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FURTHER STUDIES OF AMINOBENZACRIDINES[1]

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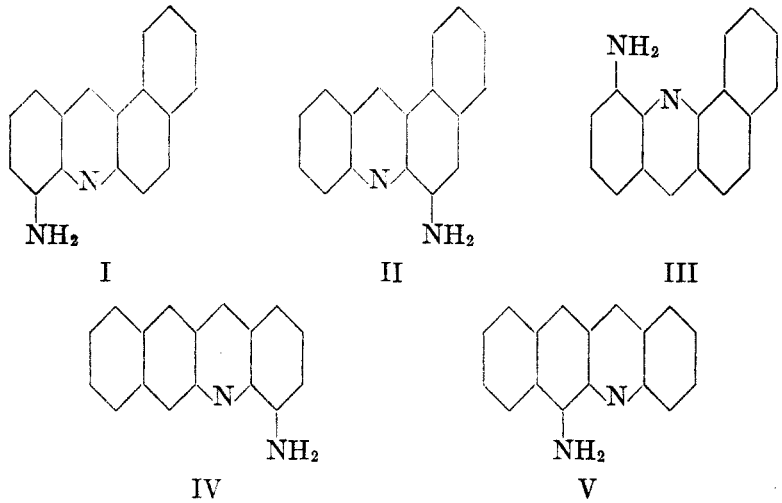
In previous publications (1, 2) from this laboratory the preparation of a series of substituted aminobenzacridines was described. The present paper describes further members of this series of compounds with special emphasis on those in which the amine group is peri rather than para to the hetero nitrogen atom. The number of possible isomers is five.



Of these I and III were made in satisfactory yields, partial syntheses of IV and V were achieved, and II was not studied, before termination of the study of this series became necessary.

2-Bromo-3-nitrobenzoic acid condensed readily with 1- or 2-naphthylamine to give a 2-naphthylamino-3-nitrobenzoic acid which was readily cyclized with phosphorus oxychloride. The acridones so obtained were reduced by stannous chloride to the corresponding aminobenzacridones and by aluminum amalgam to the desired aminoacridines (I and III). Proof of the structure of the products was obtained by diazotization of the aminobenzacridones and conversion of them to triazolobenzacridones.

Compound IV was approached by condensing 3-amino-2-naphthoic acid with *o*-nitrobromobenzene and cyclizing the product with phosphorus oxychloride. The yields in this latter step were poor. The original condensation product also was reduced to 3-(*o*-aminophenylamino)-2-naphthoic acid. This gave a cyclic amide on heating, and the desired aminobenzacridone was not obtained.

Compound V was approached by coupling 3-phenylamino-2-naphthoic acid

[1] From the Ph.D. thesis of F. M. Cowen, Purdue University, June 1947.

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with benzene diazonium chloride, reducing the dye with sodium hydrosulfite, and cyclizing the resulting 4-amino-3-phenylamino-2-naphthoic acid with phosphorus pentoxide. Here again the yields in the last step were very poor, so poor in fact that insufficient material was obtained for an analysis. The diaminonaphthoic acid diazotized satisfactorily and gave a stable N-phenyltriazolonaphthoic acid.

All attempts to alkylate I or III with side chains common to antimalarials of the Plasmoquin type were unsuccessful. The amines were recovered unchanged from treatments of the following types:

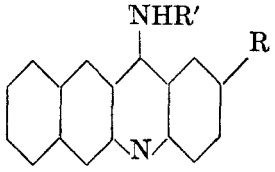
(a) Refluxing with γ-diethylaminopropyl chloride in benzene, butanol, or hexanol for fourteen hours.

(b) Refluxing first with methylmagnesium iodide and then with γ-diethylaminopropyl chloride.

(c) Refluxing with acrylonitrile (alone and with copper sulfate), or with 1-diethylamino-3-butanone, epichlorohydrin, or 2-chloro-1-nitroethane with or without solvents.

This surprising resistance to alkylation prevented us from obtaining compounds of a type suitable for antimalarial testing. It is hoped eventually to prepare a sodium derivative of I, or its *p*-toluenesulfonyl derivative and condense this with dialkylaminoalkyl halides.

