first saponified and then act in the form of methylnaphthohydroquinone. However, the potencies of the di-*n*-butyrate and di-*n*-valerate were found to be significantly greater than those of the corresponding iso-compounds with their inherent branched chains. This interesting observation may be explained by a difference in the rate of absorption, but it is also possible that these derivatives act as a whole and not in the form of a methylnaphthohydroquinone–methylnaphthoquinone equilibrium. Furthermore, the activity of the dimethyl ether is remarkably great, although in all probability this compound cannot be transformed to methylnaphthohydroquinone, considering the difficulty with which methyl ethers of phenols are split *in vitro*.

Our data confirm the results of Binkley, *et al.*,[19] namely: "In general, the activities of the diacetates of the 1,4-diols were about one-half that of the corresponding quinones." Most recently Doisy and his co-workers[20] stated, furthermore: "Only 1,4-naphthoquinones and compounds which upon oxidation in the organism might yield 1,4-naphthoquinones showed activity." In view of our observations above, particularly in conjunction with the vitamin K potency of phlorone, already reported,[18] it would seem that vitamin K activity is not confined solely to 1,4-naphthoquinones. Incidentally, anthraquinone appears to have a potency of one unit in about 2 mg.

(19) Binkley, Cheney, Holcomb, MacCorquodale, Thayer and Doisy, 98th Meeting, Am. Chem. Soc., Boston, Mass., September 12, 1939.

Summary

The preparation of several esters and an ether of 2-methyl-1,4-naphthohydroquinone is described.

The various derivatives were found to have different vitamin K potencies.

A discussion of the relationship between structure and vitamin K activity is presented.

(20) Doisy, MacCorquodale, Thayer, Binkley and McKee, Nat. Acad. Sci., Brown U. Meeting, October 23–25, 1939 [*Science*, **90**, 407 (1939)].

NEW BRUNSWICK, N. J. RECEIVED NOVEMBER 13, 1939

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Sulfanilamide Compounds. II. Arylidine Derivatives of N^1-Substituted Sulfanilamides

BY H. G. KOLLOFF AND JAMES H. HUNTER

In 1936 Buttle, Gray and Stephenson[1] reported N^1-phenylsulfanilamide to be as active against streptococcal infections in mice as sulfanilamide and on the basis of our preliminary tests N^1-(4-nitro)-phenylsulfanilamide[2] shows considerable activity against both streptococcal and pneumococcal infections. Since 1938 N^1-(2-pyridyl)-sulfanilamide[3] (Sulfapyridine, M. and B. 693) has attained a foremost position in the ranks of antibacterial agents.

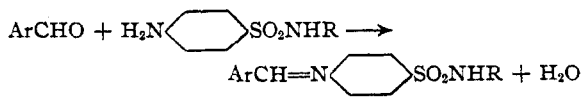
Goissedet, Despois, Galliot and Mayer[4] observed that some benzylidine sulfonamides were active and during the following year work along this line was continued by Gray, Buttle and Stephenson.[5]

The foregoing considerations suggested the preparation of a series of arylidine derivatives of the N^1-substituted sulfanilamides in order to ascertain in what respect their activity was generally affected by introducing an arylidine group.

For sake of comparison between structure and activity, the arylidine derivatives of the parent compound, sulfanilamide, have been included.

Sulfanilamide and sulfapyridine were obtained through commercial sources; N^1-phenylsulfanilamide was prepared according to Gelmo,[6] and for the preparation of N^1-(4-nitro)-phenylsulfanilamide the procedure of Webster and Powers[2] was successfully modified in that pyridine rather than dimethylaniline was used as a reaction medium.

The arylidine derivatives listed in Table I were prepared in 73% to practically quantitative yields by condensing the N^1-substituted sulfanilamides with the appropriate aldehyde in the absence of a solvent according to the equation



Purification of the new derivatives offered con-

(1) Buttle, Gray and Stephenson, *Lancet*, **1**, 1286 (1938).
(2) Webster and Powers, THIS JOURNAL, **60**, 1553 (1938).
(3) Whitby, *Lancet*, **1**, 1210 (1938).
(4) Goissedet, Despois, Galliot and Mayer, *Compt. rend. soc. biol.*, **121**, 1082 (1936).
(5) Gray, Buttle and Stephenson, *Biochem. J.*, **31**, 724 (1937).
(6) Gelmo, *J. prakt. Chem.*, [2], **77**, 374 (1908).

