[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

4-Substituted Cinnoline Derivatives[1]

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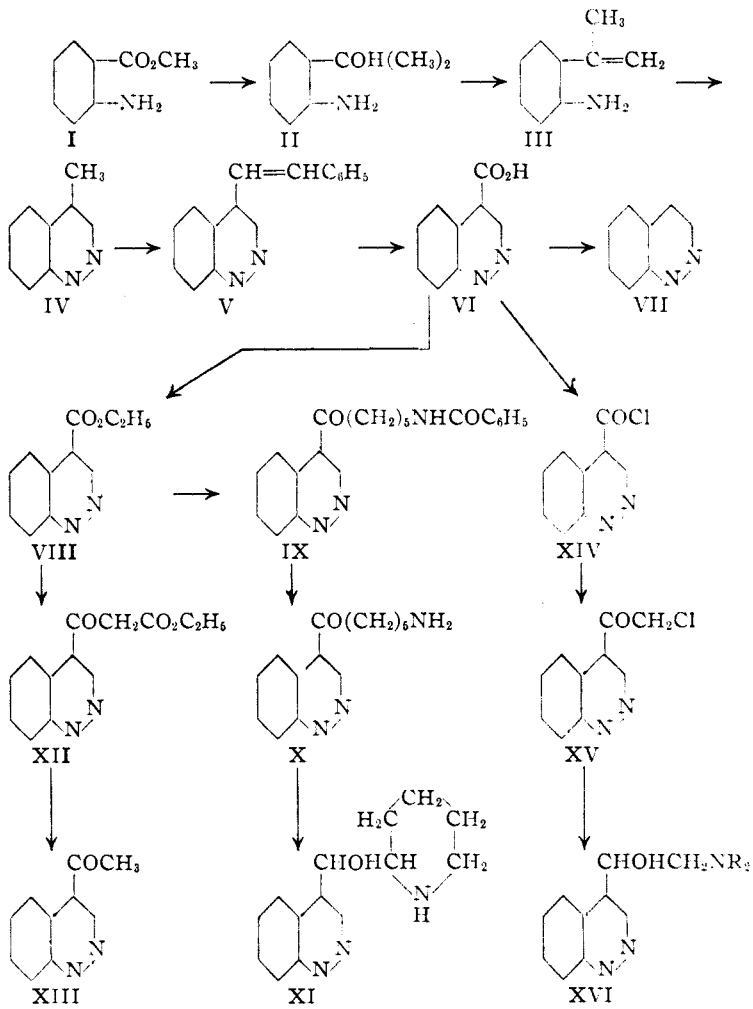
The discovery that one of the degradation products obtained by the *in vitro* action of rabbit liver on quinine was a carbostyryl analog of that drug[2] suggested the importance of the 2-position in related quinoline antimalarials and led to the preparation of many α-dialkylaminomethyl- and α-(2-piperidyl)-4-quinolinemethanols substituted in the 2-position. Since cinnoline derivatives would not be expected to undergo a degradation in the 2-position of the same sort as observed in quinine, it was of interest to introduce α-dialkylaminomethyl- and α-(2-piperidyl)-methanol side chains into the 4-position of the cinnoline ring (Compounds XI and XVI). Although this end was not achieved, a number of new 4-substituted cinnolines were prepared and are reported here.

Work on the synthesis of cinnoline derivatives is limited, but has shown that the most practical method of obtaining such compounds not containing an hydroxyl group involves the spontaneous cyclization of diazotized *o*-aminophenylethylenes (*e.g.*, III → IV), a reaction discovered by Widman[3] and studied by Stoermer[4,5] and Simpson.[6,7] It has been used mainly for the preparation of 4-aryl cinnoline derivatives. We have found that the method gives excellent yields of 4-methylcinnoline starting from methyl anthranilate (I → IV) and that condensation of the product with benzaldehyde followed by oxidation with potassium permanganate readily gives cinnoline-4-carboxylic acid (VI). The over-all yield of the latter from methyl anthranilate was 66–77%. Cinnoline (VII) is produced without difficulty by decarboxylation.

Cinnoline-4-carboxylic acid was esterified readily and the condensation of the ester (VIII) with ethyl ε-benzamidocaproate followed by mild hydrolysis gave 4-cinnolyl ε-benzamidoamyl ketone (IX). No crystalline aminoketone (X) could be obtained by hydrolysis of the ketone nor did the combined condensation and hydrolysis procedure of Sargent[8] give a crystalline material. An attempt to complete the synthesis of the piperidylmethanol (XI) without isolation of pure intermediates was not successful.