Two new derivatives of 12-aminobenz(b)acridine (VI and VII) were also prepared



VI R = —H
R' = 6-methoxy-8-quinolyl

VII R = —OCH_3
R' = —$(CH_2)_3N(C_2H_5)_2$

by condensing 3-amino-2-naphthoic acid with aniline or anisidine, cyclizing the products with phosphorus oxychloride, and condensing the chlorobenzacridines so obtained with the appropriate side chain amine in phenol. Neither of these compounds showed antimalarial activity.

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EXPERIMENTAL

Potassium 2-bromo-3-nitrobenzoate. The intermediate, potassium 2-bromo-3-nitrobenzoate, was prepared from 2-bromo-3-nitrobenzoic acid by the addition of aqueous potassium hydroxide solution to an alcoholic solution of the acid till just basic to phenolphthalein. Evaporation of the solvent gave the white salt. The bromonitrobenzoic acid was synthesized from 3-nitrophthalic acid according to the directions in Organic Syntheses (3).

2-(2'-Naphthyl)amino-3-nitrobenzoic acid (I-a). A mixture of 71 g. of potassium 2-bromo-3-nitrobenzoate, 105 g. of 2-naphthylamine, 18 g. of anhydrous potassium carbonate, 2 g. of precipitated copper, and 150 ml. of *n*-butanol was gradually heated with stirring to 110°. When the vigorous reaction had subsided, the solution was refluxed for two and three-fourths hours. The hot product was poured into 2.5 l. of cold water containing 10 g. of

potassium hydroxide, stirred, and filtered free of excess amine. The filtrate was acidified with concentrated hydrochloric acid and the precipitate filtered, washed with water, and dried. The greenish-yellow solid weighed 60 g. (78%) and was purified by two recrystallizations from dilute ethanol, reprecipitation from a basic solution, and recrystallization from glacial acetic acid. The yellow needles, m.p. 189–191°, were obtained in a 41% yield. A pure sample, obtained by several recrystallizations from dilute ethanol and methanol, melted at 190–192°.

Anal. Calc'd for $C_{17}H_{12}N_2O_4$: C, 66.23; H, 3.92.
Found: C, 66.34, 66.46; H, 3.91, 4.00.

2-(1'-Naphthyl)amino-3-nitrobenzoic acid (III-a). By a procedure similar to that used for the preparation of I-a, III-a was synthesized from potassium 2-bromo-3-nitrobenzoate and 1-naphthylamine. Care was needed to prevent too vigorous a reaction in the initial stages of the condensation. The crude acid, obtained in 62% yields, was purified by reprecipitation from a basic solution of the acid with dilute hydrochloric acid. The orange-yellow product, m.p. 200–212°, was pure enough for cyclization purposes. A sample recrystallized several times from dilute ethanol and dilute methanol gave light orange leaves, m.p. 219–220°.

Anal. Calc'd for $C_{17}H_{12}N_2O_4$: C, 66.23; H, 3.92.
Found: C, 66.22, 66.30; H, 3.93, 4.07.

3-Amino-2-(2'-naphthyl)aminobenzoic acid (I-b). A solution of 2 g. of I-a in 100 ml. of ethanol was reduced with hydrogen at three atmospheres and room temperature using 0.1 g. of platinum oxide (Adams) catalyst. When the calculated amount of hydrogen had been absorbed, the product was filtered free of catalyst, reduced in volume, and poured into an ice-water mixture. The solid product was recrystallized three times from dilute ethanol as slender, white needles, m.p. 216–218°.

Anal. Calc'd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07.
Found: C, 73.35, 73.25; H, 5.06, 4.99; N, 10.07, 10.01.

3-Amino-2-(1'-naphthyl)aminobenzoic acid (III-b). The reduction of III-a was carried out in a similar fashion to that of I-a. The crude product was purified by two recrystallizations from dilute ethanol and three recrystallizations from benzene-heptane. The light tan, leaf-like crystals melted at 153.5–154.5°.

Anal. Calc'd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07.
Found: C, 73.36, 73.46; H, 5.09, 5.18.

8-Nitro-12(7)-benz(a)acridone (I-c). A mixture of 80 g. of I-a and 360 ml. of phosphorus oxychloride was refluxed for two hours. The hot solution was poured into a mixture of 1500 g. of ice and 1.5 l. of concentrated, aqueous ammonia. The precipitate was filtered, washed with water, and hydrolyzed by suspension in boiling, dilute hydrochloric acid for one hour. The crude acridone was purified by dissolving it in a warm mixture of 1 liter of ethanol, 75 ml. of water, and 20 g. of sodium hydroxide, filtering the solution, and reprecipitating the acridone with excess dilute hydrochloric acid. The brownish-yellow precipitate, weighing 63 g. (84%), melted at 280–285°. A sample recrystallized three times from pyridine gave light orange needles, m.p. 293.5–294.5°.