TABLE I

Substituted sulfanilamide[h]	Formula	M. p., °C. (uncor.)	N, % Calcd.	N, % Found	S, % Calcd.	S, % Found	Biologic activity[i] Strep.	Biologic activity[i] Pneumo.
Sulfanilamide	$C_6H_8N_2O_2S$						7.0	4.7
N^4-Benzylidine-	$C_{13}H_{12}N_2O_2S$[c,f]	176	10.77	10.60	12.30	12.83	7.0	4.7
N^4-(4-Methoxy)-benzylidine-	$C_{14}H_{14}N_2O_3S$[d,f]	192–3	9.66	9.99	11.03	11.68	4.7	4.5
N^4-(4-Dimethylamino)-benzylidine-	$C_{15}H_{17}N_3O_2S$[d,f]	226–7	13.84	14.39	10.55	11.01	7.0	2.5
N^1-Phenyl-	$C_{12}H_{12}N_2O_2S$[g]						3.8	0.3
N^4-Benzylidine-N^1-phenyl-	$C_{19}H_{16}N_2O_2S$[b]	175–75.5	8.28	8.34	9.47	9.61	2.8	1.0
N^4-(4-Methoxy)-benzylidine-N^1-phenyl-	$C_{20}H_{18}N_2O_3S$[a]	166	7.66	7.60	8.74	8.92	3.7	0.3
N^4-(4-Dimethylamino)-benzylidine-N^1-phenyl-	$C_{21}H_{21}N_3O_2S$[d]	231	11.08	10.92	8.44	8.65	4.5	0.5
N^1-(4-Nitro)-phenyl-	$C_{12}H_{11}N_3O_4S$[g]						2.3	3.0
N^4-Benzylidine-N^1-(4-nitro)-phenyl-	$C_{19}H_{15}N_3O_4S$[b]	192	11.02	11.25	8.40	8.61	7.0	3.3
N^4-(4-Methoxy)-benzylidine-N^1-(4-nitro)-phenyl-	$C_{20}H_{17}N_3O_5S$[c]	213.5	10.21	10.40	7.79	7.76	4.7	2.7
N^4-(4-Dimethylamino)-benzylidine-N^1-(4-nitro)-phenyl-	$C_{21}H_{20}N_4O_4S$[d]	231	13.20	13.42	7.54	7.49	5.2	5.2
N^1-(2-Pyridyl)-	$C_{11}H_{11}N_3O_2S$						6.8	7.0
N^4-Benzylidine-N^1-(2-pyridyl)-	$C_{18}H_{15}N_3O_2S$[e]	245–6	12.45	12.58	9.50	9.45	6.8	4.0
N^4-(4-Methoxy)-benzylidine-N^1-(2-pyridyl)-	$C_{19}H_{17}N_3O_3S$[e]	212–12.5	11.41	11.90	8.70	8.66	5.7	4.2
N^4-(4-Dimethylamino)-benzylidine-N^1-(2-pyridyl)-	$C_{20}H_{20}N_4O_2S$[e]	238.2–40	14.72	14.64	8.42	9.25	4.8	4.7

[a] From benzene. [b] From toluene. [c] From xylene. [d] From acetone–petroleum ether. [e] Washed with ether and acetone. [f] Prepared by Gray, Buttle and Stephenson.[5] [g] From dilute alcohol. [h] Nomenclature of Crossley, Northey and Hultquist, THIS JOURNAL, **60**, 2217 (1938). [i] Results expressed on basis of average survival time, according to the method of Whitby.[3]

siderable difficulty because of both their slight solubility and their instability. When possible, the products were crystallized from benzene and its homologs or from an acetone–petroleum ether mixture. In some cases the crude products were simply washed with suitable solvents for removal of unreacted starting materials.

These arylidine derivatives, particularly the benzylidine and 4-methoxybenzylidine derivatives, hydrolyze easily. Some underwent hydrolysis merely by crystallization from dilute alcohol; for this reason water was excluded from the crystallizing media. A few compounds, N^4-(4-methoxy)-benzylidine-N^1-phenylsulfanilamide, for instance, decomposed when crystallized from high-boiling solvents such as toluene or xylene.

We are indebted to Dr. F. A. Eberly and Mr. E. A. Gibson[7] for the biological data herein reported.

These preliminary studies indicate that in general introduction of an arylidine group results in a slight, but not particularly significant, decrease in both the antistreptococcal and antipneumococcal activity; the latter was diminished to a greater extent than the former. In every instance the toxicity was found to be lowered.

(7) A detailed report of the biological study of these and other derivatives will be published elsewhere.

Further biologic studies are being made on certain compounds of this series where preliminary indications warrant.

Work on similar arylidine derivatives is now in progress in these Laboratories.

Experimental

N^4-Arylidine-N^1-substituted Sulfanilamides.—The following procedure for the preparation of **N^4-(4-methoxy)-benzylidine-N^1-(4-nitro)-phenylsulfanilamide** is typical of that used in preparing the derivatives given in Table I. Seven and forty-eight hundredths grams (0.055 mole) of anisaldehyde (Eastman Kodak Company, "Practical") was added to 14.6 g. (0.05 mole) of N^1-(4-nitro)-phenylsulfanilamide[2] (m. p. 166.5–167.5°) contained in a 500-cc. round-bottom flask, and the latter immersed one-half its depth in an oil or metal bath at 140–150°. After about five minutes the mixture liquefied and the orange-colored melt was stirred mechanically for fifteen minutes, at which time it had partially resolidified. Stirring was discontinued and the mixture heated for an additional one and three-fourths hours. Lumps of material were occasionally crushed during the heating. The crude product was cooled and thoroughly washed with five 50-cc. portions of ether; yield, 20.1 g. (98% of the theoretical). Nine grams of the crude product was crystallized from 400 cc. of xylene using a little decolorizing charcoal; yield, 5.7 g., m. p. 211–211.5° (uncorr.).

Summary

A detailed procedure is given for a general method of preparing N^4-arylidine sulfanilamides;

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.

KALAMAZOO, MICH. RECEIVED OCTOBER 25, 1939

[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).