The condensation of ethyl cinnoline-4-carboxylate with ethyl acetate and hydrolysis of the product to 4-acetocinnoline (XIII) proceeded smoothly. The ketone was oxidized with hypochlorite to give cinnoline-4-carboxylic acid but bromination of the ketone failed or gave tarry products. A compound with the composition of 4-chloroacetocinnoline (XV) was obtained in low yield by the action of diazomethane followed by

(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 California, Los Angeles.

(2) Mead and Koepfli, *J. Biol. Chem.*, **154**, 507 (1944).

(3) Widman, *Ber.*, **17**, 722 (1884).

(4) Stoermer and Fincke, *ibid.*, **42**, 3115 (1909).

(5) Stoermer and Gaus, *ibid.*, **45**, 3104 (1912).

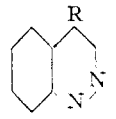
(6) Simpson and Stephenson, *J. Chem. Soc.*, 353 (1942).

(7) Simpson, *ibid.*, 447 (1943).

(8) Sargent, THIS JOURNAL, **68**, in press (1946).

TABLE I

CINNOLINE DERIVATIVES



R	M. p., °C.	Formula	Analyses, % C Calcd.	C Found	H Calcd.	H Found
—CH_3	72.5–74	$C_9H_8N_2$	74.97	75.37	5.59	5.77
—$CH{=}CHC_6H_5$	121.5–122.5	$C_{16}H_{12}N_2$	82.73	82.71	5.21	5.36
—CO_2H	195–196 dec.	$C_9H_6N_2O_2$	62.06	61.97	3.47	3.55
—$CO_2C_2H_5$	48.5–49.5	$C_{11}H_{10}N_2O_2$	65.33	65.38	4.98	5.09
—$COCH_2CO_2C_2H_5$	81.5–82	$C_{13}H_{12}N_2O_3$	63.92	63.88	4.95	4.97
—$COCH_3$	100–101	$C_{10}H_8N_2O$	69.75	70.28	4.68	4.85
—$COCH_2Cl$	95–100 dec.	$C_{10}H_7ClN_2O$	58.12	58.08	3.41	3.43
—$CO(CH_2)_5NHCOC_6H_5$	115.5–116.5	$C_{21}H_{21}N_3O_2$	72.60	72.84	6.09	6.27
—$C(NOH)CH_3$	165–165.5[a]	$C_{10}H_9N_3O$	64.16	64.36	4.85	4.94
—H[b]	Below 100	$C_8H_9ClN_2O$	52.13	52.04	4.92	4.89

[a] Softening at 156–157°. [b] Hydrochloride monohydrate.

hydrogen chloride on the unstable acid chloride of cinnoline-4-carboxylic acid (XIV). No success has attended attempts to convert the chloroketone (XV) into α-dialkylaminomethyl-4-cinnolinemethanols (XVI) either through formation and reduction of an amino ketone or by reduction of the chloroketone to a chlorohydrin and treatment of the latter with dialkylamine. This work is continuing and will be reported later.

Experimental

Analyses were carried out by Bruce F. Day and Richard Nevé. Melting points are corrected unless marked otherwise.

2-(*o*-Aminophenyl)-propene (III).—Methylmagnesium bromide was prepared from 10 g.-atoms of magnesium turnings in 1.5 liters of ether and treated dropwise during one hour at 0° under nitrogen with 250 g. (1.65 moles) of methyl anthranilate in 1 liter of ether. A Hershberg-type[9] tantalum stirrer was used. The reaction mixture was refluxed for five hours, cooled and poured into a mixture of 1200 g. of ammonium chloride and ice. Basic magnesium salts were partly neutralized by adding 700 ml. of 6 *N* hydrochloric acid and the solution extracted with ether until no more color was observed in the ether. The combined ether extracts were concentrated to 3 liters, dried over anhydrous potassium carbonate and the remaining ether removed under reduced pressure. The crude dimethyl-(*o*-aminophenyl)-methanol was dissolved in 1 liter of toluene containing 75 to 100 mg. of iodine and refluxed for thirteen hours using a separator to trap out the water produced. A total of 27.5 ml. of water was collected (93% of the theoretical amount). Toluene was removed under reduced pressure and the residue distilled from a modified Claisen flask. The yield of 2-(*o*-aminophenyl)-propene, b. p. 83.5–87.5° (1–2 mm.) was 192 g. (87%). A small sample was redistilled through a column, $n^{25}D$ 1.5676, d^{25}_4 0.9781, MR_D calcd. 43.12 (no exaltation correction), MR_D obs. 44.52.

