water. 2-Propanol (200 ml.) was added, and crystallization was allowed to proceed for two days in a refrigerator. The filtered salt (27 g.) was redissolved in water and reprecipitated by 2-propanol. The yield was 23 g. (39% over-all); m. p. 235° dec. *Anal.* Calcd. for $C_{17}H_{28}N_4Cl\cdot 2H_3PO_4$: P, 12.00. Found: P, 12.11.

7-Chloro-1-(4-diethylamino-1-methylbutylamino)-phthalazine Dihydriodide (SN-11,615-17).—The crude base was prepared in the manner previously described from 1,7-dichlorophthalazine.[4] To 21.3 g. of base (obtained from 22.5 g. of 1,7-dichlorophthalazine and 80 g. of side-chain) were added 29.8 g. of 57% hydriodic acid and 30 ml. of water. The suspension was stirred and filtered, and the insoluble material was washed with a little water. From the cooled filtrate 14.6 g. of salt was obtained; an additional 1.4 g. was obtained by concentration. The crude material was recrystallized in succession from alcohol–ether, water, and ethanol; the yield was 10.4 g. (16% over-all). The salt melted at 164.6–165.8°. *Anal.* Calcd. for $C_{17}H_{25}N_4Cl\cdot 2HI$: C, 35.4; H, 4.71. Found: C, 35.18, 35.06; H, 4.82, 4.69.

1-(4-Diethylamino-1-methylbutylamino)-phthalazine Triphosphate Monohydrate (SN-11,069-5).—The crude base was prepared from 1-chlorophthalazine[4] in the manner previously described. To 33.5 g. of base (obtained from 55 g. of 1-chlorophthalazine and 116 g. of side-chain) were added 23.4 g. of 85% phosphoric acid and 100 ml. of water. After filtration from insoluble material, the volume was brought to 150 ml. with water and 200 ml. of 2-propanol was added. Cooling overnight caused the crystallization of 18 g. of salt which was recrystallized from water and 2-propanol; yield 13.4 g. (8% over-all); m. p. 170–190°. *Anal.* Calcd. for $C_{17}H_{26}N_4\cdot 3H_3PO_4\cdot H_2O$: P, 15.54; moisture, 3.0. Found: P, 14.89, 15.03; moisture, 2.87.

Summary

The preparation of three 1-(4-diethylamino-1-methylbutylamino)-phthalazines and certain of their salts are described.

COLLEGE PARK, MD. RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE STEELE CHEMISTRY LABORATORY OF DARTMOUTH COLLEGE]

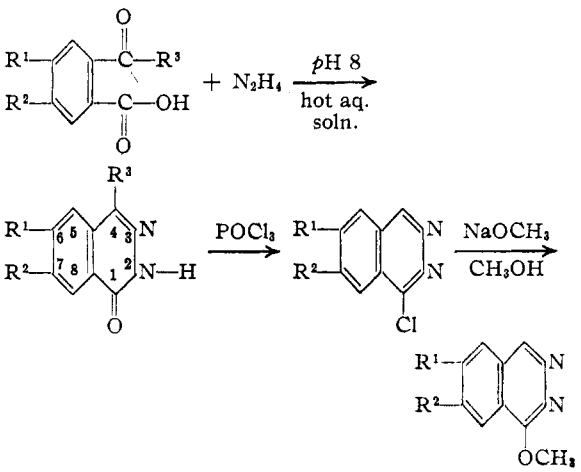
The Preparation of Some Phthalazines and Related Substances[1]

BY WYMAN R. VAUGHAN[1a] AND SPENCER L. BAIRD, JR.[1b]

The purpose of the present investigation was to prepare several 1-chlorophthalazines to be used as intermediates in the preparation of substances hoped to be of value as antimalarials. The chlorine in the 1-position of the phthalazines is relatively reactive and may be replaced by an azine residue, as will be reported elsewhere by Dr. N. L. Drake, or, as indicated in the present work, by the methoxyl group.

