[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

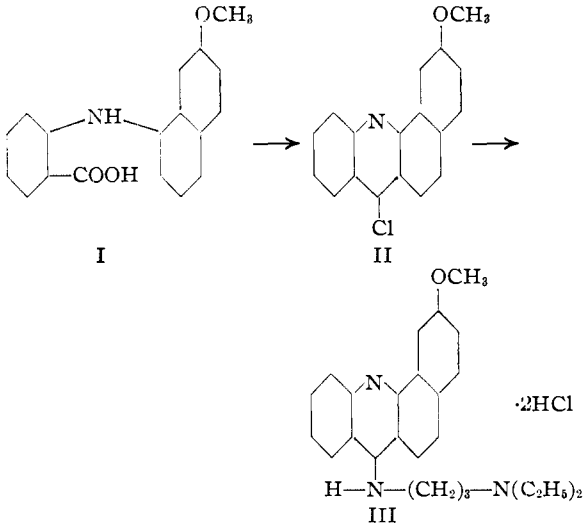
Synthesis of Substituted Aminobenzacridines[1,2]

BY G. BRYANT BACHMAN AND GEORGE M. PICHA[3]

Acridine derivatives have long been known to have marked therapeutic effects, and many of those derivatives which have a dialkylaminoalkylamino group in the 9-position are particularly effective in the treatment of malaria. As very few benzacridine derivatives of this type have been reported in the chemical literature, it was decided to prepare a number of dialkylaminoalkylaminobenzacridines, differing both in the nature of the side-chain and in the nature of the substituents on the nucleus, and to submit these for pharmacological testing. Although one synthesis of a benz[a]acridine was carried out, this investigation was largely confined to the preparation of various derivatives of benz[c]acridine.

In general, substitutions of a methoxyl group and a chlorine atom on an acridine nucleus are factors which may contribute to increased antimalarial activity. The particular derivatives selected for preparation in this work were chosen in such a manner as to determine the influence on antimalarial activity caused by altering the position of the methoxyl group in a benzacridine nucleus. A further contribution to this problem has been reported by Bachman and Wetzel.[4]

The synthesis of a typical derivative, 7-(3'-diethylaminopropylamino)-2-methoxybenz[c]acridine dihydrochloride (III), was carried out in the manner illustrated.



Condensation of the potassium salt of *o*-chlorobenzoic acid with 7-methoxy-1-naphthylamine gave N-(7'-methoxy-1'-naphthyl)-anthranilic acid (I), which was converted into 7-chloro-2-methoxybenz[c]acridine (II) by treatment with phosphorus oxychloride. Condensation of II with 3-diethylaminopropylamine in phenol solution gave III, which was purified and characterized as the dihydrochloride.

Other derivatives were prepared by carrying out the initial condensations with other benzoic acid derivatives and naphthylamines, and, in one case, by using 2-hydroxy-3-diethylaminopropylamine in the side-chain condensation. A chlorine atom was introduced into two of the final products by using the potassium salt of 2,4-dichlorobenzoic acid as a starting material. The other benzoic acid derivatives used in this work were 5-methoxyanthranilic acid, 2-chloro-5-methoxybenzoic acid, and 2-bromo-5-methoxybenzoic acid.

The synthesis of 5-methoxyanthranilic acid was accomplished by oxidizing 5-methoxyisatin with hydrogen peroxide. The statement of Halberkann[5] that 5-methoxyisatin cannot be obtained from 4-methoxyisonitrosoacetanilide is incorrect; this series of reactions was successfully carried out and was found to be a very satisfactory method for obtaining 5-methoxyanthranilic acid. The other benzoic acid derivatives were prepared by familiar reactions.

The amines used in this work were 1-naphthylamine, 2-naphthylamine, 5-methoxy-1-naphthylamine, 6-methoxy-1-naphthylamine and 7-methoxy-1-naphthylamine. The methoxynaphthylamines were all prepared by well-known procedures from the corresponding hydroxynaphthylamines.

