acetic acid in 50 ml. of water and 100 ml. of alcohol was added with stirring to 86.5 g. of ethyl benzalmalonate, and the resulting mixture was kept in a refrigerator overnight.

Reduction of 67 g. of the cyanoester in 500 ml. of alcohol at 100° with Raney nickel and hydrogen at 100 atmospheres took place in less than one hour, and gave 40.5 g. (71%) of **ethyl 2-keto-4-phenylpyrrolidine-3-carboxylate**, colorless prisms from benzene–ligroin, m. p. 119–120.5°. At higher temperatures, or in more concentrated solutions, or in ether, lower yields were obtained.

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 67.1; H, 6.4. Found: C, 67.1; H, 6.4.

Saponification of the ester with alcoholic potassium hydroxide gave a difficultly soluble potassium salt, from which there was obtained **2-keto-4-phenylpyrrolidine-3-carboxylic acid**, colorless crystals from dilute alcohol, m. p. 127–131° with decomposition.

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.4; H, 5.4. Found: C, 64.5; H, 5.3.

Distillation of the acid gave 4-phenylpyrrolidone-2, b. p. 198–200° at 10 mm., m. p. 75–76° (reported, m. p. 60°,[6] 76–77°[7]).

Reduction of 3.9 g. of 4-phenylpyrrolidone-2 with sodium in butyl alcohol gave 3-phenylpyrrolidine, isolated as its picrate (1.05 g., 12%), m. p. 163.5° (reported 164°,[8] 166°).[9]

Ethyl 2-keto-4-phenylpyrrolidine-3-carboxylate formed a white sodio derivative, difficultly soluble in alcohol, that gave back the original ester when it was acidified. A mixture of 0.05 mole of sodium ethoxide, 10 g. of ethyl 2-keto-4-phenylpyrrolidine-3-carboxylate, 7.7 g. of ethyl iodide, and 50 ml. of absolute alcohol was boiled for one hour, then cooled and diluted with water. The product was crystallized from benzene–ligroin, giving 4.96 g. (44%) of ethyl **3-ethyl-2-keto-4-phenylpyrrolidine-3-carboxylate**, colorless prisms, m. p. 118–119°.

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 69.0; H, 7.3. Found: C, 68.9; H, 7.3.

(6) Jackson and Kenner, *J. Chem. Soc.*, 1657 (1928).
(7) Winans and Adkins, THIS JOURNAL, **55**, 4167 (1933).
(8) Gitsels and Wibaut, *Rec. trav. chim.*, **59**, 1093 (1940).
(9) Späth, Wiss and Breusch, *Monatsh.*, **50**, 349 (1928).

Saponification of the alkylated ester with aqueous alkali was comparatively slow; but when a solution of 5 g. of it and 10 g. of potassium hydroxide in methanol was boiled for thirty minutes and then cooled, a crystalline potassium salt was deposited. This was removed, dissolved in water, and acidified, giving 3.9 g. (87%) of **3-ethyl-2-keto-4-phenylpyrrolidine-3-carboxylic acid**, colorless plates from dilute alcohol, that melted with decomposition at 173° or lower depending on the rate of heating.

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 67.1; H, 6.4. Found: C, 67.2; H, 6.8.

Distillation of 3.9 g. of the acid under reduced pressure gave 1.92 g. (57%) of **3-ethyl-4-phenylpyrrolidone-2**, colorless crystals, m. p. 84–85°.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.3; H, 7.9. Found: C, 76.4; H, 7.9.

A solution of 1.76 g. of 3-ethyl-4-phenylpyrrolidone-2 in 20 ml. of dry butyl alcohol was reduced with 1.5 g. of sodium. The basic product, **3-ethyl-4-phenylpyrrolidine**, b. p. approximately 140° at 15 mm., was obtained in poor yield.

Anal. Calcd. for $C_{12}H_{17}N$: C, 82.3; H, 9.7. Found: C, 82.2; H, 9.7.

The amine formed an oily benzoyl derivative. The **picrate**, yellow crystals from dilute alcohol, melted at 154–155°.

Anal. Calcd. for $C_{12}H_{17}N + C_6H_3N_3O_7$: C, 53.5; H, 5.0. Found: C, 53.8; H, 4.9.

Summary

Hydrogenation of ethyl α-carbethoxy-β-cyanovalerate and of ethyl α-carbethoxy-β-cyano-β-phenylpropionate furnished, respectively, ethyl 4-ethyl- and ethyl 4-phenyl-2-ketopyrrolidine-3-carboxylate. The sodio derivatives of these esters were ethylated, and the products were hydrolyzed and decarboxylated. The resulting pyrrolidones were reduced to pyrrolidines by treatment with sodium and butyl alcohol.

