keep the resulting compound more dispersed, water was added (175 cc.), and the hydrogen sulfide was passed into the suspension at 65°. Within one hour 7.4 g. of the gas had been absorbed. The resulting suspension of white precipitate was made alkaline with 10% sodium hydroxide (20 cc.) and then washed with water by centrifuging. After drying *in vacuo* a yield of 7 g. was obtained; m. p. 220–224°. When placed in the bath at 180°, the compound did not melt until 230–233° Found: N, 1.56; S, 51.08.

This compound (XIII) has a ratio N:S = 1:14.4, which shows that this preparation is different from the one mentioned above.

However, as in the case of (VII), it is not likely that this compound (XIII) is a molecular combination of diethanolamine with trithioformaldehyde. Both are much less soluble in acetone, ether, absolute alcohol, and benzene, and far more soluble in hot diethanolamine than the trithioformaldehyde. Furthermore, the three substances show a marked difference when submitted to sublimation, as is shown in the table.

	100°	230°
$(CH_2S)_3$	Started to sublime	Completely sublimed
(VII)	Slight sublimation with subsequent melting of sublimate	Residue melted with decomposition
(XIII)	Nothing sublimed	Residue unchanged

The analyses were done by Dr. H. K. Alber of our Microchemical Department.

Summary

Piperidine, morpholine, and diethanolamine were treated with aqueous formaldehyde to form the corresponding aminomethanols.

The 1-piperidinemethanol, 4-morpholinemethanol, and methanoldiethanolamine were treated with hydrogen sulfide under varying conditions, yielding 1-piperidinemethanethiol, 1,3-di-(1-piperidine)-2-thiapropane, 4-morpholinemethanethiol, 1,3-di-(4′-morpholine)-2-thiapropane, and polymerized thioformaldehyde derivatives of methanoldiethanolamine, respectively.

The lethal doses of the sulfur derivatives of piperidine, morpholine, and diethanolamine were determined by intravenous injections in mice.

PHILADELPHIA, PENNA. RECEIVED JULY 20, 1939

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

The Alkylation of α-Sulfonylamides[1]

BY AUSTIN POMERANTZ[2] AND RALPH CONNOR

A number of α-sulfonyl-α-alkylacetamides recently were prepared[3] by the alkylation of α-sulfonylacetamides. While this method was adequate for the compounds previously investigated, continuation of the earlier work disclosed that in certain cases the yields were low and the products difficult to purify. Since the alkylation products were of some interest as hypnotics,[4] a more complete study of this reaction was undertaken. The discussion will be limited to the ethylation of α-*n*-butylsulfonylacetamide (I) but examples of other alkylations will be given in the experimental part.

In several ethylations of α-*n*-butylsulfonylacetamide under the conditions previously used (sodium ethoxide and an alkyl halide in alcohol solution), a considerable amount of unchanged I was always present and consequently the purification of the product (α-*n*-butylsulfonyl-*n*-butyramide, II) was very difficult. The recovered starting material was not present in the reaction mixture as unreacted sodium derivative, for the solution was refluxed until it became neutral. It therefore seemed likely that the methylene group of I was not sufficiently activated to compete successfully for the sodium with the large excess of alcohol that was present[5] and that the true situation might be represented according to the equations[6]

(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.

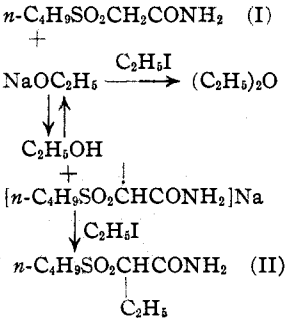
(2) Harrison Fellow in Chemistry, 1938–1939; Harrison Scholar in Chemistry, 1937–1938.

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

(4) A pharmacological examination of the compounds reported in this paper is being made under the direction of Dr. Robert S. Shelton of the Wm. S. Merrell Company and will be reported elsewhere.

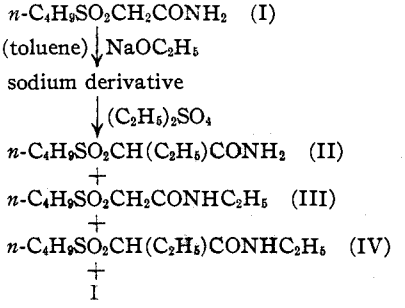
(5) Tröger and Lux [*Arch. Pharm.*, **247**, 618 (1909)] reported that α-phenylsulfonylacetamide ($C_6H_5SO_2CH_2CONH_2$) formed no sodium derivative with alcoholic sodium ethoxide. However, the alkylations of α-*p*-tolylsulfonylacetamide previously reported[3] were carried out in alcoholic solution and appeared to be more satisfactory than the alkylation of I.