The experimental data for the N-(1'-naphthyl)-anthranilic acids, 7-chlorobenz[c]acridines, and 7-(3'-diethylaminopropylamino)-benz[c]acridines which were prepared are given in Tables I, II and III.

Pharmacological Tests.—None of the substituted aminobenzacridines was found to be effective against duck malaria in low or moderate doses. The details of these tests will be described elsewhere.

Acknowledgments.—We wish to express our gratitude for financial support of this investigation by Eli Lilly and Company of Indianapolis and the Purdue Research Foundation, and to acknowledge a gift of certain chemicals by the National Aniline Division of the Allied Chemical and Dye Corporation.

Experimental

All melting points and boiling points are corrected. Except where otherwise indicated, the analyses were done by

(1) Read before the Symposium on Antimalarial Agents at the Atlantic City Meeting of the American Chemical Society, April, 1946.

(2) From the Ph.D. thesis of G. M. Picha, Purdue University, February, 1946.

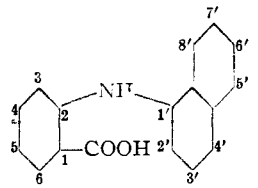
(3) Present address: G. D. Searle and Company, Chicago, Illinois.

(4) Bachman and Wetzel, *J. Org. Chem.*, in print.

(5) Halberkann, *Ber.*, **54**, 3079–3090 (1921).

TABLE I

DERIVATIVES OF N-(1′-NAPHTHYL)-ANTHRANILIC ACID

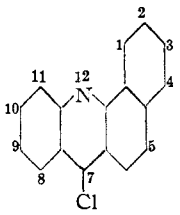


Derivative	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Unsubstituted[a]	25	207–208	$C_{17}H_{13}O_2N$				
4-Chloro	29	236–237.5	$C_{17}H_{12}O_2NCl$	68.57	68.50 68.64	4.06	4.10 4.15
5-Methoxy	24[b]	184–185.5	$C_{18}H_{15}O_3N$	73.70	73.64 73.57	5.16	5.20 5.26
5′-Methoxy	38	203–205	$C_{18}H_{15}O_3N$	73.70	73.66 73.61	5.16	5.01 4.97
4-Chloro-5′-methoxy	18	242–243	$C_{18}H_{14}O_3NCl$	65.96	65.99 66.06	4.31	4.22 4.30
6′-Methoxy	15	209–210	$C_{18}H_{15}O_3N$	73.70	73.67 73.55	5.16	5.26 5.21
7′-Methoxy	28	234–236	$C_{18}H_{15}O_3N$	73.70	73.57 73.63	5.16	5.20 5.26

[a] Reported by Ullmann, *Ann.*, **355**, 347–352 (1907), m. p. 208°. [b] The yield is that obtained from 2-bromo-5-methoxybenzoic acid. A yield of only 12% was obtained from the corresponding chloro acid.

TABLE II

DERIVATIVES OF 7-CHLOROBENZ[c]ACRIDINE

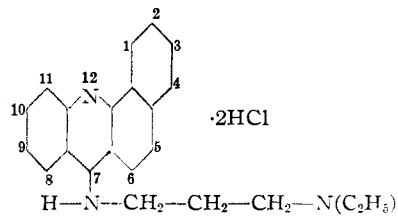


Derivative	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Unsubstituted	87	144–145	$C_{17}H_{10}NCl$	77.42	76.90 76.94	3.82	3.89 3.85
2-Methoxy	94	152–153	$C_{18}H_{12}ONCl$	73.59	73.64 73.53	4.14	4.16 4.11
3-Methoxy	91	171–172	$C_{18}H_{12}ONCl$	73.59	73.59 73.51	4.14	4.06 3.99
4-Methoxy	53	196–197	$C_{18}H_{12}ONCl$	73.59	73.65 73.53	4.14	4.19 4.09
4-Methoxy-10-chloro	50	236.5–237	$C_{18}H_{11}ONCl_2$	65.87	65.86 65.92	3.38	3.46 3.50
9-Methoxy	69	200–201	$C_{18}H_{12}ONCl$	73.59	[a]	4.14	[a]
10-Chloro	79	201–202	$C_{17}H_9NCl_2$	68.48	68.63 68.52	3.04	3.01 3.06

[a] Analytical sample lost; no more available.

