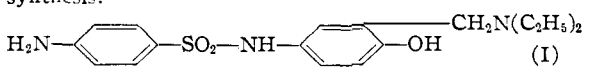
NEW COMPOUNDS

α-Diethylamino-4-sulfanilamido-o-cresol Hydrochloride

Because of the promising activity of both the sulfonamides[1] and the Mannich phenols[2] in malaria, a substance (I) which could be classified chemically both as a sulfonamide and a Mannich phenol was considered worthy of synthesis.



(I)

The proposed drug was found to be inactive in avian malaria by Dr. R. J. Porter, of the University of Michigan. It was also ineffective as an internal antiseptic in the tests by Dr. O. M. Gruhzit, of This Laboratory.

Experimental.—Hydrolysis of 23.6 g. (0.1 mole) of 4-acetamido-α-diethylamino-o-cresol was effected by treatment with 50 ml. of 20% hydrochloric acid at refluxing temperature.[2] The free base was liberated from solution by the addition of an excess of concentrated ammonia. To prevent decomposition of the 4-amino-α-diethylamino-o-cresol, the mixture was hurriedly extracted with ether. The combined extracts were washed with water, dried over magnesium sulfate and then treated with an acetone suspension of 23.3 g. (0.1 mole) of p-acetamidobenzenesulfonyl chloride. The mixture was heated on a steam-bath until the volatile solvent had been removed. It was not possible at this stage to isolate a solid product, so the residue was heated under reflux for a half hour with 250 ml. of 5% hydrochloric acid. The *p*H was adjusted to about 5 through the addition of a concentrated solution of sodium hydroxide whereupon α-diethylamino-4-sulfanilamido-o-cresol hydrochloride precipitated; yield 15 g. (39%); m. p. 234–236° (dec.). Recrystallized from boiling water containing boneblack and washed with acetone, the product became white; m. p. 236–237° (dec.).

Anal. Calcd. for $C_{17}H_{23}N_3O_3S\cdot HCl$: C, 52.91; H, 6.27. Found: C, 53.02; H, 6.45.

RESEARCH LABORATORIES
PARKE, DAVIS & COMPANY
DETROIT 32, MICHIGAN J. H. BURCKHALTER[3]

RECEIVED AUGUST 20, 1949

(1) Coggeshall, *J. Exp. Med.*, **71**, 13 (1939).

(2) Burckhalter, Tendick, Jones, E., Jones, P., Holcomb and Rawlins, THIS JOURNAL, **70**, 1363 (1948).

(3) Present address: Department of Pharmaceutical Chemistry, University of Kansas School of Pharmacy, Lawrence, Kansas.

Some New Substituted β-Nitrostyrenes[1]

In the course of other work several new substituted β-nitrostyrene derivatives have been prepared and characterized. These compounds were prepared essentially by the method outlined in Organic Syntheses[2] for the preparation of β-nitrostyrene in which the appropriate benzaldehyde was condensed with nitromethane. The compounds were characterized by melting point determination and nitrogen analysis. The nitrogen analyses were carried out using the Friedrich method as described by Clark[3] with slight modifications. The analyses and physical properties of these compounds are reported in Table I.

In addition, 3-chloro-5-nitrobenzaldehyde has not previously been reported; however, the corresponding benzoic acid has been reported by Blanksma.[4] This aldehyde was prepared by chlorination of *m*-nitro benzaldehyde in chloroform solution, using ferric chloride and iron as carrier. It was identified by qualitative elemental analysis and oxidation to the acid, this acid being identical with that reported by Blanksma.[4] It was subsequently converted to the β-nitrostyrene as reported above.

TABLE I

β-Nitrostyrene	Formula	M. p., °C.	Nitrogen, % Calcd.	Found
2,4-Dichloro-	$C_8H_5O_2Cl_2N$	110	6.42	6.38
3,4-Dichloro-	$C_8H_5O_2Cl_2N$	75	6.42	6.33
2-Chloro-5-nitro-	$C_8H_5O_4ClN_2$	142	12.25	12.21
3-Chloro-5-nitro	$C_8H_5O_4ClN_2$	126	12.25	12.30
2,3-Dimethoxy	$C_{10}H_{11}O_4N$	86.5	6.69	6.66

(1) Taken from a thesis presented by Mary E. Carter to the Graduate School, University of Florida, in partial fulfillment of the requirements for the degree of Master of Science, September, 1949.