(6) The weak acidity of the methylene group of I is not surprising in view of the fact that both the sulfone and carbonamide groups are generally considered to be relatively weak labilizing groups.[5,7] It is interesting to note, however, that when a methylene group

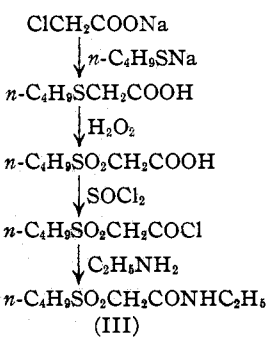


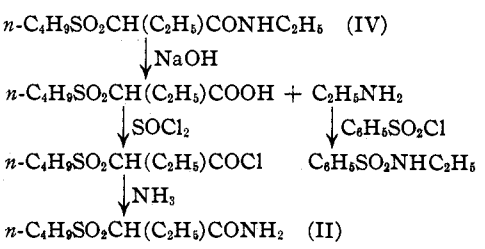
In order to avoid the effect of a high concentration of alcohol upon the above equilibrium the alkylation was next carried out in dry benzene and in dry toluene containing sodium ethoxide prepared by the reaction of sodium with the theoretical amount of alcohol. The equivalent of alcohol liberated by the reaction of I with sodium ethoxide was insufficient to interfere with the alkylation reaction since similar results were obtained whether or not this alcohol was removed before alkylation. Under these conditions the sodium derivative of I was formed quantitatively and precipitated from the hot solution as a yellow-orange oil which dried to a yellow powder. By acidification of the sodium derivative unchanged I was recovered in an amount which showed that no side reaction had occurred as a result of the sodium ethoxide treatment. The sodium derivative reacted very slowly with alkyl halides and a bromide analysis after refluxing for twenty-five hours in toluene with five equivalents of *n*-butyl bromide showed that 56% of the theoretical amount of sodium bromide had been formed. Treatment of the sodium derivative in boiling benzene with six equivalents of ethyl iodide gave a reaction mixture which was alkaline after refluxing for fifty-five hours. With ethyl sulfate the reaction was much more rapid and the alkylation mixture was neutral after refluxing for three hours. Analysis showed that the theoretical amount of sodium ethyl sulfate had been formed.

The reaction of the sodium derivative of I with ethyl sulfate in toluene gave, in addition to unchanged I, the expected *α*-*n*-butylsulfonyl-*n*-butyramide (II) and also *α*-*n*-butylsulfonyl-N-ethylacetamide (III) and *α*-*n*-butylsulfonyl-N-ethyl-*n*-butyramide (IV). The pure products were isolated in yields of 30, 7 and 0.04%, respectively. Separation was difficult, however,



and these figures do not show the relative amounts of the three compounds actually formed. It was estimated that the ratio of II to III was near to 2:1. The structure of III was established by comparison with a sample prepared by a conventional synthetic method and the identity of IV was shown by the isolation and identification of its hydrolysis products.





The results of these alkylations may be rationalized by recalling that amides undergo many reactions analogous to those generally considered typical of active methylene compounds. It may therefore be considered that in I there are two activated groups, —CH_2— and —NH_2. The data indicate that while the methylene group is somewhat the more active, their relative activity is such that both groups undergo alkylation. This possibly involves two different types of sodium derivatives, V and VI,[10] which could be interconverted by a prototropic change and which

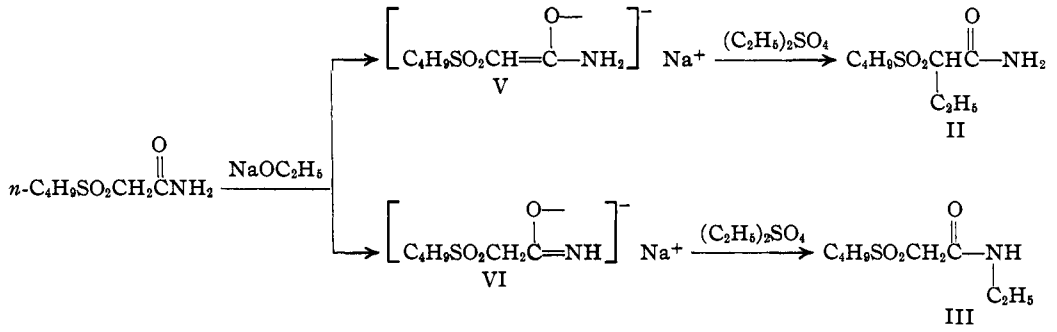
is activated by two sulfone groups[8] or by two carbonamide groups,[9] alkylation in alcoholic solution is apparently more successful than in the case of I.

(7) Gilman, "Organic Chemistry," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1938, p. 1709; Tröger and Nolte, *J. prakt. Chem.*, **101**, 136 (1920).

(8) Shriner, Struck and Jorison, THIS JOURNAL, **52**, 2060 (1930).