MINNEAPOLIS, MINNESOTA RECEIVED AUGUST 30, 1944

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

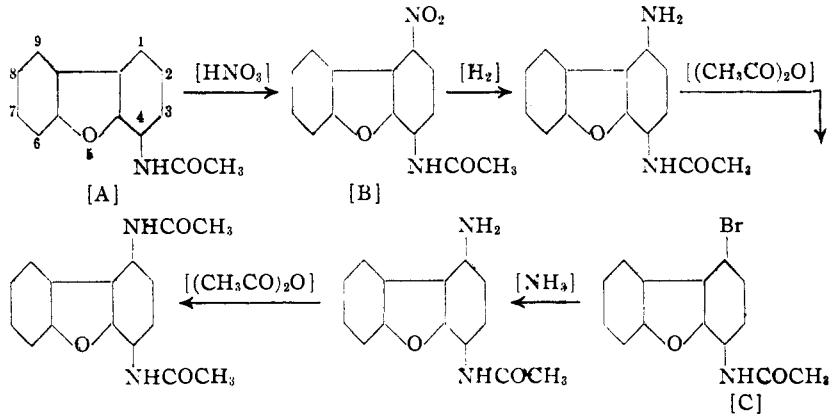
Dibenzofuran. XXII. 1-Nitrodibenzofuran[1]

BY HENRY GILMAN AND JACK SWISS[2]

Dibenzofurans having a substituent in the 1-position are of more than ordinary interest as reference compounds in cyclization processes. Nitration of dibenzofuran gives largely 3-nitrodibenzofuran. A by-product of the nitration melted at 110° and was supposed to be the 2-nitro isomer[3] or possibly the 4-nitro isomer.[4] It was later[5] shown that the 110° product was a mixture in which was contained some 2-nitrodibenzofuran. More recently[6] a nitration product melting at 91–93° was designated as the 1-nitrodibenzofuran. Subsequently, this supposed compound was resolved by further crystallization to give "a pure mononitrobiphenylene oxide melting at 126–126.5°," and purportedly shown to be the 1-nitrodibenzofuran by comparison with the 2-, 3-, and 4-nitrodibenzofurans.[7]

We do not know the structure of the product melting at 126–126.5°. It may possibly be a mixture of isomers which is very difficult to resolve, but it is not 1-nitrodibenzofuran, which we have prepared by the following sequence of reactions and which melts at 120–121°. Hydrolysis of [B], followed by deamination via the diazonium reaction, gave 1-nitrodibenzofuran. The structure of [C] was established[8a] earlier by a series of reac-

(1) Paper XXI: Gilman and Thirtle, THIS JOURNAL, **66**, 858 (1944).
(2) Present address: Research Laboratories, Westinghouse Electric and Manufacturing Co., East Pittsburgh, Pa.
(3) Borsche and Bothe, *Ber.*, **41**, 1940 (1908).
(4) Cullinane, *J. Chem. Soc.*, 2267 (1930).
(5) Gilman, Bywater and Parker, THIS JOURNAL, **57**, 885 (1935).
(6) Yamashiro, *J. Chem. Soc. Japan*, **57**, 714 (1936) [*C. A.*, **30**, 7575 (1936)].
(7) Yamasbiro, *Bull. Chem. Soc. Japan*, **16**, 61 (1941) [*C. A.*, **35**, 5111 (1941)].
(8) (a) Gilman and Van Ess, THIS JOURNAL, **61**, 1365 (1939); (b) Gilman, Jacoby and Swislowsky, *ibid.*, **61**, 954 (1939).



tions starting with the known 4-acetaminodibenzofuran.

Not only is there no agreement in melting point of our 1-nitrodibenzofuran and that reported for the product obtained by direct nitration, but the melting points of the amino compound derived by reduction of the supposed 1-nitro compound and of the corresponding acetamino compound are at variance with the melting points of 1-aminodibenzofuran[8a] and 1-acetaminodibenzofuran.[8a]

It is interesting to note that the nitration of [A] in acetic anhydride at −10° gives chiefly 3-nitro-4-acetaminodibenzofuran[8b]; whereas nitration in glacial acetic acid at 70° gives predominantly the isomeric 1-nitro-4-acetaminodibenzofuran [B].

Experimental

4-Aminodibenzofuran.—Two improved procedures[9] were developed for the preparation of this amine. In a Hofmann reaction, 20 g. (0.0836 mole) of 4-dibenzofurancarboxylic acid amide, suspended in 50 ml. of 95% ethanol and 100 ml. of 10% sodium carbonate solution, was added gradually to an ice-cooled hypobromite solution prepared from 28.8 g. (0.18 mole) of bromine and 54 g. (1.35 moles) of sodium hydroxide in 300 ml. of water. After there was no further evidence of reaction, the mixture was warmed on a steam-bath for three and one-half hours with occasional shaking, then cooled, the excess alkali partially neutralized with hydrochloric acid, and the brown product filtered. Acidification of the filtrate yielded 0.5 g. of crude 4-dibenzofurancarboxylic acid. The brown residue was extracted with ether, the ether solution was dried, and the amine hydrochloride was precipitated by passing in hydrogen chloride. The hydrochloride was decolorized by refluxing for twenty minutes in 300 ml. of water, to which 10 ml. of concd. hydrochloric acid and 2 ml. of Norite had been added. The free amine was precipitated from the filtered solution by the addition of equal volumes of concd. ammonium hydroxide and ethanol. The yield of pure amine was 9.5 g. (55%); and, in addition, 4 g. of the amide was recovered from the ether insoluble residue.

