Some alkamine-ester hydrochlorides of 3,4-dimethoxycinnamic acid have been prepared.

A pharmacological study of the first member of each series of alkamine esters, indicates that they are slightly more active than procaine as local anesthetics, but are as toxic as cocaine. Hence, their usefulness is doubtful.

CHICAGO, ILLINOIS RECEIVED SEPTEMBER 26, 1940

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Sulfanilamide Compounds. V. Arylidine Derivatives of N^4-Acetyl-N^1-(4-amino)-phenyl-sulfanilamide and N^1-(4-Amino)-phenyl-sulfanilamide

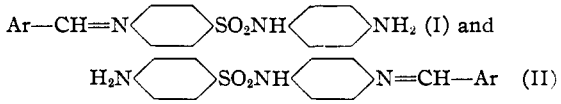
BY H. G. KOLLOFF AND JAMES H. HUNTER

In 1937 Whitby[1] reported that 4,4'-diaminobenzenesulfonanilide [N^1-(4-amino)-phenylsulfanilamide], in the form of its tartrate, was slightly more effective than sulfanilamide against experimental streptococcal infections in mice. In this respect Bauer and Rosenthal[2] found the free base to be approximately twice as active as sulfanilamide and of about the same order of toxicity; against experimental pneumococcal infections it was inferior to sulfanilamide. Gross, Cooper, and Lewis[3] concluded that N^1-(4-amino)-phenylsulfanilamide was as good as, or better than, sulfanilamide as an antistreptococcal agent in experimental infections while Webster and Powers[4] described its N^4-acetyl derivative as being moderately effective.

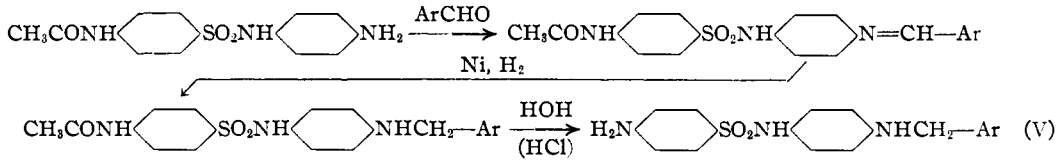
Consideration of these reports led us to extend our investigations[5,6] of N^4-arylidine derivatives of certain N^1-substituted sulfanilamides to the preparation and biologic evaluation of a number of mono- and di-arylidine derivatives of N^1-(4-amino)-phenylsulfanilamide as well as several N^4-acetyl-N^1-(4-arylidineamino)-phenylsulfanilamides.

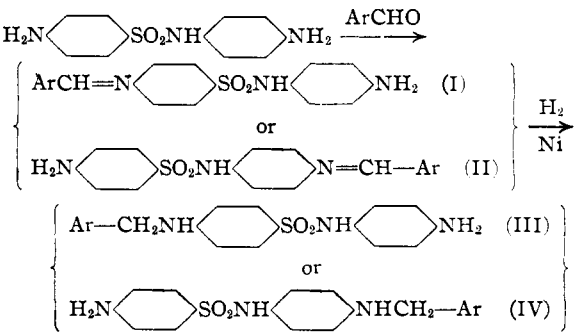
N^4-Acetyl-N^1-(4-amino)-phenylsulfanilamide and N^1-(4-amino)-phenylsulfanilamide were prepared by reduction of the corresponding nitro derivatives[4] according to the procedure of Webster and Powers.[4] When condensed with the appropriate aldehyde after the previously described[5] general procedure, these substituted sulfanilamides readily yielded their mono-arylidine derivatives. In a like manner the di-arylidine derivatives of N^1-(4-amino)-phenylsulfanilamide were obtained from the latter and slightly more than two equivalents of the requisite aldehyde. At present, all attempts to prepare the di-benzylidine derivative of this substituted sulfanilamide have resulted in the formation of the mono-benzylidine compound rather than the expected product.

