concd. hydrochloric acid, cooling precipitated the dihydrochloride quantitatively. Recrystallization from water to which a little hydrochloric acid had been added gave a product melting at 322–323°.

Anal.[13] Calcd. for $C_{12}H_{12}OCl_2N_2$: N, 10.32. Found: N, 10.50.

The free amine, obtained by addition of concd. ammonium hydroxide to the solid dihydrochloride, melted at 86–87°, and was too sensitive to air oxidation to be recrystallized by ordinary procedures.

Nitration of 1-Nitro-4-acetaminodibenzofuran.—To a suspension of 0.1 g. of 1-nitro-4-acetaminodibenzofuran in 8 ml. of acetic anhydride cooled to −10° was added dropwise with stirring 0.5 ml. of fuming nitric acid (sp. gr., 1.49). The compound melted at 286–288° after recrystallization from glacial acetic acid; and further recrystallization from acetone and then from glacial acetic acid raised the melting point to 288°.

Anal. Calcd. for $C_{14}H_9O_6N_3$: N, 13.35. Found: N, 13.46.

This compound is different from the nitration product of 3-nitro-4-acetaminodibenzofuran, and is probably 1,7-dinitro-4-acetaminodibenzofuran.

Nitration of 3-Nitro-4-acetaminodibenzofuran.—The 3-nitro-4-acetaminodibenzofuran (0.1 g.) was nitrated under the conditions described above, with the exception that twice as much nitric acid was used. When only 0.5 ml. of fuming nitric acid was used, the dinitro compound was difficult to purify, and the yield was very low. In this reaction no product separated, and the reaction mixture was poured on cracked ice. The dinitro-acetamino compound melted at 277–278° after two crystallizations from glacial acetic acid.

Anal. Calcd. for $C_{14}H_9O_6N_3$: N, 13.35. Found: N, 13.42.

A mixed m. p. determination with the 1,7(?)-dinitro-4-acetaminodibenzofuran resulted in a depression to 259°.

Direct nitration of 4-acetaminodibenzofuran gave a product which melted at 260–261° after recrystallization from glacial acetic acid and acetone. Since a further recrystallization from acetone did not change the melting point, the product was assumed to be pure and was analyzed. Its analysis (N, 13.50) checked the theoretical value for a dinitro-4-acetaminodibenzofuran. Later, however, it was found that a recrystallization (with great loss) from a large volume of toluene raised the melting point to 284°, and a mixed m. p. determination with 1,7(?)-dinitro-4-acetaminodibenzofuran was 287°. The impurity in the product melting at 260–261° was probably another dinitro compound, possibly 3,8(?)-dinitro-4-acetaminodibenzofuran. It seems reasonable to conclude that the second nitro group entered the unsubstituted nucleus in these reactions.

Summary

1-Nitrodibenzofuran, prepared by nitration of 4-acetaminodibenzofuran followed by de-acetylation and de-amination, has been shown to differ from the supposed 1-nitrodibenzofuran obtained by direct nitration of dibenzofuran. The structure of the 1-nitro-4-acetaminodibenzofuran was established by a series of transformations relating the compound to the known 1-bromo-4-acetaminodibenzofuran.

AMES, IOWA RECEIVED AUGUST 18, 1944

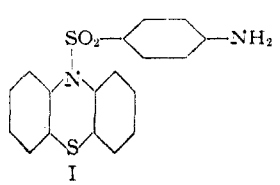
(13) The authors are grateful to H. B. Willis for this analysis.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

Phenothiazine Chemistry. I. 10-Sulfanilylphenothiazine and Other 10-Substituted Phenothiazine Derivatives[1]

BY HERBERT I. BERNSTEIN AND LEWIS R. ROTHSTEIN[2]

It was of interest to prepare certain 10-substituted phenothiazines for antimalarial testing. This was based on the fact that structural similarities exist between atabrine, *p,p'*-bis-(acetylamino)-diphenylsulfone, methylene blue, phenothiazine, and phenothiazine sulfone. The first three compounds, respectively,[3a,b,c] have previously been shown to possess antimalarial properties.



