[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Preparation and Properties of Certain Derivatives of Sulfamide

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The N-substituted sulfamides and their methods of preparation have been reviewed by Audrieth and collaborators.[1a] Such compounds are relatively few, but of a diverse nature. Very few have been prepared directly from sulfamide, probably because of its difficulty of preparation, but several indirect methods of preparation are known. N-Substituted sulfamides have been obtained from the action of primary aromatic amines or primary and secondary aliphatic amines upon sulfuryl chloride, or by the action of an amine upon an (aryl)-arylsulfonylsulfamyl chloride, an (acyl)-arylsulfamyl chloride, a dialkylsulfamyl chloride, phthalylsulfamyl chloride, or phenyl chlorosulfonate.

This paper presents the results of a study of one of these latter methods, namely, the action of a dialkylsulfamyl chloride upon various amines. The preparation of two acyl derivatives of sulfamide is also reported. The stepwise procedure used in these syntheses is illustrated by the equations

$$2R_2N{\cdot}H + Cl{\cdot}SO_2{\cdot}Cl \longrightarrow R_2N{\cdot}SO_2{\cdot}Cl + R_2NH_2{}^{+-}Cl$$
$$R_2N{\cdot}SO_2{\cdot}Cl + 2H{\cdot}NZ_2 \longrightarrow R_2N{\cdot}SO_2{\cdot}NZ_2 + Z_2NH_2{}^{+-}Cl$$

In these equations R may be an alkyl, aryl, or heterocyclic group, and Z represents an H-atom or an alkyl, aryl, or heterocyclic group. In the case of heterocyclic groups, in which the linkage is to a heterocyclic nitrogen atom, R_2 and Z_2 become R and Z, respectively.

It was found that N-alkylanilines, toluidines, xylidines, monohaloanilines, various *p*-substituted anilines and naphthylamines, as well as 2-aminopyridine and piperidine react with dimethylsulfamyl chloride to give good yields of the corresponding substituted sulfamide. Whereas *m*-nitroaniline reacted normally, *o*- and *p*-nitroanilines did not react with dimethylsulfamyl chloride under the same conditions. Likewise, *s*-tribromoaniline did not react. These facts are in accord with the postulates of relative electronegativity.

Diethylsulfamyl chloride reacts much less readily with the arylamines with which it was tried and gives products with lower melting points than the corresponding dimethyl analogs, consequently they are crystallized with difficulty.

Acyl derivatives prepared directly from sulfamide have not been reported in the literature, although Anderson[2] has prepared several such compounds. The acyl derivative reported here was prepared in the course of an unsuccessful attempt to prepare the sulfamide analog of barbituric acid, namely, $H_2C(CONH)_2SO_2$.

The tri- and tetrasubstituted alkyl and aryl sulfamides are usually white, crystalline solids which are only slightly soluble in cold but somewhat soluble in hot water. They are extremely soluble in pyridine, fairly soluble in most common organic solvents, insoluble in petroleum ether (30–60°) and soluble without decomposition in cold concentrated sulfuric acid. The trisubstituted compounds are soluble in dilute bases, due to the remaining acidic hydrogen atom on the nitrogen. Tetrasubstituted compounds, of course, are not soluble in bases. Carbon tetrachloride was found to be the most widely applicable solvent for recrystallization.

Experimental

A. Preparation of $HOOCCH_2CONHSO_2NH_2$.—The monoacid chloride of malonic acid was prepared by a standard method.[3] Upon reaction of this with sulfamide in anhydrous ether, the above compound was obtained. The crude product was recrystallized from water or aqueous methanol to give white flakes (melting at 147° uncor. with decomposition. Calculated for $C_3H_6O_5N_2$: N, 15.38. Found: N, 15.37, 15.25, 15.50).

This acid when treated with ethanol and a little sulfuric acid, gave a compound which melted at 84-85° (uncor.). The product was not analyzed, but in view of its method of preparation and properties, it is probably the ethyl ester of the above acid.

B. Preparation of Tri- and Tetrasubstituted Sulfamides.—Dimethylsulfamyl chloride and diethylsulfamyl chloride were prepared by standard procedures.[4,5] The yield of the former was raised to 80% by use of two moles of sulfuryl chloride to one mole of dimethylamine hydrochloride, the mixture being kept at 60° until evolution of hydrogen chloride ceased.

For the reaction of liquid amines, the amine (2 moles) was treated with the dialkylsulfamyl chloride (1 mole), without a solvent. The reaction takes place within a few minutes, is exothermic, and may require external cooling. The mixture soon sets to a crystalline mass, which after cooling is dissolved in ethanol. The substituted sulfamide is then precipitated by slowly pouring the alcoholic solution into crushed ice and water, which is slightly acidified with hydrochloric acid. The filtered and dried crude product may be decolorized in aqueous ethanol solution if necessary, followed by reprecipitation in water, and recrystallization.

For solid amines, the reactants in the same proportion as given above are dissolved in a minimum amount of an inert solvent such as benzene or ether. The mixture is refluxed overnight or longer, the solvent removed under vacuum and the residue treated exactly as described for the products obtained from liquid amines.

The acetyl derivative was prepared by reaction of acetyl chloride upon N,N-dimethyl-N′-phenylsulfamide in benzene.