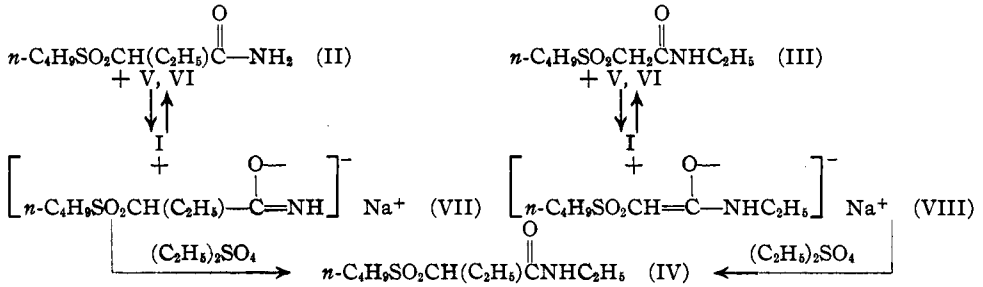
(9) Meyer, *Monatsh.*, **28** 1 (1907); Conrad and Schulze, *Ber.*, **42**, 729 (1909).

(10) Various other structures might be written for these sodium derivatives. Since a consideration of such possibilities adds nothing to the present discussion, V and VI have been arbitrarily selected to show that in one case the methylene group is involved and in the other case the —NH_2.



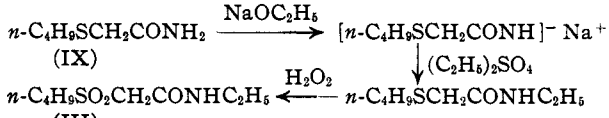
might be in dynamic equilibrium. It is also possible that the equilibrium is modified by the insolubility of the sodium derivatives; the slow rate of reaction with ethyl iodide might be construed as an indication that VI is present and not readily converted to V.[11]

The formation of a dialkylation product, IV, obviously occurred by the reaction of the monoalkylation products (II and III) with V and VI to give I and the sodium derivatives (VII and VIII) of II and III.



In the above equations the formation of only one sodium derivative from each monoalkylation product has been shown. The basis for this is the fact that the alkylation both of pure II and of pure III gave IV.[12] Furthermore, this is in accord with the view that in the system $-CH_2-\overset{O}{\overset{\|}{C}}-NH_2$ the $-CH_2-$ and $-NH_2$ are activated to approximately the same extent. Substitution of an ethyl group would change the relationship by decreasing the activity of the group to which it was attached, not only because of steric factors but also due to the fact that an alkyl group has an effect opposite to that of the common labilizing groups.[13] Therefore in II the H of $-NH_2$ is more active than that of $-CH(C_2H_5)-$ while in III the H of $-CH_2-$ is more active than that of $-NH-C_2H_5$ and the formation of sodium derivatives and their alkylation should proceed as shown above.

To compare the influence of the RS— and RSO_2— groups, the alkylation of α-(*n*-butylthio)-acetamide (IX) was investigated. The reaction of IX with sodium ethoxide in dry toluene gave a gelatinous sodium derivative. In this case an unknown side reaction apparently occurred, since only 70% of the starting material was recovered after acidification. With ethyl sulfate the sodium derivative gave an oil which was oxidized to III. It seems fairly certain that



no alkylation occurred on carbon and hence that the sodium derivative was an amide salt. Therefore, the RS— group, as would be expected, is not a labilizing group so far as this reaction is concerned. The yield of III was too low to make this a promising synthetic method.

(11) While it is well known that the sodium derivatives of amides may be converted to N-alkyl amides by the action of alkylating agents, Titherly [*J. Chem. Soc.*, **79**, 391 (1903)] observed that alkyl halides were unreactive in such syntheses while potassium alkyl sulfates reacted satisfactorily.

(12) Theoretically, II might give α-*n*-butylsulfonyl-α,α-diethylacetamide and III might give α-*n*-butylsulfonyl-N,N-diethylacetamide. Possibly these are formed in small amounts. No evidence was obtained for the former reaction. However, the crude material remaining in the mother liquors from the recrystallizations of the product from the alkylation of III was hydrolyzed and the detection of traces of diethylamine showed that alkylation of the $-NHC_2H_5$ group had occurred to a slight extent.

(13) Watson, "Modern Theories of Organic Chemistry," Oxford Press, 1937, pp. 40, 70.

Experimental Part

All melting points are uncorrected unless otherwise specified. The absolute alcohol used was the commercial material which had been further dried over lime and then treated with sodium and ethyl phthalate. Benzene and toluene were dried over sodium ribbon. The ligroin used was the fraction boiling at 70–90°.

I. Alkylation in Alcohol Solution

α-n-Butylsulfonyl-n-butyramide (II).—The reaction of α-n-butylsulfonylacetamide[3] (I) with ethyl bromide and sodium ethoxide was carried out using 0.05 molar quantities and the conditions previously[3] described. The diluted reaction mixture was concentrated under reduced pressure and chilled. The impure product weighed 7.1 g. and after repeated recrystallization from water gave 1.17 (11%) of the alkylation product (II), m. p. 124–125°. Repeated recrystallization of the residues obtained by evaporation of the aqueous mother liquors gave 1.78 g. (20%) of slightly impure starting material (I), m. p. 114–117°.

