the composition $C_{27}H_{42}O_5$. This substance has yielded certain transformation products of an interesting and new type, and a partial report of the results is made in order to indicate the lines of further investigation which are being pursued in an effort to determine the character of the terminal part of the sapogenin side chain and to effect the degradation envisioned.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASS. RECEIVED NOVEMBER 20, 1937

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

α-Sulfonyl and α,α-Disulfonyl Amides[1]

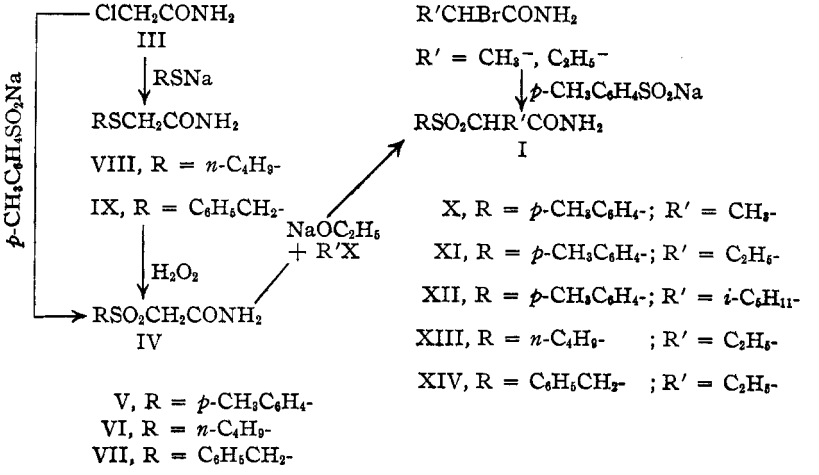
BY EDMOND L. D'OUVILLE[2] AND RALPH CONNOR

A study[3] of the lability of the methylene group in benzyl *p*-tolyl sulfone aroused our interest in other active methylene compounds containing sulfone groupings. The investigation reported here was undertaken in order to make available α-sulfonyl amides (I) and α,α-disulfonyl amides (II). In view of the fact that sulfone[4] and amide[5]

$RSO_2CHRCONH_2$ (I) $\qquad (RSO_2)_2CHCONH_2$ (II)

groups are present in certain hypnotics, the possibility that the presence of these two functions in the same molecule might give an enhanced physiological activity was the source of additional interest in these derivatives.

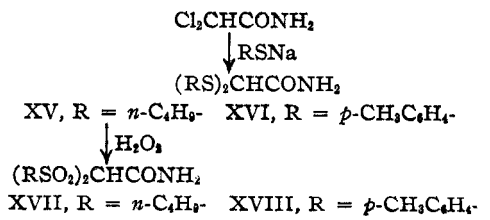
The α-sulfonyl amides (I) were prepared by the reaction of an α-halogenated amide with sodium *p*-toluenesulfinate or by the alkylation of α-sulfonylacetamides (IV). The latter were prepared from chloroacetamide and sodium *p*-toluenesulfinate[6] or from chloroacetamide and a sodium mercaptide, followed by oxidation. These reactions are summarized in the flow-sheet.



The products (I) were insoluble in cold alkali and in cold water. When the metathesis reactions were carried out under the optimum conditions described below, the different methods of synthesis of I were equally successful; the availability of the starting materials seemed to be the most important factor to be considered in selecting the method of synthesis of a given compound of this type.

The preparation of α,α-disulfonyl amides was accomplished by the reaction of dichloroacetamide with the appropriate sodium mercaptide, followed by oxidation.

The disulfonyl amides dissolved in a saturated solution of sodium carbonate and were reprecipitated by mineral acids. The alkaline hydrolysis of α,α-di-*p*-tolylsulfonylacetamide (XVIII) to give bis-*p*-tolylsulfonylmethane confirms the structure of the products and also suggests a possible practical method for the synthesis of disulfones.



(1) This communication is abstracted from a thesis submitted by Edmond L. d'Ouville in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Pennsylvania in June, 1937.

(2) Chemical Foundation Fellow.

(3) Connor, Fleming and Clayton, THIS JOURNAL, **58**, 1386 (1936).

(4) Baumann and Kast, *Z. physiol. Chem.*, **14**, 52 (1890).