(2) D. E. Worrall, "Organic Syntheses," Col. Vol. I, J. Wiley and Sons, Inc., New York, N. Y., 1941, p. 413.

(3) E. P. Clark, "Semimicro Quantitative Organic Analysis," Academic Press, Inc., New York, N. Y., 1943, p. 37–43.

(4) Blanksma, *Chem. Zentr.*, **85**, I, 538 (1914).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF FLORIDA GEORGE B. BUTLER
GAINESVILLE, FLORIDA MARY E. CARTER

RECEIVED JANUARY 9, 1950

Ephedrine-dibenzofuran-2-sulfonate

Ephedrine-dibenzofuran-2-sulfonate.—Ephedrine hydrochloride (6.05 g.) dissolved in 100 ml. of distilled water was added to a solution of 7.47 g. of dibenzofuran-2-sulfonic acid[1] in 100 ml. of distilled water at room temperature. An immediate turbidity which deepened in about five minutes to give a heavy white precipitate resulted. The precipitate was washed free of chlorides and dried under vacuum; yield 6.5 g., m. p. 196–198°. The compound is insoluble in water, ether, chloroform, benzene, dioxane, 10% sodium carbonate solution and dilute hydrochloric acid. It is slowly soluble in absolute ethanol.

Anal. Calcd. for $C_{22}H_{23}NO_5S$: N, 3.38; S, 7.75. Found: N, 3.37; S, 7.75.

The pharmacological properties of this compound will be reported elsewhere.

(1) Gilman, Smith and Oatfield, THIS JOURNAL, **56**, 1412 (1934).

SCHOOL OF PHARMACY
NORTH DAKOTA AGRICULTURAL COLLEGE
FARGO, NORTH DAKOTA CLIFTON E. MILLER

RECEIVED DECEMBER 27, 1949

p-N-Dialkylaminoazobenzenesulfonamides[1]

Several *p*-N-dialkylaminoazobenzenesulfonamides have been described in the literature[2] under the erroneous general name of diazoaminosulfanilamides. Though they are reported to have slight chemotherapeutic action, their unusual structure prompted a brief study in this laboratory of several simple derivatives. The derivatives (Table I) were easily made, with the exception of Ia, by diazotization of sulfanilamide or sulfadiazine and coupling with the appropriate secondary amine according to the method of Elks and Hey.[3] Coupling with primary amines yielded unstable derivatives which sometimes decomposed violently.

The chemical properties of all derivatives were similar, though Ia was of more therapeutic interest because of its water solubility. They can best be considered as precursors of the diazonium salts of sulfanilamide or sulfa-

(1) This research was supported by a grant from the Carnegie Foundation and the Natural Science Research Fund of Vanderbilt University.

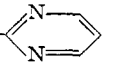
(2) Northey, "Sulfonamides and Allied Compounds," Monograph 106, p. 49, Reinhold Publishing Corp., New York, N. Y., 1948.

(3) Elks and Hey, *J. Chem. Soc.*, 441 (1943).

TABLE I

p-N-DIALKYLAMINOAZOBENZENESULFONAMIDES, *p*-$R_2N—N{=}N—C_6H_4SO_2NH_2$

Compound	R_2	Yield, %	M. p.[a]	Hydrolysis equiv. Calcd.	Hydrolysis equiv. Found	Nitrogen, % Calcd.	Nitrogen, % Found
Ia	$(HOCH_2CH_2)_2$	26	119–119.8	288	287	19.4	19.4
Ib	$(CH_3CH_2)_2$	74	132–133	258	259	21.7	21.7
Ic	$(CH_2)_5$ Piperidino	80	153–154	268	269	20.8	20.9
Id	$(CH_2CH_2O—CH_2CH_2)$ Morpholino	80	176–177	270	271.5	20.7	20.7

