only unidentified products and dinitronaphthsultam were obtained. The compound described in the present work could not be isolated from the mixture.

In other work,[4] it was shown that 1,3-dinitronaphthalene-5-sulfonic acid was formed as a minor product in the nitration of 2-nitronaphthalene-8-sulfonic acid. Evidence has also been obtained of the further sulfonation of 1,3-dinitronaphthalene-5-sulfonic acid to a disulfonic acid by heating with oleum.

EXPERIMENTAL

1,3-Dinitronaphthalene-5-sulfonic acid, sodium salt. 1,3-Dinitronaphthalene (4 g.) was added gradually to 40 ml. of 100% sulfuric acid at room temperature, and the red-black solution left 24 hr. It was then poured slowly with stirring onto an excess of ice. The mixture was heated to 60° and filtered from a little starting material, and the filtrate cooled and saturated with sodium chloride. The sodium salt was filtered and washed with brine. It was redissolved in warm water containing a little hydrochloric acid and resalted to eliminate sulfate. The air dried product weighed 10.4 g. and contained some sodium chloride. It formed a light yellow crystalline powder.

Incomplete sulfonation can be avoided by use of a larger excess of sulfuric acid or by the inclusion of a little oleum. Ordinary concentrated sulfuric acid does not sulfonate 1,3-dinitronaphthalene during 4 days' standing in the cold. The aqueous sulfonic acid solution can be salted out also by potassium chloride, giving a more granular and dense precipitate than is formed with sodium chloride.

The aqueous solution of the sodium salt becomes red with sodium or ammonium hydroxide. The latter, when mixed with a strong ammoniacal cupric sulfate solution, soon yields a crystalline powder of the sparingly soluble complex cupric-ammine salt of the sulfonic acid. The ammino-zinc salt is precipitated more slowly as crystalline grains.

The free sulfonic acid will precipitate from a solution containing a high concentration of sulfuric acid, but is dissolved by warming or on dilution with water. It was not obtained pure for analysis.

1,3-Dinitronaphthalene-5-sulfonyl chloride. A mixture of 3.9 g. of the salted sodium salt and 12 g. of phosphorus pentachloride was ground in a mortar and then placed in a lightly closed flask in an oil bath at 135°. After 1 hr., the product was cooled and stirred vigorously with ice and water until hydrolysis of the phosphorus oxychloride was complete. The solid was filtered, washed with water, and dried. The acetone solution of the material was filtered from inorganic salts and the sulfonyl chloride crystallized by gradual addition of ice water. After washing and drying, the yield was 1.3 g. Recrystallized from benzene-hexane, the sulfonyl chloride had m.p. 123–124°.

Anal. Calcd. for $C_{10}H_5N_2O_6SCl$: Cl 11.2. Found: Cl 11.4.

The percentage yields of the sodium salt of the sulfonic acid and the sulfonyl chloride were not calculated as the salt is unavoidably contaminated with sodium chloride in either case.

1,3-Dinitronaphthalene-5-sulfonamide. A solution of 1.3 g. of the sulfonyl chloride in 15 ml. of dioxane was treated at 5–10° with 5 ml. of ammonium hydroxide solution, added in portions. At first, a dark red color was produced and a precipitate rapidly formed, but after all of the ammonium hydroxide had been added the precipitate dissolved. The mixture was left in the cold bath for 15 min. and then 7 ml. of acetic acid was added during 5 min. The light red solution was treated slowly with an excess of ice water yielding a crystalline deposit of the amide. After 0.5 hr., this was filtered, washed with water, and dried. The yield of the light yellow crude product was 1.2 g. or 98%. The compound was recrystallized three times from aqueous methanol and then had m.p. 258–259°.

Anal. N as NO_2 was determined by $TiCl_3$ titration. Calcd. for $C_{10}H_7N_3O_6S$: N as NO_2, 9.43; S, 10.77. Found: $NaSNO_2$, 9.62; S, 10.30.

Conversion of the sulfonyl chloride to 1,3,5-trichloronaphthalene. A sample of the sulfonyl chloride was ground with five times its weight of phosphorus pentachloride and the mixture kept in an oil bath at 170° for 4.5 hr. The sublimed pentachloride was scraped back periodically during the heating. When cold, the product was added cautiously to ice. After complete hydrolysis, the solid was filtered, washed with water, and dried. Without further purification, the infrared spectrum was identical to that of authentic 1,3,5-trichloronaphthalene.