α-n-Butylsulfonyl-n-caproamide.—Using 0.03 molar quantities of the reagents and 125 ml. of alcohol as a solvent, the reaction of (I) with n-butyl bromide and sodium ethoxide was carried out as in the ethylation reaction. The reaction mixture was not neutral after refluxing for eight hours. Dilution with water gave no precipitate and the solution was concentrated, first under reduced pressure and then at atmospheric pressure. Several fractions of impure solid were obtained and when combined weighed 2.78 g., m. p. 104–115°. Recrystallization from water gave 1.06 g. (15%) of alkylation product, m. p. 104–105°, which was not purified further. The preparation of the pure compound is described below.

II. Alkylations with Alkyl Halides in Inert Solvents

Sodium ethoxide was prepared by the method of Cox and McElvain[14] with four modifications: (1) benzene or toluene were used instead of ether, (2) approximately 2–5% excess of absolute alcohol was used, (3) the reaction was carried out at room temperature and the completion of the reaction assured by allowing the mixture to stand overnight before use and (4) the air in the apparatus was displaced by dry nitrogen to avoid discoloration of the sodium ethoxide and a slow stream of dry nitrogen passed through the apparatus during the course of the reaction. The theoretical quantity of α-sulfonylamide was then added and the reaction mixture refluxed in an oil-bath until the formation of the insoluble sodium derivative was complete (one-half to two hours). In some cases the hot solvent was then decanted from the oily sodium derivative and replaced by fresh solvent in order to remove any unreacted starting material as well as the alcohol liberated in the reaction. However, the results did not differ in comparable runs in which decantation was omitted, so that this was not adopted as a general procedure. Evaporation of the decanted solvent in several experiments showed that the unreacted starting material was negligible and hence that the formation of the sodium derivative was complete.

An excess of the alkyl halide was then added and the reaction mixture refluxed in an oil-bath with stirring for periods up to fifty-five hours. In no case did the solution become neutral to moist litmus. The mixture was filtered through a fluted filter while hot to remove sodium halide and unreacted sodium derivative. The filtrate was concentrated and chilled to obtain the α-sulfonylamides. Further concentration of the mother liquors gave in all cases a small amount of an oil which was not successfully crystallized, although in some cases there appeared to be solid present. Since the oil was apparently a mixture of compounds similar to those described later in the discussion of the reaction of ethyl sulfate, no further attempts at characterization were made.

α-n-Butylsulfonyl-n-butyramide (II).—The sodium derivative from 6.46 g. (0.036 mole) of α-n-butylsulfonylacetamide (I) in 150 ml. of benzene was refluxed with 34.0 g. (0.22 mole) of ethyl iodide for fifty-five hours and the reaction product isolated as described above. From the benzene filtrate was obtained 1.8 g. (24%) of impure II, m. p. 117–120°. Recrystallization from water gave 1.4 g. (19%) of the pure material, m. p. 124–124.5°.

The alkaline, benzene-insoluble residue obtained by filtration of the reaction mixture was suspended in acetone, neutralized with glacial acetic acid and the solvent removed on the steam-bath. The residue was extracted repeatedly with small amounts of benzene and the extracts chilled. The first extracts appeared to consist mainly of II and the last of I. They were therefore divided into two portions; recrystallization of the less soluble portion from benzene gave a small amount of I. Recrystallization of the other fraction from water gave 1.1 g. (15%) of II, bringing the total yield of alkylation product to 2.5 g. (33% of the theoretical).

α-n-Butylsulfonyl-n-caproamide.—The sodium derivative from 4.48 g. (0.025 mole) of n-butylsulfonylacetamide (I) in 100 ml. of toluene was refluxed for twenty-five hours with stirring with 17.1 g. (0.125 mole) of n-butyl bromide. Isolation of the product by the general method described above gave 2.3 g. of impure solid, m. p. 85–95°. Recrystallization from water gave 1.1 g. (19%) of impure α-n-butylsulfonyl-n-caproamide, m. p. 107–108°. The product was very difficult to purify further but repeated recrystallizations from dilute alcohol gave analytically pure material, m. p. 110.5–111° (corr.).

Anal. Calcd. for $C_{10}H_{21}O_3NS$: N, 5.95; S, 13.62. Found: N, 5.90, 5.91; S, 13.74, 13.35.

The toluene-insoluble solid isolated by filtration of the reaction mixture was dissolved in dilute nitric acid and a solution of silver nitrate added. The silver bromide formed weighed 2.6 g., indicating 56% reaction.

