product, was also an important end-product. Acetone was found with all acids except acetic acid, in appreciable amounts, and this was not expected, except with butyric acid. The products recovered and determined analytically gave a good "accounting" of the acids subjected to oxidation. Negligible oxidation occurs in the absence of the catalysts.

The interpretation of the catalytic effects presents serious difficulties, in view of certain experimental data mentioned, if it is assumed that the rather feeble oxidizing power of hydrogen peroxide is intensified by these substances. When, however, it was considered that they promote the reduction of hydrogen peroxide by supplying hydrogen from another source (the organic acids used) to reduce it to water, and that the final oxidation of the substrate to carbon dioxide is a secondary reaction depending on the addition of water and is not due primarily to the peroxide itself, all of the known facts fall into order.

MADISON, WIS. RECEIVED APRIL 12, 1941

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF ILLINOIS]

Derivatives of N^1-Phenylsulfanilamide. II

BY G. L. WEBSTER AND S. D. GERSHON

In an earlier report, Webster and Powers[1] described a series of N^1-phenylsulfanilamide[2] derivatives in which a hydrogen atom of the phenyl group had been replaced by a nitro, amino or hydroxyl group. In this paper we describe disubstituted derivatives in which two hydrogen atoms of the phenyl group have been replaced by nitro and amino, nitro and hydroxy, amino and hydroxy, nitro and acetoxy, hydroxy and acetylamino, acetoxy and acetylamino, two acetylamino or two amino groups with the N^4-nitrogen acetylated or unacetylated. In addition to the sulfanilamide derivatives we describe eight disubstituted phenyl-4-acetylamino (or amino)-benzenesulfonates.

Most of the N^4-acetylsulfanilamide derivatives were prepared by the general method described in the experimental part. N^4-Acetyl-N^1-2-nitro-4-hydroxyphenylsulfanilamide and 3′-nitro-4′-aminophenyl-4-acetylaminobenzenesulfonate were obtained from 3-nitro-4-aminophenol in 41% and 10% yields, respectively. When the sodium acetate was replaced by an equivalent amount of sodium bicarbonate, the principal product was the sulfonate (80% yield of crude material). In the case of 5-nitro-2-aminophenol, 18% of the sulfonanilide and 11% of the sulfonate were obtained using sodium acetate. When sodium bicarbonate was used, quantitative yields of the sulfonate were obtained.

The pharmacology of the compounds described is being investigated by Dr. Perrin H. Long.

(1) Webster and Powers, THIS JOURNAL, **60**, 1553 (1938).

(2) The nomenclature has been changed to conform to that suggested by Crossley, Northey and Hultquist, *ibid.*, **60**, 2217 (1938).

Experimental Part

2-Amino-4-acetylaminophenol.—Twenty grams of 2-nitro-4-acetylaminophenol[3] was reduced catalytically (platinum) in 150 cc. of hot alcohol. Eleven grams of white crystalline product, dec. 221–222°, was obtained after crystallization from 0.5% aqueous sodium hydrosulfite. When the product was crystallized from water, using decolorizing charcoal, tan-colored crystals formed which decomposed at the same temperature.[4]

Anal. Calcd. for $C_8H_{10}O_2N_2$: N, 16.86. Found: N, 16.92, 16.96.

The 2-amino-4-acetylaminophenol was acetylated to 2,4-di-(acetylamino)-phenol, m. p. 221° (lit. 220–222°),[5] and 2,4-di-(acetylamino)-1-acetoxybenzene, m. p. 184–185° (lit. 180–182°).[5]

3-Amino-4-acetylaminophenol.—Five grams of 1-acetylamino-2-amino-4-acetoxybenzene[6] was suspended in 25 cc. of water. Thirty cc. of 10% sodium hydroxide was added, the mixture stirred until solution was complete, and filtered. The filtrate was neutralized with 35% acetic acid and placed in an ice box overnight. The red crystals (2.4 g., m. p. 187.5–188.5°) were crystallized from water, using decolorizing charcoal. One and one-tenth grams of white crystalline material, m. p. 191°, was obtained.