TABLE III

DERIVATIVES OF 7-(3′-DIETHYLAMINOPROPYLAMINO)-BENZ[c]ACRIDINE DIHYDROCHLORIDE



Derivative	Yield, %	M. p.,[a] °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Unsubstituted[b]	56	228–230	$C_{24}H_{29}N_3Cl_2$	66.97	66.75 66.87	6.79	6.79 6.92
2-Methoxy[c,f]	48	190–192	$C_{25}H_{31}ON_3Cl_2$	65.21	65.00 65.20	6.79	6.82 6.93
3-Methoxy[d]	55	242–244	$C_{25}H_{31}ON_3Cl_2$	65.21	65.06 65.15	6.79	6.89 6.92
4-Methoxy[d,f]	64	260–262	$C_{25}H_{31}ON_3Cl_2$	65.21	65.03 65.30	6.79	6.78 6.86
4-Methoxy-2′-hydroxy[b]	48	224–226	$C_{25}H_{31}O_2N_3Cl_2$	63.02	62.84 62.92	6.56	6.62 6.64
4-Methoxy-10-chloro[b,e,f]	53	224–226	$C_{25}H_{30}ON_3Cl_3$	60.67	60.86 60.73	6.11	6.20 6.19
10-Chloro[d,f]	69	253–255	$C_{24}H_{28}N_3Cl_3 \cdot 1.5H_2O$	58.60	58.47 58.49	6.35	6.25 6.45

[a] All melting points are those of anhydrous samples. [b] Recrystallized from ethanol. [c] Recrystallized from methanol–isopropyl ether. [d] Recrystallized from ethanol–isopropyl ether. [e] The free base is only moderately soluble in ether. [f] Analysis by P. D. Somers, Purdue University.

the Huffman Microanalytical Laboratories, Denver, Colorado.

Methoxy-1-naphthylamines.—The 5-,[6,7] and 7-methoxy-1-naphthylamines[8] were prepared by the method of Lockett and Short from the corresponding hydroxy-1-naphthylamines. They were purified readily by vacuum distillation: 5-methoxy-1-naphthylamine, b. p. 143–145° (5 mm.); 6-methoxy-1-naphthylamine, b. p. 178–180° (6 mm.); 7-methoxy-1-naphthylamine, b. p. 151–153° (5 mm.). The last compound was carefully purified for analysis. It formed white crystals, m. p. 75–77°.

Anal.[9] Calcd. for $C_{11}H_{11}ON$: C, 76.27; H, 6.40. Found: C, 76.5, 76.3; H, 6.8, 6.6.

5-Methoxyanthranilic Acid.—The procedure given in "Organic Syntheses"[10] for the preparation of isonitrosoacetanilide was employed for the preparation of its 4-methoxy derivative, with the substitution of an equivalent amount of *p*-anisidine for the aniline. The yields from a large number of runs averaged 85% of a tan, crystalline product. Four recrystallizations from ethanol–water gave large white plates, m. p. 181–182°. Although reference to this compound has been made in the literature,[5] no physical constants or analytical data are reported.

Anal. Calcd. for $C_9H_{10}O_3N_2$: C, 55.66; H, 5.20. Found: C, 55.74, 55.83; H, 5.36, 5.48.

5-Methoxyisatin was prepared from 4-methoxyisonitrosoacetanilide by a procedure analogous to that given in "Organic Syntheses"[10] for the preparation of isatin. The average yield of 5-methoxyisatin (m. p. 185–190°) was 46%. A recrystallized sample (glacial acetic acid) was obtained as lustrous, almost black needles, m. p. 200–201°; reported by Halberkann,[5] who prepared it from 5-methoxydioxindole, m. p. 201–202°. The identity of this compound was confirmed by preparation of two of the derivatives described by Halberkann, N-acetyl-5-methoxyisatin, m. p. 143° (reported, m. p. 144–145°), and 9-methoxyindophenazine, m. p. 251° (reported m. p. 247°).