Acknowledgment. Appreciation is expressed to W. Morgan Padgett II, Dietrich Heinritz, and A. J. Valerga for spectral measurements and analytical determinations, and to Dr. J. Hyman for encouragement during the course of the work.

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(4) D. C. Morrison, unpublished work, Hyman Laboratories, Inc.

Preparation of Some Additional Sulfonylureas[1]

GERALD F. HOLLAND

Received August 23, 1960

Two sulfonylureas, 1-*n*-butyl-3-(4-tolylsulfonyl)-urea (tolbutamide) and 1-(4-chlorobenzenesulfonyl)-3-*n*-propylurea (chlorpropamide), are clinically effective as hypoglycemic agents.[2,3] Research in our laboratory, as well as in others,[4–8] has been underway for some time to prepare antidiabetic agents of even superior therapeutic usefulness. This note reports some further compounds prepared in this program.

(1) For preceding papers see W. M. McLamore, G. M. Fanelli, S. Y. P'an, and G. D. Laubach, *Ann. N. Y. Acad. Sci.*, **74**(3), 443 (1959); G. F. Holland, D. A. Jaeger, R. L. Wagner, G. D. Laubach, W. M. McLamore, and S. Y. P'an, *J. Med. Phar. Chem.*, **3**(1) 99 (1961).

(2) R. Levine, "The Effects of the Sulfonylureas and Related Compounds in Experimental and Clinical Diabetes," *Ann. N. Y. Acad. Sci.*, **71**(1), 1–292 (1957).

(3) M. G. Goldner, "Chlorpropamide and Diabetes Mellitus," *Ann. N. Y. Acad. Sci.*, **74**(3), 413–1028 (1959).

(4) D. R. Cassady, C. Ainsworth, N. R. Easton, M. Livezey, M. V. Sigal, Jr., and E. Van Heyningen, *J. Org. Chem.*, **23**, 923 (1958).

(5) F. J. Marshall and M. V. Sigal, Jr., *J. Org. Chem.*, **23**, 927 (1958).

(6) E. Haack, *Arzneimittel-Forsch.*, **8**(7a), 444 (1958).

(7) H. Ruschig, C. Korger, W. Aumueller, H. Wagner, and R. Weyer, *Arzneimittel-Forsch.*, **8**(7a), 448 (1958).

(8) S. Onisi, *J. Phar. Soc. Japan*, **79**, 559, 628, 632, (1959).

TABLE 1

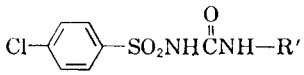
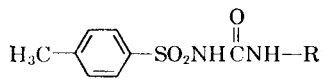
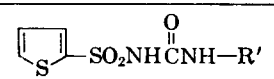
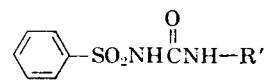
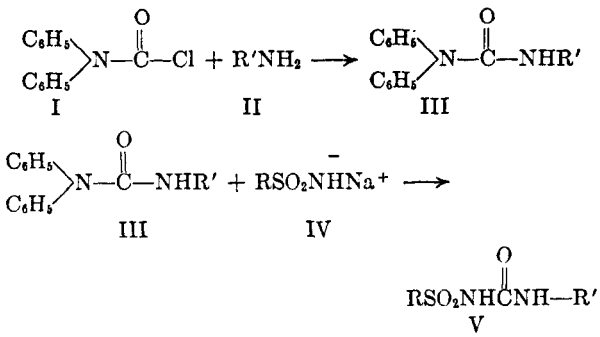
R′	Method	Yield, %	M.P.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
										
