tablets resulted in recovery values of 96.4 and 98.2% EEME by gas chromatography, while analysis by thin-layer chromatography led to a 95.5% recovery value. The above tablets were prepared by adding levels of EEME (from a spectrophotometrically standardized stock solution of EEME in methanol) to an appropriate amount of an excipient mixture containing either CDAP or ENT. After drying, the mixture was tableted and assayed. The excipients used were cornstarch, lactose, and magnesium stearate.

The results of analyses of synthetic mixtures of ENT plus EEME or CDAP plus EEME are shown in Table II, an indication that cyclohexane extracts EEME quantitatively in the presence of either CDAP or ENT.

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4,4′-Dibromodiphenyldisulfimide as a Reagent for the Identification of Organic Bases I. Preparation of the Reagent and Derivatives of Some Antihistamines

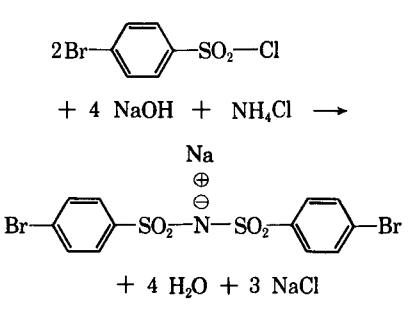
By EDWARD A. JULIAN* and ELMER M. PLEIN

A procedure for the synthesis of a new reagent, 4,4′-dibromodiphenyldisulfimide, which reacts with all classes of amines and produces crystalline derivatives suitable for the determination of various physical properties of value in analytical work, is reported. Melting points for the 4,4′-dibromodiphenyldisulfimide derivatives of 21 antihistamines are also presented.

DISULFIMIDE compounds ($R\text{-}SO_2\text{-}NH\text{-}SO_2\text{-}R$) have been suggested as reagents for the preparation of derivatives of some medicinal amines (1, 2). It is the purpose of this paper to report the synthesis of a new disulfimide reagent, 4,4′-dibromodiphenyldisulfimide, which reacts with primary, secondary, and tertiary amines and to report on the use of this reagent in the preparation of some medicinal amine derivatives of antihistamine drugs.

The synthesis of disulfimide compounds and their use in preparing derivatives were reported as early as 1854 (3). Most of the disulfimides synthesized (4–6) have been aromatics with halide substitutions in positions 3 and 4. Procedures reported in the literature for the preparation of disulfimide compounds (7, 8) were not applicable for the preparation of 4,4′-dibromodiphenyldisulfimide, so a new method was devised.

Two moles of *p*-bromobenzenesulfonyl chloride was reacted with ammonium chloride and sodium hydroxide to give sodium-4,4′-dibromodiphenyldisulfimide.



The sodium salt of the reagent can be treated with acid for conversion to the acid imide.

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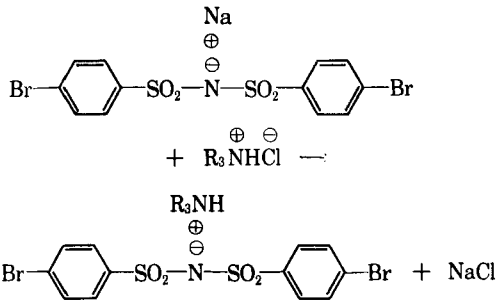
Amine derivatives were prepared from the sodium salt of the reagent and acid salts of the amines according to the following reaction



EXPERIMENTAL

Preparation of Sodium-4,4′-dibromodiphenyldisulfimide.—In a 1-L. three-necked flask fitted with a stirrer, a dropping funnel and a thermometer was placed a solution of 100 Gm. (0.39 mole) of *p*-bromobenzenesulfonyl chloride (Eastman Kodak Co.) in 450 ml. of dioxane and 10.35 Gm. (0.195 mole) of ammonium chloride. Stirring was begun, and the temperature of the mixture was reduced to 10° by immersing the flask in an ice bath. Approximately 62.8 ml. of 50% w/v sodium hydroxide solution (0.78 mole) was slowly added by means of the dropping funnel. The temperature of the mixture gradually rose to 20–25° but was not allowed to go higher. The addition of sodium hydroxide solution was continued until the pH of the reaction mixture reached 8 (determined with pHydrion paper).

