tilled to give 2.2 g. (18%) of product, b.p. 78° (25 mm.), $n^{27}D$ 1.5283. Karmas and Spoerri[31] give the b.p. of this compound as 94–96° (65 mm.), $n^{25}D$ 1.5302.

(B) A similar experiment with 11.0 g. (0.10 mole) of the 3-methylpyrazine-1-oxide (m.p. 80–82°) gave a 4.0-g. residue which, on distillation, gave 1.2 g. (10.4%) of product, b.p. 80° (27 mm.).

Both compounds gave identical ultraviolet and infrared absorption spectra ($CHCl_3$ solution), which in turn, were identical with the spectra of an authentic sample of 2-chloro-3-methylpyrazine.[32]

(31) G. Karmas and P. E. Spoerri, THIS JOURNAL, **74**, 1582 (1952).

Absorption Spectra.—Ultraviolet absorption spectra were obtained on a Beckman DU spectrophotometer, with 1-cm. quartz cuvets. Infrared absorption spectra were obtained on a Perkin–Elmer model 21 recording spectrophotometer either as chloroform solutions, carbon disulfide solutions or potassium bromide disk preparations.[33]

(32) Obtained from the Wyandotte Chemicals Corp. by the courtesy of Dr. Phelps Trix.

(33) The authors are indebted to Dr. Oscar Auerbach, Assistant Director, Professional Services for Research, V. A. Hospital, East Orange, N. J., for loan of the infrared spectrophotometer.

BRONX 68, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE COLLEGE OF LIBERAL ARTS OF TEMPLE UNIVERSITY]

The Synthesis of 2-Amino-5-pyrimidinesulfonamide and Some of its Derivatives

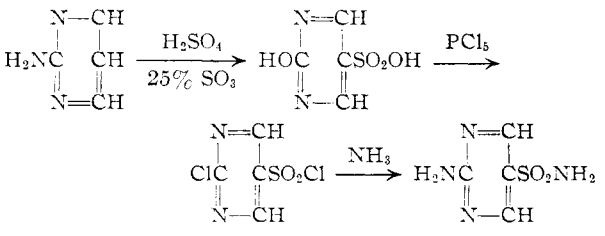
BY WILLIAM T. CALDWELL AND GERALD E. JAFFE

RECEIVED MARCH 23, 1959

2-Amino-5-pyrimidinesulfonamide and a number of its N^1,N^4-substituted derivatives have been prepared from 2-chloro-5-pyrimidinesulfonyl chloride, readily obtainable from 2-aminopyrimidine in two steps.

The therapeutic value of sulfanilamide led naturally to the preparation of many of its derivatives and analogs such as sulfadiazine[1] on the one hand and 2-amino-5-pyridinesulfonamide,[2] 3-amino-6-pyridinesulfonamide[3] and 2-amino-5-thiazolesulfonamide[4] on the other. Because of the efficacy of sulfadiazine, the preparation of 2-amino-5-pyrimidinesulfonamide and its derivatives has seemed intriguing, particularly in view of the fact that such a comparatively simple compound has not yet been described in the literature. The reason for this is, doubtless, that the obviously requisite intermediates such as 2-acetamido-5-pyrimidinesulfonyl chloride or 2-nitro-5-pyrimidinesulfonyl chloride are not readily accessible.

After many abortive experiments, we have found a simple sequence of reactions by which we have prepared the primary objective of our work, 2-amino-5-pyrimidinesulfonamide, as well as a number of its derivatives; this sequence is illustrated by the transitions



These reactions, some of which are described below, involve first the conversion of 2-aminopyrimidine into an unanticipated, deaminated product, 2-hydroxy-5-pyrimidinesulfonic acid, which is readily convertible into 2 - chloro - 5 - pyrimidinesulfonyl chloride. The latter, in turn, serves as an intermediate for preparing 2-amino-5-pyrimidinesulfonamide and N^1,N^4-disubstituted derivatives thereof; unfortunately, it is not suited to the preparation of N^1-monosubstituted sulfonamides. Attempts to prepare 2-acetamido-5-pyrimidinesulfonyl chloride have so far been unsuccessful in our hands; both 2-aminopyrimidine and 2-acetamidopyrimidine, when treated with chlorosulfonic acid, yielded 2-amino-5-pyrimidinesulfonic acid. The latter was obtained unchanged after attempts to acetylate it, and when treated with phosphorus pentachloride formed only refractory products.

We wish to thank Eli Lilly and Co. for carrying out pharmacological tests and the Temple University Committee on Research and Publications for a grant-in-aid.

The tests so far reported on these compounds indicate that they have no significant value pharmacologically.

(1) R. O. Roblin, J. H. Williams, P. S. Winnek and J. P. English, THIS JOURNAL, **62**, 2002 (1940).