4-Picolyl	A	46	165–166	$C_{13}H_{12}ClN_3O_3S$	47.93	3.71	12.90	47.87	3.85	12.77
2-(6-CH_3)picolyl	A	47	171–172	$C_{14}H_{14}ClN_3O_3S$	49.48	4.15	12.37	49.29	4.13	12.13
$CH_2CH_2COOCH_3$	A	65	102–103	$C_{11}H_{13}ClN_2O_5S$	41.19	4.09	8.73	41.01	3.98	8.88
C_6H_5CONH	A		205–207	$C_{14}H_{12}ClN_3O_4SNa$	44.75	2.95	11.18	44.75	3.21	10.75
1-$C_{10}H_7$	A	39	153–154	$C_{17}H_{13}ClN_2O_3S$	56.59	3.63	7.77	56.85	3.34	7.75
2-$ClC_6H_4CH_2$	A	71	154–155	$C_{14}H_{12}Cl_2N_2O_3S$	46.81	3.37	7.80	47.20	3.62	7.73
4-$ClC_6H_4CH_2$	A	67	195–196	$C_{14}H_{12}Cl_2N_2O_3S$	46.81	3.37	7.80	47.02	3.44	7.51
4-$CH_3OC_6H_4CH_2$	A	75	189–190	$C_{15}H_{15}ClN_2O_4S$	50.77	4.26	7.90	50.77	4.36	7.80
4-$CH_3C_6H_4CH_2$	A	90	203–204	$C_{15}H_{15}ClN_2O_3S$	53.17	4.46	8.27	53.04	4.58	8.57
2,4-$(Cl)_2C_6H_3CH_2$	A	55	158–159	$C_{14}H_{11}Cl_3N_2O_3S$	42.71	2.82	7.12	42.73	2.79	7.46
3,4-$(Cl)_2C_6H_3CH_2$	A	32	172–173	$C_{14}H_{11}Cl_3N_2O_3S$	42.71	2.82	7.12	42.51	2.82	7.28
2-$NO_2C_6H_4$	B	54	156–157	$C_{13}H_{10}ClN_3O_5S$	43.89	2.83	11.81	44.07	2.71	11.89
3-$NO_2C_6H_4$	B	26	167–168	$C_{13}H_{10}ClN_3O_5S$	43.89	2.83	11.81	43.60	2.84	11.89
4-$NO_2C_6H_4$	B	68	242–244	$C_{13}H_{10}ClN_3O_5S$	43.89	2.83	11.81	43.83	3.07	11.70
3,4-$(CH_3O)_2C_3H_3CH_2CH_2$	A		156–157	$C_{17}H_{19}ClN_2O_5S$	51.19	4.80	7.02	51.36	4.79	7.44
d-$C_6H_5CH_2CH(CH_3)$	A	80	152–153	$C_{16}H_{17}ClN_2O_3S$	54.47	4.86	7.94	54.82	5.10	7.81
CH_2CH_2CN	A	80	190–191	$C_{10}H_{10}ClN_3O_3S$	41.74	3.50	14.60	42.22	3.48	14.85
2-(5,6,7,8-Tetrahydro)-naphthyl	A	30	170–171	$C_{17}H_{17}ClN_2O_3S$	55.96	4.70	7.68	55.98	4.90	7.84
										
4-Picolyl	A	50	154–157	$C_{14}H_{15}N_3O_3S$	55.06	4.95	13.76	55.10	4.75	13.71
2-(6-CH_3)picolyl	A	65	146–147	$C_{15}H_{17}N_3O_3S$	56.42	5.37	13.16	56.36	5.57	13.18
$CH_2CH_2COOCH_3$	A	67	120–121	$C_{12}H_{16}N_2O_5S$	47.99	5.37	9.33	48.13	5.32	9.31
C_6H_5CONH	A		178–181	$C_{15}H_{15}N_3O_4S$	54.04	4.54	12.61	54.34	4.49	12.31
1-$C_{10}H_7$	A	61	138–140	$C_{18}H_{16}N_2O_3S$	63.51	4.74	8.23	63.41	4.85	8.07
2-$ClC_6H_4CH_2$	A	74	160–161	$C_{15}H_{15}ClN_2O_3S$	53.17	4.46	8.27	53.24	4.57	8.03
4-$ClC_6H_4CH_2$	A	14	199–200	$C_{15}H_{15}ClN_2O_3S$	53.17	4.46	8.27	53.41	4.85	8.59
		18		$C_{15}H_{14}ClN_2O_3SNa$	49.93	3.91	7.77	50.14	3.77	7.35
4-$CH_3OC_6H_4CH_2$	A	75	191–192	$C_{16}H_{18}N_2O_4S$	57.48	5.43	8.38	57.68	5.32	8.80
4-$CH_3C_6H_4CH_2$	A	94	195–196	$C_{16}H_{18}N_2O_3S$	60.37	5.70	8.80	60.23	6.02	8.41
2,4-$(Cl)_2C_6H_3CH_2$	A	75	152–153	$C_{15}H_{14}Cl_2N_2O_3S$	48.26	3.78	7.51	48.43	4.18	7.46
3,4-$(Cl)_2C_6H_3CH_2$	A	47	196–197	$C_{15}H_{14}Cl_2N_2O_3S$	48.26	3.78	7.51	48.19	4.04	7.93
2-$NO_2C_6H_4$	B	55	168–169	$C_{14}H_{13}N_3O_5S$	50.14	3.91	12.53	50.33	4.23	12.56
3-$NO_2C_6H_4$	B	19	184–185	$C_{14}H_{13}N_3O_5S$	50.14	3.91	12.53	50.01	4.05	12.73
4-$NO_2C_6H_4$	B	40	226–227	$C_{14}H_{13}N_3O_5S$	50.14	3.91	12.53	50.99	4.53	12.54
3,4-$(CH_3O)_2C_6H_3CH_2CH_2$	A	22	148–150	$C_{18}H_{22}N_2O_5S$	57.12	5.86	7.40	57.55	5.76	7.47
CH_2CH_2CN	A	79	177–179	$C_{11}H_{13}N_3O_3S$	49.42	4.90	15.72	49.55	5.03	15.66
2-(5,6,7,8-Tetrahydro)-naphthyl	A	58	169–170	$C_{18}H_{20}N_2O_3S$	62.76	5.85	8.14	62.99	5.94	8.14

