TABLE II

DERIVATIVES OF PHENYL-4-AMINOBENZENESULFONATE

| | Compound | Dec. pt., °C.[a] | Yield, % | Crystd. from | Formula | Nitrogen, % Calcd. | Nitrogen, % Found | Sulfur, % Calcd. | Sulfur, % Found |
|---|---|---|---|---|---|---|---|---|---|
| | (—)-Phenyl-4-acetylaminobenzenesulfonate | | | | | | | | |
| 17 | 3′-Nitro-4′-acetamino- | 211–212 | 92 | 35% AcOH | $C_{16}H_{15}O_7N_3S$ | 10.68 | 10.57 | 8.15 | 7.88 |
| 18 | 3′-Nitro-4′-amino-[c] | 231–232 | 58 | 35% AcOH | $C_{14}H_{13}O_6N_3S$ | 11.96 | 12.06 | 9.13 | 9.14 |
| 19 | 2′-Amino-5′-nitro- | 212 | 50 | 35% AcOH | $C_{14}H_{13}O_6N_3S$ | 11.96 | 12.01 | 9.13 | 8.83 |
| 20 | 2′,5′-Diamino-[d] | 159–160 | 55 | 1% $Na_2S_2O_4$ | $C_{14}H_{15}O_4N_3S$ | 13.08 | 12.89 | 9.98 | 10.04 |
| 21 | 2′,5′-Diacetylamino-[e] | 268 | | 40% AcOH | $C_{18}H_{19}O_6N_3S$ | 10.37 | 10.23 | 7.91 | 7.93 |
| 22 | 2′-Acetylamino-5′-nitro-[f] | 217–217.5 | 55[b] | 50% EtOH | $C_{16}H_{15}O_7N_3S$ | 10.68 | 10.74 | 8.15 | 8.08 |
| | (—)-Phenyl-4-aminobenzenesulfonate | | | | | | | | |
| 23 | 3′-Nitro-4′-amino-[g] | 166.5–167.5 | 93 | 25% AcOH | $C_{12}H_{11}O_5N_3S$ | 13.59 | 13.52 | 10.37 | 10.14 |
| 24 | 2′-Amino-5′-nitro-[h] | 217–218 | 58 | 30% AcOH | $C_{12}H_{11}O_5N_3S$ | 13.59 | 13.34 | 10.37 | 10.13 |

[a,b] See Table I for significance. [c] This compound was prepared from 3-nitro-4-aminophenol, N-acetylsulfanilyl chloride and sodium bicarbonate (in place of sodium acetate) following the general directions described for the preparation of $N^4$-acetyl-$N^1$-disubstituted phenylsulfanilamide compounds. When deacetylated it yielded compound 23 and gave no depression with the latter in a mixed decomposition point determination. [d] Prepared by catalytic reduction of compound 19. [e] Prepared by acetylation of compound 20. [f] One-tenth mole of 2-acetylamino-5-nitrophenol was treated with 0.16 mole of N-acetylsulfanilyl chloride and 0.16 mole of sodium bicarbonate following the general directions described for the preparation of the sulfonates; 39% of 2-acetylamino-5-nitrophenol was recovered by extraction of the product with 5% sodium hydroxide followed by acidification with acetic acid. [g] This compound was acetylated with acetic anhydride in 25% acetic acid solution to form compound 18. The amino group ortho to the nitro group is not acetylated under these conditions. No depression in decomposition point occurred in a mixed decomposition point determination. [h] This compound was prepared from compound 19 (99% yield) and 22 (90% yield). No depression in a mixed decomposition point determination indicated that the compound prepared from 19 and 19 itself were sulfonates.

tions of 5% hydrochloric acid. The acid insoluble material ($N^4$-acetyl-$N^1$-2-nitro-4-hydroxyphenylsulfanilamide, 2.9 g., 41%) was recrystallized from 25% alcohol. The decomposition point (217°) was depressed by the presence of the sulfonate.