(2) C. Naegeli, W. Kündig and H. Bradenburger, *Helv. Chim. Acta*, **21**, 1746 (1938).

(3) W. T. Caldwell and E. C. Kornfeld, THIS JOURNAL, **64**, 1695 (1942).

(4) H. J. Backer and J. A. K. Buisman, *Rec. trav. chim.*, **63**, 228 (1944).

Experimental

2-Hydroxy-5-pyrimidinesulfonic Acid.—To 400 ml. of fuming sulfuric acid (25% SO_3) was added cautiously 95 g. (1 mole) of 2-aminopyrimidine. The temperature was then raised to 180° and kept there for five hours. After cooling, the contents of the flask were poured upon 4 kg. of crushed ice and the white solid filtered off; yield, after recrystallization from water, 42 g. (23.8%), m.p. above 300°.

Anal. Calcd. for $C_4H_4N_2O_4S$: C, 27.27; H, 2.29; N, 15.90. Found: C, 27.45; H, 2.47; N, 15.95.

2-Chloro-5-pyrimidinesulfonyl Chloride.—A mixture of 104.3 g. (0.5 mole) of phosphorus pentachloride and 35.2 g. (0.2 mole) of 2-hydroxy-5-pyrimidinesulfonic acid was heated in an oil-bath at 180° under reflux. After two hours, the material formed a tan-colored liquid which was refluxed for an additional two hours. To the cooled liquid, 400 ml. of benzene was added and the solution filtered. Upon concentration under diminished pressure, a light tan-colored solid remained which was placed in a Soxhlet apparatus and continuously extracted with 500 ml. of petroleum ether (b.p. 30–60°) for 16 hours. This solution was concentrated to one-half of its original volume and then cooled. After filtering and drying, the yield of white, crystalline product was 37 g. (87%), m.p. 66–67°.

Anal. Calcd. for $C_4H_2Cl_2N_2O_2S$: C, 22.55; H, 0.95; N, 13.15; Cl, 33.28. Found: C, 22.79; H, 0.97; N, 12.94; Cl, 33.18.

2-Amino-5-pyrimidinesulfonamide.—A mixture of 2.13 g. (0.01 mole) of 2-chloro-5-pyrimidinesulfonyl chloride and

TABLE I

2-AMINOPYRIMIDINE-5-SULFONAMIDE AND SOME OF ITS N¹,N⁴-DISUBSTITUTED DERIVATIVES[a]

Reagent	M.p., °C.	Crystn. solvent	Yield, %	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Ammonia	283–285	Water	48.3	$C_4H_6N_4O_2S$	27.58	27.61	3.47	3.51	32.17	31.93
Methylamine	194–195	Water	90.5	$C_6H_{10}N_4O_2S$	35.63	35.72	4.98	5.03	27.71	27.41
Dimethylamine	200–201	Ethanol–water	86.5	$C_8H_{14}N_4O_2S$	41.72	41.94	6.13	6.22	24.33	24.14
Ethylamine	191–192	2-Propanol–water	58.5	$C_8H_{14}N_4O_2S$	41.72	41.58	6.13	6.20	24.33	24.30
Diethylamine	72–73	Ethanol–water	83.2	$C_{12}H_{22}N_4O_2S$	50.32	50.37	7.74	7.66		
n-Propylamine	162–163	2-Propanol–water	82.3	$C_{10}H_{18}N_4O_2S$	46.49	46.55	7.02	7.02	21.69	21.69
n-Butylamine	165–167	Ethanol–water	80.5	$C_{12}H_{22}N_4O_2S$	50.32	50.39	7.74	7.64	19.57	19.46
Allylamine	165–167	Ethanol–water	88.4	$C_{10}H_{14}N_4O_2S$	47.23	47.11	5.55	5.54	22.03	22.03
Cyclohexylamine	156–158	2-Propanol–water	90.2	$C_{16}H_{26}N_4O_2S$	56.77	56.85	7.74	7.88	16.55	16.65
Pyrrolidine	215–217	2-Propanol–water	85.1	$C_{12}H_{18}N_4O_2S$	51.04	50.94	6.43	6.44	19.84	19.84
N-Methylpiperazine	180–182	Water	83.5	$C_{14}H_{24}N_6O_2S$	49.39	49.34	7.11	7.23	24.69	24.72
Morpholine	223–224	2-Propanol–water	78.3	$C_{12}H_{18}N_4O_4S$	45.85	46.09	5.77	5.88	17.82	17.76
Piperidine	199–200	2-Propanol–water	81.4	$C_{14}H_{22}N_4O_2S$	54.14	54.06	7.14	7.26	18.05	18.12

[a] Prepared from 2-chloro-5-pyrimidinesulfonyl chloride with the reagents listed in column 1 under the same conditions as described for the reaction with methylamine.

of 4.8 g. (0.05 mole) of ammonium carbonate was heated at 100° for three hours. After cooling, the contents of the flask were poured into 25 ml. of water, the precipitate filtered off and recrystallized from water; yield of white needles, 0.84 g. (48%), m.p. 283–285°. The same product is obtained from the chloride by using concentrated ammonium hydroxide or a solution of dry ammonia in tetrahydrofurane.