Anal. Calc'd for $C_{17}H_{10}N_2O_3$: C, 70.34; H, 3.47; N, 9.65.
Found: C, 70.31, 70.42; H, 3.48, 3.55; N, 9.64, 9.71.

11-Nitro-7(12)-benz(c)acridone (III-c). By a similar procedure to that described above for the preparation of I-c, III-a was converted to III-c in 73% yields of reprecipitated product. In order to hydrolyze the chloronitrobenzacridine (III-d), it was necessary to reflux the suspension for nine hours in 6 *N* hydrochloric acid. A sample, recrystallized three times from pyridine, gave orange needles, m.p. 272–274°.

Anal. Calc'd for $C_{17}H_{10}N_2O_3$: C, 70.34; H, 3.47.
Found: C, 70.31, 70.42; H, 3.45, 3.40.

12-Chloro-8-nitrobenz(a)acridine (I-d). A mixture of 2.4 g. of I-c and 10 ml. of phosphorus oxychloride was refluxed two and one-half hours. The warm product was poured into a mixture of 75 ml. of concentrated, aqueous ammonia and 200 g. of ice. When the excess

phosphorus oxychloride had been destroyed, the suspension was extracted with chloroform; the chloroform extracts were dried and evaporated to dryness. The light yellow solid was crystallized from hot, dry benzene as 0.7 g. (27%) of long, slender, light yellow needles. One rapid recrystallization from dry benzene gave a compound melting at 218–219°. The product was dried *in vacuo* over phosphorus pentoxide, since it was readily hydrolyzed to the acridone (I-c) by moisture.

Anal. Calc'd for $C_{17}H_9ClN_2O_2$: Cl, 11.49. Found: Cl, 11.47, 11.56.

7-Chloro-11-nitrobenz(c)acridine (III-d). When III-c was refluxed with phosphorus oxychloride and isolated by a similar procedure to that employed for I-d, 2.4 g. (89%) of reddish-orange needles, crystallized once from benzene, was obtained. Two recrystallizations from the same solvent gave light yellow needles with a greenish fluorescence, m.p. 252.5–253.5°.

Anal. Calc'd for $C_{17}H_9ClN_2O_2$: C, 66.13; H, 2.94; Cl, 11.49.
Found: C, 66.09, 65.98; H, 2.94, 2.98; Cl, 11.50, 11.57.

8-Amino-12(7)benz(a)acridone (I-e). A suspension of 3.5 g. of I-c, 4.5 ml. of concentrated hydrochloric acid, and 14 ml. of ethanol was heated on a steam-bath for nine hours with a solution of 10.8 g. of stannous chloride dihydrate in 10.8 ml. of concentrated hydrochloric acid. The product was isolated according to the direction of Lehmstedt and Schrader (4). Crystallization from pyridine gave 1.5 g. (48%) of glistening brown plates, m.p. 313–315° (d.). Recrystallization from ethanol gave yellow needles, m.p. 317–318° (d.).

Anal. Calc'd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76.
Found: C, 78.48; 78.38; H, 4.68; 4.77; N, 10.71, 10.60.

11-Amino-7(12)-benz(c)acridone (III-e). The preparation and isolation of III-e were accomplished by a procedure identical with that for the preparation of I-e but starting with III-c. The moist product was not purified but was used directly in the preparation of III-g. A small sample crystallized from ethanol as small yellow needles, m.p. 325–326° (d.).

Anal. Calc'd for $C_{17}H_{12}N_2O$: N, 10.76. Found: N, 10.53, 10.46.

13-Triazolo(fg)benz(a)acridone (I-f). The diazotization of 1 g. of I-e by the method of Lehmstedt and Schrader gave 0.7 g. (67%) of flat leaf-like, light yellow crystals, crystallized from benzene. Recrystallization from this same solvent gave a compound melting at 226–228° (d.).

Anal. Calc'd for $C_{17}H_9N_3O$: C, 75.27; H, 3.34.
Found: C, 75.30, 75.39; H, 3.35, 3.30.