Anal. Calcd. for $C_8H_{10}O_2N_2$: N, 16.86. Found: N, 16.70

The monoacetyl compound was acetylated to 3,4-di-(acetylamino)-phenol, m. p. 212° (lit. 214–215°),[6] and to 3,4-di-(acetylamino)-1-acetoxybenzene, m. p. 185–186° (lit. 187–188°).[6]

Preparation of N^4-Acetyl-N^1-disubstituted Phenylsulfanilamides.—One-tenth mole of disubstituted aniline

(3) Girard, *Bull. soc. chim.*, [4] **35**, 772 (1924).

(4) This compound has been reported with a decomposition point of 248° [Höchster Farbw., German Patent 164,295; *Chem. Zentr.*, **76**, II, 1701 (1905)] and 249° [Cassella and Co., German Patent 162,069; *Chem. Zentr.*, **76**, II, 865 (1905)].

(5) Kehrmann and Bahatrian, *Ber.*, **31**, 2399 (1898).

(6) Fieser and Martin, THIS JOURNAL, **57**, 1836 (1935).

TABLE I

DERIVATIVES OF N^1-PHENYLSULFANILAMIDE

	Compound	Dec. pt., °C.[a]	Yield, %	Crystd. from	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
				N^4-Acetyl-N^1-(—)-phenylsulfanilamide					
1	3-Nitro-4-hydroxy-	236	72	50% AcOH	$C_{14}H_{13}O_6N_3S$	11.96	11.89	9.13	9.06
2	2-Hydroxy-5-acetylamino-	239–240	55	30% AcOH	$C_{16}H_{17}O_5N_3S$	11.56	11.37	8.82	8.56
3	2-Nitro-4-hydroxy-	217	41[b]	25% EtOH	$C_{14}H_{13}O_6N_3S$	11.96	11.77	9.13	9.05
4	2-Acetylamino-5-acetoxy-[c]	200–201	50	5% AcOH	$C_{18}H_{19}O_6N_3S$	10.37	10.29	7.91	7.86
5	2-Acetylamino-5-hydroxy-[d]	239–240	52	15% AcOH	$C_{16}H_{17}O_5N_3S$	11.56	11.46	8.82	8.92
6	2-Hydroxy-4-nitro-	222–223	18[b]	50% EtOH	$C_{14}H_{13}O_6N_3S$	11.96	11.80	9.13	9.21
7	3-Nitro-4-amino-	258–259	63	65% AcOH	$C_{14}H_{14}O_5N_4S$	16.00	15.86	9.15	9.17
8	3,4-Diamino-	230–231	65	1% $Na_2S_2O_4$ in 50% EtOH	$C_{14}H_{16}O_3N_4S$	17.49	17.34	10.01	9.86
9	2,5-Diacetylamino-[e]	227–228	35	6% AcOH	$C_{18}H_{20}O_5N_4S$	13.85	13.64	7.93	7.79
10	Acetyl-N^1-3-nitro-4-acetoxy-	191	56	40% AcOH	$C_{15}H_{17}O_8N_3S$	9.6.	9.65	7.36	7.28
				N^1-(—)-Phenylsulfanilamide					
11	3-Nitro-4-hydroxy-	189	68	25% AcOH	$C_{12}H_{11}O_5N_3S$	13.59	13.70	10.37	10.28
12	3-Amino-4-hydroxy-[f]	204	70[b]	Water-CO_2 atm.	$C_{12}H_{13}O_3N_3S$	15.05	14.95	11.48	11.39
13	2-Amino-5-hydroxy-[g]	205	42	1% $Na_2S_2O_4$ in 2% AcOH[i]	$C_{12}H_{13}O_3N_3S$	15.05	14.72	11.48	11.63
14	3-Nitro-4-amino-[h]	223–224	63	45% AcOH	$C_{12}H_{12}O_4N_4S$	18.17	17.95	10.40	10.18
15	3,4-Diamino-	208–209	52	1% $Na_2S_2O_4$ in 50% EtOH	$C_{12}H_{14}O_2N_4S$	20.13	20.16	11.52	11.54
16	2-Hydroxy-5-amino-	167–168	54	1% $Na_2S_2O_4$	$C_{12}H_{13}O_3N_3S$	15.05	15.00	11.48	11.47

