It gave 1.1 g. (33%) of crude β-aminoisopropyl disulfide dihydrochloride, m.p. 202–210°. After recrystallization from ethanol, it melted at 223.5–226°.

Cyclization of N-(hydroxyalkyl)benzamides to 2-thiazolines or 5,6-dihydro-1,3,4-thiazines. These preparations were carried out by heating the amides with phosphorus pentasulfide; the results are summarized in Table III. The following example is typical of the procedure used.

2-Phenyl-5-methyl-2-thiazoline from N-(2-hydroxypropyl)-benzamide. A mixture of 16 g. of *N*-(2-hydroxypropyl)-benzamide,[18] 10 g. of phosphorus pentasulfide, and 250 ml. of toluene was refluxed for 12 hr. The toluene was decanted from a gummy residue which remained in the flask. The residue was warmed on a steam bath with 10% sodium hydroxide solution. The basic solution was extracted with ether and the ether layer was combined with the toluene and extracted with 10% hydrochloric acid. The acid extracts were neutralized and extracted with ether. After drying of the ether solution, removal of solvent, and distillation of the residual oil, 4.8 g. (30%) of 2-phenyl-5-methyl-2-thiazoline was obtained; b.p. 146–149°/18 mm. The picrate prepared from this sample had m.p. 153–155°, undepressed when mixed with the product obtained from *N*-allylbenzthionamide.

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[CONTRIBUTION FROM THE W. A. NOYES LABORATORY OF CHEMISTRY, UNIVERSITY OF ILLINOIS]

Syntheses and Properties of Some *N*-Substituted Sulfamides

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Received May 25, 1960

Reactions of dialkylsulfamyl chlorides with ammonia or with aliphatic, aromatic, and heterocyclic amines have been employed to synthesize seventeen new *N*-substituted derivatives of sulfamide of the types $R_2NSO_2NH_2$, R_2NSO_2NHR, and $R_2NSO_2NR_2$. These compounds have been characterized in terms of analysis, melting or boiling point, refractive index, and infrared spectrum. Two intense absorption bands in the 1140–1145 cm.$^{-1}$ and 1320–1350 cm.$^{-1}$ regions are associated with S—O vibrations in the —SO_2— group. The compounds are either low-melting crystalline solids or high-boiling oily liquids. Certain of the solids show promise as derivatives for the characterization of amines.

Of the various known aquo-ammono sulfuric acids, sulfamide is of particular interest because of the many analogies, both formal and actual, between its chemistry and that of urea. Like urea, it is capable of forming derivatives in which alkyl or aryl groups are bonded to one or both of the nitrogen atoms. Such *N*-substituted derivatives may be of the types $RNHSO_2NH_2$, $RNHSO_2NHR$, $R_2NSO_2NH_2$, R_2NSO_2NHR, or $R_2NSO_2NR_2$, where the R-groups may be the same or different. Most of these classes are represented by a few known compounds,[1] but the total information available on them is limited. It has been of interest, therefore, to investigate in detail methods of synthesis and both chemical and physical properties for a number of such compounds.

All of these substances can be regarded as ammonolysis or aminolysis products of sulfuryl chloride. Their direct formation from sulfuryl chloride, however, is often complicated by lack of control or the production of polymeric products.[1] Sulfuryl chloride reacts readily with secondary aliphatic amines or saturated heterocyclic amines to yield disubstituted sulfamyl chlorides, R_2NSO_2Cl. From these by reaction with ammonia, primary, or secondary amines, compounds of the types $R_2NSO_2NH_2$, R_2NSO_2NHR, or $R_2NSO_2NR_2$, respectively, are more conveniently prepared than by any other procedure. Secondary aromatic amines, however, are apparently insufficiently basic to yield comparable sulfamyl chlorides and undergo preferential ring chlorination on treatment with sulfuryl chloride. Primary amines give a variety of products with sulfuryl chloride, but sulfamyl chlorides of the type $RNHSO_2Cl$ are apparently not among them.

The present communication is concerned with the ammonolysis and aminolysis products obtainable from diethyl and cyclopentamethylene sulfamyl chlorides as typical starting materials. These compounds were obtained either by treating the sulfamyl chloride with liquid ammonia or by refluxing in admixture with the appropriate amine in an inert solvent such as chloroform, benzene, or ether. Reactions with aliphatic amines were complete in twelve hours; those with aromatic amines required up to twenty-four hours.