7-Triazolo(fg)benz(c)acridone (III-f). In a similar fashion 0.9 g. (60%) of III-f, crystallized from benzene, was obtained from 1.4 g. of III-e. Two recrystallizations from benzene gave light yellow, fibrous needles, m.p. 212–213° (d.).

Anal. Calc'd for $C_{17}H_9N_3O$: C, 75.27; H, 3.34.
Found: C, 75.14, 75.08; H, 3.40, 3.43.

8-Aminobenz(a)acridine (I). The reduction of 24.2 g. of I-c to 8-aminobenz(a)acridan and the subsequent oxidation to the acridine (I) was carried out by the method of Albert and Ritchie (5). A 100% excess of aluminum foil was used in the reduction. Only a few drops of 10% ferric chloride solution (oxidizing agent) were necessary, indicating complete, or almost complete, oxidation during the isolation of the product. The alcoholic extracts were reduced to a volume of 100 ml. and diluted with 750 ml. of water. The greenish-yellow precipitate (20 g.) was extracted with ether. The ether extracts were evaporated to dryness and extracted with ether. Removal of the solvent gave an orange-brown residue which was extracted with heptane. Evaporation of the heptane gave 1.5 g. (7%) of a solid which was recrystallized twice from ethanol as light yellow needles, m.p. 175–177°.

Anal. Calc'd for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.47.
Found: C, 83.60, 83.47; H, 4.94, 4.99; N, 11.46, 11.34.

The ether-insoluble fraction (13 g.) was recrystallized several times from dilute pyridine as light yellow plates, m.p. 315–317° (d.). An analysis indicated it was the aminoacridone (I-e).

Anal. Calc'd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76.
Found: C, 78.42, 78.53; H, 4.63, 4.68; N, 10.76, 10.84.

11-Aminobenz(c)acridine (III). Moist, crude III-e, obtained by the reduction of III-c with stannous chloride was reduced, as above, with aluminum-mercury amalgam. The oxidative step with 10% ferric chloride solution indicated that oxidation had been completed during isolation. The orange-yellow solid from two extractions with ether and heptane weighed 8.5 g. [32% based on the nitroacridone (III-c) used in the preliminary reduction]. Several recrystallizations from ethanol and heptane gave yellow, fibrous needles, m.p. 150–151°.

Anal. Calc'd for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.47.

Found: C, 83.51, 83.38; H, 4.91, 4.81; N, 11.45, 11.31.

3-(2'-Nitrophenyl)amino-2-naphthoic acid (IV-a). A mixture of 12.5 g. of 3-amino-2-naphthoic acid (6), 50 g. of 2-bromonitrobenzene, 50 g. of anhydrous potassium carbonate, 0.15 g. of precipitated copper, and 120 ml. of cyclohexanol was refluxed, with stirring, for three hours at 150°. The dark red solution was poured into 1500 ml. of water containing 15 g. of potassium hydroxide. Cyclohexanol and unreacted 2-bromonitrobenzene were removed by steam distillation from the solution whose volume was maintained at about 1500 ml. by the occasional addition of water. Filtration and acidification of the filtrate with excess concentrated hydrochloric acid gave a brown precipitate which was filtered while hot (85°). The solid product was redissolved in a solution of 1500 ml. of water and 12 g. of sodium hydroxide, reprecipitated with excess concentrated hydrochloric acid, filtered white hot, and the filter cake washed with hot water till the washings were no longer acid. The reprecipitation process was repeated and an orange-brown precipitate obtained which weighed 53 g. (70% based on 2-bromonitrobenzene). The crude acid was readily purified by recrystallizations from glacial acetic acid and ethyl acetate. A pure sample, recrystallized several times from ethanol as orange needles, melted at 247–248°.

Anal. Calc'd for $C_{17}H_{12}N_2O_4$: C, 66.23; H, 3.92; N, 9.09.

Found: C, 66.18, 66.31; H, 3.91, 4.00; N, 9.01, 8.96.