α-p-Tolylsulfonyl-n-caproamide.—The sodium derivative from 9.45 g. (0.044 mole) of α-p-tolylsulfonylacetamide[3] in 150 ml. of dry toluene was refluxed with stirring for nineteen hours with 24.3 g. (0.18 mole) of n-butyl bromide. The product was 5.05 g. of impure material, m. p. 128–138°. Several recrystallizations from dilute alcohol gave 3 g. (25%) of the pure alkylation product, m. p. 165.5–166° (corr.).

Anal. Calcd. for $C_{13}H_{19}O_3NS$: N, 5.20; S, 11.90. Found: N, 5.18, 5.15; S, 11.93, 11.60.

α-Benzyl-α-p-tolylsulfonylacetamide.—The sodium derivative from 14.62 g. (0.07 mole) of a α-p-tolylsulfonylacetamide in 200 ml. of dry toluene was refluxed with

(14) Fieser, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1937, Vol. XVII, p. 54.

stirring for eighteen hours with 15.4 g. (0.12 mole) of benzyl chloride. The impure product weighed 4.3 g. but was separated by repeated recrystallization from dilute methanol into the starting material, α-*p*-tolylsulfonylacetamide, and 1.6 g. of the alkylation product.

The toluene-insoluble material was washed with dilute hydrochloric acid, dried and recrystallized from dilute alcohol. The weight of α-benzyl-α-*p*-tolylsulfonylacetamide from this source was 7.6 g., making the total yield of the product 9.2 g. (44%), m. p. 203–204° (corr.).

Anal. Calcd. for $C_{16}H_{17}O_3NS$: N, 4.62; S, 10.57. Found: N, 4.61, 4.58; S, 10.47.

III. Alkylations with Ethyl Sulfate in Toluene

Ethylation of α-*n*-Butylsulfonylacetamide (I).—The sodium derivative prepared from 76.7 g. (0.43 mole) of I in 700 ml. of dry toluene by the procedure mentioned above was refluxed with stirring with 72.6 g. (0.47 mole) of freshly distilled ethyl sulfate. The reaction mixture became neutral after three and one-half hours but heating was continued until the total reaction time was seven hours. At the end of this time the solution was no longer alkaline to moist litmus and the sodium ethyl sulfate obtained by filtering the hot solution weighed 62.0 g. (98% of the theoretical). The filtrate was concentrated and chilled, giving 43.9 g. of impure material, m. p. 100–108°. Repeated recrystallization from water gave 27.0 g. (30%) of pure α-*n*-butylsulfonyl-*n*-butyramide (II). The water was evaporated from the combined filtrates from these recrystallizations and the residue recrystallized repeatedly from a mixture of benzene and alcohol. While the separation of I from mixtures with II was very difficult, this procedure gave a considerable amount of unchanged I.

Further concentration of the toluene filtrate of the original reaction mixture gave a thick oil which could not be crystallized. The solvent was removed completely and the residue distilled under reduced pressure in a modified Claisen flask. The fraction (29 g.) boiling at 168–177° (2 mm.) was a viscous liquid which partly solidified in the receiver but which could not be crystallized by ordinary methods. However, using methanol as a solvent and a cooling bath of dry-ice–acetone, 9.3 g. of impure solid was isolated. Recrystallization of this product from a mixture of benzene and ligroin gave 6.2 g. (7%) of α-*n*-butylsulfonyl-N-ethylacetamide (II), m. p. 73–73.5° (corr.), which was identical with the synthetic material described later. The methanol solution obtained by filtration after the dry-ice–acetone treatment stood for some time at room temperature and a crystal growth of α-*n*-butylsulfonyl-N-ethyl-*n*-butyramide (IV), 0.4 g. (0.04%), m. p. 63–64°, was formed. This was identical with the definitely characterized material described later. Attempts to crystallize the remainder of the material were unsuccessful but it appeared to be a mixture of III and IV. In other experiments repeated attempts to separate III and IV satisfactorily were unsuccessful; small amounts were separated by crystallization and none at all by distillation.

Ethylation of α-*n*-Butylsulfonyl-N-ethylacetamide (III).—Thirty-one grams (0.15 mole) of III (prepared as described later in this paper) was refluxed with stirring for two and one-half hours in 400 ml. of dry toluene containing one equivalent of sodium ethoxide. The sodium derivative precipitated as a white granular solid. There was then added 28.2 g. (0.18 mole) of freshly distilled ethyl sulfate and the mixture refluxed in an oil-bath with stirring for two and one-half hours. This alkylation was relatively rapid; the reaction mixture had become neutral to litmus within one hour. The hot solution was filtered to remove the sodium ethyl sulfate which, when dry, weighed 20.0 g. (91% of the theoretical). The filtrate was concentrated and chilled but there was no crystallization. Removal of all of the solvent gave a thick oil which was distilled in a modified Claisen flask. The fraction (31.0 g.) boiling at 174–178° (3 mm.) was a viscous liquid boiling almost entirely at 174° (3 mm.). This distillate remained an oil for two weeks but solidified when seeded with α-*n*-butylsulfonyl-N-ethyl-*n*-butyramide (IV) isolated from the above ethylation. Recrystallization was very difficult but was accomplished by using methanol as a solvent and dry-ice in acetone as a cooling bath. The pure product weighed 16.4 g. (47%), m. p. 64–65°. Evaporation of the methanol gave an oil from which no additional pure solid was obtained. The hydrolysis of 4.9 g. of this impure material was carried out by refluxing with 60 ml. of 17% sulfuric acid for fifty hours. The solution was made alkaline, steam-distilled, and the distillate collected in dilute hydrochloric acid. A Hinsberg separation was carried out on the distillate, using *p*-toluenesulfonyl chloride.[15] There were isolated 1.5 g. of N-ethyl-*p*-toluenesulfonamide, m. p. 59–60°, and 0.15 g. of N,N-diethyl-*p*-toluenesulfonamide, m. p. 56–58°. These products did not depress the melting points of authentic samples of the proper amides.

