[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

α-Alkylsulfonylamides[1]

BY AUSTIN POMERANTZ[2] AND RALPH CONNOR

In the previous study[3] of α-sulfonylamides the most effective hypnotic was α-*n*-butylsulfonyl-*n*-butyramide. Since this was the only purely aliphatic derivative investigated, the synthesis of a series of α-alkylsulfonylamides was undertaken. From the results described in the preceding paper[4] it seemed advisable to avoid the alkylation reaction previously employed and attention was therefore directed toward the reaction of mercaptides with α-bromoamides, followed by oxidation.

$$RSNa + R'_2CBrCONH_2 \longrightarrow RSCR'_2CONH_2 \xrightarrow{H_2O_2} RSO_2CR'_2CONH_2$$

$$R' = -H \text{ or } -C_nH_{2n+1}$$

Using conditions somewhat similar to those previously described,[3] the reactions of ethyl, *n*-propyl and *n*-butyl mercaptans with chloroacetamide, α-bromopropionamide, α-bromo-*n*-butyramide, α-bromoisobutyramide, α-bromo-*n*-valeramide, α-bromoisovaleramide and α-bromo-*n*-caproamide were carried out and the α-(alkylthio)-amides oxidized to the corresponding α-alkylsulfonylamides.[5] This synthesis proved to be satisfactory; the results are given in the experimental part. The sulfides were readily purified by crystallization but in several cases developed a slight odor of mercaptan on long standing. The oxidations were generally satisfactory but in a few cases the sulfones were rather difficult to purify.

The method of synthesis makes the structures of the products fairly certain. Furthermore, α-*n*-butylsulfonyl-*n*-butyramide and α-*n*-butylsulfonyl-*n*-caproamide were identical with the compounds previously prepared by the alkylation method.[4] The only reactions about which there seemed to be any uncertainty were those of α-bromoisobutyramide. Considering the behavior of the corresponding ester with the sodium derivatives of active methylene compounds,[6] it seemed possible that a mercaptide might cause the elimination of hydrogen bromide from α-bromoisobutyramide with the formation of α-methylacrylamide; addition of mercaptan to the conjugated system would give a β-(alkylthio)-amide isomeric with the desired product. However, β-(*n*-butylthio)-isobutyramide was prepared by the reaction of *n*-butyl mercaptan with α-methylacrylamide.[7]

$$n\text{-}C_4H_9SH + CH_2{=}C(CH_3)CONH_2 \xrightarrow{\text{piperidine}} n\text{-}C_4H_9SCH_2CH(CH_3)CONH_2$$

The product differed from that obtained by metathesis; this establishes the fact that the α-bromoamides react normally with mercaptides to give α-alkylthio derivatives.

Experimental Part

Melting points are uncorrected unless otherwise specified. The acids and mercaptans were products of the Eastman Kodak Company. The ligroin used was the fraction boiling at 70–90°. Pure α-bromopropionamide was obtained in 70% yields from methyl α-bromopropionate[8] but the ethyl ester gave unsatisfactory results. Some of the other α-bromoamides were prepared from the α-bromo acid chlorides by the method of Bischoff.[9] The most satisfactory general method was the bromination of the fatty acids and isolation of the pure α-bromo acids by the method described for α-bromo-*n*-caproic acid.[10] The α-bromo acid chlorides were prepared by the method described for *n*-butyryl chloride[11] and were satisfactory for use without distillation. They were converted to the amides by the use of ammonium hydroxide as described below. All but two of the α-bromoamides had been prepared previously.[9]

α-Bromoamides.—The middle neck of a 1-liter, three-necked, round-bottomed flask was fitted with a mechanical stirrer and gas outlet tube. A gas inlet tube long enough to extend below the surface of the reaction mixture and a dropping funnel were inserted in the other necks. The flask was immersed in an ice–salt-bath, 235 ml. of concentrated ammonium hydroxide added and ammonia gas bubbled into the cold solution over a period of about one hour. The crude acid chloride from one mole of α-bromo acid was then added dropwise over a period of about three hours. During this time the temperature of the ammoniacal solution was maintained at about 0° and ammonia gas passed into the mixture continuously. The in-

(1) This communication is constructed from a thesis submitted by Austin Pomerantz in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Pennsylvania in June, 1939.

