenyl sulfoximine from 0.06 mole of methyl *p*-tolyl sulfoxide[10] and 0.1 mole of hydrazoic acid. It was obtained as white needles, slightly soluble in water, soluble in most organic solvents, insoluble in petroleum ether: m.p. 66–68°; yield 2 g. (20%).

Anal. Calcd. for $C_8H_{11}NOS$: N, 8.27. Found: N, 8.37.

Methyl *p*-nitrophenyl sulfoximine was prepared in the same manner as the diphenyl sulfoximine using 0.05 mole of methyl *p*-nitrophenyl sulfoxide[11] and 0.1 mole of hydrazoic acid. After recrystallization from methanol, it was obtained as pale yellow prisms, soluble in most organic solvents; m.p. 139–141°; yield 2.2 g. (25%).

Anal. Calcd. for $C_7H_8N_2O_3S$: N, 13.98. Found: N, 13.95.

4-Aminophenyl Methyl Sulfoximine.—4-Nitrophenyl methyl sulfoximine (0.5 millimole) was dissolved in 10 cc. of acetic acid, 3.5 g. of stannous chloride in 4 cc. of concentrated hydrochloride acid was added, then boiled for a few minutes, concentrated to dryness *in vacuo*, dissolved in water, made alkaline with sodium hydroxide and the solution extracted with chloroform. After removal of the chloroform

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(6) H. R. Bentley, E. E. McDermott and J. K. Whitehead, *Nature*, **165**, 735 (1950).

(7) F. G. Mann and D. Purdie, *J. Chem. Soc.*, 1549 (1935).

(8) All m.p.'s are uncorrected.

(9) C. E. Colby and C. S. McLoughlin, *Ber.*, **20**, 197 (1887).

(10) T. Zincke and W. Frohneberg, *ibid.*, **43**, 843 (1910).

(11) T. Zincke and S. Lenhardt, *Ann.*, **400**, 14 (1913).

the residue was dissolved in acetone and recrystallized from acetone–petroleum ether. The resulting white prisms were soluble in water and most organic solvents; m.p. 120–122°.

Anal. Calcd. for $C_7H_{10}N_2OS$: N, 16.45: Found: N, 16.72.

BELLEVILLE, N. J. RECEIVED JUNE 26, 1950

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS UNIVERSITY]

The Systems Ag_2SO_4–Rb_2SO_4–H_2O and Ag_2SO_4–Cs_2SO_4–H_2O at 25°[1]

BY WERNER C. VON DOHLEN[2] AND EDWARD L. SIMONS

The solubility measurements here reported have been made as an extension of the study of the equilibrium relations in aqueous systems involving silver sulfate and the alkali sulfates.[3]

Materials.—C.P. grade silver sulfate was further purified by recrystallization from concentrated sulfuric acid.[4] The rubidium sulfate was prepared from recrystallized rubidium nitrate[5] and the cesium sulfate from cesium dichloroiodide[6] which had been twice recrystallized from 9 molal hydrochloric acid.[7] All salts, after drying at 250°, were stored in glass-stoppered weighing bottles in a calcium chloride desiccator.

Solubility Determinations.—Complexes of known composition were made up by weight in 8-inch ignition tubes fitted with an internal stirrer, similar to that shown by Purdon and Slater.[8] At least two days were allowed for the attainment of equilibrium in a constant temperature water-bath. The 25° solubilities were measured at 25.00 ± 0.05°, the 35° solubilities at 34.90 ± 0.05°. To prevent photochemical decomposition of the silver sulfate, the solubility tubes were wrapped in aluminum foil. Samples for analysis were taken in the usual way by means of pipets fitted with filter paper tips.

The analytical method involved determination of the silver sulfate concentration by titration with ammonium thiocyanate, using the Volhard indicator, and of the water concentration by the loss in weight on evaporation and drying for eight hours at 110° followed by overnight heating at 250°.