It is apparent that interaction of molecular equivalents of an aldehyde and N^1-(4-amino)-phenylsulfanilamide can yield a mono-arylidine derivative of two possible structures, *i. e.*



We have shown that compounds 8 and 9 of Table I have the type II structure by means of the following scheme





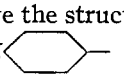
If (I) is the correct structural type, then com-

(1) Whitby, *Lancet*, **1**, 1518 (1937).
(2) Bauer and Rosenthal, *Pub. Health Reports*, **53**, 40 (1938).
(3) Gross, Cooper and Lewis, *Proc. Soc. Exptl. Biol. Med.*, **38**, 375 (1938).
(4) Webster and Powers, THIS JOURNAL, **60**, 1553 (1938).
(5) Kolloff and Hunter, *ibid.*, **62**, 158 (1940).
(6) Kolloff and Hunter, *ibid.*, **62**, 1647 (1940).

TABLE I

Number	Substituted sulfanilamide[a]	M. p., °C. (uncor.)	Formula	Nitrogen, % Calcd.	Found
1	Sulfanilamide	165	$C_6H_8N_2O_2S$[b]	16.28	16.30
2	N^4-Acetyl-N^1-(4-amino)-phenyl-	230–231	$C_{14}H_{16}N_3O_3S$[c]	13.78	13.96
3	N^1-(4-Amino)-phenyl-	155	$C_{12}H_{13}N_3O_2S$[c]	15.97	15.52
4	N^4-Acetyl-N^1-(4-benzylidineamino)-phenyl-	206.5–207	$C_{21}H_{19}N_3O_3S$[d]	10.69	10.88
5	N^4-Acetyl-N^1-(4-(*p*-methoxy)-benzylidineamino)-phenyl-	246.5–247.5	$C_{22}H_{21}N_3O_4S$[d]	9.93	9.82
6	N^4-Acetyl-N^1-(4-(*p*-dimethylamino)-benzylidineamino)-phenyl-	242	$C_{23}H_{24}N_4O_3S$[e]	12.85	12.91
7	N^4-Acetyl-N^1-(4-(*p*-nitro)-benzylidineamino)-phenyl-	255.5–257.5	$C_{21}H_{18}N_4O_5S$[e]	12.78	12.98
8	N^1-(4-Benzylidineamino)-phenyl-	225	$C_{19}H_{17}N_3O_2S$[e]	11.96	11.18
9	N^1-(4-(*p*-Methoxy)-benzylidineamino)-phenyl-	204–205	$C_{20}H_{19}N_3O_3S$[e]	11.02	10.96
10	N^1-(4-(*p*-Dimethylamino)-benzylidineamino)-phenyl-	214–215	$C_{21}H_{22}N_4O_2S$[e]	14.21	14.74
11	N^1-(4-(*p*-Nitro)-benzylidineamino)-phenyl-	223–224	$C_{19}H_{16}N_4O_4S$[e]	14.13	14.60
12	N^4-(*p*-Methoxy)-benzylidine-N^1-(4-(*p*-methoxy)-benzylidine-amino)-phenyl-	183–184	$C_{28}H_{25}N_3O_4S$[f]	8.42	8.95
13	N^4-(*p*-Dimethylamino)-benzylidine-N^1-(4-(*p*-dimethylamino)-(benzylidineamino)-phenyl-	238.2	$C_{30}H_{31}N_5O_2S$[f]	13.32	13.11
14	N^4-(*p*-Nitro)-benzylidine-N^1-(4-(*p*-nitro)-benzylidineamino)-phenyl-	230	$C_{26}H_{19}N_5O_6S$[g]	13.22	13.32

[a] Nomenclature of Crossley, Northey and Hultquist, THIS JOURNAL, 60, 2217 (1938). [b] From water. [c] From dilute alcohol. [d] From abs. alcohol. [e] From acetone–petroleum ether. [f] From xylene. [g] From chloroform and Skelly Solvent "B."

pounds (III) and (V) should, among other dissimilarities, have different melting points or at least should exhibit a lowered mixed melting point. On the other hand, if type (II) is correct, compounds (IV) and (V) should be identical. We have found that when Ar equals  and  , the specific compounds corresponding to types (IV) and (V) have been obtained, and have proved identical in every respect. So far we have been unable to prove the structure of those in which Ar equals  and  by this procedure. However, on the basis of the close similarity among these four compounds we are, for the present, assuming that these latter two mono-arylidine derivatives likewise belong to the type (II) class.