(5) Volwiler and Tabern, THIS JOURNAL, **58**, 1352 (1936).

(6) Tröger and Hille, *J. prakt. Chem.*, [2] **71**, 201 (1905).

The syntheses reported here were satisfactory after a study of the metathesis reactions involving the sulfinates and mercaptides had shown the proper conditions for minimizing side reactions. Early in the investigation it became obvious that the reaction with α-halogenated amides was more complex than the formation of sulfides and sulfones from simple alkyl halides. The nature of the halogen in the amides is presumably enough like that of phenacyl halides[7] to cause oxidation of the sulfinates and mercaptides. While no oxidation products were isolated in the experiments reported in this paper, their presence was indicated by the difficulty of purification of the metathesis products formed under conditions such that the yields were low (*i. e.*, under conditions favorable for oxidation).

After a number of experiments it was found that higher yields of metathesis products could be obtained by carrying out the reactions at room temperature or lower. In no case did this fail to improve the yield and in some instances it made an otherwise impracticable reaction successful. The results of some of our experiments are summarized in Table I.

Pharmacological Data.—The pharmacological investigation of these compounds has been carried out through the kindness of Dr. Robert S. Shelton of the Wm. S. Merrell Co. and will be reported elsewhere. Preliminary tests show that some of the products are sufficiently active hypnotics to justify the examination of other members of these series. In addition, it is planned to synthesize other types of compounds containing the sulfone grouping combined with other hypnotic groups.

TABLE I

THE INFLUENCE OF TEMPERATURE UPON THE YIELDS OF METATHESIS PRODUCTS

Product	Yield, % Cold[a]	Hot[b]
n-$C_4H_9SCH_2CONH_2$	65	30
$C_6H_5CH_2SCH_2CONH_2$	75	4
(p-$CH_3C_6H_4S)_2CHCONH_2$	75	35
(n-$C_4H_9S)_2CHCONH_2$	55	30
p-$CH_3C_6H_4SO_2CH_2CONH_2$	75[c]	55[d]

[a] The reactants in alcohol solution or suspension were mixed at 0°, allowed to come to room temperature as the ice-bath melted and to stand for three to five days at room temperature. [b] The reactants were mixed, immediately heated to boiling and refluxed for one hour. [c] The reaction stood for thirty days at room temperature. [d] The reaction mixture was refluxed for four hours.

(7) Kohler and Potter, THIS JOURNAL, **58**, 2166 (1936). These authors found that the principal products from the reaction of sodium p-thiocresolate with phenacyl chloride were p-tolyl phenacyl sulfoxide and acetophenone; similarly, the reaction of sodium p-toluenesulfinate with tribenzoylmethyl chloride gave no metathesis, but only oxidation-reduction.

Experimental Part

All melting points are corrected unless otherwise specified. The analytical data for the new compounds are given in Table II. α-Bromopropionamide and dichloroacetamide were prepared in 60% yields from methyl α-bromopropionate and ethyl dichloroacetate by the method described[8] for chloroacetamide. This reaction was unsatisfactory with ethyl α-bromobutyrate; none of the amide crystallized from the cold solution and extraction with ether gave a product containing much unreacted ester. A 15% yield of α-bromobutyramide was obtained by concentrating the aqueous layer.

I. α-p-Tolylsulfonylamides by Metathesis

Equivalent quantities of sodium p-toluenesulfinate and the appropriate α-halogenated amide were refluxed in alcohol for the times stated below and the product precipitated by dilution with water.

α-p-Tolylsulfonylacetamide[6] **(V).**—The product obtained by refluxing 106 g. (0.6 mole) of anhydrous sodium p-toluenesulfinate and 56 g. (0.6 mole) of chloroacetamide in 300 ml. of alcohol for four hours was recrystallized from water. The yield of purified product was 70 g. (55%), m. p. 166–167° (uncorr.). Higher yields were obtained (see Table I) by condensation at room temperature but the reaction was so slow under such conditions that reaction under reflux was more practical.

α-p-Tolylsulfonylpropionamide (X).—A mixture of 21 g. (0.1 mole) of sodium p-toluenesulfinate hydrate and 15.2 g. (0.1 mole) of α-bromopropionamide in 200 ml. of alcohol was refluxed for six hours. Recrystallization of the product from dilute alcohol gave 15 g. (55%), m. p. 168–168.5°.