In a Bucherer reaction, by an adaptation of the method used for the preparation of 4,6-diaminodibenzofuran,[10] a mixture of 2 g. (0.0109 mole) of 4-hydroxydibenzofuran, 15 ml. of concd. ammonium hydroxide, and 7.5 g. of sodium metabisulfite dissolved in 15 ml. of water was heated for twenty hours at 185–195° in a sealed tube. Extraction of the solid reaction product with 5% potassium hydroxide gave on acidification a 10% recovery of 4-hydroxydibenzofuran. The alkali insoluble part was extracted by refluxing with 5% hydrochloric acid, to give 0.9 g. (45%) of pure 4-amine when the combined extracts were made alkaline with ammonium hydroxide.

Nitration of 4-Acetaminodibenzofuran.—One gram (0.0044 mole) of 4-acetaminodibenzofuran[11] was dissolved in 15 ml. of glacial acetic acid and warmed to 70°. Two milliliters (0.0476 mole) of fuming nitric acid (sp. gr., 1.49) was added dropwise with stirring, in a period of two minutes, during which the temperature rose momentarily to 85°. The solution was maintained at a temperature of 65–75° for twenty minutes, and then about 25 ml. of water was added slowly with stirring. Recrystallization from glacial acetic acid and then from 95% ethanol gave 0.7 g. (59%) of light yellow needles melting at 216°.

Anal. Calcd. for $C_{14}H_{10}O_4N_2$: N, 10.35. Found: N, 10.31.

1-Nitro-4-aminodibenzofuran.—Hydrolysis of 0.5 g. of the nitro-acetamino compound by refluxing with a mixture of 15 ml. of concd. hydrochloric acid and 15 ml. of 95% ethanol, followed by filtration and treatment with ammonium hydroxide, gave 1-nitro-4-aminodibenzofuran which melted at 219–220° after crystallization from ethanol.

Anal. Calcd. for $C_{12}H_8O_3N_2$: N, 12.28. Found: N, 12.23 and 12.39.

1-Nitrodibenzofuran.—To a solution of 0.4 g. (0.00176 mole) of 1-nitro-4-aminodibenzofuran in 2.5 ml. of 48% sulfuric acid and 12.5 ml. of 95% ethanol warmed to 80° on a steam-bath, was added dropwise and with stirring a solution of 1.2 g. (0.0174 mole) of sodium nitrite in 2.5 ml. of water. The compound melted at 120° after steam distillation, and recrystallization from ethanol gave 0.125 g. (33%) of straw colored needles melting at 120–121°.

Anal. Calcd. for $C_{12}H_7O_3N$: N, 6.57. Found: N, 6.75 and 6.78.

1-Amino-4-acetaminodibenzofuran.—Reduction of 1 g. of 1-nitro-4-acetaminodibenzofuran in 50 ml. of 95% ethanol with about 1 g. of Raney nickel catalyst[12] at a hydrogen pressure of 47 lb. and in a shaking machine, gave 1-amino-4-acetaminodibenzofuran which melted at 202° after crystallization from ethanol.

Anal. Calcd. for $C_{14}H_{12}O_2N_2$: N, 11.68. Found: N, 11.64.

1,4-Diacetaminodibenzofuran.—[I] After refluxing 0.5 g. (0.00195 mole) of 1-amino-4-acetaminodibenzofuran for thirty minutes in 15 ml. of benzene containing the calculated quantity of acetic anhydride, there was obtained an 80% yield of the 1,4-diacetamino compound which melted at 307–308° subsequent to crystallization from glacial acetic acid.

[II] Into each of two Carius tubes was placed 150 ml. of concd. ammonium hydroxide and an intimate mixture of 3 g. of 1-bromo-4-acetaminodibenzofuran and 3 g. of cuprous bromide, and the tubes were then heated at 175° for thirty hours. Acetic anhydride was then added to the dried benzene extract. The yield of diacetamino compound melting at 307–308° was 2.5 g. (45%), and a mixed m. p. determination showed the compound to be the same as that obtained in procedure [I].

Anal. Calcd. for $C_{16}H_{14}O_4N_2$: N, 9.93. Found: N, 9.99.

1,4-Diaminodibenzofuran Dihydrochloride.—After refluxing a solution of 2.5 g. of 1,4-diacetaminodibenzofuran for two hours with 35 ml. of 95% ethanol and 35 ml. of

(9) See Kirkpatrick and Parker, THIS JOURNAL, **57**, 1123 (1935).

(10) Gilman and Cheney, *ibid.*, **61**, 3149 (1939).

(11) Prepared in accordance with the directions of Kirkpatrick and Parker, *ibid.*, **57**, 1123 (1935).

(12) Covert and Adkins, *ibid.*, **54**, 4116 (1932).

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

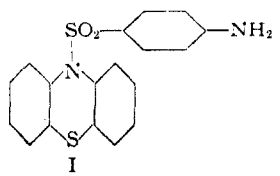
(13) The authors are grateful to H. B. Willis for this analysis.

[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).