As observed in earlier instances,[5,6] one of the characteristics of the arylidine derivatives is their ease of hydrolytic decomposition, thus imposing the necessity of avoiding water in their preparation and purification. Considerable loss was encountered during purification owing to sparing solubility and poor recovery.

The biologic activity of the arylidine derivatives will be published elsewhere at a future date.

Experimental

The preparation of N^1-(4-benzylidineamino)-phenylsulfanilamide will illustrate the general procedure by which the arylidine derivatives listed in Table I were prepared, and proof of its structure will exemplify the method used to locate the position of the arylidine group in compounds 8 and 9.

N^1-(4-Benzylidineamino)-phenylsulfanilamide.—A mixture of 5.26 g. (0.02 mole) of N^1-(4-amino)-phenylsulfanilamide and 2.33 g. (0.022 mole, 2.22 cc.) of benzaldehyde, contained in a 200-cc. round-bottomed flask was heated in a bath at 140° for one and one-quarter hours with occasional stirring. When cool, the benzal derivative was finely ground and repeatedly washed with ether; yield, 6.8 g.; m. p. 224–225° (uncor.). Recrystallization from an acetone–petroleum ether mixture gave a flesh-colored product melting at 225° (uncor.).

Proof of the Structure of N^1-(4-Benzylidineamino)-phenylsulfanilamide.—Nine and five-tenths grams (0.03 mole) of the crude N^1-(4-benzylidineamino)-phenylsulfanilamide was dissolved in 150 cc. of hot dioxane (Eastman Kodak Co. "Histological"), boiled briefly with a little decolorizing charcoal, filtered, and washed with 50 cc. of dioxane. Four grams of Raney nickel[7] was added to the filtrate and the mixture hydrogenated at approximately three atmospheres of hydrogen and 50–58°. After absorption of hydrogen had ceased, the mixture was filtered, washed with a little dioxane, and the filtrate diluted with 500 cc. of water. When cold, the precipitate was collected, washed with water, and air-dried; yield, 5.5 g. (52%). Repeated crystallizations from alcohol gave white needles melting constantly at 175–175.5° (uncor.).

A mixture of approximately equal parts of these crystals and N^1-(4-benzylamino)-phenylsulfanilamide,[6] m. p. 174–175° (uncor.), melted at 174–175° (uncor.). Since these compounds are identical, it follows that the arylidine group in the above monobenzylidine derivative of N^1-(4-amino)-phenylsulfanilamide must be attached to the nitrogen of the N^1-(4-amino) group rather than that of the N^4-amino group.

(7) Covert and Adkins, THIS JOURNAL, 54, 4116 (1932).

Summary

A series of arylidine derivatives of N^4-acetyl-N^1-(4-amino)-phenylsulfanilamide and N^1-(4-amino)-phenylsulfanilamide have been prepared and their antibacterial efficacy against β-hemolytic streptococci and pneumococci will be reported elsewhere.

KALAMAZOO, MICHIGAN RECEIVED SEPTEMBER 9, 1940

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

Chain Reactions in Aqueous Solutions Containing Ozone, Hydrogen Peroxide and Acid