There is not an abundant literature relating to the preparation of simple phthalazine derivatives. However, phthalazones have been prepared from hydrazine and *ortho*phthalaldehydic acid (or a substance which readily yields this acid),[2] or from phthalonic acid and hydrazine.[3,4,5] Phthalazones alkylated in the 1- or 4-position have been prepared by a similar procedure from hydrazine and *ortho*acylbenzoic acids.[6]

Both phthalaldehydic acid and phthalonic acid have been used in the present work. The reaction of these compounds with hydrazine yielded a phthalazone or a phthalazone-4-carboxylic acid which was readily decarboxylated to give a phthalazone. The phthalazones were converted into the 1-chlorophthalazines by treatment with phosphorus oxychloride.[2] In addition to 1-chlorophthalazine and 1-methoxyphthalazine which were already known,[2] several new 1-chlorophthalazines were prepared, and the corresponding 1-methoxy derivatives were prepared from them. The general reaction may be represented as



I, R^1 = Cl; R^2 = H; R^3 = H
II, R^1 = H; R^2 = Cl; R^3 = H
III, R^1 = H; R^2 = CH_3O; R^3 = H
IV, R^1 = H; R^2 = CH_3O; R^3 = COOH; CO_2 is removed before the $POCl_3$ reaction

The phthalaldehydic acids for the preparation of the 6- and 7-chlorophthalazones (I and II) were not isolated but were introduced as 5-chloro- and 6-chloro-3-bromophthalides, respectively, which were prepared from the corresponding chlorophthalides by direct bromination. However, when the benzene ring carried a methoxyl group,

(1) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Dartmouth College.

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(2) Gabriel and Neumann, *Ber.*, **26**, 521 (1893).

(3) Rothenburg, *J. prakt. Chem.*, **51**, 140 (1895).

(4) Fränkel, *Ber.*, **33**, 2808 (1900).

(5) Gabriel, *ibid.*, **36**, 3373 (1903).

(6) Gabriel and Neumann, *ibid.*, **26**, 705 (1893); Gabriel and Eschenbach, *ibid.*, **30**, 3022 (1897); Paul, *ibid.*, **32**, 2014 (1899); Rowe and Peters, *J. Chem. Soc.*, 1331 (1933).

such bromination was unsatisfactory as would be expected.

An interesting observation was made in this connection: tests indicated that sulfuryl chloride could be used to chlorinate the methylene group of 6-chlorophthalide in the presence of dibenzoyl peroxide as a catalyst.[7] The 3,6-dichlorophthalide so produced could be used in place of the 3-bromo compound. The optimum conditions were not determined, but exploratory work indicated about 38% monochlorination at 160° when the sulfuryl chloride containing the peroxide catalyst was added dropwise beneath the surface of 6-chlorophthalide in chlorobenzene solution. It was thought that the Kharasch procedure might be used to chlorinate 6-methoxyphthalide, but nuclear chlorination appeared to take place even under the mildest conditions when the latter substance was treated under the conditions noted.

It was necessary, therefore, to prepare 5-methoxyphthalaldehydic acid by another procedure.[8] A small sample of the desired 7-methoxyphthalazone (III) was prepared from this acid, but further investigation proved that it was simpler to oxidize 2-methyl-4-methoxyacetophenone[9] to 4-methoxyphthalonic acid by the use of aqueous permanganate,[8] and without isolating this acid, to add hydrazine, acidify, and collect the precipitate. It was then a simple matter to isolate 7-methoxyphthalazone-4-carboxylic acid (IV) and to decarboxylate it to the desired phthalazone (III).

The preparation of the 1-chlorophthalazines from the phthalazones presented no difficulty although several of the former compounds appeared to decompose on standing. The 1-methoxyphthalazines are stable.

Experimental[10]

6-Chlorophthalazone (I).—The bromination of 5-chlorophthalide[11] was carried out according to the procedure of Shriner and Wolf[12] with the following modifications: the 5-chlorophthalide was maintained at 165° for the first hour of bromine addition, 160° for the second hour, and 150–155° for the remainder of the addition. Bromine was used up at the rate of about 1.5 g. per hour with the carbon dioxide stream carrying the bromine passing at the rate of 72 bubbles per minute. The yield of 3-bromo-5-chlorophthalide, b. p. 132–135° (1.5 mm.), was 90%. This material was hydrolyzed and converted to 6-chlorophthalazone,[2] m. p. 268–272° (uncor.). Upon recrystallization from glacial acetic acid the 6-chlorophthalazone formed coarse white needles, m. p. 272.2–273.5°; over-all yield, 57%.