The compounds prepared are listed in Table I, together with important data pertaining to their syntheses and properties. The tri- and tetra-substituted sulfamides are either colorless oils or white crystalline solids. They dissolve readily in the common organic solvents but are insoluble in cold water and only slightly soluble in boiling water. Recrystallization is best effected from *n*-heptane, carbon tetrachloride, or ether. The formation of characteristically and sharply melting compounds with many amines suggests that the sulfamyl chlorides may be useful reagents for the characterization of such amines.

No systematic investigation of the infrared spectra of the *N*-substituted sulfamides has been reported. The spectra of a number of related *N,N*-disubstituted sulfonamides contain strong bands, which have been ascribed,[2,3] respectively, to the

(1) L. F. Audrieth, M. Sveda, H. H. Sisler, and M. J. Butler, *Chem. Revs.*, 26, 49 (1940).

TABLE I

PROPERTIES AND ANALYSES OF TRI- AND TETRA-SUBSTITUTED SULFAMIDES

Compound	Formula	Yield, %	M.P.[a]	B.P.,[a] Mm.	n_D^t	Carbon		Hydrogen		Nitrogen	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
N,N-Diethylsulfamide	$C_4H_{12}N_2O_2S$	53	44	—	—	31.57	31.49	7.95	7.72	18.41	18.49
N,N-Diethyl-*N'*-butylsulfamide	$C_8H_{20}N_2O_2S$	50	—	87/0.1	1.4510^{25}	46.16	45.90	9.68	9.56	13.45	13.59
N,N-Diethyl-*N'*-cyclohexylsulfamide	$C_{10}H_{22}N_2O_2S$	60	49	—	—	51.28	51.00	9.47	9.40	11.95	11.85
N,N-Diethyl-*N'*-phenylsulfamide	$C_{10}H_{16}N_2O_2S$	61	—	171/2.5	$1.5260^{25.5}$	52.64	52.48	7.06	7.11	12.28	11.95
N,N-Diethyl-*N',N'*-dibutylsulfamide	$C_{12}H_{28}N_2O_2S$	65	—	88/0.15	1.4500^{25}	54.53	54.35	10.68	10.65	10.60	10.75
N,N-Diethyl-*N'*-cyclohexyl-*N'*-methyl sulfamide	$C_{11}H_{24}N_2O_2S$	52	—	101–102/0.2	1.4726^{24}	53.21	53.40	7.74	9.78	11.28	11.16
N,N-Diethyl-*N'*-phenyl-*N'*-methyl sulfamide	$C_{11}H_{18}N_2O_2S$	50	—	98/0.1	1.5160^{25}	54.55	54.32	9.49	7.16	11.56	11.35
N-Cyclopentamethylene-*N'*-cyclohexyl sulfamide	$C_{11}H_{22}N_2O_2S$	65	75	—	—	53.64	53.62	9.00	8.99	11.37	11.26
N-Cyclopentamethylene-*N'*-2-naphthyl sulfamide	$C_{15}H_{18}N_2O_2S$	20	115–116	—	—	62.05	61.81	6.25	6.32	9.65	9.63
N-Cyclopentamethylene-*N'*-phenyl sulfamide	$C_{11}H_{16}N_2O_2S$	42	83	—	—	54.98	55.18	6.71	6.69	11.66	11.39
N-Cyclopentamethylene-*N'*-benzyl sulfamide	$C_{12}H_{18}N_2O_2S$	42	100–101	—	—	56.67	56.71	7.13	7.33	11.02	11.00
N-Cyclopentamethylene-*N'*-*p*-tolyl sulfamide	$C_{12}H_{18}N_2O_2S$	55	97–98	—	—	56.67	56.91	7.13	7.20	11.02	10.94
N-Cyclopentamethylene-*N'*-methyl-*N'*-cyclohexyl sulfamide	$C_{12}H_{24}N_2O_2S$	45	—	134/0.5	1.4970^{22}	55.34	55.11	9.29	9.20	10.75	10.46
N-Cyclopentamethylene-*N'*-*m*-tolyl sulfamide	$C_{12}H_{18}N_2O_2S$	70	123–124	—	—	56.67	56.83	7.13	7.15	11.02	10.74
N-Cyclopentamethylene-*N'*-*o*-tolyl sulfamide	$C_{12}H_{18}N_2O_2S$	62	94	—	—	56.67	56.87	7.13	7.11	11.02	10.74
N-Cyclopentamethylene-4-morpholine sulfamide	$C_9H_{18}N_2O_3S$	81	71–72	—	—	46.14	46.27	7.74	7.70	11.96	11.93
N-Cyclopentamethylenesulfamide	$C_5H_{12}N_2O_2S$	55	120	—	—	36.57	36.82	7.36	7.31	17.06	16.88