Anal. Calcd. for $C_4H_6N_4O_2S$: C, 27.58; H, 3.47; N, 32.17. Found: C, 27.61; H, 3.51; N, 31.93, 32.49.

2-Methylamino-5-pyrimidine-N-methylsulfonamide.—Two grams of methylamine was bubbled into 50 ml. of cooled benzene and then 2.13 g. (0.01 mole) of 2-chloro-5-pyrimidinesulfonyl chloride in 50 ml. of benzene was added with stirring during a period of 15 minutes. After stirring for an additional 15 minutes, the white product was filtered off and washed with water to remove methylamine hydrochloride. Crystallization from water afforded 1.83 g. (90.5%) of white crystals, m.p. 194–195°.

Anal. Calcd. for $C_6H_{10}N_4O_2S$: C, 35.63; H, 4.98; N, 27.71. Found: C, 35.72; H, 5.03; N, 27.41.

2-Amino-5-pyrimidinesulfonic Acid.—Forty-seven and one-half grams (0.5 mole) of finely powdered 2-aminopyrimidine was added very slowly with vigorous stirring to 300 ml. of chlorosulfonic acid cooled in a bath of ice and salt to 10°. After all of the 2-aminopyrimidine had been added, the mixture was refluxed for 8 hours, cooled and poured carefully upon crushed ice. After standing overnight in a refrigerator the solid was filtered off, washed well with cold water and recrystallized from water. The yield of white crystals, m.p. 305–307° dec., was 22.8 g. (28%).

Anal. Calcd. for $C_4H_5N_3O_3S$: C, 27.42; H, 2.88; N, 24.00. Found: C, 27.82; H, 3.03; N, 24.02.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND THE ENGINEERING EXPERIMENT STATION, GEORGIA INSTITUTE OF TECHNOLOGY]

Spiroaminobarbituric Acids. I[1]

BY JAMES A. STANFIELD AND PHILLIP M. DAUGHERTY

RECEIVED OCTOBER 2, 1958

The synthesis of several nitrogen-substituted alkyl, substituted alkyl and aryl derivatives of spiropiperidine-4′,5-barbituric acid is reported. It has been observed that the stability of the spiro-1′-methylpiperidine-4′,5-barbituric acid is of the same order of magnitude as barbital and is somewhat more stable than the spirotetrahydropyran- or the spirocyclopentanebarbituric acids. The pharmacological examinations of the 1′-phenyl- and the 1′-(2-phenylethyl)- compounds are also reported.

Cyclic diimides, prepared by condensing urea or its derivatives with various substituted malonic esters, form an important group of compounds many of which have a depressant action on the central nervous system. Such compounds, the barbiturates, are valuable sedatives and soporifics. Among these, the most useful are those compounds having two substituents, usually alkyl, at the number 5 position. Close analogs of these, the spirobarbiturates, many of which incorporated a spirocarbocyclic system involving the 5-position, have been prepared by previous investigators in the field.[2] The most recent effort along these lines, however, was the preparation of a spironitrogen system, *i.e.*, spiro-1′-benzenesulfonylpiperidine-4′,-5-barbituric acid.[3] This present work reports the preparation of several spiro-1′-alkyl- or arylpiperidine-4′,5-barbituric acids, two possible approaches to the synthesis of compounds of this type being outlined in Figs. 1 and 2.

(1) A portion of this material was presented at the 130th Meeting of the American Chemical Society in Atlantic City, N. J., September, 1956, and is taken in part from the Ph.D. thesis submitted to the Graduate School of the Georgia Institute of Technology by Phillip M. Daugherty in May, 1957.

(2) (a) A. W. Dox and L. Yoder, THIS JOURNAL, **43**, 677 (1921); (b) **43**, 1366 (1921); (c) O. Kamm and J. H. Waldo, *ibid.*, **43**, 2223 (1921); (d) A. C. Cope, P. Kovacic and M. Burg, *ibid.*, **71**, 3658 (1949); (e) W. J. Doran and E. M. Van Heyningen, U. S. Patents 2,561,688 and 2,561,689 (July, 1951); (f) J. Buchi, K. Leuenberger and R. Lieberherr, *Farm. Sci. e tec. (Pavia)*, **6**, 430 (1951); and (g) G. Giacomello and P. Malatesta, *ibid.*, **6**, 684 (1951).

(3) G. S. Skinner, H. R. Krysiak and J. A. Perregrino, THIS JOURNAL, **77**, 2248 (1955).