[a] All decomposition points are uncorrected; the rate of heating alters the decomposition point; 2° per minute was used. [b] Crude yield. [c] In preliminary work, this compound crystallized as a monohydrate which lost its water of crystallization at 141–143° (in the melting point tube) then resolidified to decompose at 198°. The monohydrate lost its water very slowly at 100°. Calcd. for $C_{18}H_{19}O_6N_3S \cdot H_2O$: 9.92% N; found 10.01% N. [d] Prepared as described in experimental part and by partial deacetylation of compound 4 with dilute alkali. [e] Used 0.15 mole of the acid chloride for its preparation. [f] Prepared by the reduction of compound 1 with stannous chloride; deacetylation occurred in the acid solution used. [g] Prepared by the deacetylation of compound 5. [h] In the preparation of this compound by deacetylation of compound 7 the insoluble hydrochloride was filtered from the alcohol–hydrochloric acid solution, dissolved by the addition of 20% sodium hydroxide and precipitated by acidification with acetic acid. [i] The solvent was warmed with charcoal, filtered and the filtrate used for crystallization of the compound.

compound, 0.11 mole of sodium acetate and 0.11 mole of crystallized[7] N-acetylsulfanilyl chloride were stirred in 300 cc. of water at room temperature for thirty minutes followed by one and one-half hours at 55–60°[8] and a final twenty minutes at 75°. The mixture was cooled, filtered and the insoluble material washed with water.

Preparation of N^1-Disubstituted Phenylsulfanilamides. The appropriate N^4-acetyl derivative was deacetylated as described by Webster and Powers,[1] using sodium bicarbonate to neutralize the acid present (in place of ammonia water) for compounds easily oxidized.

Preparation of Disubstituted Phenyl-4-acetylamino(or amino)-benzenesulfonates.—One-tenth mole of the substituted phenol, 0.12 mole of N-acetylsulfanilyl chloride and 0.12 mole of sodium bicarbonate in 600 cc. of water were stirred for thirty minutes at room temperature, followed by one hour at 55–60°.[8] The mixture was cooled, filtered and the insoluble material washed well with water.

The appropriate acetyl derivatives were deacetylated by the method described by Webster and Powers[1] for the preparation of N^1-substituted phenylsulfanilamides.

N^4-Acetyl-N^1-acetyl-N^1-3-nitro-4-acetoxyphenylsulfanilamide.—Ten grams of N^4-acetyl-N^1-3-nitro-4-hydroxyphenylsulfanilamide was refluxed gently for two hours with enough acetic anhydride to completely dissolve it (50 cc.). The solvent was then distilled *in vacuo* and the residue dissolved in 75 cc. of hot alcohol. Hot water was added to a permanent turbidity which was cleared with alcohol. The solution was allowed to cool. To the oily product 600 cc. of water and ice were added, the resulting solid (12 g.) removed by filtration and crystallized from 40% acetic acid using charcoal. Seven grams of pale yellow solid, insoluble in 5% sodium hydroxide, was obtained.

N^4-Acetyl-N^1-2-nitro-4-hydroxyphenylsulfanilamide.—Three and one-tenth grams of 3-nitro-4-aminophenol, 2.7 g. of sodium acetate trihydrate and 4.7 g. of N-acetylsulfanilyl chloride in 100 cc. of water were treated according to the general method. The insoluble material was extracted with 100 cc. of 5% sodium hydroxide and filtered leaving 0.7 g. (10%) of 3′-nitro-4′-aminophenyl-4-acetylamino-benzenesulfonate as insoluble material. The latter was crystallized from 35% acetic acid twice. It decomposed at 231–232° and in a mixed melting point with the known sulfonate, obtained by acetylation of 3′-nitro-4′-aminophenyl-4-aminobenzenesulfonate, gave no depression.

The alkaline extract was acidified with acetic acid and the resulting precipitate extracted with two 100-cc. por-

(7) Pence and Winter, THIS JOURNAL, 61, 2977 (1939).
(8) Thermometer in bath.

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.

CHICAGO, ILLINOIS RECEIVED MARCH 19, 1941

[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).