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Aliphatic Sulfenamides

BY RANDOLPH T. MAJOR AND LOUIS H. PETERSON

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Several N,N-dialkylalkanesulfenamides, R_2NSR', have been made by the interaction of dialkylamines and alkanesulfenyl thiocyanates, R'SSCN. The hydrolysis of N,N-diethylethanesulfenamide by potassium hydroxide in methanol and by dilute hydrochloric acid was studied. The toxicity and local anesthetic and chemotherapeutic properties of several N,N-dialkylalkanesulfenamides have been reported.

In the course of studies of organic derivatives of hydroxylamine it was felt that a comparison with some analogous sulfenamides might be of interest. Some of the sulfenamides with rather special structures have found use as rubber accelerators and as intermediates in the synthesis of medicinally important sulfonamides. Few aliphatic sulfenamides have been described.[1-6]

A method of making alkyl substituted sulfenamides of broad utility was sought. Some difficulty was encountered in preparing N,N-diethylethanesulfenamide by the procedure of Peyron and Lapaine.[2] It has been found that N,N-dialkylethanesulfenamides may be prepared by the reaction of alkanesulfenyl thiocyanates[7] with secondary amines.

$$RSSCN + 2R_2NH \longrightarrow RSNR_2 + R_2NH\cdot HSCN\downarrow$$

As yet alkyl substituted sulfenamides have not been prepared by the interaction of primary amines with alkanesulfenyl thiocyanates.

Unlike alkyl substituted hydroxylamines, R_2NOR, the N,N-dialkylalkanesulfenamides do not appear basic in aqueous solution but behave more like amides. They decompose slowly at room temperature. However, N,N-diethylethanesulfenamide was not changed appreciably by treatment with caustic soda at room temperature overnight. On the other hand, it could be hydrolyzed by heating with potassium hydroxide in methanol or by shaking with dilute hydrochloric acid. Hydrolysis with caustic potash in methanol gave diethylamine and diethyl disulfide, while hydrochloric acid gave diethylamine hydrochloride, diethyl disulfide and diethyl disulfoxide.[8] It would appear that this latter compound has a thiosulfonate structure.[9]

Dr. J. M. Sprague of our West Point, Pa., research laboratories has been kind enough to arrange for the biological testing of the N,N-dialkylalkanesulfenamides. He has reported that none of the compounds showed any local anesthetic activity in the rabbit cornea when tested at 1% concentration. The acute toxicity of these compounds to mice intraperitoneally was

Compounds	LD_{50} i.p. mice (in oil), mg./kg.
$C_2H_5SN(C_2H_5)_2$	73.3
$C_3H_7SN(C_3H_7)_2$	1000 (approx.)
$C_3H_7SN(C_4H_9)_2$	>1000
$C_5H_{11}SN(C_4H_9)_2$	>1000
$t\text{-}C_4H_9SN(C_4H_9)_2$	>1000

Both N,N-diethylethanesulfenamide and N,N-di-*n*-propyl-*n*-propanesulfenamide inactivated PR8 influenza virus *in vitro* at 1600 μmolar, whereas at the same concentrations the other sulfenamides were inactive.

N,N-Di-*n*-butyl-*n*-hexanesulfenamide inhibited *Staph. aureus* at low concentration (6.25 μmolar) in broth, but this effect was abolished in the presence of 10% horse serum. The other sulfenamides tested were less active.

Dr. Solotorovsky of the Merck Institute for Therapeutic Research has reported that N,N-diethylethanesulfenamide was an active antituberculosis agent in a concentration of 0.5% in the diet of tubercular mice.

We are indebted to Mr. R. N. Boos and associates for microanalyses and to Mr. F. A. Bacher and associates for ultraviolet spectra.

Experimental

Alkanesulfenyl Thiocyanates, RSSCN.—Alkanesulfenyl thiocyanates were prepared by the method of Lecher and Wittwer[10] when the alkane was ethane, *n*-propane, trimethylmethane and *n*-hexane. Subsequent to the reaction of the mercaptan with thiocyanogen in dry ether, the solution was washed with ice-water until no red color indicating thiocyanate ion was obtained with ferric chloride. The water extracts were re-extracted with ether before being discarded. Ordinarily, the combined ether solutions after being dried with magnesium sulfate were used in the subsequent reactions without further purification because of the ease of decomposition of these thiocyanates. However, trimethylmethanesulfenyl thiocyanate was distilled, b.p. 31–32° (0.4 mm.), yield 83%, λ_{max} 270 mμ, $E^{1}\%$ 13.6, ε 200; and *n*-hexanesulfenyl thiocyanate was distilled, b.p. 73–75° (0.65 mm.), yield, 71% λ_{max} 272 mμ, $E^{1}\%$ 11.4, ε 199.

