anh. ether and transferred immediately to a vacuum desiccator. The red solid was very hygroscopic and became a dark oil on exposure to air. The weight of crude hydrochloride was 22.7 g. (calcd. 24.3 g.). It was converted to the free base in only 29% yield by suspending 10 g. in a mixture of 300 ml. of benzene and 150 ml. of water containing 15 g. of sodium bicarbonate and shaking for thirty minutes on a mechanical shaker. The aqueous layer contained much black, insoluble material; it was shaken similarly twice more with 100-ml. portions of benzene and the combined benzene extracts were decolorized with brief boiling, concentrated to 150 ml. *in vacuo* and diluted with 50 ml. of hexane. Overnight cooling gave 1.5 g. of red crystals and addition of 300 ml. more hexane with further cooling gave an additional gram. This material had a decomposition point of about 90°. It gave yellow crystals on recrystallization from benzene and hexane; these decomposed on standing.

The liberation of the free base was accomplished in about the same yield without adding the sodium bicarbonate.

Summary

4-Methylcinnoline was prepared in excellent yields from methyl anthranilate and converted to cinnoline-4-carboxylic acid through 4-styrylcinnoline. The acid was decarboxylated readily to cinnoline. Attempts to convert the carboxyl group to α-dialkylaminomethyl- or α-(2-piperidyl)-methanol groups were unsuccessful.

LOS ANGELES, CALIF. RECEIVED APRIL 5, 1946

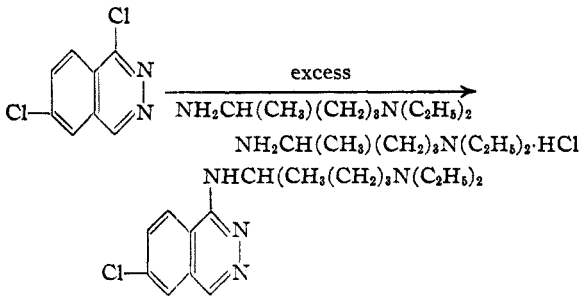
[CONTRIBUTION FROM THE LABORATORIES OF THE UNIVERSITY OF MARYLAND]

Synthetic Antimalarials. Some 1-(4-Diethylamino-1-methylbutylamino)-phthalazines[1]

BY NATHAN L. DRAKE AND RICHARD M. PECK

In the course of the search for superior antimalarials numerous heterocyclic substances bearing structural resemblances to the active 4-aminoquinolines were studied; among these were certain 1-(4-diethylamino-1-methylbutylamino)-phthalazines. The present paper describes the preparation and properties of three such substituted phthalazines and certain of their salts; the activity of these drugs in avian malaria will be treated elsewhere.[2]

The method of preparation of these substances follows closely that employed in the preparation of 4-dialkylaminoalkylaminoquinolines and is described by the formulas



The desired 1-chlorophthalazine is heated with an excess of a suitable diamine until condensation is complete and the product is worked up without distillation. In the cases studied alkylation occurred at temperatures (below 100°) considerably below those necessary when 4,7-dichloroquinoline was used with the same diamine. Extensive decomposition of the nucleus invariably accompanied alkylation and it proved impossible to obtain pure base. The substances were therefore isolated and purified as salts, and an indeterminate amount of product was lost during separation of the salts from the by-products. An attempt to distil one of the substances was unsuccessful due to very extensive decomposition at the elevated temperature; consequently, salts were prepared directly from the crude base, after the latter had been washed free from excess side chain; the salts were recrystallized for analysis and submission for testing.

Experimental[3]

6-Chloro-1-(4-diethylamino-1-methylbutylamino)-phthalazine (SN-11,614).—A mixture of 27.8 g. of 1,6-dichlorophthalazine[4] and 87 g. of purified noval diamine was stirred and heated at 87–100° (temperature of reactants) for three and one-half hours. The reaction was sufficiently exothermic so that an appreciable temperature differential was established between the oil-bath and the reactants. When the internal temperature dropped below the bath temperature, the reaction was assumed to be complete.

The mixture was cooled and 200 ml. of ether and 50 ml. of 20% sodium hydroxide were added. The layers were separated and the ethereal solution was exhaustively extracted with water to remove excess side-chain. The ether was removed by distillation *in vacuo*, and the oily residue was slurried successively with two 100-ml. portions of Skellysolve F which were decanted. The remaining oil, after heating under reduced pressure to remove petroleum ether, weighed 27 g. Attempts to purify the compound were unsuccessful; it was therefore converted to the diphosphate which was easier to purify.

6-Chloro-1-(4-diethylamino-1-methylbutylamino)-phthalazine Diphosphate (SN-11,614-5).—To 25.2 g. of the crude base were added 26.0 g. of 85% phosphoric acid and 100 ml. of water. The suspension was centrifuged to remove a small amount of insoluble amorphous material, and the supernatant liquid was filtered and diluted to 150 ml. with

(1) This work was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Maryland.

(2) The Survey Number, designated SN, identifies a drug in the files of the Survey of Antimalarial Drugs. The activities of these compounds will be tabulated in a forthcoming monograph. See, "A Survey of Antimalarial Drugs, 1941–1945," F. Y. Wiselogle, editor, to be published by Edwards Bros., Ann Arbor, Mich.

(3) Micro-analyses by Miss Eleanor Werble of this Laboratory.

(4) Supplied by Dr. E. Hartshorn, Dartmouth College, see THIS JOURNAL, **68**, in press (1946).

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]

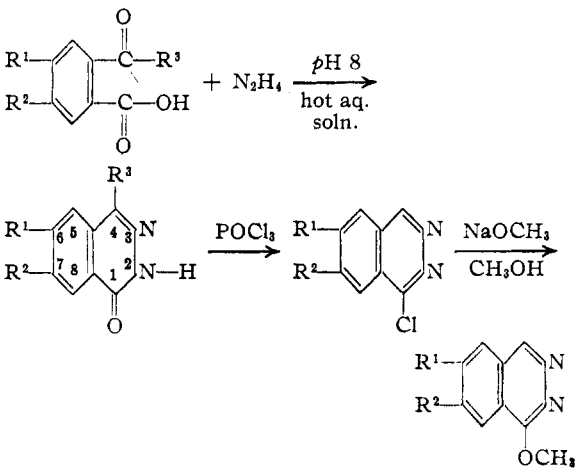
The Preparation of Some Phthalazines and Related Substances[1]

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).