The structure of the pure IV was established by refluxing 1.8 g. of the product for twenty-two hours with 35 ml. of 10% sodium hydroxide solution. The ethylamine evolved was absorbed in dilute hydrochloric acid and converted to N-ethylbenzenesulfonamide,[15] m. p. 56–57°. The saponification mixture was acidified with dilute hydrochloric acid, extracted with ether, and the extracts dried over sodium sulfate. The ether was removed by evaporation and the crude acid converted to the acid chloride and then the amide,[16] m. p. 124–124.5°. The identities of both derivatives were confirmed by mixed melting points with synthetic samples.

Ethylation of *n*-Butylsulfonyl-*n*-butyramide (II).—Forty-five grams (0.22 mole) of II[17] was refluxed with stirring for two hours in 400 ml. of dry toluene containing one equivalent of sodium ethoxide. The sodium derivative was soluble in hot and cold toluene. There was then added 36.9 g. (0.24 mole) of freshly distilled ethyl sulfate and the mixture refluxed in an oil-bath with stirring for eight and one-half hours. The reaction mixture was neutral; it was filtered while hot to remove the sodium ethyl sulfate which, when dry, weighed 30.0 g. (93% of the theoretical). The filtrate was concentrated and cooled and 4.67 g. (10%) of unchanged II, m. p. 117–119°, obtained. The solvent was removed completely and the thick oily residue distilled in a modified Claisen flask. In addition to

(15) Hickinbottom, "Reactions of Organic Compounds," Longmans, Green and Company, London, 1936, p. 263.

(16) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1935, p. 144.

(17) The material used in this reaction was identical with that obtained by alkylation but was prepared by a method to be described in a later paper.

the customary fore-run of ethyl sulfate, there was obtained 40.8 g., b. p. 172–178° (3–4 mm.), which solidified when seeded with α-*n*-butylsulfonyl-N-ethyl-*n*-butyramide (IV). Recrystallization from a mixture of benzene and ligroin gave 30.5 g. (60%) of impure IV, m. p. 58–61°. Several recrystallizations gave 24 g. (47%) of the pure material, m. p. 64.5–65° (corr.), which did not depress the melting points of the material obtained by the ethylation of III or that obtained as one of the products from the ethylation of I.

Anal. Calcd. for $C_{10}H_{21}O_3NS$: N, 5.95; S, 13.62. Found: N, 5.91, 5.90; S, 13.72, 13.68.

Ethylation of α-(*n*-Butylthio)-acetamide.—The sodium derivative was prepared by refluxing with stirring 74.7 g. (0.51 mole) of α-(*n*-butylthio)-acetamide[8] for two and one-half hours in 800 ml. of dry toluene containing an equivalent amount of sodium ethoxide. The sodium derivative was soluble in hot toluene but precipitated as a gelatinous mass on cooling. The sodium derivative was refluxed with stirring for eight and one-half hours with 82.5 g. (0.54 mole) of freshly distilled ethyl sulfate. At the end of this period the reaction mixture was neutral to moist litmus. The sodium ethyl sulfate obtained by filtration of the hot solution weighed 70 g. (93% of the theoretical). The filtrate was concentrated and the oily residue distilled in a modified Claisen flask. Fraction 1, 12.7 g., distilled at 73–81° (4–6 mm.). Ethyl sulfate was shown to be present in this mixture by the formation of barium sulfate. Another component of the fraction was probably ethyl α-(*n*-butylthio)-acetate[18] which is reported[19] to boil at 89–90° (10 mm.). Fraction 2, 47.5 g., distilled at 122–125° (4 mm.). Considerable decomposition occurred during distillation and the residue was large. The entire fraction was dissolved in 270 ml. of 1:1 acetic acid–acetic anhydride mixture and treated with 70 ml. of 30% hydrogen peroxide according to the method already described.[8] At the end of the oxidation period the excess peroxide was decomposed by manganese dioxide and the solvent removed under reduced pressure. The residue was an oil which dissolved in hot benzene and was precipitated as a solid by the addition of ligroin. The product thus obtained weighed 41.11 g., corresponding to approximately 75% of the theoretical for the oxidation step. Crystallization from benzene gave 5 g. of I, m. p. 117–118°, and the addition of ligroin to the filtrate gave 24.1 g. of impure III, m. p. 65–67° (23% of the theoretical, based on α-(*n*-butylthio)-acetamide). Since the separation of I and III in other experiments was fairly easy, it seems safe to say that the product of the oxidation was III contaminated with relatively small amounts of I. Several recrystallizations of the impure III raised its melting point to 72°.