N,N-Dialkylalkanesulfenamides, R_2NSR'.—A solution of from 0.07 to 0.15 mole of sulfenyl thiocyanate in dry ether[11] was added slowly to a cold solution of twice the molecular proportions of dialkylamine in dry ether. A precipitate (generally an oil) separated at once. The reaction mixture was stirred for half an hour.[12] The precipitate was then separated. The remaining ether solution was washed with water until it was free of thiocyanate ion according to tests with ferric ion. The ether solution was then dried over

(1) H. Reinboldt and E. Motzkus, *Ber.*, **72B**, 657 (1939).
(2) L. Peyron and J. Lapaine, *Compt. rend.*, **227**, 132 (1948).
(3) L. T. Eby, U. S. Patent 2,474,237, June 28, 1949.
(4) W. A. Schulze, C. H. Short and W. W. Crouch, *Ind. Eng. Chem.*, **42**, 916 (1950).
(5) F. O. Edmonds, U. S. Patent 2,554,097, May 22, 1951.
(6) N. Kharasch, S. J. Potempa and H. L. Wehrmeister, *Chem. Revs.*, **39**, 269 (1946).
(7) H. Lecher and M. Wittwer, *Ber.*, **55**, 1474 (1952).
(8) Fr. Fichter and F. Braun, *ibid.*, **47**, 1531 (1914).
(9) R. Connor in H. Gilman's "Organic Chemistry," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 912.
(10) The mercaptan must be added slowly to the thiocyanogen to avoid excess mercaptan, which would react with the sulfenyl thiocyanate to form a disulfide.
(11) Normally a solution of crude, undistilled alkanesulfenyl thiocyanate was used. The exceptions were trimethylmethanesulfenyl thiocyanate and *n*-hexanesulfenyl thiocyanate which were distilled before being redissolved in ether for this reaction.
(12) In the preparation of N,N-di-*n*-butyltrimethylmethanesulfenamide the reaction mixture was stirred for 1.5 hr.

magnesium sulfate. After removal of the ether by distillation the residual oil was distilled twice *in vacuo*.

N,N-Diethylethanesulfenamide: yield 31%, b.p. 61°, (38 mm.) $n^{26}D$ 1.4500. *Anal.* Calcd. for $C_6H_{15}NS$: C, 54.08; H, 11.35; N, 10.51; S, 24.06. Found: C, 54.66; H, 11.32; N, 9.95; S, 23.74.

N,N-Dipropylpropanesulfenamide: yield 30%, b.p. 74° (5 mm.), $n^{25}D$ 1.4533. *Anal.* Calcd. for $C_9H_{21}NS$: C, 61.65; H, 12.07; S, 18.29. Found: C, 61.77; H, 11.71; S, 18.04.

N,N-Di-*n*-butylpropanesulfenamide: yield 70%, b.p. 56–57° (0.32 mm.), $n^{27.5}D$ 1.4543. *Anal.* Calcd. for $C_{11}H_{25}NS$: C, 64.96; H, 12.39; S, 15.76. Found: C, 64.45; H, 12.38; S, 15.98.

N,N-Di-*n*-butyltrimethylmethanesulfenamide: yield 77%, b.p. 60–62° (0.67 mm.), $n^{28}D$ 1.4539–1.4542. *Anal.* Calcd. for $C_{12}H_{27}NS$: C, 66.29; H, 12.52; S, 14.75. Found: C, 66.68; H, 12.78; S, 14.92.

N,N-Di-*n*-butylhexanesulfenamide: yield 68%, b.p. 74–76° (0.001 mm.), $n^{28}D$ 1.4570–1.4574. *Anal.* Calcd. for $C_{14}H_{31}NS$: C, 68.50; H, 12.73; S, 13.07. Found: C, 68.78; H, 12.75; S, 13.40.

Hydrolysis of N,N-Diethylethanesulfenamide. (a) With Potassium Hydroxide in Methanol.—Ten grams of N,N-diethylethanesulfenamide (0.75 mole) was dissolved in 150 ml. of 1 *N* KOH in methanol. The solution was refluxed for 3 hr., at which time the absorption spectrum of a sample had stabilized with an ultraviolet absorption plateau in the region of 240–255 mμ. The solution was then distilled at atmospheric pressure. Fractions boiling at 65–67.5° were collected. They gave positive nitroprusside tests for disulfides,[13] became cloudy when diluted with water and had ultraviolet spectra maxima at 249 mμ. The combined fractions were diluted with water, acidified with dilute HCl and extracted with ether. The ether extract was dried and the ether was removed by distillation. The residue, 1.4 g., appeared to be diethyl disulfide, $n^{29}D$ 1.4991.[14] The aqueous layer was concentrated to a solid residue, yield 7 g. (0.064 mole), m.p. 220–222°, mixed m.p. with authentic diethylammonium chloride 222–224°.