3-(2'-Aminophenyl)amino-2-naphthoic acid (IV-b). A mixture of 4.5 g. of IV-a, 10 ml. of ethanol, and 5.8 ml. of concentrated hydrochloric acid was heated on a steam-bath for six hours with a solution of 14 g. of stannous chloride dihydrate in 14 ml. of concentrated hydrochloric acid. The slurry was cooled, filtered free of excess acid liquors, and dissolved in 80 ml. of 2 *N* sodium hydroxide solution. After heating the solution for ten minutes on a steam-bath, it was acidified with glacial acetic acid. The suspension was made alkaline with concentrated, aqueous ammonia and filtered. The filter cake was washed with dilute ammonia and the washings added to the filtrate. Acetic acid was added to *p*H 6 and the yellow precipitate was filtered, washed with water, and dissolved in 500 ml. of ethanol. After treatment with Norit and concentration to a volume of 350 ml., the solution was allowed to cool. The yellow needles which deposited were added to those obtained by further concentration of the mother liquors for a total yield of 3.2 g. (89%). The product was purified by reprecipitation at *p*H 6 and two recrystallizations from methanol. The bright yellow needles melted at 219.5–220°, with the evolution of a gas, resolidified and remelted at 255–256°. This behavior can be attributed to the formation of the internal amide (IV-c).

Anal. Calc'd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07.

Found: C, 73.44, 73.48; H, 5.09, 5.04.

Internal amide of 3-N-(2'-aminophenyl)amino-2-naphthoic acid (IV-c). A small quantity of IV-b was heated in purified mineral oil to 230°. When foaming had ceased, the mixture was cooled and diluted with petroleum ether, and recrystallized once from dilute ethanol, once from petroleum ether-ethanol, and finally from methanol as bright yellow plates, m.p. 255.5–256.5°.

Anal. Calc'd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65.

Found: C, 78.45, 78.58; H, 4.79, 4.72.

4-Nitro-12(5)-benz(b)acridone (IV-d). A mixture of 1 g. of IV-a and 5 ml. of phosphorus oxychloride was refluxed for two hours. The hot solution was poured into an ice-concentrated aqueous ammonia mixture. When the excess phosphorus halides had been destroyed, the solid was removed and refluxed with dilute hydrochloric acid for two hours. The deep red precipitate was filtered, washed with water, and recrystallized twice from

dilute pyridine as 0.1 g. (11%) of beautiful dark red plates with a greenish fluorescence, m.p. 309–310°.

Anal. Calc'd for $C_{17}H_{10}N_2O_3$: C, 70.34; H, 3.47.
Found: C, 70.40, 70.47; H, 3.65, 3.69.

4-Amino-3-N-phenylamino-2-naphthoic acid (*V-a*). A solution of 9.6 g. of sulfanilic acid monohydrate, 3.5 g. of potassium carbonate, and 50 ml. of water was heated and stirred till all of the solid had dissolved. After cooling in an ice-bath to 15°, a solution of 3.7 g. of sodium nitrite in 10 ml. of water was added. The resulting solution was immediately poured into a well-stirred mixture of 10.6 ml. of concentrated hydrochloric acid and 60 g. of ice. The suspension was placed in an ice-bath for fifteen minutes. The mixture of the white diazonium salt was then poured into a previously prepared solution of 13.2 g. of VI-a, 19.1 g. of potassium carbonate, 100 ml. of water, 50 ml. of methanol, and 125 g. of cracked ice. The solution of the red dye was allowed to stand at room temperature for one hour, then heated to 45–50° and 23 g. of sodium hydrosulfite cautiously added. When all of the reducing agent had been added, the yellow-orange mixture was heated at 80° until foaming subsided. The product was cooled to room temperature and carefully acidified with 15 ml. of glacial acetic acid. The yellow precipitate was quickly filtered, washed with water, and dried *in vacuo*. The yield was 13 g. (94%) of a solid which readily oxidized on exposure to the air. The acid was analyzed as the monohydrochloride monoethanolate by treating an ether solution of V-a with excess hydrogen chloride and recrystallizing the solid three times from ethanol-isopropyl ether, as small, light yellow needles, m.p. 233–236°(d.). A gas was evolved above 150°.

Anal. Calc'd for $C_{17}H_{15}ClN_2O_2 \cdot C_2H_5OH$: C, 63.24; H, 5.87; Cl, 9.83.
Found: C, 63.33, 63.43; H, 5.83, 5.78; Cl, 9.72, 9.65.