TABLE I *Continued*

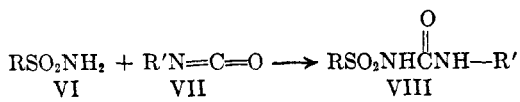
R′	Method	Yield, %	M.P.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
										
4-FC_6H_4	A	62	195–197	$C_{11}H_9FN_2O_3S_2$	43.99	3.02	9.33	44.02	2.97	8.96
2-$CH_3OC_6H_4$	A	81	176–177	$C_{12}H_{12}N_2O_4S_2$	46.16	3.87	8.97	46.10	4.59	8.79
3-$CH_3OC_6H_4$	A	66	106–108	$C_{12}H_{12}N_2O_4S_2$	46.16	3.87	8.97	46.42	3.88	9.12
4-$(CH_3)_2NC_6H_4$	A	65	199–200	$C_{13}H_{15}N_3O_3S_2$	48.00	4.65	12.92	47.51	4.75	12.43
3,4-$(CH_3)_2C_6H_3$	A	75	133–135	$C_{13}H_{14}N_2O_3S_2$	50.32	4.55	9.03	50.18	4.59	8.92
2,4-$(CH_3O)_2C_6H_3$	A	73	153–154	$C_{13}H_{14}N_2O_5S_2$	45.62	4.12	8.19	45.79	4.14	7.84
2,5-$(CH_3O)_2C_6H_3$	A	82	172–173	$C_{13}H_{14}N_2O_5S_2$	45.62	4.12	8.19	45.70	4.26	8.07
3,4-$(CH_3O)_2C_6H_3$	A	66	168–170	$C_{13}H_{14}N_2O_5S_2$	45.62	4.12	8.19	45.68	4.24	8.32
4-CH_3O-2-$CH_3C_6H_3$	A	51	155–157	$C_{13}H_{14}N_2O_4S_2$	47.85	4.33	8.59	47.68	4.49	8.47
4-Cl-2,5-$(CH_3O)_2C_6H_2$	A	86	195–196	$C_{13}H_{13}ClN_2O_5S_2$	41.43	3.48	7.43	41.65	3.49	7.33
$CH_2CH_2CH_2OCH_3$	A	57	114–115	$C_9H_{14}N_2O_4S_2$	38.85	5.07	10.07	39.00	5.22	9.54
4-Picolyl	A	28	152–153	$C_{11}H_{11}N_3O_3S_2$	44.43	3.73	14.13	44.71	3.71	3.78
										
1-$C_{10}H_7$	A	34	169–170	$C_{17}H_{14}N_2O_3S$	62.56	4.32	8.59	62.56	4.59	8.66
2-$NO_2C_6H_4$	B	39	140–142	$C_{12}H_{11}N_3O_5S$	48.59	3.45	13.08	48.94	2.85	13.48
3-$NO_2C_6H_4$	B	39	185–186	$C_{13}H_{11}N_3O_5S$	48.59	3.45	13.08	48.50	3.59	13.06
4-$NO_2C_6H_4$	B	70	244–245	$C_{13}H_{11}N_3O_5S$	48.59	3.45	13.08	48.60	3.53	13.08
d-$C_6H_5CH_2CH(CH_3)$	B	83	143–144	$C_{16}H_{18}N_2O_3S$	60.35	5.70	8.80	60.72	5.72	9.06
CH_2CH_2CN	A	83	172–173	$C_{10}H_{11}N_3O_2S$	47.42	4.38	16.59	47.63	4.64	16.51

The sulfonylureas were prepared by either of two following routes, and are described in Table I.