I

10-Sulfanilylphenothiazine (I) was prepared by the condensation of *p*-acetylaminobenzenesulfonyl chloride and phenothiazine in pyridine, followed by hydrolysis of the resulting 10-*p*-acetylaminobenzenesulfonylphenothiazine with alkali. The hydrochloride of I was prepared by passing dry hydrogen chloride gas into an ethereal solution of I, and its composition established by neutral equivalent determination.

The compound I was also prepared in another manner. This involved the condensation of *p*-nitrobenzenesulfonyl chloride with phenothiazine followed by reduction of the resulting 10-*p*-nitrobenzenesulfonylphenothiazine. The compound so obtained readily reacted with acetic anhydride to form the acetylamino compound described above.

10-*p*-Toluenesulfonylphenothiazine was prepared from the corresponding acid chloride and phenothiazine by a condensation similar to those described above.

10-Methyl and 10-ethylphenothiazine had been prepared by Bernthsen[4] by heating phenothiazine and the necessary halide in the corresponding al-

(1) Presented before the Organic Division of the American Chemical Society, April 5, 1944.

(2) Submitted by L. R. Rothstein in partial fulfillment for the degree of Master of Science.

(3) (a) Goodman and Gilman, "Pharmacological Basis of Therapeutics," The Macmillan Co., N. Y., 1941, 918–921; (b) Marshall, *et al.*, *J. Pharm. Exptl. Therapy*, **75**, 89 (1942); (c) Fourneau, *et al.*, *Ann. inst. Pasteur*, **46**, 514–541 (1942).

(4) Bernthsen, *Ann.*, **230**, 88–94 (1885).

cohol at 100° in a sealed tube.[5] It was found that the halide was unnecessary, and only a little hydrogen chloride need be passed into the alcoholic solution of phenothiazine, and the sealed tube heated to 130–150°. The 10-methyl derivative was thus prepared in 60% yield, the ethyl in only 35%, and the higher alcohols would not react at all. Olefin and ether formation from the alcohols were often detected.

Preliminary investigation seems to indicate that the ease of oxidation of 10-substituted phenothiazines to the corresponding sulfones is dependent upon the nature of the 10-substituent. Bernthsen[6] has demonstrated that while 10-methylphenothiazine is readily converted to the sulfone by permanganate oxidation, 10-acetylphenothiazine is almost completely inactive under similar conditions. We have found that the 10-ethyl compound can also be converted to its sulfone by this method. However, the tosyl derivative could be oxidized only to the sulfoxide by a similar procedure while the acetyl-sulfanilyl derivative did not react at all. Also, Barnett[7] has shown that the 10-methyl compound is readily converted to its sulfoxide by treatment with 30% hydrogen peroxide whereas it was found here that neither the tosyl derivative nor the acetyl-sulfanilyl compound reacted under the same conditions.

Ethyl 10-phenothiazine carboxylate,[8] on the other hand, was readily converted to its sulfone by permanganate oxidation. Alkaline hydrolysis of the latter gave a 90% yield of phenothiazine sulfone. Bernthsen[9] has previously described an inferior method for the preparation of phenothiazine sulfone involving the action of hydrogen iodide on 10-methylphenothiazine sulfone.

Pharmacological findings will be reported later.

Experimental[10]

10-*p*-Acetylaminobenzenesulfonylphenothiazine.—To a mixture of 20 g. of dry phenothiazine and 25 cc. of pyridine, 23 g. of *p*-acetylaminobenzenesulfonyl chloride was added in 0.5-g. portions over a period of a half hour. The reaction mixture was warmed on a hot-plate long enough to bring about complete solution and was then allowed to cool to room temperature. Twelve hours later, the reaction mixture had gelled to a brownish-red tar. It was triturated with 20 cc. of alcohol, filtered, and washed with 10-cc. portions of alcohol to remove the excess pyridine. The crude material was recrystallized from alcohol, using Norite; wt. 20.0 g., m. p. 204–206°. The mother liquor was diluted with water. Numerous recrystallizations of the resulting precipitate yielded an additional 12 g., a total yield of 80%.

