[CONTRIBUTION FROM THE VENEREAL DISEASE RESEARCH LABORATORY, U. S. PUBLIC HEALTH SERVICE]

N^1-(Aminoalkyl)-sulfanilamides and N^1-(Acetamidoalkyl)-sulfanilamides

BY LAWRENCE H. AMUNDSEN[1] AND LENA A. MALENTACCHI[1]

These compounds have been prepared for biological testing in order to aid in evaluating the possible therapeutic utility of sulfanilamides with N^1-aliphatic substituents containing amino groups.

The N^1-(aminoalkyl)-sulfanilamides were prepared from the monoacetylated diamines by the usual condensation with N-acetylsulfanilyl chloride and subsequent hydrolysis. To obtain the N^1-(acetamidoalkyl)-sulfanilamides, the monoacetylated diamines were condensed with *p*-nitrobenzenesulfonyl chloride and the products were reduced. In these condensations there is a tendency for the acetyl group to be hydrolyzed off the diamine with the consequent formation of the highly insoluble N,N′-alkylenebissulfonamides, some of which were also prepared directly from the unsubstituted diamines for identification. This tendency can be considerably reduced by carrying out the condensations in a neutral solution, substituting sodium bicarbonate for the usual alkaline reagents. Better results have also been obtained by adding a solvent that dissolves at least partially the sulfonyl chloride. Chloroform or ethylene chloride was satisfactory.

When this work was interrupted the series was being extended to include the analogous compounds from tetramethylenediamine. The symmetrically disubstituted products had already been obtained and are included in the tables.

TABLE I

p-NITROBENZENESULFONAMIDES

Substituent	Yield, %	Cryst. from	M. p., °C.	Formula	Sulfur, % Calcd.	Found	
N-(β-Acetamidoethyl)-	11.34	Water, EtOH, MeOH	147.5–148.5	$C_{10}N_{13}N_3O_5S$	11.16	11.03	11.01
N-(γ-Acetamidopropyl)-	63.33	Water	162.8–163.8	$C_{11}H_{15}N_3O_5S$	10.68	10.37	10.30
N,N′-Ethylenebis-		Ethylene chlorohydrin	282.1–283.2	$C_{14}H_{14}N_4O_8S_2$	14.89	14.64	14.69
N,N′-Trimethylenebis-		95% EtOH	224.5–225.5	$C_{15}H_{16}N_4O_8S_2$	14.44	14.20	14.24
N,N′-Tetramethylenebis-		95% EtOH	205–206	$C_{16}H_{18}N_4O_8S_2$	13.98	13.38	13.40

TABLE II

SULFANILAMIDES

Substituent	Yield, %	Cryst. from	M. p., °C.	Formula	Sulfur, % Calcd.	Found	
N^4-Acetyl-N^1-(β-acetamidoethyl)-	43.1	Water	176.0–176.5	$C_{12}H_{17}N_3O_4S$	N, 14.04	14.25	14.17
N^1-(β-Acetamidoethyl)-	44.0	Ethanol–water	225.2–225.7	$C_{10}H_{15}N_3O_3S$	12.45	12.16	12.23
N-(β-Aminoethyl)-dihydrochloride	Prev. rep.[a]						
N^4-Acetyl-N^1-(γ-acetamidopropyl)-	33.6	Water	150.6–151.6	$C_{13}H_{19}N_3O_4S$	10.23	10.24	10.26
N^1-(γ-Acetamidopropyl)-	14.9	Water	161.0–161.5	$C_{11}H_{17}N_3O_3S$	11.81	11.63	11.69
N^1-(γ-Aminopropyl)-dihydrochloride	Not detd.	EtOH–ether	130–133 (dec.)	$C_9H_{17}Cl_2N_3O_2S$	10.61	10.65	10.62
$N^1,N^{1\prime}$-Trimethylene-bis-(N^4-acetyl-)	Not detd.	95% EtOH	224.5–225.5	$C_{15}H_{16}N_4O_8S$	14.44	14.20	14.24
$N^1,N^{1\prime}$-Tetramethylene-bis-(N^4-acetyl-)	Not detd.	50%, 95% EtOH	218[b]	$C_{20}H_{26}N_4O_8S$	13.38	12.77	12.76

[a] Amundsen and Malentacchi, *Science*, **93**, 286 (1941). [b] Taken by dropping the tube containing the material into the preheated bath. The sample resolidified and melted again at 241–242° (cor.). A sample that had been heated for two hours at 210° also melted at 241–242° (cor.). The usual technique when applied to this compound gave wide and indefinite melting point ranges, usually about 210–225° (cor.).