α-p-Tolylsulfonyl-n-butyramide (XI).—A mixture of 10.5 g. (0.05 mole) of sodium p-toluenesulfinate hydrate and 8.4 g. (0.05 mole) of α-bromo-n-butyramide in 100 ml. of alcohol was refluxed for two hours. The yield without purification was 10.0 g. (80%), m. p. 167–168° (uncorr.). (The synthesis of this product by another method is described in Part IV of the experimental.)

II. Mercaptides with Chloroamides

To a sodium ethoxide solution prepared by dissolving sodium in absolute alcohol was added the equivalent amount of the thiol compound and the mixture cooled to 0° in an ice–salt bath. The theoretical amount of the chloroamide was added to the cold mixture and the mixture allowed to come to room temperature as the ice-bath melted (this required about three hours). After standing at room temperature for three to five days, the reaction mixture was poured on chipped ice.

α-(n-Butylthio)-acetamide[9] **(VIII).**—The diluted reaction mixture was extracted with four 125-ml. portions of ether, the extracts dried over sodium sulfate and the ether removed on the steam-bath. The solid was recrystallized from ligroin (b. p. 90–120°). The product

(8) "Organic Syntheses," John Wiley and Sons, Inc., New York, Coll. Vol. I, 1932, p. 479.

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

TABLE II

ANALYTICAL DATA ON NEW COMPOUNDS

Compound	Empirical formula	Calculated			Found				
		Mol. wt.	N, %	S, %	Mol. wt.[a]	N,[b] %		S,[c] %	
VI	$C_6H_{13}O_3NS$	179	7.82	17.89	192	7.93	7.94	17.9	18.1
VIII[d]	$C_6H_{13}ONS$	147	9.53	...	143	9.60	9.76	.....	
XI	$C_{11}H_{15}O_3NS$	241	5.82	13.31	...	5.95		13.0	13.1
XII	$C_{14}H_{21}O_3NS$	283	4.94	11.32	280	5.20	5.11	11.7	11.3
XIII	$C_8H_{17}O_3NS$	207	6.76	15.50	218	6.70	6.69	15.2	15.6
XIV	$C_{11}H_{15}O_3NS$	241	5.82	13.31	244	5.91	5.96	13.2	13.2
XV	$C_{10}H_{21}ONS_2$	235	5.96	27.3	232	5.97	5.89	27.8	27.2
XVI	$C_{16}H_{17}ONS_2$	303	4.62	21.17	302	4.72	4.79	21.0	20.7
XVII	$C_{10}H_{21}O_5NS_2$	299	4.68	21.50	308	4.73	4.76	21.3	21.6[e]
XVIII	$C_{16}H_{17}O_5NS_2$	367	3.82	17.42	356	3.79	3.88	17.5[e]	17.1[e]

[a] Determined by Mr. W. S. Young by the procedure of Rast, using a turpentine thermometer. [b] Micro Dumas. [c] The micro method of Elek and Hill [THIS JOURNAL, **55**, 3479 (1933)] was used unless otherwise specified. [d] Calcd.: C, 48.91; H, 8.90. Found: C, 48.95; H, 8.79. This analysis was carried out by Mr. Wm. McClellan. [e] The open fusion method of Emerson [THIS JOURNAL, **52**, 1219 (1930)] was used.

from 36 g. (0.4 mole) of *n*-butyl mercaptan and 37.4 g. (0.4 mole) of chloroacetamide in 250 ml. of sodium methoxide solution weighed 38.5 g. (65%), m. p. 50.5–52°. This product was suitable for oxidation, but further recrystallization raised its melting point to 57–58°.[10]

α-(Benzylthio)-acetamide (IX).—The diluted reaction mixture from 31 g. (0.25 mole) of benzyl mercaptan and 23.4 g. (0.25 mole) of chloroacetamide in 150 ml. of sodium ethoxide solution gave 40 g. of crude product, m. p. 93–95° (uncorr.). Recrystallization from ligroin gave 34 g. (75%), m. p. 97–98°.

α,α-(Bis-*n*-butylthio)-acetamide (XV).—The product obtained by dilution of the reaction mixtures from 18 g. (0.2 mole) of *n*-butyl mercaptan and 13 g. (0.1 mole) of dichloroacetamide in 125 ml. of sodium ethoxide solution was recrystallized from ligroin (b. p. 90–120°). The yield of recrystallized product was 12.7 g. (55%), m. p. 102–104°, which upon further recrystallization melted at 104.5–105°.