Anal. Calcd. for $C_9H_{11}N$: C, 81.15; H, 8.33. Found: C, 81.10; H, 8.25.

The olefin darkened on standing although the change in refractive index was very slight.

The toluene distillate from the dehydration gave 5 g. of a white solid, m. p. 182–192°, by treatment with ethereal hydrogen chloride. This was shown to be mainly aniline hydrochloride, m. p. 196.5–197.5°, and presumably arose from impurities in the methyl anthranilate. When the toluene was treated with more ethereal hydrogen chloride and diluted with ether another solid, m. p. 166–172°, was obtained. This was the impure hydrochloride of 2-(*o*-aminophenyl)-propene; the pure hydrochloride, m. p. 163–168.5°, was obtained from the pure olefin and showed no mixed m. p. depression with the 166–172° material; the m. p. of a mixture with aniline hydrochloride was depressed.

4-Methylcinnoline (IV).—A solution of 174 g. (1.3 moles) of 2-(*o*-aminophenyl)-propene in 875 ml. of water and 97 ml. (3.5 equivalents) of concd. sulfuric acid was diazotized in an ice-salt-bath by the dropwise addition of 90 g. of sodium nitrite in 195 ml. of water with stirring. About ninety minutes were required for the addition to maintain the temperature below 5° and small additional amounts of sodium nitrite solution were required so that a very slight excess was present. The diazotized solution was diluted to 12 liters with ice and water, stored in the dark at room temperature for three days, made basic with 150 g. of sodium hydroxide in 150 ml. of water and extracted for ten or eleven hours in a continuous extractor[10] with benzene. Removal of the benzene under reduced pressure gave 168–170 g. (89–90%) of 4-methylcinnoline, m. p. 63–70°. A second extraction (thirteen hours) of the aqueous solution yielded only 1.3 g. of less pure product. The crude product was used without purification. One recrystallization from hexane gave light orange crystals, m. p. 73–74.5°, which developed a deep red color in acid solution. The analytical sample was purified by distillation, b. p. 135–137° (3 mm.), sublimation at 110° and 3 mm. and two more recrystallizations from hexane. The product, m. p. 72.5–74°, was light yellow, and gave a light yellow color in acid solution. Treatment with picric acid in ether gave red-brown crystals which became pale green after decolorizing and recrystallizing twice from alcohol. The m. p. of the picrate was 176–177°.

4-Styrylcinnoline (V).—The directions of Ainley and King[11] for 4-styrylquinoline were followed. A mixture of 72 g. (0.5 mole) of crude 4-methylcinnoline, 250 ml. of benzaldehyde and 32 g. of anhydrous zinc chloride was refluxed for five hours, cooled in an ice-bath and treated with 300 ml. of benzene and 300 ml. of 2 *N* hydrochloric acid. A yellow-green solid precipitated and the mixture was heated to boiling on a water-bath for an hour with initial swirling, cooled in ice and filtered. After thorough washing with benzene the solid hydrochloride was dried overnight at 80° and converted to the free base by shaking for one hour with 600 ml. of 3 *N* sodium hydroxide. The dark yellow solid was filtered, washed thoroughly with water and dried to constant weight at 80°. The weight of crude material, m. p. 113–118°, was slightly more than the theoretical. The product was purified by recrystallization from methanol and vacuum sublimation.

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

(10) Wilson, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1941, Coll. Vol. I, 2nd ed., p. 277.

(11) Ainley and King, *Proc. Roy. Soc.* (London), **125B**, 60 (1938).