Experimental

N-(β-Acetamidoethyl)-*p*-nitrobenzenesulfonamide.—A mixture of 20.4 g. (0.2 mole) of N-acetylethylenediamine,[2] 44.2 g. (0.2 mole) of *p*-nitrobenzenesulfonyl chloride, 25.2 g. (0.3 mole) of sodium bicarbonate, 100 cc. of water, and 100 cc. of chloroform was shaken mechanically for seven hours. The solid material was filtered off and extracted with 300 cc. of hot acetone. From the acetone-insoluble residue N,N′-ethylenebis-(*p*-nitrobenzenesulfonamide) was obtained by extraction with ethylene chlorohydrin. Water was added to the acetone filtrate until precipitation was complete. The solid was filtered off and extracted with hot water, from which the product crystallized upon cooling. The material that had failed to dissolve in hot water melted at 186.2–187.2° (cor.) after two crystallizations from ethanol. It was insoluble in both hydrochloric acid and sodium hydroxide and analytical data indicated that it was bis-(*p*-nitrophenyl) sulfoxide (calcd. for $C_{12}H_8N_2O_5S$: C, 49.25; H, 2.75; S, 10.96. Found: C, 48.95, 48.90;

(1) Present address: Department of Chemistry, University of Connecticut, Storrs, Connecticut.

(2) Hill and Aspinall, THIS JOURNAL, **61**, 822 (1939); Aspinall, *ibid.*, **63**, 852 (1941).

H, 2.59, 2.52; S, 10.50, 10.82. Since bis-(*p*-nitrophenyl) sulfoxide is reported[3] to melt at 173° additional evidence for the identity of our product was sought. We, therefore, heated a sample of it with fuming nitric acid and obtained a substance melting at 254–255° (259–260° cor.), which checks well with the melting point 254° reported by Witte[3] for bis-(*p*-nitrophenyl) sulfone.

N-(γ-Acetamidopropyl)-*p*-nitrobenzenesulfonamide.—This compound was prepared from N-acetyltrimethylenediamine[4] by the same procedure used for the previous compound except that the solid that was filtered off from the reaction mixture was crystallized directly from water.

N⁴-Acetyl-N¹-(β-acetamidoethyl)-sulfanilamide.—A mixture of 8.16 g. (0.08 mole) of N-acetylethylenediamine,[2] 22.8 g. (0.096 mole) of N-acetylsulfanilyl chloride, 10.08 g. (0.12 mole) of sodium bicarbonate, 80 cc. of water, and 200 cc. of chloroform was shaken mechanically for seven hours. The solution then was filtered and the solid product recrystallized.

N¹-(β-Acetamidoethyl)-sulfanilamide.—A solution of 2.8 g. (0.01 mole) of N-(β-acetamidoethyl)-*p*-nitrobenzenesulfonamide in 75 cc. of 95% ethanol was shaken at room temperature with 0.1 g. of Raney nickel catalyst and hydrogen under three atmospheres pressure. The mixture was centrifuged, the clear solution then was evaporated to dryness, and the residue was purified by crystallization.

N⁴-Acetyl-N¹-(γ-acetamidopropyl)-sulfanilamide.—A mixture of 5.8 g. (0.05 mole) of N-acetyltrimethylenediamine,[4] 11.7 g. (0.05 mole) of N-acetylsulfanilyl chloride, 6.2 g. (0.075 mole) of sodium bicarbonate, 32 cc. of water and 25 cc. of chloroform was shaken mechanically for seven hours and the solid product was filtered off.

N¹-(γ-Acetamidopropyl)-sulfanilamide.—A solution of 1.5 g. (0.005 mole) of N-(γ-acetamidopropyl)-*p*-nitrobenzenesulfonamide in 75 cc. of 95% ethanol was shaken for twenty-four hours under a pressure of three atmospheres of hydrogen with 0.1 g. of Raney nickel catalyst promoted with a trace of Adams platinum oxide catalyst. The mixture was centrifuged and the clear solution was evaporated to dryness to obtain the product.