[a] Melting points and boiling points are uncorrected.

symmetric and antisymmetric vibrations of the S—O bonds in the —SO_2— group, near 1160 cm.$^{-1}$ and 1350 cm.$^{-1}$ Absorption in the 1300–1350 cm.$^{-1}$ region is also characteristic of sulfones but not of sulfides.[4] The Raman spectra of sulfamide and trisulfimide show the frequencies 1163 cm.$^{-1}$ and 1350 cm.$^{-1}$, characteristic again of symmetric and antisymmetric vibrations within the —SO_2— group.[5] It has been of interest, therefore, to compare these data with those obtained for the compounds described herein.

Significant data from the infrared spectra of chloroform or carbon tetrachloride solutions of nine *N*-substituted sulfamides of the types described above are given in Table II. Corresponding spectral data for four compounds of the type RNHSO_2NHR, prepared in another connection,[6] are given also for comparison. Characteristic absorptions in the 1140–1145 cm.$^{-1}$ and 1320–1340 cm.$^{-1}$ regions undoubtedly reflect, respectively, symmetric and antisymmetric vibrations within the —SO_2— group. A third band at 3280 cm.$^{-1}$ is found only for the di- and tri-substituted compounds and is due to the N—H stretching vibration. This band is particularly apparent for the RNHSO_2NHR compounds. Assignment of absorptions in the 1070-cm.$^{-1}$ region to the S—N bond is open to some question.[3] Neither of the first two bands is dis-

TABLE II

INFRARED DATA FOR *N*-SUBSTITUTED SULFAMIDES

Compound	Frequency, Cm.$^{-1}$		
	S—O	S—O	N—H
N-Cyclopentamethylene-*N'*-*p*-tolylsulfamide	1140	1332	3280
N-Cyclopentamethylene-*N'*-phenylsulfamide	1142	1320	3280
N-Cyclopentamethylene-*N'*-methyl-*N'*-cyclohexylsulfamide	1142	1320	—
N,N-Diethyl-*N'*-cyclohexylsulfamide	1142	1320	3280
N,N-Diethylsulfamide	1150	1342	3280
N,N-Diethyl-*N'*-butylsulfamide	1142	1320	3280
N,N-Diethyl-*N',N'*-dibutylsulfamide	1142	1320	—
N,N-Diethyl-*N'*-methyl-*N'*-cyclohexylsulfamide	1142	1325	—
N,N-Diethyl-*N'*-methyl-*N'*-phenylsulfamide	1142	1340	—
N,N'-Dipropylsulfamide	1147	1320	3280
N,N'-Dibutylsulfamide	1145	1315	3280
N,N'-Dicyclohexylsulfamide	1142	1320	3280
N,N'-Diamylsulfamide	1145	1320	3280

(2) R. Adams and J. J. Tjepkema, *J. Am. Chem. Soc.*, **70**, 4204 (1948).

(3) J. N. Baxter, J. Cymerman-Craig, and J. B. Willis, *J. Chem. Soc.*, **1955**, 669.

(4) K. C. Schreiber, *Anal. Chem.*, **21**, 1168 (1949).

(5) H. J. Hofmann and K. Andress, *Z. anorg. allgem. Chem.*, **248**, 234 (1956).

(6) T. Moeller and A. Vandi, Contract DA-11-022-ORD-2956, Quarterly Progress Report No. 2, University of Illinois, Nov. 30, 1959.

placed particularly among the compounds examined by change from an aliphatic to an aromatic substituent.

EXPERIMENTAL

Sulfamyl chlorides. Diethylsulfamyl chloride was prepared as described by Binkley and Degering.[7] *N*-Pentamethylene sulfamyl chloride was prepared by Denivelle's procedure[8] as modified by Audrieth and von Brauchitsch.[9] The compounds boiled at 62°/0.02 mm. and 95°/1 mm., respectively.

N-Substituted sulfamides. Ammonolysis could be effected with liquid ammonia but not in the presence of a diluting solvent. As the procedure followed in all aminolysis reactions was essentially the same, only one synthesis of this type is described. With diethylsulfamyl chloride, chloroform is a suitable solvent; with pentamethylenesulfamyl chloride, benzene is better.