The acid solution was neutralized with sodium bicarbonate and yielded 0.5 g. (16%) of 3-nitro-4-aminophenol, m. p. 149°, which when recrystallized from water melted at 152–153°.

## Summary

The preparation of a number of disubstituted derivatives of $N^1$-phenylsulfanilamide and $N^4$-acetyl-$N^1$-phenylsulfanilamide in which two hydrogen atoms of the phenyl group are replaced by nitro and amino, nitro and hydroxy, amino and hydroxy, nitro and acetoxy, hydroxy and acetylamino, acetoxy and acetylamino, two acetylamino or two amino groups is described.

Eight disubstituted phenyl-4-acetylamino (or amino)-benzenesulfonates are described.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

# Syntheses in the Pyrazine Series. III. The Amination of 2,5-Dimethylpyrazine. The Synthesis of 3-Sulfanilamido-2,5-dimethylpyrazine

BY ROBERT R. JOINER AND PAUL E. SPOERRI

Since the preparations of aminopyrazine and some of its homologs, as given in the literature, are either very lengthy or give poor yields, it seems appropriate, in view of the present interest in amino heterocyclics, to devise simpler and better methods of preparation. 2,5-Dimethylpyrazine was first investigated, since it can be prepared readily from acetone by the method of Gabriel and Pinkus.[1] Direct amination with sodamide would then yield 3-amino-2,5-dimethylpyrazine. This reaction already has been described by Tschitschibabin and Shukina[2] but they were unable to obtain better than 10% yields. Repetition of this work confirmed their results. On investigating the course of the reaction by measuring the evolution of hydrogen, the reaction was found to be 90% complete in four hours.

We found that by replacing the xylene, which Tschitschibabin used as his solvent, with di-

(1) Gabriel and Pinkus, *Ber.*, **26**, 2197 (1893).

(2) Tschitschibabin and Shukina, *J. Russ. Phys.-Chem. Soc.*, **62**, 1189 (1930).

methylaniline, and increasing the temperature to about 165°, we could obtain yields of 35% of 3-amino-2,5-dimethylpyrazine.

This amine was condensed with N-acetylsulfanilyl chloride in the presence of dry pyridine to yield 3-($N^4$-acetylsulfanilamido)-2,5-dimethylpyrazine. This compound was hydrolyzed and recrystallized first from ethanol and then from water, m. p. 227–228° (cor.). Its chemotherapeutic action is being investigated.

## Experimental

**3-Amino-2,5-dimethylpyrazine.**—7.2 grams of 2,5-dimethylpyrazine was dissolved in 17 cc. of dimethylaniline, 11 g. of sodium amide was added and the reaction mixture heated to 165° in an oil-bath for two hours. The reaction mixture was poured upon 100 g. of ice, the solution saturated with potassium carbonate and extracted with ether. After the ether extract was dried with anhydrous potassium carbonate, the ether was removed by distillation. The residue was distilled under reduced pressure and 2.9 g. of 3-amino-2,5-dimethylpyrazine, b. p. 119–122° at 10 mm., was obtained (35%). The 3-amino-2,5-dimethylpyrazine was recrystallized from benzene; m. p. 111–112° (Tsch. 111°), m. p. of picrate 205° (Tsch. 205°).

**3-($N^4$-Acetylsulfanilamido)-2,5-dimethylpyrazine.**—To 1.057 g. (1 mol) of 3-amino-2,5-dimethylpyrazine dissolved in 2.2 cc. of dry pyridine there was added gradually 2.068 g. (1.02 mol) of N-acetylsulfanilyl chloride, the temperature being kept below 50°. The reaction mixture was then heated on a steam-bath for one hour. A solution of 0.368 g. (1.1 mols) of sodium hydroxide in 1.75 cc. of water was added slowly and the heating continued for two to three minutes. The solution was cooled, 10 cc. of water added, and the pyridine was removed under reduced pressure, water being added to maintain the volume. Crude 3-($N^4$-acetyl sulfanilamido)-2,5-dimethylpyrazine separated as a yellow solid; filtered and recrystallized twice from water, m. p. 238–239°, yield 1.6 g. (57%).