(2) Harrison Fellow in Chemistry, 1938–1939; Harrison Scholar in Chemistry, 1937–1938.

(3) d'Ouville and Connor, THIS JOURNAL, **60**, 33 (1938).

(4) Pomerantz and Connor, *ibid.*, **61**, 3139 (1939).

(5) The pharmacological examination of these compounds is being carried out under the direction of Dr. Robert S. Shelton of the Wm. S. Merrell Company and will be reported elsewhere.

(6) Rydon, *J. Chem. Soc.*, 1444 (1936).

(7) The authors are grateful to the Rohm and Haas Company for a generous supply of α-methylacrylamide.

(8) Jacobs and Heidelberger, "Org. Syntheses," Coll. Vol. I, p. 147.

(9) Bischoff, *Ber.*, **30**, 2312 (1897).

(10) Clarke and Taylor, "Org. Syntheses," Coll. Vol. I, p. 108.

(11) Helferich and Schaefer, "Org. Syntheses," Coll. Vol. I, p. 142.

TABLE I

α-(ALKYLTHIO)-AMIDES

Compound	M. p. (corr.), °C.	Nitrogen, %[a] Calcd.	Found	Sulfur, %[b] Calcd.	Found
$C_2H_5SCH_2CONH_2$	50.5–51[c]	11.8	11.9	26.90	26.90
$C_2H_5SCH(CH_3)CONH_2$	65–65.5	10.5	10.5	24.07	24.24
n-$C_3H_7SCH(CH_3)CONH_2$	56.5–57	9.52	9.45	21.78	21.86
n-$C_4H_9SCH(CH_3)CONH_2$	60.5–61.5	8.69	8.66	19.88	19.66
$C_2H_5SCH(C_2H_5)CONH_2$	100.5–101	9.52	9.47	21.78	21.80
n-$C_3H_7SCH(C_2H_5)CONH_2$	78–78.5	8.69	8.64	19.88	20.02
n-$C_4H_9SCH(C_2H_5)CONH_2$	65–65.5	7.99	7.94	18.29	18.22
$C_2H_5SC(CH_3)_2CONH_2$	93.5–94	9.52	9.46	21.78	21.84
n-$C_3H_7SC(CH_3)_2CONH_2$	95–95.5	8.69	8.66	19.88	19.83
n-$C_4H_9SC(CH_3)_2CONH_2$	107.5–108	7.99	7.95	18.29	18.37
$C_2H_5SCH(n$-$C_3H_7)CONH_2$	101.5–102	8.69	8.72	19.88	19.92
n-$C_3H_7SCH(n$-$C_3H_7)CONH_2$	98.5–99	7.99	7.95	18.29	18.36
n-$C_4H_9SCH(n$-$C_3H_7)CONH_2$	64.5–65	7.40	7.38	16.94	16.85
$C_2H_5SCH(i$-$C_3H_7)CONH_2$	111–111.5	8.69	8.65	19.88	19.62
n-$C_3H_7SCH(i$-$C_3H_7)CONH_2$	98.5–99	7.99	7.97	18.29	18.54
n-$C_4H_9SCH(i$-$C_3H_7)CONH_2$	75–75.5	7.40	7.32	16.94	17.07
$C_2H_5SCH(n$-$C_4H_9)CONH_2$	84.5–85	7.99	7.90	18.29	18.25
n-$C_3H_7SCH(n$-$C_4H_9)CONH_2$	100.5–101	7.40	7.44	16.94	17.06
n-$C_4H_9SCH(n$-$C_4H_9)CONH_2$	86.5–87	6.89	6.87	15.77	15.99

[a] Nitrogen analyses were made by the semi-micro Kjeldahl method. The values reported are the average of two determinations which did not differ more than 0.07% from the mean. [b] Sulfur analyses were made by the macro Parr bomb procedure. [c] This compound is included because the melting point had previously been reported[14] as 44°. The values for α-(n-propylthio)-acetamide and α-(n-butylthio)-acetamide agreed with those previously observed.[3,15]

soluble product was separated by filtration, washed with a small amount of cold water, dried and recrystallized from benzene or a mixture of benzene and ligroin. The yield of recrystallized material was 50–70% based on the α-bromo acid.

α-Bromo-n-valeramide.—The purified material melted at 78.5–79° (corr.).

Anal. Calcd. for $C_5H_{10}ONBr$: N, 7.78. Found: N, 7.77, 7.87.