Heterocyclic amines such as piperidine react so vigorously that it is necessary to dissolve the amine in an inert solvent, then slowly add the dialkylsulfamyl chloride to

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(1) Abstract of a thesis submitted to the Faculty of Purdue University by Keith Wilson Wheeler in partial fulfillment of the requirements for the degree of Doctor of Philosophy, February, 1944.

(1a) Audrieth, Sveda, Sisler and Butler, *Chem. Revs.*, **26**, 49–94 (1940).

(2) Anderson, M.S. Thesis, Purdue University, 1943.

(3) Staudinger and Ott, *Ber.*, **41**, 2211 (1908).

(4) Behrend, *Ann.*, **222**, 116 (1884).

(5) Binkley and Degering, THIS JOURNAL, **61**, 3250 (1939).

TABLE I

TRI- AND TETRASUBSTITUTED SULFAMIDES

Sulfamide	Yield, %	M. p., °C. (cor.)	N Analyses, %		
			Calcd.	Found	
N,N,N'-Trimethyl-N'-phenyl-	96	45.5- 46.0	13.07	12.87	13.02
N,N-Dimethyl-N'-					
-ethyl-N'-phenyl-	88	31.5- 32.0	12.27	12.36	12.37
-*o*-tolyl-	95	104.8-105.2	13.07	12.88	12.94
-*m*-tolyl-	94	80.5- 81.0	13.07	12.98	12.98
-2,4-dimethylphenyl-	87.5	132.0-132.5	12.28	12.17	12.32
-*o*-chlorophenyl-	81.5	75.5- 76.0	11.94	11.78	11.85
-*m*-chlorophenyl-	94	88.2- 88.7	11.94	11.76	11.86
-*p*-chlorophenyl-	80	56.5- 57.1	11.94	11.80	11.93
-*p*-bromophenyl-	87	78.8- 79.3	10.04	9.95	9.95
-*p*-iodophenyl-	69	83.6- 84.2	8.59	8.64	8.50
-*m*-nitrophenyl-	72	126.7-127.0	17.14	(Dumas) 17.1	17.2
-*p*-dimethylaminophenyl-	62	108.6-109.3	17.28	17.32	17.25
-*p*-anisyl-	78.5	55.6- 56.2	12.04	12.10	12.08
-*p*-carbethoxyphenyl-	85	125.0-125.4	10.27	10.09	10.15
-acetyl-N'-phenyl-	74	92.3- 92.7	11.56	11.53	11.59
-1-naphthyl-	87	107.3-107.7	11.18	11.22	11.20
-2-naphthyl-	86	110.0-110.4	11.18	11.08	11.20
-cyclopentamethylene-	74	55.5- 56.2	14.57	14.37	14.41
-2-pyridyl-	53.5	130.7-131.2	20.88	20.86	20.87
N,N-Diethyl-N'-					
-*o*-tolyl-	85	64.6- 65.2	11.54	11.38	11.47
-*m*-tolyl-	88	47 - 48	11.54	11.65	11.59
-2,4-dimethylphenyl-	84	74.7- 75.0	10.91	10.72	10.78
-*o*-chlorophenyl-	78.5	49.4- 49.7	10.64	10.70	10.61
-*p*-anisyl-	72	56.3- 56.8	10.83	10.86	10.96

the solution, accompanied by external cooling with ice. The reaction mixture is then treated as in the procedure given for solid amines.

Nitrogen analyses were made by the Kjeldahl procedure, except in the case of the nitro compound which was analyzed by the Dumas method. In the Kjeldahl procedure, the ammonia was absorbed in boric acid and titrated directly, using the mixed indicator proposed by Ma and Zuazaga.[6]

Melting points were determined by means of a set of calibrated, total-immersion thermometers. In all cases these compounds sinter slightly a few degrees before the melting point.

The new compounds prepared by these general procedures are listed in Table I. In addition, the known compounds, N,N-dimethyl-N'-phenylsulfamide and N,N-dimethyl-N'-*p*-tolylsulfamide,[4,7] were prepared and included to complete the series.

Summary

Over a score of derivatives of sulfamide have been prepared by the condensation of dialkylsulfamyl chloride with various amines such as N-alkylanilines, toluidines, xylidines, monohaloanilines, *p*-substituted anilines, and naphthylamines, as well as 2-aminopyridine and piperidine.

The tri- and tetrasubstituted alkyl and aryl sulfamides are usually white crystalline solids, which are only slightly soluble in cold water but more soluble in hot water. These compounds are fairly soluble in most organic solvents, very soluble in pyridine, and soluble without decomposition in cold, concentrated sulfuric acid. They are insoluble in petroleum ether. The N,N,N'-trisubstituted sulfamides are soluble in dilute bases, as are the mono- and disubstituted derivatives. For recrystallization and purification, carbon tetrachloride was the most satisfactory general solvent.

These compounds are comparatively stable, much more so than is sulfamide. Some of these derivatives, according to preliminary tests, have desirable physiological activity.

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(6) Ma and Zuazaga, *Ind. Eng. Chem., Anal. Ed.*, **14**, 280 (1942).

(7) Battegay and Meybeck, *Compt. rend.*, **194**, 187 (1932).