N,N-Diethylsulfamide. One hundred milliliters of liquid ammonia was placed in a three necked flask fitted with a mechanical stirrer, an outlet tube, and a small separatory funnel and immersed in a bath of Methyl Cellosolve and Dry Ice to maintain the temperature at −70°. Twenty grams (0.117 mole) of diethylsulfamyl chloride was added dropwise with vigorous agitation over a period of 2 hr. The resulting solution was stirred for 2 hr. and then kept at room temperature in order to permit evaporation of the excess of ammonia. The residue was dissolved in hot ether, the solution filtered, and the ether removed from the filtrate under vacuum. The product was recrystallized twice from ether.

N,N-Diethyl-N'-cyclohexylsulfamide. Seventeen and one-tenth grams (0.1 mole) of diethylsulfamyl chloride, 20.0 g. (0.2 mole) of cyclohexylamine, and 50 ml. of chloroform were placed in a flask equipped with a reflux condenser. The solution was then refluxed at 70° for 12 hr. The solvent was removed by distillation, and the dark residue was shaken with water and ether in a separatory funnel. The ether layer was dried over anhydrous calcium chloride. Removal of the ether by distillation left a dark oily residue which, upon fractional distillation, yielded a colorless, viscous oil. Upon standing, this solidified to a crystalline mass. Final purification was effected by recrystallization from *n*-heptane.

Infrared spectra. These were measured with a Perkin-Elmer Model 21 instrument, using a sodium chloride prism.

Acknowledgment. Support received for this investigation under Contract DA-11-022-ORD-2956 with the Feltman Research and Engineering Laboratory, Ordnance Corps, Picatinny Arsenal, Dover, N. J., is gratefully acknowledged.

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(7) W. W. Binkley and E. F. Degering, *J. Am. Chem. Soc.*, 61, 3250 (1939).

(8) L. Denivelle, *Bull. soc. chim. France*, [5], 3, 2143 (1936).

(9) L. F. Audrieth and M. von Brauchitsch, *J. Org. Chem.*, 21, 426 (1956).

[CONTRIBUTION FROM SMITH KLINE AND FRENCH LABORATORIES AND TEMPLE UNIVERSITY RESEARCH INSTITUTE]

Synthesis of Phenothiazines. VI. Certain 2-Substituted Phenothiazines and Their 10-Aminoalkyl Derivatives

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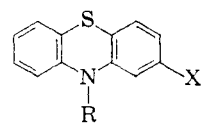
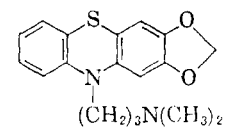
Received July 25, 1960

2-Dimethylaminophenothiazine, 2,3-methylenedioxyphenothiazine, 2-cyanophenothiazine and phenothiazine-2-carboxamides were synthesized. Several 10-aminoalkyl derivatives of these compounds and of 2-acetylphenothiazine and its oxime were prepared for pharmacological evaluation.

Various investigators have found that introduction of certain substituents such as chlorine or the trifluoromethyl group in the 2-position of 10-dimethylaminopropylphenothiazine (promazine) (Ia) produces agents having enhanced tranquilizing and antiemetic activities.[2] In the course of our studies on the chemistry and pharmacology of 2-substituted phenothiazines[3] related to Ia, we synthesized derivatives Ib–d, II and several compounds derived from 2-acetylphenothiazine listed in Table I.





II

Ia. X = H, R = $(CH_2)_3N(CH_3)_2$
b. X = $N(CH_3)_2$, R = $(CH_2)_3N(CH_3)_2$
c. X = $CON(CH_3)_2$, R = $(CH_2)_3N(CH_3)_2$
d. X = CN, R = $CH_2CH(CH_3)CH_2N(CH_3)_2$

2-Dimethylaminophenothiazine (IV) was prepared by the Ullman route starting with *N,N*-dimethyl-4-bromoaniline (III).[4]

An attempt to obtain IV by thionation of 3-dimethylaminodiphenylamine (Bernthsen method) was unsuccessful.

Alkylation of IV with 3-dimethylaminopropyl chloride was carried out in the usual way to yield

(1) Research Institute of Temple University.

(2) See E. A. Nodiff, S. Lipschutz, P. N. Craig, and M. Gordon, *J. Org. Chem.* 25, 60 (1960) (Paper III of this series) and references therein.

(3) Paper IV of this series: P. N. Craig, M. Gordon, J. J. Lafferty, B. M. Lester, A. M. Pavloff, and C. L. Zirkle, *J. Org. Chem.*, 25, 944 (1960).

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