Cinnoline-4-carboxylic Acid (VI).—Following the directions of Ainley and King[11] for the preparation of cinchoninic acid, 46.4 g. (0.2 mole) of crude, powdered 4-styrylcinnoline suspended in 500 ml. of water and 500 ml. of pyridine was stirred and cooled in ice and salt while 80.5 g. (0.51 mole, 95%) of potassium permanganate was added in small portions so that the temperature remained below 2°. The addition required ninety-five minutes; the mixture was stirred fifteen minutes with cooling, allowed to warm to room temperature and stirred for three hours longer. A Hershberg-type stirrer[9] is recommended. The mixture was filtered using a filter aid and the manganese dioxide was shaken twice with 0.1 *N* sodium hydroxide to remove additional product. The filtrate was concentrated to 500 ml. at 50° and 40 mm. using an antifoam device when necessary and the concentrate was filtered and acidified to *p*H 3 with 6 *N* hydrochloric acid. The yellow cinnoline-4-carboxylate was filtered, washed with water and dried to constant weight at 60°. Contaminating benzoic acid was removed by shaking for one hour with 200 ml. of ether. The product after filtering and washing with ether weighed 27.4 g. (83%). It could be purified by decolorizing in dilute sodium carbonate solution and acidifying carefully or by recrystallizing from large volumes of methanol. The neutral equivalent was determined on a carefully purified sample. Calcd.: 174.16. Found: 173.9, 173.3. The decomposition point depended upon the rate of heating.

Cinolinne (VII).—Cinnoline-4-carboxylic acid was decarboxylated by heating 5.0 g. with 25 g. of benzophenone under nitrogen for ninety minutes in a bath at 155–165° following a procedure described by Schofield and Simpson.[12] The reaction mixture was dissolved in 180 ml. of ether and extracted with 100 ml. of 1 *N* hydrochloric acid in three portions. The hydrochloric acid extracts were combined, washed once with ether, cooled in an ice-bath, saturated with potassium carbonate and extracted with ether. The red ether solution was dried over anhydrous potassium carbonate, decolorized and treated with excess ethereal hydrogen chloride with ice cooling. Light yellow crystals of cinnoline hydrochloride monohydrate were obtained in 72% yield (3.84 g.). This material melted gradually below 100°, sublimed above this temperature as the anhydrous compound and then melted at 154–156° (reported[13] 156–160°). For analysis it was sublimed at 110–115° (3 mm.) and recrystallized from absolute ethanol and ether. The hydrochloride was converted to the free base with 6 *N* sodium hydroxide, taken up in benzene and distilled under reduced pressure. Cinnoline was obtained as a pale yellow solid, m. p. 37–38°, under nitrogen. On exposure to air at 20–25° it liquefied within thirty seconds and became green on standing overnight. A picrate, m. p. 196–196.5° (reported[13] 190°), and methiodide, m. p. 168–170.5° (dec.) when placed in the m. p. bath at 163° (reported[13] 169°) were prepared.

Less pure cinnoline could also be obtained in lower yields by heating the acid without solvent (above 190°) or in nitrobenzene.

Ethyl Cinnoline-4-carboxylate (VIII).—Crude cinnoline-4-carboxylic acid was esterified by refluxing with absolute alcohol and sulfuric acid for three hours. The crude ester dissolved in boiling hexane leaving a black tar and crystallized after the solution was concentrated. The yield was 77% of bright yellow plates. Saponification equivalent. Calcd.: 202.21. Found: 203.7.

The ester was also obtained in 83% yield by adding a benzene solution of the acid chloride to absolute alcohol. The acid chloride was prepared by refluxing the acid with thionyl chloride in benzene; it decomposed if the benzene was removed even at reduced pressure. Excess thionyl chloride was removed by distillation of the benzene while the volume was maintained with fresh benzene. The acid chloride could be precipitated from benzene solution with petroleum ether, but soon decomposed. An attempt to prepare it with phosphorus pentachloride gave a tar from which no ester could be isolated after reaction with alcohol.

(12) Schofield and Simpson, *J. Chem. Soc.*, 512 (1945).

(13) Busch and Rast, *Ber.*, **30**, 521 (1897).