IV. Reactions of Amides with Sodium Ethoxide

The general procedure was to prepare sodium ethoxide in benzene by the method already described, add an equivalent amount of the amide and reflux in an oil-bath for the periods of time stated below. Glacial acetic acid was then added in 10% excess of the theoretical amount and heating continued until the mixture was neutral to moist litmus.

α-*n*-Butylsulfonylacetamide (I).—To 150 ml. of benzene containing sodium ethoxide was added 4.05 g. (0.023 mole) of I and the mixture refluxed for two and one-half hours. After treatment with glacial acetic acid as described above, the hot solution was filtered, concentrated and chilled. The amount of I recovered was 3.40 g. (84%), m. p. 116–117°. Considering the mechanical losses that might be expected, it seems safe to say that no appreciable side reactions arise from the action of sodium ethoxide on I. Evidence for the complete conversion of I to the sodium derivative has been mentioned earlier in the experimental part.

α-(*n*-Butylthio)-acetamide (IX).—To 100 ml. of benzene containing sodium ethoxide was added 6.01 g. (0.041 mole) of the amide and the mixture refluxed for five hours. After treatment with glacial acetic acid as described above, the hot solution was filtered, concentrated, and the amide precipitated by the addition of ligroin. The recovery was 4.16 g. (69%), m. p. 55–56°. The poor recovery and the large residue after distillation of the alkylation product as mentioned above both suggest that the reaction of sodium ethoxide with α-(*n*-butylthio)-acetamide gives other products in addition to the sodium derivative.

V. Preparation of α-*n*-Butylsulfonyl-N-ethylacetamide

α-(*n*-Butylthio)-acetic Acid.[20]—This compound was prepared from sodium chloroacetate and sodium *n*-butylmercaptide.[21] An aqueous solution of sodium chloroacetate was prepared by mixing a concentrated aqueous solution containing 66.2 g. (0.7 mole) of chloroacetic acid with a concentrated aqueous solution containing 28 g. (0.7 mole) of sodium hydroxide and diluting with water to a total volume of 150 ml. The solution was placed in a 1-liter, three-necked, round-bottomed flask equipped with a mechanical stirrer and a dropping funnel and immersed in an ice–salt bath. A solution of 75.5 ml. (63.1 g., 0.7 mole) of *n*-butyl mercaptan and 28.0 g. (0.7 mole) of sodium hydroxide in 110 ml. of water was added, with stirring, over a period of one and one-half hours. The reaction mixture was allowed to come to room temperature as the freezing bath melted and after standing overnight was heated on the steam-bath for three hours. The solution was transferred to a separatory funnel, an excess of concentrated sulfuric acid added and the oily upper layer separated. The aqueous layer was extracted with two 100-ml. portions of ether, the extracts added to the original acid layer and the solution dried over calcium chloride. The ether was removed on the steam-bath and the residue distilled in a modified Claisen flask. The product weighed 93.4 g. (90%), b. p. 125–130° (5–6 mm.).

α-*n*-Butylsulfonylacetic Acid.[20]—A solution of 93.4 g. (0.63 mole) of α-(*n*-butylthio)-acetic acid in 630 ml. of 1:1 acetic acid–acetic anhydride mixture was chilled in an ice–salt bath and a one-third excess (172 ml.) of 30% hydrogen

(18) In the alkylation of the α-sulfonylamides, as well as in this case, it often was noted that a fraction corresponding to the ethyl ester was present unless freshly dried alcohol was used. Apparently the slightest traces of moisture cause saponification and the salt formed is converted to the ester by the ethyl sulfate: $RSO_2CH_2CONH_2 \xrightarrow{NaOH} RSO_2CH_2COONa \xrightarrow{(C_2H_5)_2SO_4} RSO_2CH_2COOC_2H_5$.

(19) Uyeda and Reid, THIS JOURNAL, **42**, 2385 (1920).

(20) The conditions for these reactions were worked out in this Laboratory by Mr. Gordon Urquhart.

(21) This reaction had been described previously by Uyeda and Reid.[19] Since certain modifications were made in their directions and higher yields obtained, our method has been described in detail.

peroxide solution added slowly to the cold mixture. The solution was allowed to come to room temperature as the ice-bath melted and stand at room temperature overnight.[22] Manganese dioxide[23] was added, the solution transferred to a Claisen flask and the solvent removed under reduced pressure. The solid residue was dissolved in a mixture of ether and acetone, dried over sodium sulfate and the solvent removed on the water-bath. The yield of crude product was 88 g. (77%), m. p. 59–62°. Recrystallization from toluene gave the pure acid, m. p. 67.5–68.5° (corr.).