(b) With Dilute Hydrochloric Acid.—Eighteen grams of N,N-diethylethanesulfenamide (0.135 mole) was added to 135 ml. of cold 2.5 *N* HCl and shaken. After an hour the mixture was extracted with ether. The ether extract was distilled. A fraction, b.p. 42–43° (11 mm.), redistilled, 44–46° (15 mm.), $n^{27}D$ 1.4991, yield about 2.8 g. (0.023 mole), which must have been diethyl disulfide was obtained.

Anal. Calcd. for $C_4H_{10}S_2$: C, 39.30; H, 8.24. Found: C, 39.52; H, 8.03.

Another fraction, b.p. 122–124° (11 mm.), redistilled, 72–74° (1 mm.), $n^{27}D$ 1.4976, yield about 3.22 g. (0.021 mole), which must have been the product described by Fichter and Braun as diethyl disulfoxide was obtained.

Anal. Calcd. for $C_4H_{10}S_2O_2$: C, 31.15; H, 6.53; S, 41.57. Found: C, 31.39; H, 6.71; S, 41.82.

The above described hydrochloric acid solution from a previous hydrolysis of N,N-diethylethanesulfenamide (2.66 g., 0.02 mole), after extraction with ether, was evaporated *in vacuo*. The residue, m.p. 220–222°, weighed 2.2 g. (0.02 mole); recrystallized from methanol–ether, m.p. 224–225°; mixed m.p. with authentic diethylamine hydrochloride, 223–225°.

(13) E. Walker, *Biochem. J.*, **19**, 1082 (1925).

(14) R. Nasini, *Ber.*, **15**, 2882 (1882), reports $n^{20}D$ 1.50633.

RAHWAY, NEW JERSEY

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH LABORATORY]

Some 5-(Oxoalkyl)-2-thiohydantoins and Their Derivatives

BY S. ARCHER, MARY JACKMAN UNSER AND E. FROELICH

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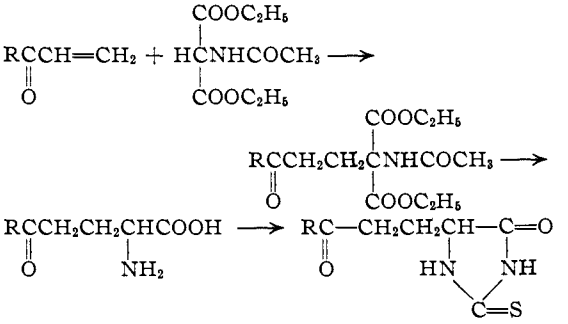
A number of 5-(2-oxoalkyl)-2-thiohydantoins were prepared by condensing the appropriate 1-chloro-2-alkanones with ethyl acetamidomalonate and hydrolyzing the intermediate esters to the amino acids and finally converting these to the thiohydantoins. The requisite amino acids for the preparation of the 5-(3-oxoalkyl)-2-thiohydantoins were obtained by hydrolysis of the adducts of alkyl vinyl ketones and ethyl acetamidomalonate. The thiohydantoins and the isonicotinoylhydrazones derived therefrom were examined for tuberculostatic activity.

In a previous communication[1] it was reported that a few members of a series of 5-(alkyl)-2-thiohydantoins showed appreciable antituberculosis activity when administered to mice infected with *M. tuberculosis* H37Rv. The maximally effective drug in this group was 5-(*n*-heptyl)-2-thiohydantoin; higher and lower homologs as well as isomers thereof showed decreased activity.

In a further study of this problem it appeared to us that there was a similarity between the alkyl naphthoquinones of Fieser[2] which possess antimalarial activity and our compounds in the sense that both series were characterized by the presence of lipophilic chains coupled to nuclei containing polar groups. Since it had been shown in the antimalarial work that oxygenation of the side-chain of certain active members increased therapeutic effectiveness it was decided to prepare a series of 5-(2 and 3-oxoalkyl)-2-thiohydantoins for examination as antituberculosis agents.

Two members of the 5-(3-oxoalkyl)-2-thiohydantoin class were prepared according to the equations



The alkyl vinyl ketones, prepared as previously described,[3] condensed readily with ethyl acetamidomalonate in the expected manner[4] to furnish crystalline adducts which were hydrolyzed to the amino acids which were, in turn, converted to the desired thiohydantoins.

(1) E. Froelich, *et al.*, THIS JOURNAL, **76**, 3099 (1956).

(2) L. F. Fieser, *et al.*, *ibid.*, **70**, 3151 (1948).

(3) S. Archer, W. B. Dickinson and M. J. Unser, *J. Org. Chem.*, in press.

(4) O. A. Moe and D. J. Warner, THIS JOURNAL, **70**, 2763 (1948).