**3-Sulfanilamido-2,5-dimethylpyrazine.**—1.128 grams (1 mol) of 3-($N^4$-acetyl sulfanilamido)-2,5-dimethylpyrazine and 1.75 cc. of 6*N* hydrochloric acid (3 mols) were mixed together to form a paste which was then heated slowly to 100° and held at this temp. for eight to ten minutes, during which time the paste slowly became a clear red liquid. The solution was poured upon 10 g. of cracked ice, and clarified by stirring ten minutes in the cold with activated carbon. The yellow solution was carefully neutralized to *p*H 6 with 10% sodium hydroxide solution and the yellow precipitate filtered off and recrystallized once from ethanol and twice from water, yield 0.9 g. (92%), m. p. 227–228° (cor.).

*Anal.* Calcd. for $C_{12}H_{14}O_2N_4S$: C, 51.76; H, 5.07; N, 20.14. Found: C, 51.93; H, 5.28; N, 20.18.

A qualitative test for the free amino group by the method of E. K. Marshall[3] was positive.

## Summary

1. 3-Amino-2,5-dimethylpyrazine was prepared in yields of 35%.

2. 3-Sulfanilamido-2,5-dimethylpyrazine was prepared.

(3) E. K. Marshall, *J. Biol. Chem.*, **122**, 263 (1936).

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[CONTRIBUTION FROM THE STAMFORD RESEARCH LABORATORIES OF THE AMERICAN CYANAMID COMPANY]

# Studies in Chemotherapy. III. Sulfones[1]

BY RICHARD O. ROBLIN, JR., JAMES H. WILLIAMS AND GEORGE W. ANDERSON

In 1937 Buttle, Fourneau[2] and their co-workers reported a high degree of chemotherapeutic activity for 4,4′-diaminodiphenylsulfone and, to a lesser extent, its diacetyl derivative.[3] Since that time several other groups of investigators[4] have confirmed the original reports. From the results of all these investigations it may be concluded that 4,4′-diaminodiphenylsulfone, while it is too toxic to be of much practical value, is probably the most active of all the bacterial chemotherapeutic agents which have been studied up to the present time. In spite of this high degree of activity, relatively few attempts have been made to reduce the toxicity of this compound. Moreover, those cases in which this result was accomplished[5] involved the formation of acyl or Schiff base derivatives which were probably broken down slowly *in vivo* to liberate 4,4′-diaminodiphenylsulfone before they became therapeutically active.

This paper describes the preparation and properties of a series of sulfones many of which are

(1) Presented in part before the Division of Medicinal Chemistry, St. Louis meeting of the American Chemical Society, April 10, 1941.

(2) Buttle, Stephenson, Smith, Dewing and Foster, *Lancet*, **232I**, 1331 (1937); Fourneau, Tréfouël, Tréfouël, Nitti and Bovet, *Compt. rend.*, **204**, 1763 (1937).

(3) Fromm and Wittmann, *Ber.*, **41**, 2264 (1908).

(4) Bauer and Rosenthal, *U. S. Pub. Health Repts.*, **53**, 40 (1938); Raiziss, Severac, Moetsch and Clemence, *Proc. Soc. Expti. Biol. Med.*, **39**, 339 (1938); Feinstone, Dissertation, Johns Hopkins University, School of Hygiene and Public Health (1939); Marshall, Litchfield and White, *J. Pharmacol.*, **69** (1) 89; (2) 166 (1940).

(5) (a) Fourneau, Tréfouël, Tréfouël, Nitti and Bovet, *Compt. rend.*, **205**, 299 (1937); (b) Buttle, Dewing, Foster, Gray, Smith and Stephenson, *Biochem. J.*, **32**, 1101 (1938).