α,α-(Bis-*p*-tolylthio)-acetamide (XVI).—Dilution of the reaction mixture from 12.4 g. (0.1 mole) of *p*-thiocresol and 6.4 g. (0.05 mole) of dichloroacetamide in 75 ml. of sodium ethoxide solution gave 15.5 g. of crude product. Recrystallization from alcohol gave 11.5 g. (75%), m. p. 172.5–173.5°.

III. Oxidation of Sulfides

The sulfide was dissolved in glacial acetic acid–acetic anhydride mixture (five parts by volume of acid to one of anhydride) and maintained at 0–10° while 30% hydrogen peroxide (30–35% excess over the theoretical quantity) was added slowly. The mixture was allowed to come to room temperature and stand for two to five days. The optimum time for the oxidation was not determined but there was no indication of incomplete oxidation after two days of standing and no detrimental effects were observed after five days. Complete solubility of the sulfide at the beginning of the oxidation was not essential.

α-*n*-Butylsulfonylacetamide (VI).—The sulfone obtained from VIII by oxidation according to the above method was too soluble to be precipitated by dilution with water. Therefore the excess peroxide was decomposed by the addition of manganese dioxide and the solvent removed under reduced pressure while the temperature of the solution was maintained at 40°. When crystals began to appear 150 ml. of water was added. The product from 38.5 g. (0.26 mole) of α-(*n*-butylthio)-acetamide in 235 ml. of acetic acid–acetic anhydride solvent was recrystallized from water. The yield of purified material was 35.1 g. (75%) of white crystalline material, m. p. 119–119.5°.

α-Benzylsulfonylacetamide[11] (VII).—Dilution with 100 ml. of ice water of the reaction mixture from 30 g. (0.165 mole) of α-(benzylthio)-acetamide in 60 ml. of solvent gave 30 g. (85%) of α-benzylsulfonylacetamide, m. p. 175–176° (uncorr.). Recrystallization of 10 g. of the crude material from water gave 8 g., m. p. 178.5–179°.

α,α-Bis-*n*-butylsulfonylacetamide (XVII).—The addition of 300 ml. of ice water to the reaction mixture from 12 g. (0.05 mole) of α,α-(bis-*n*-butylthio)-acetamide in 60 ml. of solvent precipitated XVII. Recrystallization from alcohol gave 11 g. (75%), m. p. 180.5–181.5°.

α,α-Bis-*p*-tolylsulfonylacetamide (XVIII).—The product from 10 g. (0.033 mole) of α,α-(bis-*p*-tolylthio)-acetamide in 60 ml. of solvent crystallized from the reaction mixture. The solid was washed with water, dissolved in 5% sodium carbonate solution and filtered. Acidification of the filtrate gave 9.5 g. (75%) which after recrystallization from alcohol melted at 195–196°.

Bis-(*p*-tolylsulfonyl)-methane (XIX) was prepared by refluxing 3 g. of XVIII for forty-five minutes with 75 ml. of 4% aqueous sodium hydroxide solution. The reaction mixture was acidified and the solid product recrystallized from dilute alcohol. The yield of purified material was 2.0 g. (75%), m. p.[12] 133.5–134° (uncorr.).

IV. Alkylation of α-Sulfonylamides

The α-sulfonylamide to be alkylated was added to a sodium ethoxide solution prepared by dissolving the theoretical amount of sodium in absolute alcohol. A 1% excess of the alkyl bromide was added and the mixture refluxed on the water-bath until neutral (about four

(10) Although Uyeda and Reid[9] reported that this compound melted at 65°, repeated recrystallization did not raise the melting point of our product above 58° and our material was analytically pure.

(11) Lesser and Mehrländer, *Ber.*, **56**, 1642 (1923).

(12) Fromm, Forster and Scherschswitski, *Ann.*, **394**, 343 (1912).

hours). The crude product was obtained by diluting the reaction mixture with ice and water.