Anal. Calcd. for $C_8H_5ON_2Cl$: C, 53.20; H, 2.79. Found: C, 53.14; H, 2.85.

1,6-Dichlorophthalazine.—The procedure for the preparation of this substance was the same as that described by Gabriel and Neumann[2] for 1-chlorophthalazine. A mixture of 8 g. of 6-chlorophthalazone and 73 g. (31 ml.) of phosphorus oxychloride yielded 9.9 g. of crude 1,6-dichlorophthalazine. Recrystallization of this material from 350 ml. of carbon tetrachloride yielded 6 g. (70%) of fine white needles, m. p. 150–151° (uncor.) with decomposition.

Anal. Calcd. for $C_8H_4N_2Cl_2$: Cl, 35.63. Found: Cl, 35.57.

1-Methoxy-6-chlorophthalazine.—A solution of 1,6-dichlorophthalazine in methanol was treated with sodium methoxide (equivalent amount). The methoxy compound was obtained by evaporation of the methanol, extraction of the residue with water, and finally recrystallization of the water-insoluble residue from ligroin (70–90°) to yield coarse pale green-yellow needles, m. p. 116.0–116.6°.

Anal. Calcd. for $C_9H_7ON_2Cl$: C, 55.54; H, 3.63. Found: C, 55.63; H, 3.91.

7-Chlorophthalazone (II).—The 6-chlorophthalide required for this preparation was prepared from phthalide[13] by nitration,[14] reduction to 6-aminophthalide by catalytic hydrogenation in glacial acetic acid over palladium–barium sulfate, and replacement of the amino group by chlorine by the Sandmeyer reaction. By carrying out the latter reaction initially at −5° and with efficient mechanical stirring a yield of 78.4% of relatively pure 6-chlorophthalide, m. p. 109.6–110.0°, was obtained. Conversion[12] of this substance to 3-bromo-6-chlorophthalide was carried out at the lowest temperature at which the reaction would proceed (115–120°) in order to minimize tar formation. The product, b. p. 119–122° (3 mm.), was not itself analyzed but was converted into 5-chlorophthalaldehydic acid by boiling with water. The acid was recrystallized from water, yielding white needles, m. p. 122–124° (uncor.), which proved to be unstable on long standing.

Anal. Calcd. for $C_8H_5O_2Cl$: C, 52.05; H, 2.73. Found: C, 51.84; H, 2.93.

The bulk of the 3-bromo-6-chlorophthalide was transformed into 7-chlorophthalazone.[2] The yellow hydrazone which separated almost immediately was converted into the desired phthalazone by boiling the reaction mixture for ten to fifteen minutes. All of the phthalazone was precipitated at a *p*H slightly greater than 7 and was filtered off. The filtrate was acidified and boiled, and upon cooling, a small quantity of 6-chlorophthalide was recovered. Corrected for this recovery, the conversion of 3-bromo-6-chlorophthalide into 7-chlorophthalazone, m. p. 246.5–246.7°, was effected in 95% yield. A sample recrystallized from alcohol (white feathery needles) for analysis showed no alteration in the melting point.

Anal. Calcd. for $C_8H_5ON_2Cl$: C, 53.20; H, 2.79. Found: C, 53.24; H, 2.90.

1,7-Dichlorophthalazine.—The procedure of Gabriel and Neumann[2] was modified somewhat to accommodate the properties of the desired compound. The phosphorus oxychloride solution was allowed to boil with refluxing for not more than fifteen minutes, and then it was cooled rapidly and poured onto crushed ice. Cold water was added with vigorous stirring, and the solution was filtered. The filtrate was made alkaline (*p*H 8) with 50% potassium hydroxide solution, care being taken to keep the temperature below 15°. An orange precipitate separated and was filtered off and dried in air at room temperature. Purification was effected by solution of the product in 6 *N* hydrochloric acid and filtration. The filtrate was then made neutral or slightly alkaline with 50% potassium hydroxide solution (temperature < 15°), and the resulting precipitate was filtered off and dried in air on a piece of porous plate. The 1,7-dichlorophthalazine thus obtained melted at 156–158° (uncor.) with decomposition;[15] yield 66.5%. Repeated recrystallization of the crude product from carbon tetrachloride yielded white

(7) Kharasch, THIS JOURNAL, **61**, 2142 (1939).