The precipitated product was filtered off by means of a Büchner funnel and washed free of alkali with water. The product was then dissolved in a mixture of water and dioxane (1:4) at 65° on a water bath, and the solution was filtered. The solution was allowed to cool and the sodium salt of 4,4′-dibromodiphenyldisulfimide crystallized in 40% of theoretical yield (0.195 mole, 93.2 Gm.). Solubility of the product was determined as 1:200 in water at room temperature and 1:50 in water at 65°.

Anal.—Calcd. for $C_{12}H_8O_4Br_2NaNS_2$: N, 2.94%. Found: N, 2.97% by the micro-Dumas method.

The free acid form of the reagent was obtained by adding 100 ml. of concentrated hydrochloric acid to the warm (65°) solution of product in water–dioxane mixture described above, filtering the solution and allowing the acid imide to crystallize as the solution cooled. The yield averaged 40%, the compound melted at 232–233° and had a water solubility of 1:500 at 65°.

Anal.—Calcd. for $C_{12}H_9Br_2NS_2O_4$: N, 3.08%. Found: N, 3.13% by the micro-Dumas method.

Preparation of 4,4′-Dibromodiphenyldisulfimide Derivatives.—Successively, 0.3 Gm. of sodium 4,4′-dibromodiphenyldisulfimide and 0.25 Gm. of the amine salt were dissolved in a hot ethanol–water mixture (1:1). The derivative precipitated out within minutes to several hours and was then recrystallized from a minimal amount of methanol–*n*-amyl acetate solution (1:1). The compounds were analyzed for nitrogen by the micro-Dumas method, their melting points were determined by means of a Kofler micro hot stage (Table I).

TABLE I.—ANALYTICAL DATA AND MICROMELTING POINTS OF 4,4′-DIBROMODIPHENYLDISULFIMIDE DERIVATIVES OF SOME ANTIHISTAMINES

4,4′-Dibromodiphenyldisulfimide Derivative	Micro M.p.,[a] °C.	N, % Calcd.	N, % Found[b]
Antazoline	146–147	7.78	7.56
Bromdiphenhydramine	124	3.55	3.72
Brompheniramine	138	5.43	5.22
Chlorcyclizine	168	5.56	5.78
Chlorothen	99	7.46	7.43
Chlorpheniramine	132–133	5.76	5.56
Clemizole	127–128	7.18	7.09
Cyclizine	165	5.82	5.77
Dexbrompheniramine	128–129	5.43	5.32
Diphenhydramine	115–117	3.95	4.03
Diphenylpyraline	147	3.80	3.86
Doxylamine	145	5.80	5.63
Meclizine	189	4.97	4.90
Methapyrilene	142	7.82	7.73
Phenyltoloxamine	107	3.94	3.72
Pyrrobutamine	138–139	3.66	3.91
Sandostene	150	5.67	5.84
Thenyldiamine	117–118	7.82	7.70
Thonzylamine	117–118	9.19	9.36
Tripelennamine	144	7.89	7.90
Zolamine	129	7.52	7.20
4,4′-Dibromodiphenyldisulfimide	232–233	3.08	3.13
Sodium 4,4′-dibromodiphenyldisulfimide	...	2.94	2.97

[a] The Kofler micromelting point hot stage (30–350° C.), A. H. Thomas and Co., Philadelphia, Pa., was used. [b] Analyses were determined by the micro-Dumas method.

DISCUSSION AND RESULTS

In synthesizing the reagent, the mixture was cooled to prevent the reaction from becoming too volatile. The sodium salt of the reagent can be converted to the acid imide, which has a melting point of 232–233°, but another compound, 4-bromobenzenesulfonamide, with a melting point of 162–166°, has appeared, perhaps because some hydrolysis has occurred during synthesis of the reagent.

Analytical data (for nitrogen) and the micromelting points of 4,4′-dibromodiphenyldisulfimide derivatives of some medicinal amines of the antihistamine group are listed in Table I. With most antihistamines studied, crystalline disulfimide derivatives with sharp melting points were obtained. Satisfactory derivatives were not obtained for buclizine, carbinoxamine, dexchlorpheniramine, isothipendyl, methaphenilene, orphenadrine, pheniramine, promethazine, pyrilamine, rotoxamine, and triprolidine because they oiled out—or for dimethindene and phenindamine, which, upon analysis for nitrogen, did not meet the standards.

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