3-Phenylnaphtho(1.2)triazole-4-carboxylic acid (*V-b*). Crude V-a (5.6 g.) was dissolved in a warm solution of 3 g. of sodium bicarbonate and 1.6 g. of sodium nitrite in 200 ml. of water. The cooled mixture was treated with 35 ml. of concentrated hydrochloric acid, added dropwise over a period of fifteen minutes, and allowed to stand an additional fifteen minutes. Neutralization with sodium acetate gave a purple precipitate. The product was purified by reprecipitation and three recrystallizations from glacial acetic acid. The small, white needles melted at 325–327°(d.).

Anal. Calc'd for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.83.
Found: C, 70.54, 70.42; H, 3.80, 3.85.

6-Amino-12(5)-benz(b)acridone (*V-c*). A solution of 13 g. of V-a and 43 ml. of 85% phosphoric acid was stirred at 100° while 110 g. of phosphorus pentoxide was added over a period of one-half hour. The temperature was allowed to rise to 155° during the addition and then heated at 150–160° for one-fourth hour. The viscous solution was poured into a mixture of 500 g. of ice and 600 ml. of concentrated, aqueous ammonia. The dark purple precipitate weighed 12.5 g. Continuous extraction of the product with 300 ml. of benzene gave a solution with a greenish fluorescence. The benzene solution was chromatographed on an aluminum oxide column and the column was developed with a 2:1 heptane-acetone mixture. The well-defined greenish-yellow layer was eluted with acetone and the acetone solution evaporated to dryness. Crystallization of the solid from ethanol gave small, brownish-yellow plates with a green fluorescence, m.p. 308–309°. There was not enough for an analysis.

3-N-Phenylamino-2-naphthoic acid (*VI-a*). A mixture of 280 g. (3 moles) of aniline and 167 g. (0.89 mole) of 3-hydroxy-2-naphthoic acid was refluxed for sixty-six hours. The cooled mixture was diluted with 100 ml. of ether and filtered. The yellow crystalline product was washed with ether. The washings and filtrate were combined, reduced in volume, and the recovered solid added to the above product. The powdered crude anilide was suspended in a warm solution of 1.5 l. of water and 40 g. of sodium hydroxide, filtered, and the moist filter cake treated with additional dilute sodium hydroxide solution, filtered, washed with water, and dried. The yellow, base-insoluble product weighed 130 g. (45%). A small sample recrystallized from glacial acetic acid gave greenish-yellow needles, m.p. 167–171°. Reported (7) 168–169.5°.

The anilide (106 g.) was hydrolyzed by refluxing the solid in a solution of 450 ml. of ethanol, 120 ml. of water, and 120 g. of potassium hydroxide for eight hours. The mixture was diluted with 3 l. of water, filtered, and the filtrate acidified with concentrated hydrochloric acid. The yellow solid, obtained in 97% yield (80 g.), was crystallized from ethanol as bright yellow needles, m.p. 239–241°. Four recrystallizations from four different solvents, ethanol, ethyl acetate, methanol, and benzene, gave light yellow needles, m.p. 239–240° (sintering at 236.5°). Reported by Schöpff m.p. 235–237°.

Anal. Calc'd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98.
Found: C, 77.51, 77.62; H, 4.90, 4.84.

3-N-(4'-Methoxyphenyl)amino-2-naphthoic acid (VII-a). 3-Hydroxy-2-naphthoic acid was converted to 3-amino-2-naphthoic acid by the procedure described in Organic Syntheses. 3-Bromo-2-naphthoic acid was obtained from this acid by the method of Kenner *et al.* (8). The crude product was purified by solution in dilute sodium hydroxide, treatment with Norit, filtration, and reprecipitation with concentrated hydrochloric acid.

A mixture of 3.3 g. of 3-bromo-2-naphthoic acid, 10.2 g. of *p*-anisidine, 2.1 g. of anhydrous potassium carbonate, and 0.05 g. of copper powder was heated at 180–190° for two hours. The mixture was poured into cold water containing 1 g. of sodium hydroxide, allowed to stand till the excess anisidine had solidified, and filtered. The filtrate was acidified with concentrated hydrochloric acid and the yellow precipitate purified by reprecipitation and recrystallization from ethanol. The bright yellow needles (1.0 g., 26%) melted at 234–238° (sintering). A small sample recrystallized from ethanol, melted at 237–239°. Reported by Wilke (9), m.p. 240°.

Anal. Calc'd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15.
Found: C, 73.63, 73.78; H, 5.24, 5.28.