α-*p*-Tolylsulfonyl-*n*-butyramide (XI).—The crude product from the ethylation of 51 g. (0.24 mole) of α-*p*-tolylsulfonylacetamide (V) in 250 ml. of absolute alcohol weighed 33 g. (60%). Three recrystallizations from benzene gave 21 g. (35%), m. p. 175–175.5°.

α-*p*-Tolylsulfonyl-α-isoamylacetamide (XII).—From 26 g. (0.12 mole) of V in 100 ml. of absolute alcohol a crude yield of 26 g. (76%), m. p. 133–135° (uncorr.) was obtained. After recrystallization from dilute alcohol the product weighed 15 g. (44%), m. p. 151.5–152°.

α-*n*-Butylsulfonyl-*n*-butyramide (XIII).—From 8.5 g. (0.05 mole) of α-*n*-butylsulfonylacetamide (VI) in 200 ml. of sodium ethoxide solution only 3.0 g. of product was obtained by dilution with ice and water. An additional 2.0 g. was obtained by concentrating the filtrate. The combined products were recrystallized from ligroin. The yield of purified material was 4.2 g. (40%), m. p. 125–125.5°.

α-Benzylsulfonyl-*n*-butyramide (XIV).—The product from 21.3 g. (0.1 mole) of α-benzylsulfonylacetamide (VII) in 200 ml. of sodium ethoxide solution was recrystallized from 1 l. of boiling water. The purified product weighed 14 g. (62%), m. p. 196–198°.

Ackowledgment.—The authors are grateful to the Faculty Research Committee of the University of Pennsylvania for a grant to aid this investigation.

Summary

The preparation of α-sulfonyl (I) and α,α-disulfonyl (II) derivatives of amides has been investigated. The influence of temperature on the yields of metathesis products from mercaptides and sulfinates has been described.

$RSO_2CHR'CONH_2$ (I) $(RSO_2)_2CHCONH_2$ (II)

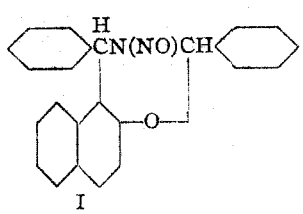
PHILADELPHIA, PENNA. RECEIVED NOVEMBER 12, 1937

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

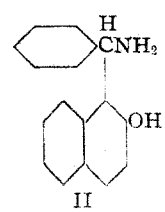
The Action of Nitrous Acid on Phenyl-beta-Naphtholaminomethane. III

BY FRANCIS EARL RAY AND WALTER R. HAEFELE

A previous paper of this title[1] explained the formation of N-nitroso-1,3-diphenyl-4,2-β-naphtho-iso-oxazine, I, and 1,6-dinitro-2-naphthol from phenyl-β-naphtholaminomethane, II, and nitrous acid by assuming a preliminary dissociation of the amine into benzaldehyde, β-naphthol and ammonia.



I

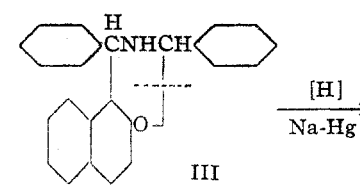


II

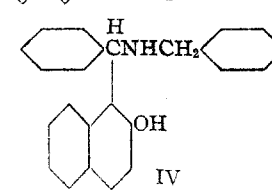
We now wish to report further on reactions of this type. While some of the structures can be advanced only tentatively, the present status of the work is recorded inasmuch as the authors are unable, at this time, to continue the research.

The iso-oxazine, III, as well as the nitroso derivative, I, give no reaction with ferric chloride. When, however, the iso-oxazine, III, is reduced with sodium amalgam, the compound obtained melts at 143° and gives a strong violet color with ferric chloride.

(1) Ahmed and Hemphill with Ray, THIS JOURNAL, **56**, 2403 (1934).



III



IV

The iso-oxazine does not form a salt but the reduction product readily forms stable, crystalline salts. Analyses and molecular weight determinations all point to the compound being phenyl-β-naphthol-N-benzylaminomethane, IV. In distinction from the iso-oxazine this compound is not hydrolyzed by boiling hydrochloric acid.

Evidently reduction attacked the molecule at the carbon–oxygen bond as shown by the dotted line in III.

The nitroso-iso-oxazine, I, was reduced under similar conditions and white needles melting at 141° were obtained. At first it was thought that this substance was identical with that obtained above, but a mixed melting point showed almost