One hundred grams of crude 5-methoxyisatin was dissolved in one liter of 5% sodium hydroxide solution and oxidized by the dropwise addition of 150 cc. of 30% hydrogen peroxide. The solution was made distinctly acidic with hydrochloric acid and filtered from an insoluble residue. The filtrate was evaporated to dryness on a steam-bath, and the dry residue was extracted with 600 cc. of hot ethanol in three portions. When the extracts were cooled and diluted with ether, 56 g. (49%) of the hydrochloride precipitated. It was converted to the free base (94%, m. p. 148–150°) by treating it with the equivalent amount of sodium hydroxide. Sublimation (15 mm.) gave long, white needles, m. p. 151°. Reported by Pschorr,[11] m. p. 150°, by Friedlaender,[12] m. p. 179–180°.

2-Chloro- and 2-Bromo-5-methoxybenzoic Acids.—These acids were both prepared in about 80% yields by the Sandmeyer reaction from 5-methoxyanthranilic acid. The chloro acid was recrystallized from ethanol–water and then sublimed. It formed pale yellow needles, m. p. 172.5–173.0°. Reported by Mazzara,[13] who prepared it otherwise, m. p. 170–171°.

The bromo acid was also prepared in 82% yield by brominating *m*-methoxybenzoic acid in hot water with the calculated amount of bromine introduced slowly below the surface of the liquid. Both methods gave white crystals, m. p. 160°; reported by Pschorr,[11] m. p. 161–162°.

N-(1′-Naphthyl)-anthranilic Acids (see Table I).—The preparation of N-(7′-methoxy-1′-naphthyl)-anthranilic acid is typical for all members of this series. A mixture of 40 g. of 7-methoxy-1-naphthylamine, 43 g. of the potassium salt of *o*-chlorobenzoic acid, 20 g. of potassium carbonate, 120 cc. of amyl alcohol and 1 g. of copper powder was heated at 125° for eight hours. The reaction mixture was poured into potassium hydroxide solution, and the amyl alcohol was removed by distillation with steam. The residual solution was filtered, and the filtrate was added slowly to dilute hydrochloric acid to precipitate the product. After one or more reprecipitations from basic solution, the product was recrystallized from ethanol, acetone or a mixture of these solvents.

Using 6-methoxy-1-naphthylamine and the potassium salt of *o*-chlorobenzoic acid, it was necessary to run the condensation for twelve hours at 130° in order to obtain a satisfactory yield.

The condensation between 1-naphthylamine and 2-chloro-5-methoxybenzoic acid (or the corresponding bromo acid) was carried out by heating a solution of the free acid in 4–5 parts by weight of 1-naphthylamine, along with potassium carbonate and copper powder. This condensation was run for two hours at 180–185°.

N-(2′-Naphthyl)-anthranilic Acid.—This compound was prepared in a manner analogous to the procedure for the corresponding derivatives of 1-naphthylamine. The yield was 41%, m. p. 210–211°; reported by Ullmann,[14] m. p. 212°.

7-Chlorobenz[c]acridines (see Table II).—The preparation of 7-chloro-2-methoxybenz[c]acridine is typical for all members of this series, with the exceptions noted below and in Table II. Eighteen grams of N-(7′-methoxy-1′-naphthyl)-anthranilic acid was suspended in 135 g. of redistilled phosphorus oxychloride, and the mixture was refluxed for two hours, giving a dark, viscous solution. Most of the excess phosphorus oxychloride was removed by distillation, and the residual solution was poured into a mixture of ammonia, ice, and sufficient chloroform (800 cc.) to dissolve the product after one hour of continual stirring. The chloroform solution was dried, filtered, and allowed to evaporate; it deposited a yellow, crystalline product. With some derivatives the product thus obtained was satisfactory for use without purification. Samples of all members of this series were recrystallized from dry benzene, dry heptane, or a mixture of these solvents.

