the preparation of N^4-(4-methoxy)-benzylidine-N^1-(4-nitro)-phenylsulfanilamide is described as an example.

On the basis of preliminary biological studies, introduction of the arylidine group causes some diminution in activity, and a significant decrease in toxicity.

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[CONTRIBUTION FROM THE NICHOLS CHEMICAL LABORATORY OF NEW YORK UNIVERSITY]

Sulfanilyl Derivatives of Pyridine and Quinoline Amines

BY ROBERT WINTERBOTTOM

Since the discovery by Whitby[1] of the therapeutic action of 2-sulfanilamidopyridine, numerous compounds of similar structure have been prepared. This paper describes the preparation of sulfanilamides containing a pyridine or a quinoline ring. The sulfanilyl derivatives of 5, 6, 7, and 8 aminoquinoline[2] were published by Bobranski while this research was in progress. Their physical properties correspond with those of the same compounds prepared in this Laboratory. Although there are many references in the literature to 2-sulfanilamidopyridine, its detailed method of synthesis has never appeared; for this reason its preparation has been included.

The aminoquinolines, with the exception of 3-aminoquinoline, were prepared from the corresponding nitroquinolines by catalytic reduction using Raney nickel. The yields were slightly better than those obtained by using iron and acetic acid.[3] Attempts to prepare 7-nitroquinoline by nitration of quinoline with lithium nitrate in acetic anhydride[4] failed to give appreciable yields. Diacetyl orthonitric acid was tried because of its peculiar orienting effects but was ineffective. 7-Nitroquinoline, prepared by the Skraup reaction using metanitraniline, upon catalytic reduction gave an aminoquinoline corresponding in physical properties to that prepared by Hamer.[5] It melted at 74–75.5° and not at 189° as described by earlier workers.[6] 3-Aminoquinoline was prepared from the corresponding bromo compound by treatment with aqueous ammonia at 200°.[7]

The sulfanilamides were prepared by condensing recrystallized acetylsulfanilyl chloride with the appropriate amine in pyridine solution. 5-N^4-Acetylsulfanilamido-2-acetylaminopyridine was prepared from 5-amino-2-acetylaminopyridine by Bauer's[8] method employing acetone. A sample of 2-acetylamino-5-aminopyridine was obtained through the courtesy of the Pyridium Corporation. The crude acetyl derivatives were recrystallized from ethanol or propanol. In cases where no suitable solvent could be found, the crude products were washed and dried before analysis, or prepared by acetylation of the free amine. In all cases, except that of 2-N^4-acetylsulfanilamidopyridine, removal of the acetyl group was effected by boiling for a half hour with 12% hydrochloric acid. This treatment causes rupture of the sulfonamide linkage when applied to 2-N^4-acetylsulfanilamidopyridine. When the hydrolysis was carried out in alcoholic hydrochloric acid solution, the sulfonamide link remained intact.

Experimental Part

7-Aminoquinoline.—7-Nitroquinoline (10 g., 0.058 mole), dissolved in 100 cc. of acetone, was reduced in a low pressure Parr hydrogenator in the presence of 0.6 g. (0.001 mole) of Raney nickel. Reduction was complete in one hour. The acetone was then allowed to evaporate. The product separated as an oil which soon solidified. Upon recrystallization from water, light yellow needles were obtained; yield: 8 g. (95%), m. p. 74–75.5°.

The same procedure was utilized for 5- and 8-aminoquinoline, using ethanol as the solvent. Recrystallization from ligroin and petroleum ether have yields of 75 and 69%, respectively.

2-Sulfanilamidopyridine.—Acetylsulfanilyl chloride (10 g.) and 2-aminopyridine (4 g.) were dissolved in 34 cc. of acetone containing 5 cc. of pyridine. Upon standing overnight 5 g. of almost pure product separated as a white deposit. The filtrate upon dilution with water gave an additional 4 g. For analysis it was recrystallized from acetone as small white needles. Removal of the acetyl group was effected by treating 1 g. of the crude acetyl compound with 10 cc. of ethanol and 2 cc. of concd. hydro-

(1) Whitby, *Lancet*, **1**, 1210 (1938).
(2) Bobranksi, *Arch. Pharm.*, **277**, 75 (1938).
(3) Dikshoorn, *Rec. trav. chim.*, **48**, 153 (1929).
(4) Bacharach, *et al.*, *ibid.*, **52**, 413 (1933).
(5) Hamer, *J. Chem. Soc.*, **119**, 1434 (1921).
(6) Claus and Massau, *J. prakt. Chem.*, **48**, 174 (1893).
(7) Renshaw and Friedman, THIS JOURNAL, **61**, 3320 (1939).
(8) Bauer, *ibid.*, **61**, 613 (1939).