α-Bromo-n-caproamide.—The purified material melted at 58.5–59° (corr.).

Anal. Calcd. for $C_6H_{12}ONBr$: N, 7.22. Found: N, 7.27, 7.28.

α-(Alkylthio)-amides.—To a sodium ethoxide solution prepared by dissolving sodium in absolute alcohol (approximately 50 ml. of alcohol per 0.1 gram atom of sodium) was added an equivalent amount of the mercaptan. The mixture was cooled in an ice–salt-bath[12] to 0° and the α-haloamide added in portions with shaking. The mixture was kept in the ice-bath during the mixing, since the reaction was noticeably exothermic. The mixture was shaken frequently and allowed to come to room temperature as the bath melted. After standing at room temperature for two to five days the reactions were complete, except those involving α-bromoisobutyramide; in these cases the reactions were carried out for two weeks at room temperature. The insolubility of the amide and the decreased reactivity of the tertiary halogen probably combined to retard the reaction of α-bromoisobutyramide.

After the reaction was complete most of the alcohol was removed from the mixture under reduced pressure. In most cases the amides were fairly insoluble in water and were isolated by pouring the distillation residue on chipped ice and collecting the solid product on a filter. The aqueous filtrates contained small amounts of the α-(alkylthio)-amides which were readily removed by ether extraction. The solvent was removed on the steam-bath, the residues dissolved in hot dilute alcohol, decolorized with charcoal and crystallized by the addition of more water. The amount of material so obtained was usually small, especially with the higher homologs.

The α-(alkylthio)-acetamides and α-(ethylthio)-propionamide were too soluble in water to be isolated in good yields by the above method. In these cases the residues remaining after the removal of the solvent were diluted with water (one to two times the original volume of the reaction mixtures) and extracted with four 100-ml. portions of ether. The extracts were dried over sodium sulfate and the ether removed on the steam-bath. The residues were oils but were readily crystallized from ligroin; in a few cases a little benzene was added to increase the solubility. The properties and analyses of the products are given in Table I.

Using 0.15 to 0.30 mole of reactants, the amount of α-(alkylthio)-amides averaged 88%. α-(Ethylthio)-propionamide (64% yield) was the only product obtained in less than 80% yield.

β-(n-Butylthio)-isobutyramide.[13]—A mixture of 14.0 ml. (11.7 g., 0.13 mole) of n-butyl mercaptan, 11.1 g. (0.13 mole) of α-methylacrylamide[7] (m. p. 107.5–110°) and 0.5 ml. of piperidine in 50 ml. of absolute alcohol was

(12) The effect of temperature upon this reaction has already been described.[8]

(13) The procedure is that used by Nicolet, THIS JOURNAL, **57**, 1098 (1935), for α,β-unsaturated esters and ketones.

(14) Claesson, *Bull. soc. chim.*, [2] **23**, 444 (1875).

(15) Uyeda, *J. Chem. Soc. Jap.*, **50**, 687 (1929).

TABLE II

α-ALKYLSULFONYLAMIDES[a]