N,N'-Trimethylenebis-(*p*-nitrobenzenesulfonamide).—A solution of 0.741 g. (0.01 mole) of trimethylenediamine[5] in 10 cc. (0.06 mole) of 6 *N* sodium hydroxide was cooled in an ice-bath and 4.432 g. (0.02 mole) of *p*-nitrobenzenesulfonyl chloride was added. The mixture was shaken for an hour, acidified and filtered. The solid was dissolved in sodium hydroxide solution, precipitated with hydrochloric acid, filtered, and crystallized. The other N,N'-alkylenebissulfonamides were prepared by substantially the same procedure. Tetramethylenediamine was used in the form of its dihydrochloride, so with it the quantity of sodium hydroxide was increased to 0.08 mole. These substances are all very insoluble and therefore require relatively large volumes of solvents for recrystallization. Even then they go into solution slowly.

(3) Witte, *Rec. trav. chim.*, **51**, 299 (1932).

(4) Aspinall, THIS JOURNAL, **62**, 2160 (1940).

Summary

Some sulfanilyl and related derivatives have been prepared from ethylenediamine, trimethylenediamine, and tetramethylenediamine.

(5) Amundsen and Malentacchi, *ibid.*, **67**, 493 (1945).

STATEN ISLAND, NEW YORK RECEIVED OCTOBER 30, 1945

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF WASHINGTON UNIVERSITY]

Some Basic Barbituric Acid Derivatives

BY JOHN H. GARDNER,[1] FRANK H. BOPP[2] AND ROBERT F. PRINDLE[3]

Some time ago, Guggenheim pointed out that barbituric acid derivatives must have at least one acidic hydrogen if they are to have hypnotic activity.[4] Those with one N-hydrogen replaced by an alkyl group are characterized by a shorter duration of activity. It seemed of interest to prepare some of these compounds in which an N-hydrogen has been replaced by a basically substituted alkyl group to determine whether such a product would be an effective hypnotic. While a few such compounds have been described,[5] no pharmacological properties have been reported. In this investigation, we have prepared the β,4-morpholine-ethyl derivatives of barbital and of amytal. The first of these was subjected to a preliminary pharmacological examination by Mr. L. W. Rowe of Parke, Davis and Co. He found no evidence of hypnotic action in white mice, guinea pigs or dogs.

(1) Present address: J. T. Baker Chemical Co., Phillipsburg, N. J.

(2) Present address: American Can Co., Maywood, Ill.

(3) Present address: Strong Cobb & Co., Cleveland, Ohio.

(4) M. Guggenheim, "Festschrift Emil Barell," F. Hoffmann-LaRoche and Co., Basel, 1936, p. 171.

(5) E. Gryszkiewicz-Trochimowski, *Arch. Chem. Farm.*, **2**, 1 (1934).

Experimental

β,4-Morpholine-ethylurea.—A mixture of 8.4 g. of β,4-morpholine-ethylamine and 7.9 g. of nitrourea in 40 cc. of alcohol was warmed gently. The reaction soon started and proceeded without further heating until the evolution of gas was complete. The mixture was then boiled for a few minutes and most of the alcohol evaporated on the steam-bath. On cooling, the product crystallized; yield 6.1 g. (53.5%), m. p. 173–174° from alcohol.

Anal. Calcd. for $C_7H_{15}O_2N_3$: N, 24.28. Found: N, 24.55, 24.73.

5,5-Diethyl-1-(β,4-morpholine-ethyl)-barbituric Acid Hydrochloride.—Condensation of 5.2 g. of β,4-morpholine-ethylurea and 6.5 g. of ethyl diethylmalonate was carried out in a solution of 2.8 g. of sodium in the smallest amount of absolute alcohol. The mixture was boiled five hours, cooled, diluted with water, made just acid to congo red, and most of the alcohol removed on the steam-bath by a current of air. The residue was extracted with ether. On standing for several days, the aqueous solution deposited long, white needles. These were filtered off and additional crystals obtained by chilling the mother liquor: yield 3.85 g. (38.5%), m. p. 255–256° from alcohol.

Anal. Calcd. for $C_{14}H_{23}O_4N_3.HCl$: N, 12.59; Cl, 10.95. Found: N, 12.98, 12.39; Cl, 11.10, 10.78.

5-Ethyl-5-iso-amyl-1-(β,4-morpholine-ethyl)-barbituric Acid Hydrochloride.—In a similar manner, ethyl ethyl-iso-amylmalonate was condensed with β,4-morpholine-ethylurea; yield 38%, m. p. 90–92°.

Anal. Calcd. for $C_{17}H_{29}O_4N_3.HCl$: N, 11.18. Found: N, 11.14, 11.02.