Those derivatives which had a methoxyl group in the 4-position (to a limited extent in the 9-position also) were always contaminated with darkly colored by-products, whose removal necessitated additional recrystallizations.

Those derivatives which had a chlorine atom in the 10-position were relatively insoluble in chloroform, and it was necessary to remove part of the product by filtration.

12-Chlorobenz[a]acridine.—This compound was prepared in a manner analogous to the procedure for derivatives of benz[c]acridine. The yield was 87%, m. p. 156–158°. Recrystallization (benzene–heptane) to constant melting point gave large, yellow crystals, m. p. 158°.

Anal. Calcd. for $C_{17}H_{10}NCl$: C, 77.42; H, 3.82. Found: C, 77.43, 77.43; H, 3.87, 3.85.

Derivatives of 7-(3′-Diethylaminopropylamino)-benz[c]-acridine Dihydrochloride (see Table III).—The preparation of 7-(3′-diethylaminopropylamino)-2-methoxybenz[c]acridine dihydrochloride is typical for all members of this series. A mixture of 10.6 g. of 7-chloro-2-methoxybenz[c]acridine, 5.17 g. (a 10% excess) of 3-diethylaminopropylamine, and 32 g. of anhydrous, redistilled phenol was heated at 110° for two and one-half hours, giving a dark red, very viscous solution. Precautions were taken to ensure that all reactants and the reaction vessel were free from traces of moisture. The reaction mixture was poured into a solution of 70 g. of potassium hydroxide in 500 cc. of water, and the free base which separated was extracted with ether. The ether solution of the free base was dried and filtered, and the filtrate was treated with dry hydrogen chloride until precipitation of the gummy (occasionally solid) dihydrochloride was complete. This product was recrystallized two or more times from a suitable solvent (*cf.* Table III) containing enough hydrogen

(6) Lockett and Short, *J. Chem. Soc.*, 788 (1939).

(7) Butenandt and Schramm, *Ber.*, **68**, 2087 (1935).

(8) Davis, *Chem. News*, **74**, 302 (1896). No physical constants nor analytical data are given.

(9) Analysis by P. D. Somers, Purdue University.

(10) "Organic Syntheses," **5**, 71–74 (1925).

(11) Pschorr, *Ann.*, **391**, 23–29 (1912).

(12) Friedlaender, *Ber.*, **49**, 963–964 (1916).

(13) Mazzara, *Gazz. chim. ital.*, **29**, I, 378–379 (1899).

(14) Ullmann, *Ann.*, **355**, 347–352 (1907).

chloride to make the solution acidic to congo red paper. The yields were determined largely by the recovery which each recrystallization solvent permitted, as the condensation reaction itself was almost quantitative.

One derivative was prepared by using 2-hydroxy-3-diethylaminopropylamine as the side-chain.

Whenever the dihydrochloride was obtained as a hydrate, a sample of the anhydrous form (very hygroscopic) was prepared for characterization by heating the hydrate at 140°, or by recrystallizing it from an inert solvent containing thionyl chloride.

12-(3'-Diethylaminopropylamino)-benz[a]acridine Dihydrochloride.—This compound was prepared in a manner analogous to the procedure used for the corresponding benz[c]acridine derivatives. The yield after two recrystallizations from propanol–dibutyl ether was 31% of very small, yellow needles, m. p. 250–252° by the instantaneous method.

Anal. Calcd. for $C_{24}H_{29}N_3Cl_2$: C, 66.97; H, 6.79. Found: C, 67.06, 67.15; H, 6.75, 6.82.

Summary

A series of dialkylaminoalkylaminobenzacridines has been prepared for testing as antimalarials.