BY HENRY TAUBE[1] AND WILLIAM C. BRAY

In a continuation of the work of Rothmund and Burgstaller[1a,2] on the rate of interaction of ozone and hydrogen peroxide in acidic aqueous solutions, the two reactions that occur

$$H_2O_2 + O_3 = H_2O + 2O_2 \quad (A)$$
$$2O_3 = 3O_2 \quad (B)$$

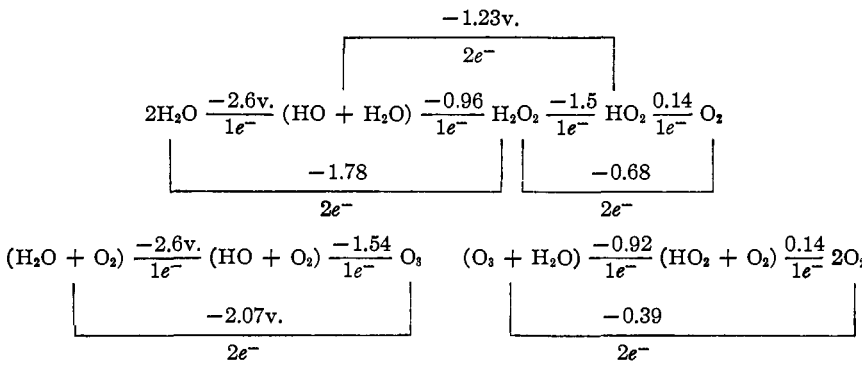
have been proved to be chain reactions. The effect of adding various inhibitors and catalysts has been investigated and the kinetics in the presence of one inhibitor, chloride ion, has been studied in detail. The only mechanism which we have found to correlate all the results of the present work requires the presence of the free radicals *hydroxyl* and *perhydroxyl* as intermediates in these homogeneous reactions.

A chain mechanism involving both these substances, HO and HO_2, has been suggested by a number of investigators to explain the decomposition of hydrogen peroxide solutions under various conditions, *e. g.*, in the presence of enzymes,[3] at certain surfaces,[3] at metallic cathodes,[4] during the oxidation of ferrous ion[5] and in the presence of light.[6] It is to be noted that the decomposition occurs at surfaces in nearly all these instances, including the photodecomposition.[7]

Weiss[8] has advocated a similar mechanism for the OH^- catalyzed decomposition of ozone, and has used both mechanisms to explain the results of Rothmund and Burgstaller[1a]; but the experimental data are not extensive enough to prove or disprove chain mechanisms for these reactions.

Approximate values of the standard potentials of the various one and two electron couples in the oxygen system of compounds are presented below in the form used by Latimer[9] for other systems. Except in the case of the HO couples, these energy data are in agreement with the values selected by Latimer and by Bray.[2] The heat of dissociation of HO has now been decreased from about 116 kcal. to 104, a value which has been accepted by many investigators.[10]

STANDARD POTENTIALS IN ACID SOLUTIONS AT 25°



These charts show clearly the relation of HO and HO_2 to the better known oxidation states of oxygen, and facilitate the calculations of the standard free energy changes for reactions of these radicals.

(1) Abraham Rosenberg Research Fellow, 1939–40.

(1a) Rothmund and Burgstaller, *Monatsh.*, **38**, 295–303 (1917).

(2) Bray, THIS JOURNAL, **60**, 82–87 (1938).

(3) Haber and Willstätter, *Ber.*, **64**, 2855 (1931).

(4) Weiss, *Trans. Faraday Soc.*, **31**, 1547–1557 (1934).

(5) Haber and Weiss, *Proc. Roy. Soc.* (London), **A147**, 332–351 (1934). A non-chain mechanism has been suggested by Bray and Gorin, THIS JOURNAL, **54**, 2124–2125 (1932).

(6) Kornfeld, *Z. physik. Chem.*, **B29**, 205–214 (1935). This article contains references to earlier work on the photodecomposition.

(7) Rice, THIS JOURNAL, **48**, 2106 (1926).

(8) Weiss, *Trans. Faraday Soc.*, **31**, 668–681 (1935).

(9) Latimer, "Oxidation Potentials," Prentice-Hall, Inc., New York, N. Y., 1938.

(10) (a) Bonhoeffer and Reichert, *Z. physik. Chem.*, **A139**, 75–97 (1929); (b) Herzberg, *ibid.*, **B10**, 189–192 (1930); (c) Bates and Lavin, THIS JOURNAL, **55**, 81 (1933); (d) Mecke, *Trans. Faraday Soc.*, **30**, 209 (1934).