(8) Chakravarti, Swaminathan and Venkataraman, *J. Ind. Chem. Soc.*, **17**, 264 (1940).

(9) Noller and Adams, THIS JOURNAL, **46**, 1889 (1924).

(10) Melting points are corrected unless otherwise noted.

(11) Levy and Stephens, *J. Chem. Soc.*, 867 (1931).

(12) Shriner and Wolf, "Organic Syntheses," Vol. 23, 1943, p. 74.

(13) We are indebted to the National Aniline Division, Allied Chemical and Dye Corporation, New York, for a generous supply of this material.

(14) Borsche, *Ber.*, **67**, 675 (1934).

(15) The decomposition point was taken at 1° per minute rise, the capillary being introduced at 150°.

or very pale yellow needles, m. p. 161–162° (uncor.) with decomposition.[15] The substance is very sensitive to warm alcohols or water.

Anal. Calcd. for $C_8H_4N_2Cl_2$: C, 48.27; H, 2.03. Found: C, 48.23; H, 2.32.

1-Methoxy-7-chlorophthalazine.—A small portion of the crude 1,7-dichlorophthalazine was transformed into 1-methoxy-7-chlorophthalazine by the same procedure employed for 1-methoxy-6-chlorophthalazine. The product consisted of pale yellow needles, m. p. 134.9–135.9°, after recrystallization from ligroin (70–90°).

Anal. Calcd. for $C_9H_7ON_2Cl$: C, 55.54; H, 3.63. Found: C, 55.65; H, 3.84.

6-Hydroxyphthalide.—A mixture of 4.0 g. (0.27 mole) of 6-aminophthalide, 25 ml. of water, and 1 ml. of concentrated sulfuric acid was treated, with good cooling (0–5°), with a solution of 2.2 g. of sodium nitrite in 10 ml. of cold water. To the resulting solution of diazonium salt, 20 ml. of concentrated sulfuric acid was added slowly and with good cooling, the final solution being about 50% sulfuric acid. This solution was slowly introduced beneath the surface of 50 ml. of boiling 50% sulfuric acid (120–125°). The reaction mixture was boiled for two minutes after complete addition and then was cooled to room temperature and diluted to 250 ml. with water. It was then extracted with several portions of ether (totaling 500 ml.), and the yellow ethereal extracts were combined and extracted with 5% sodium bicarbonate solution until the bicarbonate extracts were nearly colorless. The ether solution was dried over magnesium sulfate, filtered, and evaporated to dryness to give 3.0 g. of a pale yellow product, m. p. 200–201°; yield 74%. Additional product was obtained by acidification of the bicarbonate extracts followed by ether extraction of the acid solution. The dried, filtered ethereal extract was evaporated to dryness, and the residue was boiled with 25 ml. of water containing 2 drops of concentrated hydrochloric acid in order to close the lactone ring of 6-hydroxyphthalide. The resulting solution was treated with Darco and filtered hot. The filtrate was cooled to 0° to give 0.25 g. of pale yellow crystals, m. p. 199–201°; total yield of 6-hydroxyphthalide 80.2%. Upon recrystallization from water, flat white needles, m. p. 200.5–201.2°, were obtained.

Anal. Calcd. for $C_8H_6O_3$: C, 64.00; H, 4.03. Found: C, 63.99; H, 4.30.

The 6-hydroxyphthalide was readily converted to 6-methoxyphthalide by treatment with methyl sulfate in an alkaline medium. The white needles obtained upon recrystallization from water melted at 119.5–120.1°, which agrees with recorded data for 6-methoxyphthalide prepared by another procedure.[16]

Anal. Calcd. for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 65.51; H, 5.14.