TABLE I

Compound[a]	M. p., °C. (corr.)	Formula	Nitrogen, % Calcd.	Found[b]
2-N^4-Acetylsulfanilamidopyridine	226–227	$C_{13}H_{13}N_3O_3S$	14.42	14.60
2-Sulfanilamidopyridine	190–191	$C_{11}H_{11}N_3O_2S$	16.86	16.68
3-N^4-Acetylsulfanilamidopyridine	272–275 dec.	$C_{13}H_{13}N_3O_3S$	14.42	14.14
3-Sulfanilamidopyridine	248–251 dec.	$C_{11}H_{11}N_3O_2S$	16.86	16.61
5-N^4-Acetylsulfanilamido-2-acetylaminopyridine	288–291 dec.	$C_{15}H_{16}N_4O_4S$	16.09	15.81
5-Sulfanilamido-2-aminopyridine	210–211	$C_{11}H_{12}N_4O_2S$	21.20	20.94
3-N^4-Acetylsulfanilamidoquinoline	250–253 dec.	$C_{17}H_{15}N_3O_3S$	12.31	12.23
3-Sulfanilamidoquinoline	185–186 dec.	$C_{15}H_{13}N_3O_2S$	14.04	14.20
5-N^4-Acetylsulfanilamidoquinoline[c]	256–258	$C_{17}H_{15}N_3O_3S$	12.31	12.52
5-Sulfanilamidoquinoline[c]	228–230	$C_{15}H_{13}N_3O_2S$	14.04	14.15
6-N^4-Acetylsulfanilamidoquinoline[c]	285–287	$C_{17}H_{15}N_3O_3S$	12.31	12.12
6-N^4-Acetylsulfanilamidoquinoline hydrochloride	238–240	$C_{17}H_{16}ClN_3O_3S$	11.12	11.06
6-Sulfanilamidoquinoline[c]	202–204	$C_{15}H_{13}N_3O_2S$	14.04	13.86
8-N^4-Acetylsulfanilamidoquinoline[c,d]	193–194	$C_{17}H_{15}N_3O_3S$	12.31	12.02
8-Sulfanilamidoquinoline[c,d]	194–195	$C_{15}H_{13}N_3O_2S$	14.04	13.87

[a] Nomenclature according to Crossley, Northey and Hultquist, THIS JOURNAL, 60, 2217 (1938). [b] Dumas. [c] Previously prepared by Bobranski.[2] [d] Previously prepared by A. D. Choudhury, *et al.*, *J. Ind. Chem. Soc.*, 14, 733 (1937).

chloric acid. After refluxing for twenty minutes, the reaction mixture was diluted with water and made basic with ammonium hydroxide. It was recrystallized from ethanol; yield, 0.67 g. (75%).

5 - N^4 - Acetylsulfanilamido - 2 - acetylaminopyridine.—Using the same procedure as above, 3.0 g. of 5-amino-2-acetylaminopyridine and 4.0 g. of acetyl sulfanilyl chloride gave 6.0 g. (94%) of crude 5-N^4-acetylsulfanilamido-2-acetylaminopyridine. This was converted to 5-sulfanilamido-2-aminopyridine by the same procedure used below for 3-sulfanilamidoquinoline.

3-Sulfanilamidoquinoline.—3-Aminoquinoline (2.5 g.) and acetylsulfanilyl chloride (4.0 g.) were dissolved in 30 cc. of dry pyridine. After heating for two hours on the steam-bath, the reaction mixture was poured into 400 cc. of cold water. The product separated as a white crystalline mass weighing 5.4 g. when dry. For analysis a small amount was washed successively with water and ethanol and dried at 100°. One gram of the crude acetyl compound was boiled for a half hour with 25 cc. of 12% hydrochloric acid. Upon cooling and neutralizing with ammonium hydroxide, the sulfonamide was obtained; yield 0.8 g. (91%). It was recrystallized from ethanol.

Summary

An improved method of preparation of the 5, 7, and 8-aminoquinolines as well as the preparation of certain sulfanilamido derivatives of pyridine and quinoline amines is described.

The results obtained by Bobranski[2] are confirmed.

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Amines Related to 2,5-Dimethoxyphenethylamine.[1] I

BY RICHARD BALTZLY AND JOHANNES S. BUCK

Preliminary pharmacological work has indicated that some amines containing the 2,5-dimethoxyphenyl group show activity comparable with that of similar phenolic amines, and also that they probably will be active orally. It therefore became important to prepare, for pharmacological examination, as complete a series as possible of amines (as hydrochlorides) containing the 2,5-dimethoxyphenethyl grouping, the optimal C–C–N side chain being present in all cases.

(1) This work is part of a joint research being carried out in collaboration with a pharmacological group at the above laboratories.

Six series of 2,5-dimethoxyphenethylamines were prepared, in each series the primary, secondary, tertiary and quaternary compounds being made. Included in the series are the analogs of practically all the known pharmacologically active amines containing the phenethyl group (that is, containing the C–C–N side chain).

The present paper deals with the preparation and properties of the amines with no hydroxyl group in the side chain. One hydrochloride has been described previously.

The formulas of the primary amines are