TABLE I

SYSTEMS Ag_2SO_4–H_2O– AND Rb_2SO_4 OR Cs_2SO_4 AT 25 OR 35°

Liquid solution			C, Orig. complex, R, wet residue			
Wt. % Ag_2SO_4	Wt. % Rb_2SO_4	Density		Wt. % Ag_2SO_4	Wt. % Rb_2SO_4	Solid phase[a]
		(1) Rb_2SO_4 at 25°				
0.833[b]		1.004[b]				A
0.79	5.85	1.052	C	15.26	5.00	A
0.92	12.99	1.126	C	14.33	11.20	A
1.10	20.45	1.200	C	15.10	17.58	A
1.18	24.41	1.252	C[c]	20.1	19.1	A
1.23	26.13	1.272	C[c]	13.6	22.6	A
1.30	28.95	1.316	C	14.98	25.03	A
1.33	30.85	1.336	C[c]	11.1	27.5	A
1.37	32.93	1.359	C	10.09	29.96	A
1.38	33.66	1.375	C	6.15	33.43	A + B
1.37	33.61	1.373	C[c]	6.2	35.9	A + B
1.38	33.63	1.378	C	2.49	37.47	A + B
1.38	33.63	1.361	C	1.38	38.81	A + B
1.38	33.63	1.372		Average		A + B
0.62	33.72	1.355	C	0.51	45.12	B
	33.77	1.348				B
		(2) Cs_2SO_4 at 25°				
	Wt. % Cs_2SO_4				Wt. % Cs_2SO_4	
0.833[b]		1.004[b]				A
.76	5.93	1.055	C	15.02	5.06	A
.86	13.94	1.136	C	14.96	11.95	A
.98	20.52	1.211	C	15.00	17.61	A
1.07	27.53	1.306	C	14.86	23.69	A
1.19	35.16	1.411	C	15.04	30.15	A
1.22	36.19	1.420	R	90.89	3.69	A
1.28	41.19	1.514	C	14.79	35.52	A
1.38	46.96	1.623	C	14.88	40.37	A
1.43	48.11	1.635	R	84.20	7.78	A
1.43	51.99	1.743	C	14.97	44.84	A
1.53	57.94	1.871	R	84.57	9.16	A
1.57	62.74	2.005	C	15.45	53.79	A
1.57	62.99	2.011	R	77.75	14.22	A
1.57	63.72	2.048	C[c]	8.8	58.6	A + D
1.58	63.71	2.049	C[c]	6.3	65.4	A + D
1.57	63.80	2.054	C[c]	3.1	67.0	A + D
1.57	63.79	2.045	C	1.45	66.60	A + D
1.57	63.76	2.049		Average		A + D
0.57	64.21	2.016	C	0.49	69.45	D
	64.53	2.007				D
		(3) Cs_2SO_4 at 35°				
1.80	64.28	2.057	C[c]	9.8	61.0	A + D
1.80	64.27	2.048	C[c]	6.9	62.5	A + D
1.80	64.22	2.068	C	5.01	65.01	A + D
1.80	64.31	2.059	C[c]	3.2	67.1	A + D
1.80	64.27	2.058		Average		A + D

[a] A = Ag_2SO_4; B = Rb_2SO_4; D = Cs_2SO_4. [b] Ref. 3. [c] These complexes were not prepared directly from the pure components, but by the addition of salts and water as needed to other complexes. No extrapolation errors were calculated for these data.

Results.—The data (in weight per cent.) are shown in Table I. Both systems are simple, the only solid phases being the pure salts, as determined by the algebraic extrapolation[9] of the tie lines through the original complexes or wet residues. The extrapolation errors averaged 0.30 and 0.26% for the rubidium and cesium systems, respectively. The density values, obtained by using calibrated pipets in the sampling of the saturated liquids for analysis, are relatively less precise and dependable than the analytical results themselves. At 35° only the isothermally invariant point was determined for the cesium system.

Summary

1. The ternary systems silver sulfate–rubidium

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[1] Abstracted from a dissertation submitted by Werner C. von Dohlen in May, 1950, to the School of Chemistry of Rutgers University in partial fulfillment of the requirements for the degree of Bachelor of Science with Special Honors in Chemistry.

[2] Department of Chemistry, Brown University, Providence, R. I.

[3] Simons and Ricci, THIS JOURNAL, **68**, 2194 (1946).

[4] Archibald, "The Preparation of Pure Inorganic Substances," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 66.

[5] Ref. 4, p. 50.

[6] Ref. 4, p. 52.

[7] Bender and Strehlow, THIS JOURNAL, **70**, 1996 (1948).

[8] Purdon and Slater, "Aqueous Solution and the Phase Diagram," Edward Arnold and Co., London, 1946, p. 68.

[9] Hill and Ricci, THIS JOURNAL, **53**, 4306 (1931).