Method A



Method B



EXPERIMENTAL[9]

Method A. Preparation of the triarylureas (III). To 300 ml. of absolute ethanol there was added 1 mole of the amine and 2.3 moles of diphenylcarbamyl chloride. This mixture was heated to reflux for 16 hr., concentrated *in vacuo*, and the residue extracted with chloroform and water. The chloroform layer was separated, washed with *N* hydrochloric acid and water, and dried over sodium sulfate. Chloroform was removed *in vacuo* and the resulting product crystallized from 95% ethanol.

All the triarylureas (III) were prepared by this procedure with the exception of those having a basic function, in which case the acid wash was omitted.

Preparation of the sulfonylureas (V). A mixture of 0.034 mole of the triarylurea (III) and 0.034 mole of the sodium salt of the sulfonamide (IV) was heated in 50 ml. of dimethylformamide at 100° for 16 hr. After cooling, the dimethylformamide mixture was diluted with 100 ml. of 2% sodium carbonate solution and extracted twice with ether. The aqueous layer was cooled and acidified with *N* hydrochloric acid. The white crystalline product that separated was collected by suction filtration and dried.[10]

All of the method A preparations essentially followed this procedure, except that in the preparation of compounds containing a basic function the alkaline aqueous layer was carefully acidified in the cold to *p*H 4, and the product that separated was collected and dried.

Method B. Preparation of the sulfonylureas (VIII). To a mixture of 30 ml. of triethylamine and 15 ml. of dimethylformamide was added 0.064 mole of the sulfonamide (VI) and 0.064 mole of the isocyanate (VII). After being stirred overnight, the mixture was diluted with 100 ml. of water and extracted twice with ether. The aqueous layer was collected and acidified in the cold with *N* hydrochloric acid. The product was collected by suction filtration and dried.

(9) All melting points are uncorrected.

(10) Method A gives in most cases high yields of the desired product; low yields in a few cases can be attributed to the fact that no effort was made to purify the commercially available amines. In two cases, the sodium salt of the sulfonylurea was insoluble in water, both these compounds were analyzed and tested as such.

Acknowledgment. The author wishes to thank Mrs. Joyce Abrams and Mr. Robert Sacco for assistance in the preparation of these compounds.

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The Preparation and Attempted Chlorosulfonation of *N,N*-Dimethylbenzylamine Sulfur Trioxide

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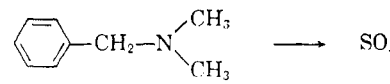
Received July 13, 1960

Some aminomethylbenzenesulfonyl chlorides were desired for studies on the preparation of aminomethylthiophenols. The chlorosulfonation of *N,N*-dimethylbenzylamine in chloroform solution and in the absence of a solvent gave us, unexpectedly, *N,N*-dimethylbenzylamine sulfur trioxide (also called the anhydro sulfate salt of *N,N*-dimethylbenzylamine) to which we have assigned the structure:



The following amine sulfur trioxide salts have previously been reported in the literature: the salt of pyridine, *N,N*-dimethylaniline, and trimethylamine.[1,2]

An attempt to rearrange dimethylbenzylamine sulfur trioxide to a dimethylaminomethylbenzenesulfonic acid by heating in a chloroform solution at reflux for five hours was unsuccessful.

Treatment of *N,N*-dimethylbenzylamine sulfur trioxide with an excess of chlorosulfonic acid produced a homogeneous pale-yellow solid which showed properties characteristic of both a sulfonyl chloride and of an amine sulfur trioxide salt. However, the chlorosulfonation reaction was accompanied by the evolution of sulfur dioxide indicating that there was an extensive oxidation of the amine sulfur trioxide salt. Various conditions, such as variation of reaction temperature, length of reaction time, amount of chlorosulfonic acid used and inverse addition, were employed in an unsuccessful attempt to prevent the oxidation reaction. The only analogy to this oxidation reaction that has been reported in the literature is the treatment of *N,N*-dimethylaniline with the phenyl ester of chlorosulfonic acid in the cold in which the salt of structure

(1) H. H. Sisler and L. F. Audrieth, *Inorganic Syntheses*, Vol. II, W. C. Fernelius, ed., McGraw-Hill, New York, 1946, pp. 173–175.

(2) O. W. Willcox, *Am. Chem. J.*, **32**, 446 (1904).