Anal.[11] Calcd. for $C_{20}H_{16}N_2S_2$: C, 60.58; H, 4.08; N, 7.08. Found: C, 60.93; H, 4.18; N, 7.28.

10-Sulfanilylphenothiazine (I).—To 1200 cc. of boiling ethyl alcohol were added 20.0 g. of the acetylamino compound, 70 g. of potassium hydroxide, and 1.0 g. of sodium hydrosulfite. The reaction mixture was refluxed for three hours and then poured into an aqueous solution of sodium hydrosulfite. The precipitate was filtered and recrystallized from alcohol. Hydrosulfite as well as charcoal was used in this process to prevent oxidation of the amine. The pure compound, m. p. 182–184°, was obtained in 85% yield. Its mixed m. p. with the acetylamino compound was 182–204°.

Anal. Calcd. for $C_{18}H_{14}O_2N_2S_2$: C, 61.03; H, 3.95. Found: C, 61.49; H, 3.91.

Dry hydrogen chloride gas was passed into an ethereal solution of 0.5 g. of the amine until precipitation of the amine hydrochloride was complete. The latter was identified as such by titration with standard alkali, using phenolphthalein as the indicator.

Anal. Calcd. for $C_{18}H_{14}O_2N_2S_2 \cdot HCl$: neut. equiv., 390. Found: neut. equiv., 382.

The instability of the amine hydrochloride in water was shown by washing it with several portions of cold water and determining the acid content of the combined wash liquids.

Anal. Calcd.: neut. equiv., 390. Found: neut. equiv., 359.

10-*p*-Nitrobenzenesulfonylphenothiazine and its Reduction Product.—To a mixture of 5.0 g. of phenothiazine and 5 cc. of pyridine, 5.6 g. of *p*-nitrobenzenesulfonyl chloride was added slowly enough so that the temperature of the reaction mixture never rose above 50°. The reaction mixture was heated, allowed to stand, triturated with alcohol and purified in a manner identical with that of the acetylamino compound described above. The pure nitro compound, recrystallized from alcohol, was obtained in 60% yield, m. p. 175–176°.

Anal. Calcd. for $C_{18}H_{12}O_4N_2S_2$: C, 56.25; H, 3.13. Found: C, 56.48; H, 3.29.

To 50 cc. of an alcoholic solution containing 0.4 g. of the nitro compound were added 0.5 g. stannous chloride, 10 cc. of concd. hydrochloric acid, and a few granules of twenty-mesh tin. The reaction mixture was refluxed until the characteristic yellow color of the nitro compound had disappeared. The colorless solution was cooled to room temperature and sodium hydrosulfite was added to decompose the stannous chloride double salt. The stannous sulfide formed was removed by filtration and extracted with hot alcohol. The filtrate and extracts were then poured into water yielding a precipitate which, upon recrystallization from alcohol, melted at 182–184°. The yield was 70%; mixed m. p. with the 10-sulfanilylphenothiazine (I) described above, 182–184°.

When 0.2 g. of the reduction product just described was refluxed with 10 cc. of acetic anhydride for ten minutes and the reaction mixture cooled and diluted with water, a white crystalline compound precipitated which melted at 203–206°. This m. p. was not depressed by admixture with the acetylamino compound.

10-*p*-Toluenesulfonylphenothiazine.—Equimolar quantities of phenothiazine and *p*-toluenesulfonyl chloride in a pyridine solution were treated as in the condensations described above. An 80% yield of white needles, m. p. 155–156°, was obtained by recrystallization from alcohol.