12-Chlorobenz(b)acridine (VI-b). A mixture of 70 g. of VI-a and 390 g. of phosphorus oxychloride was refluxed for one and three-fourths hours. Most of the excess oxychloride was removed by distillation and the dark purple residue was poured into a mixture of ammonia, ice, and chloroform. When hydrolysis of the phosphorus oxychloride was complete, the chloroform solution was dried, filtered, and evaporated to dryness. The orange solid was recrystallized from dry benzene as 50 g. (71%) of orange-red needles, m.p. 174–175°. An analytical sample was prepared by two recrystallizations from benzene. The orange, fibrous needles melted at 173.5–174.5°. Reported by Schöpff (10), m.p. 165°.

Anal. Calc'd for $C_{17}H_{10}ClN$: C, 77.42; H, 3.82.
Found: C, 77.46, 77.32; H, 3.81, 3.88.

12-Chloro-2-methoxybenz(b)acridine (VII-b). By the same procedure described above, VII-a was converted to VII-b in 78% yields of once-crystallized product. A pure analytical sample, recrystallized from benzene as light orange, fibrous needles, melted at 211.5–212°.

Anal. Calc'd for $C_{18}H_{12}ClNO$: C, 73.59; H, 4.12; Cl, 12.07.
Found: C, 73.59, 73.46; H, 4.13, 4.20; Cl, 12.04, 12.11.

5(12)-Benz(b)acridone (VI-c). A small quantity of VI-b was refluxed with dilute hydrochloric acid for one hour. The insoluble acridone was filtered, washed with water, and recrystallized three times from dilute pyridine as golden-yellow plates with a greenish fluorescence, m.p. 305–306°. Reported by Schöpff, m.p. 304–305°.

Anal. Calc'd for $C_{17}H_{11}NO$: C, 83.24; H, 4.52; N, 5.71.
Found: C, 83.25, 83.39; H, 4.52, 4.58; N, 5.69, 5.75.

2-Methoxy-5(12)-benz(b)acridone (VII-c). The hydrolysis of VII-b in a 3:1 mixture of glacial acetic acid and dilute hydrochloric acid was accomplished by refluxing the suspension for one hour. The orange-brown product was recrystallized three times from pyridine as orange plates with a greenish fluorescence, m.p. 335–337°. Reported by Wilke, m.p. 175°.

Anal. Calc'd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76.
Found: C, 78.52, 78.63; H, 4.80, 4.86.

12-(6'-Methoxy-8'-quinolylamino)benz(b)acridine (VI). A mixture of 10 g. of VI-b, 7 g. of freshly distilled 8-amino-6-methoxyquinoline, and 30 g. of phenol was heated in an oil-bath at 105–115° for two hours. The dark red solution was poured into a solution of 25 g. of potassium hydroxide in 500 ml. of water. The orange solid was filtered, washed with

water, and crystallized from dilute pyridine as 12 g. (79%) of bright orange needles, m.p. 292–293°.

Anal. Calc'd for $C_{27}H_{19}NO_3$: C, 80.77; H, 4.77; N, 10.47.
Found: C, 80.75, 80.79; H, 4.80, 4.90; N, 10.45, 10.37.

12-(3'-Diethylamino-1'-propylamino)-2-methoxybenz(b)acridine (VII). Compound VII-b (7.4 g.) was heated in an oil-bath with 3.6 g. of 3-diethylamino-1-propylamine and 22 g. of phenol for one-half hour at 90–100°. The dark red solution was then heated at 100–110° for two hours. The cooled product was poured into a vigorously stirred solution of 25 g. of potassium hydroxide in 250 ml. of water and the gummy solid extracted with ether. The dry ether extracts were treated with hydrogen chloride until precipitation of the dark hydrochloride was complete. The gummy precipitate was crystallized from a mixture of ethanol, dioxane, and isopropyl ether as 5.3 g. (46%) of dark red crystals, m.p. 233°. Recrystallization from the same solvent mixture gave dark red, hygroscopic, minute crystals, m.p. 234–235° (d.), dried over phosphorus pentoxide *in vacuo* at 100°.

Anal. Calc'd for $C_{25}H_{31}Cl_2N_3O$: C, 65.21; H, 6.79.
Found: C, 64.97, 64.96; H, 6.65, 6.59.

SUMMARY

The preparation of various aminobenz(a, b, and c)acridines has been studied, especially with a view to obtaining the amino group in a peri rather than the para position to the hetero nitrogen atom.

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