4-Cinnolyl ϵ-Benzamidoamyl Ketone (IX).—A modification of the method of Ainley and King[11] was used. To a stirred benzene suspension of sodamide (from 2.07 g., 0.09 g.-atom of sodium) was added 26.3 g. (0.1 mole) of ethyl ϵ-benzamidocaproate[14] in 75 ml. of dry benzene and the reaction mixture was stirred and refluxed in an oil-bath for one hour. A solution of 12.1 g. (0.06 mole) of 4-carbethoxycinnoline in 50 ml. of benzene was added dropwise during thirty minutes and the mixture stirred and heated at 85–90° for eight hours. The black, homogeneous solution was cooled to room temperature and dissolved in 400 ml. of water. Carbon dioxide was bubbled rapidly through the solution for fifteen minutes, the oil that separated was taken up in chloroform, and the aqueous layer was heated with decolorizing charcoal at 100° for one hour and filtered. The filtrate was acidified with 6 *N* hydrochloric acid and gave 1.7 g. (16% recovery) of cinnoline-4-carboxylic acid. Chloroform was removed from the oil under reduced pressure and the dark residue was heated on a steam-bath for ninety minutes with 250 ml. of 18% hydrochloric acid. The reaction mixture was poured on ice, basified with potassium carbonate and extracted with chloroform. The chloroform was washed twice with dilute sodium carbonate, once with water, and the chloroform was removed under reduced pressure. The dark oil solidified when cooled and weighed 9.7 g. (47%). It was recrystallized from methanol. The m. p. and analysis are given in Table I.

Attempts to hydrolyze the benzamido group according to the directions of Ainley and King[11] gave benzoic acid but the basic material was an oil and gave oily salts even when carefully purified 4-cinnolyl ϵ-benzamidoamyl ketone was used as the starting product. The oily product was brominated according to the procedure of Ainley and King[11] but the solid that was obtained in low yield decomposed readily to a tar and could not be purified. Ring closure and reduction were attempted using the procedure of Sargent[8] but without success.

4-Acetocinnoline (XIII).—The condensation[15] was carried out by refluxing 30 g. (0.15 mole) of ethyl cinnoline-4-carboxylate and 26.4 g. (0.30 mole) of ethyl acetate with 0.23 mole of sodium ethoxide in 70 ml. of benzene for seventeen hours. The product was hydrolyzed by adding 120 ml. of hot 54% sulfuric acid, removing benzene by distillation, refluxing the acid solution for two and one-half hours and pouring into a solution of 135 g. of potassium carbonate in ice and water (375 g.). A dark green solid precipitated and was collected and dried overnight *in vacuo;* it was then extracted in a Soxhlet extractor with hexane for ten hours to yield 15.8 g. (61%) of dark yellow 4-acetocinnoline. Recrystallization from hexane gave 12.6 g. (49%) of pure material, m. p. 100–101°. The oxime was prepared.

A 91% yield of the ketoester (XII) was obtained by isolating a product before hydrolysis and decarboxylation. It was purified by recrystallization from alcohol, and was converted to 4-acetocinnoline without difficulty.

4-Acetocinnoline was oxidized with potassium hypochlorite[16] to cinnoline-4-carboxylic acid (77% yield).

4-Cinnolyl Chloromethyl Ketone (XIV).—A benzene solution of the acid chloride prepared from 17.4 g. (0.10 mole) of cinnoline-4-carboxylic acid was added dropwise during thirty minutes to a cooled, methylene chloride solution containing 1 mole of diazomethane[17] in an all-glass apparatus with stirring. The reaction mixture was allowed to stand at room temperature overnight; it was then cooled to 0° and 250 ml. of ether saturated with hydrogen chloride was added with stirring during twenty-five minutes. After two hours of stirring in the cold and one and one-half hours at room temperature the dark red precipitate was collected on a sintered glass funnel, washed with

(14) This ester was supplied by Dr. C. C. Price and co-workers of the University of Illinois.

(15) Koelsch, *J. Org. Chem.*, **10**, 34 (1945).

(16) Newman and Holmes, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1943, Coll. Vol. II, p. 429.

(17) Lutz, THIS JOURNAL, **68**, 1288 (1946).

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.

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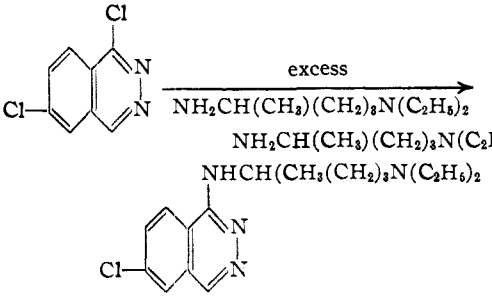
[CONTRIBUTION FROM THE LABORATORIES OF THE UNIVERSITY OF MARYLAND]

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).