Anal. Calcd. for $C_6H_{12}O_4S$: S, 17.79. Found: S, 17.76, 17.91.

α-*n*-Butylsulfonyl-N-ethylacetamide (III).—Crude α-*n*-butylsulfonylacetic acid (40.5 g., 0.225 mole) was placed in an Erlenmeyer flask which was connected by a wide rubber tube to the neck of a three-necked, round-bottomed flask. The acid chloride was prepared by adding the solid acid slowly to thionyl chloride and treating according to the method described for *n*-butyryl chloride.[24] Ethylamine, generated from the hydrochloride by the addition of concentrated alkali and heating, was passed through a tube of soda-lime and bubbled into 250 ml. of dry ether in a 1-liter, three-necked, round-bottomed flask surrounded by an ice–salt bath. When the increase in weight of the ethereal solution was 26 g. (0.58 mole of ethylamine) the flask was fitted with a reflux condenser, a mercury-sealed stirrer and a dropping funnel, kept in the cooling bath, and the acid chloride added dropwise. The reaction mixture stood overnight and the ether then distilled on the steam-bath and replaced by dry benzene during the distillation. The resulting benzene solution was filtered while hot through a fluted filter, concentrated, and the product precipitated by the addition of ligroin and chilling. The product weighed 37.6 g. (81%), m. p. 60–65°, but was contaminated with *n*-butylsulfonylacetic acid. It was dissolved in cold benzene, washed with a saturated solution of sodium bicarbonate, dried over sodium sulfate and recrystallized from a benzene–ligroin mixture. The pure product so obtained weighed 17.4 g., m. p. 73–73.5° (corr.). Concentration of the mother liquor gave an additional 7.4 g., m. p. 70–71°, making the total yield of product 24.8 g. (53%).

Anal. Calcd. for $C_8H_{17}O_3NS$: N, 6.76; S, 15.47. Found: N, 6.69, 6.71; S, 15.36, 15.55.

(22) A longer oxidation period would probably give better results.

(23) Manganese dioxide was used in small amounts, since it formed a manganese salt of the product. Nevertheless, it appeared to assist in the decomposition of the excess peroxide and was always used.

(24) Gilman, "Organic Syntheses," John Wiley and Sons, New York, N. Y., 1932, Coll. Vol. I, p. 142.

Summary

The alkylationi n alcohol of α-alkylsulfonylamides ($RSO_2CH_2CONH_2$) was complicated by the fact that the compounds were not acidic enough to form sodium derivatives satisfactorily in the presence of a considerable amount of alcohol. In inert solvents alkyl halides were not very reactive but ethyl sulfate reacted readily with the sodium derivative of α-*n*-butylsulfonylacetamide (I). The products of this reaction were, in addition to unchanged starting material, α-*n*-butylsulfonyl-*n*-butyramide (II), α-*n*-butylsulfonyl-N-ethylacetamide (III) and α-*n*-butylsulfonyl-N-ethyl-*n*-butyramide (IV). Under similar conditions both II and III gave IV. The results may be interpreted as evidence that in the system $—CH_2—CO—NH_2$ of this series, two types of sodium derivatives are formed and that the $—CH_2—$ and $—NH_2$ are activated to about the same extent. Introduction of an alkyl substituent on either $—CH_2—$ or $—NH_2$ decreases the relative reactivity of the group to which the alkyl substituent is attached and subsequent alkylation occurs on the other active group.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Reductive Alkylation of Aromatic Primary Amines. II[1]

BY WILLIAM S. EMERSON AND W. D. ROBB

In view of earlier success with the reductive alkylation of aniline[1] it seemed advisable to test the generality of this reaction with other aromatic primary amines. For this purpose we selected *p*-toluidine, *p*-anisidine and α- and β-naphthylamines.

Using the procedure previously described[1] ethyl-α-naphthylamine was prepared in 88% yield, ethyl-, *n*-butyl- and benzyl-β-naphthylamine, and ethyl- and *n*-butyl-*p*-toluidine in 50 to 64% yields. These amines were identified by the formation of known salt or amide derivatives.

The new substances, N-*n*-butyl-α-naphthylamine and N-ethyl- and N-*n*-butyl-*p*-anisidine, were also prepared by this method. Their properties, as well as those of the new benzamide of benzyl-α-naphthylamine, are given in Table I.

N,N-Dialkylarylamines.—In the alkylation of *p*-toluidine and *p*-anisidine with *n*-butyraldehyde, a high boiling fraction was obtained. Three grams of this material was boiled with 20 cc. of acetic

(1) For paper I, see Emerson and Walters, THIS JOURNAL, 60, 2023 (1938).