Anal. Calcd. for $C_{19}H_{15}O_2NS_2$: C, 64.55; H, 4.27. Found: C, 64.52; H, 4.29.

10-Methyl- and 10-Ethylphenothiazines.—A series of syntheses of 10-substituted phenothiazines was attempted with the use of alcohols rather than of the alkyl halides which Bernthsen[4] had employed. A 1.0 g. sample of phenothiazine and 10 cc. of methyl alcohol were placed in a tube and hydrogen chloride gas was bubbled through the mixture for three minutes. The tube was then sealed and placed in an oven at 130–150° for twelve hours. It was then chilled in ice and opened. The pressure developed during the methylation was thought to be due to the formation of dimethyl ether. As the pressure within

(5) It has since been reported that the 10-methyl compound can easily be prepared by simply refluxing a methyl alcohol solution of phenothiazine and methyl iodide for several days, B. P. DeLaney, private communication.

(6) Bernthsen, *Ann.*, **230**, 95 (1885).

(7) Barnett and Smiles, *J. Chem. Soc.*, **95**, 188 (1910).

(8) Fraenkel, *Ber.*, **18**, 1845 (1885).

(9) Bernthsen, *ibid.*, **39**, 1807 (1906).

(10) Melting points uncorrected.

(11) We wish to thank Dr. T. S. Ma of the University of Chicago for performing all the microanalyses recorded in this paper.

the tube dissipated, the reaction mixture solidified. Fractional recrystallizations of the crude material from alcohol yielded 60% of the theoretically calculated amount of 10-methylphenothiazine; m. p. 99–100°, known m. p. 99–100°.[4]

An identical run was made using absolute ethyl alcohol. In this case, only 35% of the calcd. 10-ethyl compound was isolated; m. p. 101–102°, known m. p. 101–102°.[4]

Similar reactions were run with *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, *n*-amyl, and benzyl alcohols. In all but the last case, however, phenothiazine was recovered quantitatively, even at temperatures of 180° for forty-eight hours. A 1–2 cc. water layer always formed in the course of these reactions and the characteristic odor of olefin could be detected upon opening the tubes. In the case of the *n*-butyl alcohol run, besides olefin formation, 3 cc. of a liquid having the characteristic odor of di-*n*-butyl ether, b. p. 135–140°, was isolated by fractional distillation from an initial charge of 10 cc. of the alcohol. The benzyl alcohol run gave an unworkable red oil.

10-Ethylphenothiazine Sulfone.—To 20 cc. of boiling water was added 1.0 g. of 10-ethylphenothiazine. The mixture was stirred until the ethyl compound had completely melted and a potassium permanganate solution containing 1.5 g. of permanganate and 45 cc. of water was added over a period of an hour. The reaction mixture was cooled, filtered, and the residue extracted with boiling alcohol. The combined extracts were then diluted with water and the resultant precipitate recrystallized from alcohol; wt. 0.65 g. (57% of the calcd.), m. p. 162–163°.

Anal. Calcd. for $C_{14}H_{13}O_2NS$: C, 65.14; H, 5.02. Found: C, 64.84; H, 5.06.

10-Toluenesulfonylphenothiazine Sulfoxide.—An attempt to oxidize 10-tosylphenothiazine by the above procedure failed in aqueous media. Therefore, acetone was used as a solvent to increase its solubility. To a refluxing acetone solution of 1.0 g. of the tosyl compound was added, dropwise, a saturated aqueous potassium permanganate solution until the purple color remained. The reaction mixture was diluted with water and then treated in an analogous manner to the 10-ethyl-sulfone above except that acetone was used in the extractions. Recrystallization from alcohol yielded 0.75 g. (74% of the calcd.), m. p. 246–248°.

Anal. Calcd. for $C_{19}H_{15}O_3NS_2$: C, 61.78; H, 4.06. Found: C, 61.81; H, 3.97.