Compound	M. p. (corr.), °C.	Nitrogen, %[b] Calcd.	Found	Sulfur, %[b] Calcd.	Found
$C_2H_5SO_2CH_2CONH_2$	98.5–99[c]	9.27	9.17	21.21	21.11
n-$C_3H_7SO_2CH_2CONH_2$	104–104.5[d]	8.48	8.37	19.40	19.44
$C_2H_5SO_2CH(CH_3)CONH_2$	126–126.5[e]	8.48	8.47	19.40	19.47
n-$C_3H_7SO_2CH(CH_3)CONH_2$	122–122.5	7.82	7.82	17.89	17.91
n-$C_4H_9SO_2CH(CH_3)CONH_2$	114–114.5	7.25	7.19	16.59	16.54
$C_2H_5SO_2CH(C_2H_5)CONH_2$	168–168.5	7.82	7.81	17.89	17.74
n-$C_3H_7SO_2CH(C_2H_5)CONH_2$	137–137.5	7.25	7.28	16.59	16.70
$C_2H_5SO_2C(CH_3)_2CONH_2$	92.5–93[f]	7.82	7.78	17.89	17.79
n-$C_3H_7SO_2C(CH_3)_2CONH_2$	99.5–100.5[f]	7.25	7.56[h]	16.59	...[h]
n-$C_4H_9SO_2C(CH_3)_2CONH_2$	77.5–78[f]	6.76	6.68	15.47	15.27
$C_2H_5SO_2CH(n$-$C_3H_7)CONH_2$	117.5–118	7.25	7.27	16.59	16.39
n-$C_3H_7SO_2CH(n$-$C_3H_7)CONH_2$	125–125.5	6.76	6.74	15.47	15.48
n-$C_4H_9SO_2CH(n$-$C_3H_7)CONH_2$	125–125.5[g]	6.33	6.34	14.49	14.39
$C_2H_5SO_2CH(i$-$C_3H_7)CONH_2$	122–123.5	7.25	7.15	16.59	16.50
n-$C_3H_7SO_2CH(i$-$C_3H_7)CONH_2$	116–117	6.76	6.79	15.47	15.49
n-$C_4H_9SO_2CH(i$-$C_3H_7)CONH_2$	126.5–127[g]	6.33	6.33	14.49	14.51
$C_2H_5SO_2CH(n$-$C_4H_9)CONH_2$	112–112.5[g]	6.76	6.76	15.47	15.46
n-$C_3H_7SO_2CH(n$-$C_4H_9)CONH_2$	119–119.5[g]	6.33	6.29	14.49	14.24

[a] Unless otherwise noted, the sulfones were recrystallized from water. The properties of α-n-butylsulfonylacetamide, α-n-butylsulfonyl-n-butyramide and α-n-butylsulfonyl-n-caproamide agreed with those previously reported.[3,4] [b] See Table I, footnotes [a] and [b]. [c] Recrystallized from alcohol. [d] Recrystallized from benzene–alcohol. [e] Recrystallized from benzene–methanol. [f] Recrystallized from benzene–ligroin. [g] Recrystallized from dilute alcohol. [h] See the remarks about the impure nature of this compound in the discussion of the preparation of α-alkylsulfonylamides.

heated on the steam-bath for six and one-half hours. Most of the alcohol was then removed by distillation and the solution poured on chipped ice. The crude material weighed 12.3 g. (54%), m. p. 52–53°. Recrystallization from ligroin gave a pure product, m. p. 54.5–55° (corr.).

Anal. Calcd. for $C_8H_{17}ONS$: N, 7.99; S, 18.29. Found: N, 8.01, 8.09; S, 18.35.

α-Alkylsulfonylamides.—The sulfide was dissolved in a mixture of equal parts by volume of glacial acetic acid and acetic anhydride, using about 100 ml. of this solvent per 0.1 mole of sulfide. The solution was cooled in an ice–salt-bath and maintained at approximately 0° while 30% hydrogen peroxide was added slowly. Approximately 27 ml. of peroxide (30–35% excess) was used per 0.1 mole of sulfide. The mixture was allowed to come slowly to room temperature as the ice-bath melted and to stand at room temperature for at least three days. A small amount of manganese dioxide was added carefully to decompose the excess peroxide, the solution transferred to a Claisen flask and the solvent entirely removed under a pressure of not more than 30 mm. The solid residue was dissolved in a proper solvent, in most cases water, decolorized with charcoal and allowed to crystallize. In many cases a pure product was obtained from the first crystallization but the caproamides and α-n-ethylsulfonyl-n-valeramide were difficult to purify and required several recrystallizations. The oxidation of α-(n-propylthio)-isobutyramide was quite unsatisfactory (28%) and its abnormality verified by check runs. In this case the product gave a cloudy melt, the analytical data were unsatisfactory and numerous recrystallizations from benzene–ligroin and from acetone (using dry-ice) did not improve the product. The yields of α-alkylsulfonylamides averaged 72%, using 0.1 to 0.2 mole of sulfide. The products are described in Table II.

Summary

The reactions of the sodium mercaptides from ethyl, n-propyl and n-butyl mercaptans with seven α-haloamides have been carried out and the twenty-one α-(alkylthio)-amides oxidized to the corresponding sulfones, which are under examination as hypnotics. The metathesis reaction of the α-bromoamides was shown to be normal by the synthesis of the β-isomer from the reaction of n-butyl mercaptan with α-methylacrylamide. The preparation of α-bromoamides, including two not previously reported, has been described.

PHILADELPHIA, PENNA. RECEIVED AUGUST 30, 1939