2-(*p*-N-DIALKYLAMINOAZOSULFANILAMIDO)-PYRIMIDINES, *p*-$R_2N—N{=}N—C_6H_4SO_2NH$— 

IIb	$(CH_3CH_2)_2$	71	205° (dec.)	...	...	25.1	25.2
IIc	$(CH_2)_5$	71	235° (dec.)	...	...	24.3	24.0

[a] Melting points were taken with a partial immersion thermometer (ASTM specification).

diazine in their chemical reactions. In water or dilute alkali they were quite stable at room temperature but somewhat thermolabile. In acid solution they slowly evolved nitrogen with the formation of the appropriate dialkylamine and an insoluble, amorphous dye similar in characteristics to that isolated by Kleiderer and Shonle.[4]

The anti-bacterial qualities of Ia were tested by the geometric series dilution method and the paper disc method on several standard organisms. The results indicated that the antibacterial activity of Ia was slight in comparison with sulfanilamide in non-buffered solutions but comparable in buffered solutions.

A. General Method of Preparation.—A 1-liter beaker, equipped with mechanical stirrer and surrounded by an ice–salt-bath, was charged with 40 g. (0.23 mole) of sulfanilamide (Eastman Kodak Co.), 100 ml. of concentrated hydrochloric acid and 400 ml. of water. When temperature of the contents had reached 0–5°, a solution of 16.6 g. (0.24 mole) of sodium nitrite in 50 ml. of water was added dropwise until diazotization was complete (starch–iodide paper). The clear, yellow solution was cautiously neutralized by dropwise addition of 22 g. (0.3 mole) of diethylamine (or other secondary amines) followed by moderately fast addition of 136 g. (1.0 mole) of sodium acetate trihydrate dissolved in water. The temperature was maintained at 5° or below during the entire operation. The appearance of a flocculent, orange precipitate at any stage indicated hydrolysis and/or coupling of the diazonium compound with the hydrolysis product or free sulfanilamide. The desired compound (Ib, c, d, IIb, c) precipitated during addition of sodium acetate as a colorless or light-brown, easily filterable solid. The product was washed thoroughly with water and recrystallized from water–alcohol mixtures.

B. Preparation of *p*-N-Diethanolaminoazobenzenesulfonamide (Ia).—Ia was more difficult to prepare because of its solubility in water and acetic acid. The following modification was the best of many attempted: the diazotization was carried out as in Part A. The cold, stirred solution was then neutralized carefully with 84 g. (1.0 mole) of solid sodium bicarbonate or until carbon dioxide evolution was no longer evident. The solution, after neutralization, was yellow to orange in color and contained an appreciable amount of flocculent precipitate. It was then poured in a thin stream into a previously cooled (0–5°) and stirred solution of 32.6 g. (0.31 mole) of diethanolamine (Eastman Kodak Co., redistilled) in 150 ml. of water. The solution turned orange-red and deposited a red gum which was removed mechanically. After addition was complete, the solution was filtered to remove any other precipitate (the filtration was difficult if the amount of precipitate was appreciable) and allowed to cool overnight in an ice-box. The light brown or cream-colored needles were separated by filtration and recrystallized from water, m. p. 119–119.8°, 11 g. (28%). Concentration of the mother liquor under reduced pressure yielded a second crop of 5–10 g. of less pure compound. Continuous extraction with ethyl acetate could be used in place of the concentration process.

C. Hydrolysis of Dialkylaminoazobenzenesulfonamides.—An accurately weighed sample (0.2–0.3 g.) was suspended or dissolved in a solution of 20 ml. of alcohol, 20 ml. of water and 10 ml. of standard 0.1 *N* acid. The solution turned yellow and finally deposited a flocculent, brown precipitate. The hydrolysis was complete in six hours at 70° or several days at room temperature. By back-titration with standard 0.1 *N* alkali using a glass electrode, the molecular weight of the azo compound could be determined from the secondary amine hydrochloride equivalent.

DEPARTMENT OF CHEMISTRY
VANDERBILT UNIVERSITY
NASHVILLE, TENN.

D. E. PEARSON
W. C. HOLLAND
H. P. MIDGETT

RECEIVED NOVEMBER 21, 1949

(4) Kleiderer and Shonle, U. S. Patent 2,117,251, May 10, 1938; *C. A.*, **32**, 5162 (1938).