Attempts to prepare the above sulfoxide and 10-*p*-acetylaminophenothiazine sulfoxide by Barnett's method[7] failed, no observable reaction having occurred after 3 g. samples of the tosyl and acetylamino compounds had been bottled and allowed to stand for two weeks in a solution consisting of 20 cc. of 30% hydrogen peroxide, an equal volume of acetone, and a few drops of a sodium ethoxide solution.

When a glacial acetic acid solution of the acetylamino compound was treated with chromic acid, a black, tarry oxidate was formed with 50% recovery of the unreacted starting material. Shriner had previously found this procedure satisfactory in the oxidation of various sulfides.[12]

Sulfone of Ethyl 10-Phenothiazine-carboxylate.—To a refluxing solution containing 300 cc. of glacial acetic acid, 100 cc. of water, and 60 g. of ethyl 10-phenothiazine-carboxylate,[8] was added 65 g. of potassium permanganate dissolved in 300 cc. of water. The permanganate solution was preheated to about 90° and was added slowly enough to prevent frothing. The mixture was refluxed for twenty minutes, cooled, diluted with water, and filtered. The residue was extracted with acetone, the extracts poured into water and the resulting precipitate recrystallized from acetone. The pure sulfone, wt. 55 g., m. p. 215–216°, was obtained in 83% yield.

Anal. Calcd. for $C_{15}H_{13}O_4NS$: C, 59.41; H, 4.39. Found: C, 60.43, 58.97; H, 4.39, 4.82.

Phenothiazine Sulfone.—To 50 g. of the above sulfone dissolved in an excess of alcohol, 30 g. of potassium hydroxide was added and the reaction mixture refluxed for thirty minutes. The reaction could be followed by the precipitation of potassium carbonate. The hot solution was cooled and diluted with water and the precipitated phenothiazine sulfone recrystallized from alcohol; wt. 35 g. (90% of the calcd.), m. p. 257–258°, known m. p. 258°.[8]

Summary

1. Several 10-substituted phenothiazines including 10-sulfanilylphenothiazine have been prepared.

2. 10-Methyl- and 10-ethylphenothiazine were prepared by the action of the corresponding alcohols on phenothiazine.

3. Phenothiazinesulfone has been prepared by a new and superior method and it has been suggested that the ease of oxidation of 10-substituted phenothiazines is dependent upon the nature of the 10-substituent.

(12) Shriner, Struck and Jorison, THIS JOURNAL, **52**, 2060 (1930).

CHICAGO 16, ILLINOIS RECEIVED JUNE 30, 1944

[CONTRIBUTION FROM THE BAILEY CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS]

Amphiprotic Substances. I. The Systems Acetamide–Ammonia and Acetamide–Acetic Acid

BY HARRY H. SISLER, ARTHUR W. DAVIDSON, RAYMOND STOENNER AND LUTHER L. LYON

It is a well-known experimental fact that ammonia and simple amines stand high in the Brønsted scale of basicity. This has been explained in terms of the high electron-donating or proton-accepting tendency which, because of the unshared pair of electrons on its nitrogen atom, resides in the amide group. That the acid amides are much less basic is equally well known, and this fact has been attributed to the electron affinity of the carbonyl group, which serves to decrease markedly the electron density about the nitrogen atom. Acetamide, like other simple acid amides, shows so little tendency to accept protons from the strongest acid available in aqueous solution, *viz.*, the hydronium ion, and so little tendency to release protons to the strongest base available in aqueous solution, *viz.*, the hydroxyl ion, that it is ordinarily thought of as a neutral substance. Conductivity studies of solutions of acetamide and barium hydroxide in water have shown that the acid dissociation constant of acetamide is 8×10^{-16}, which is of the same order of magnitude as that of water itself.[1]

(1) Branch and Clayton, THIS JOURNAL, **50**, 1680 (1928).