LAFAYETTE, INDIANA RECEIVED MARCH 30, 1946

[CONTRIBUTION FROM THE LABORATORIES OF THE UNIVERSITY OF MARYLAND]

Synthetic Antimalarials. The Preparation of Certain Derivatives of Sulfanilamide[1]

BY NATHAN L. DRAKE, CHARLES M. EAKER, JOHN A. GARMAN, KENNETH E. HAMLIN, JR., ROBERT A. HAYES, STUART T. HAYWOOD, RICHARD M. PECK, ROBERT K. PRESTON, JOHN STERLING, JR., JOHN O. VAN HOOK AND EDWARD WALTON

Conflicting reports on the value of sulfanilamide in the treatment of malaria are to be found in the earlier literature; a review of some of these papers has been made by Sinton,[2] whose work indicated that sulfanilamide itself was of no value in human malaria, of little or no value in avian malaria, but did, however, have a definite effect upon *P. Knowlesi* in monkeys. Walker and Van Dyke[3] have shown that sulfathiazole, sulfadiazine and sulfanilamide, in this order, are effective against *P. lophurae* in ducklings. Coggeshall[4] and co-workers, employing sulfadiazine, showed it to be effective against all forms of human malaria.

When it thus became apparent that the sulfa drugs were effective against malaria, and when it appeared[5] that sulfadiazine was a causal prophylactic in avian malaria, investigations were undertaken with the object of finding a more active drug which might act as a causal prophylactic in man.

The present paper describes the preparation of twenty-two drugs which were synthesized for this purpose. Data concerning the activity of the compounds will be found elsewhere.[6]

The sulfanilamide derivatives were prepared by coupling N-acetylsulfanilyl chloride with the appropriate amine or amine salt, followed by hydrolysis, in some cases with acid and in others with base, to remove the acetyl group. The amines in some instances are known compounds, and were prepared by methods reported in the literature or were obtained from stock. In many instances the precursor of the desired amine was prepared by a known series of reactions, and this compound was converted to the desired amine by an appropriate method. In a few cases neither the amine nor any of its immediate precursors are reported in the literature, and methods of synthesis were devised for these compounds.

The coupling was carried out in pyridine solution at temperatures varying from 60 to 100°, and for times ranging from one to four hours in all cases except that of 3-chloro-4-dimethylaminosulfanilanilide (SN-5069). In this instance 2-chloro-N^1,N^1-dimethyl-*p*-phenylenediamine in ether solution was stirred and refluxed with N-acetylsulfanilyl chloride in the presence of anhydrous sodium carbonate for one and one-half hours. Coupling in pyridine was not used in this case because all attempts to isolate the free amine resulted in extensive decomposition; the reduction mixture from 2-chloro-4-nitro-N,N-dimethylaniline, therefore, was coupled directly with N-acetylsulfanilyl chloride as described above without isolating the 2-chloro-N^1,N^1-dimethyl-*p*-phenylenediamine.

N^1-(2-Hydroxy-3-camphanyl)-sulfanilamide was prepared by a Meerwein–Ponndorf reduction of α-(N-acetylsulfanilamido)-camphor, followed by acid hydrolysis. The α-(N-acetylsulfanilamido)-camphor was prepared in the usual manner by coupling α-aminocamphor with N-acetylsulfanilyl chloride in pyridine.

p-Aminobenzenesulfinic acid was prepared by the standard method[7,8] starting with N-acetylsulfanilyl chloride.

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

(2) Sinton, Hutton and Shute, *Ann. Trop. Med.*, **33**, 37–44 (1939).

(3) Walker and Van Dyke, *Proc. Soc. Exptl. Biol. Med.*, **48**, 368 (1941); *C. A.*, **35**, 567 (1942).

(4) Coggeshall, Maier and Best, *J. Am. Med. Assoc.*, **117**, 1077 (1941).

(5) "Antimalarial Drugs, 1941–1945," F. Y. Wiselogle, editor, Chapter V, in press.

(6) "Antimalarial Drugs, 1941–1945," published by the Survey of Antimalarial Drugs, in press. Drugs described herein are identified by the SN number used in this monograph.

(7) Smiles and Bere, "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., p. 7.

(8) Tensen and Linquist, *Dansk. Tids. Farm.*, **14**, 129 (1940); *C. A.*, **35**, 3987 (1941).