7-Methoxyphthalazone-4-carboxylic Acid (IV).—A mixture of 22.0 g. (0.134 mole) of 2-methyl-4-methoxyacetophenone[9] and 11 g. of potassium carbonate in 220 ml. of water was heated to 100° and treated with portions of a hot solution of 82.5 g. of potassium permanganate in 825 ml. of water.[8] The reaction mixture was vigorously stirred with a wire stirrer,[17] and the color of the permanganate solution was allowed to disappear after each addition before addition of the next portion of the reagent. After addition of the final portion, the reaction mixture was maintained at 100° for half an hour. It was then cooled and filtered, and the residue was thoroughly washed with water, the washings being collected with the filtrate. The clear filtrate containing 4-methoxyphthalonic acid was heated to about 90° and the *p*H was adjusted to 8. A solution of 19.5 g. of hydrazine sulfate (excess) and 6.1 g. of sodium hydroxide in 65 ml. of hot water was added. The resulting solution was then evaporated to one half its volume on a hot plate by means of an air stream, and the concentrated solution was strongly acidified with hydrochloric acid. A yellow precipitate formed, and after the mixture had cooled to room temperature, it was filtered; and the dried residue weighed 20.4 g. It was extracted twice with 80-ml. portions of methanol, and the residue from this treatment weighed 14.5 g. (49.2%) and melted with the evolution of carbon dioxide at 229–230°. A small sample was recrystallized from glacial acetic acid in which it is difficultly soluble even at the boiling point. The purified 7-methoxyphthalazone-4-carboxylic acid, m. p. 230.8–231.0° with the evolution of carbon dioxide, forms a white crystalline powder.

Anal. Calcd. for $C_{10}H_8O_4N_2$: C, 54.55; H, 3.66. Found: C, 54.47; H, 3.93.

7-Methoxyphthalazone (III): A. From 5-Methoxyphthalaldehydic Acid.—The 5-methoxyphthalaldehydic acid was prepared according to the method of Chakravarti,[8] and it was converted into the phthalazone by the usual procedure.[2]

B. From 7-Methoxyphthalazone-4-carboxylic Acid.—A finely powdered sample of 7-methoxyphthalazone-4-carboxylic acid in a round-bottom flask plugged loosely with cotton was carefully melted over a smoky flame. The flask was cooled when the evolution of carbon dioxide had ceased. If the acid is pure, this procedure may be carried out practically quantitatively.

The product from either A or B may be recrystallized from water to give white needles, m. p. 221.9–222.2°.

Anal. Calcd. for $C_9H_8O_2N_2$: C, 61.36; H, 4.58. Found: C, 61.30; H, 4.81.

1-Chloro-7-methoxyphthalazine.—Treatment of 7-methoxyphthalazone with a slight excess of phosphorus oxychloride as described above for 1,7-dichlorophthalazine afforded a relatively pure product, m. p. 140.7–141.8° with decomposition; yield 84%. Repeated recrystallization from carbon tetrachloride yielded rather fine yellow needles, m. p. 144.9–145.5° with decomposition.

Anal. Calcd. for $C_9H_7ON_2Cl$: C, 55.54; H, 3.63. Found: C, 55.50; H, 3.65.

1,7-Dimethoxyphthalazine.—This substance was prepared from 1-chloro-7-methoxyphthalazine by the same procedure used for the preceding 1-methoxy derivatives. Recrystallization of the crude substance from ligroin (70–90°) yielded pale yellow needles, m. p. 125.6–125.9°.

Anal. Calcd. for $C_{10}H_{10}O_2N_2$: C, 63.14; H, 5.30. Found: C, 62.97; H, 5.60.

Acknowledgment.—The authors wish to express their appreciation to Professor Elden B. Hartshorn for his kind advice and suggestions.

Summary

The following new phthalazones have been prepared: 6-chloro-, 7-chloro- and 7-methoxyphthalazone, and 7-methoxyphthalazone-4-carboxylic acid. 6-Hydroxyphthalide and 5-chlorophthalaldehydic acid also have been prepared.

The following new phthalazines have been prepared: 1,6-dichloro-, 1,7-dichloro-, 1-chloro-7-methoxy-, 6-chloro-1-methoxy-, 7-chloro-1-methoxy- and 1,7-dimethoxyphthalazine.

The chlorine in the 1-position of the phthalazines is relatively reactive and may be replaced readily by methoxyl.

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(16) Fritsch, *Ann.*, **296**, 344 (1897).

(17) Hershberg, *Ind. Eng. Chem., Anal. Ed.*, **8**, 313 (1936).