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HETEROCYCLIC BASIC COMPOUNDS. XV. BENZACRIDINE DERIVATIVES[1]

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Several benzacridine derivatives, analogous to the known acridine and quinoline antimalarials, Atabrin (1), Camoquine (2), and Chloroquin (3), have been synthesized during the search of a superior drug for the treatment of malaria. Bachman and co-workers (4–6) have prepared a series of benz[*c*]-acridines and when this work became known to us, our investigations in this series, which are reported in Table I, were discontinued and our efforts directed towards the benz[*a*]acridine derivatives. This latter group of compounds, reported in Table II, proved to be significantly more active against a blood induced *gallinaceum* malarial infection in chicks than the benz[*c*]acridines; however, none showed any indication of being equal to the corresponding *acridine* derivatives in antimalarial activity. Data on the pharmacological activity of these compounds are to be found in the tables published by the Survey of Antimalarial Drugs[5] (7). Dobson, Hutchinson, and Kermack (19) have reported the preparation of several benz[*a*]- and benz[*c*]-acridines and these results are in accord with their findings.

The methods for the preparation of 7-substituted benz[*a*]acridines from β-naphthylamine and its derivatives and for the preparation of 12-substituted benz[*c*]acridines from α-naphthylamine and its derivatives have been well delineated (4–6, 8), and are summarized by the equations on page 360.

The analogous studies in the acridine series by Albert and Linnel (9) proved helpful in choosing conditions for the formation of the *substituted* anthranilic acids. The yields in the preparation of the anthranilic acids were never good, although they were consistently higher in the reactions with β-naphthylamine than with α-naphthylamine. In fact the reaction of 2,4-dichlorobenzoic acid with α-naphthylamine failed to produce any isolatable anthranilic acid derivative; instead a 67 % yield of 4-chlorobenzoic acid was obtained. This corresponds to the experience of Albert and Linnel (9) who obtained 4-nitrobenzoic acid as a by-product in the reaction of 2-chloro-4-nitrobenzoic acid with *p*-nitroaniline. The ring closures with phosphorus oxychloride were uniformly good; the yields

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[5] Pharmacological studies have been conducted in the laboratories of Parke, Davis and Co.

TABLE I

BENZ[c]ACRIDINES

SN No.[a]	SUBSTITUENTS	YIELD, %	M.P., °C.	DERIVATIVE M.P., °C.	FORMULA	ANALYSIS					
						Calc'd			Found		
						C	H	N	C	H	N
	7-Cl[b]	96	143								
	7-Cl, *10*-Cl, *5*-OCH_3	80	194		$C_{18}H_{11}Cl_2NO$	65.87	3.38		65.97	3.64	
8,007	$NH(CH_2)_2NC_4H_8O$[c]	72	123–124		$C_{24}H_{25}N_3O$			11.32			11.54
8,009	$NH(CH_2)_5NC_5H_{10}$[d]	57		234–236[e]	$C_{27}H_{31}N_3 \cdot 2HCl$			8.91			8.69
8,008	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	29		209–211[e]	$C_{26}H_{29}N_3 \cdot 3HCl$			8.52			8.42
11,652	NHC_6H_3-*3'*-$CH_2N(C_2H_5)_2$-*4'*-OH	33		251–255[e]	$C_{28}H_{27}N_3O \cdot 2HCl$	68.01	5.91		67.66	6.19	
	NHC_6H_3-*3'*-$CH_2N(C_2H_5)_2$-*4'*-OH, *10*-Cl, *5*-OCH_3	14		264[e]	$C_{29}H_{23}ClN_3O_2 \cdot 2HCl \cdot 2H_2O$	58.41	5.76		58.81	5.51	

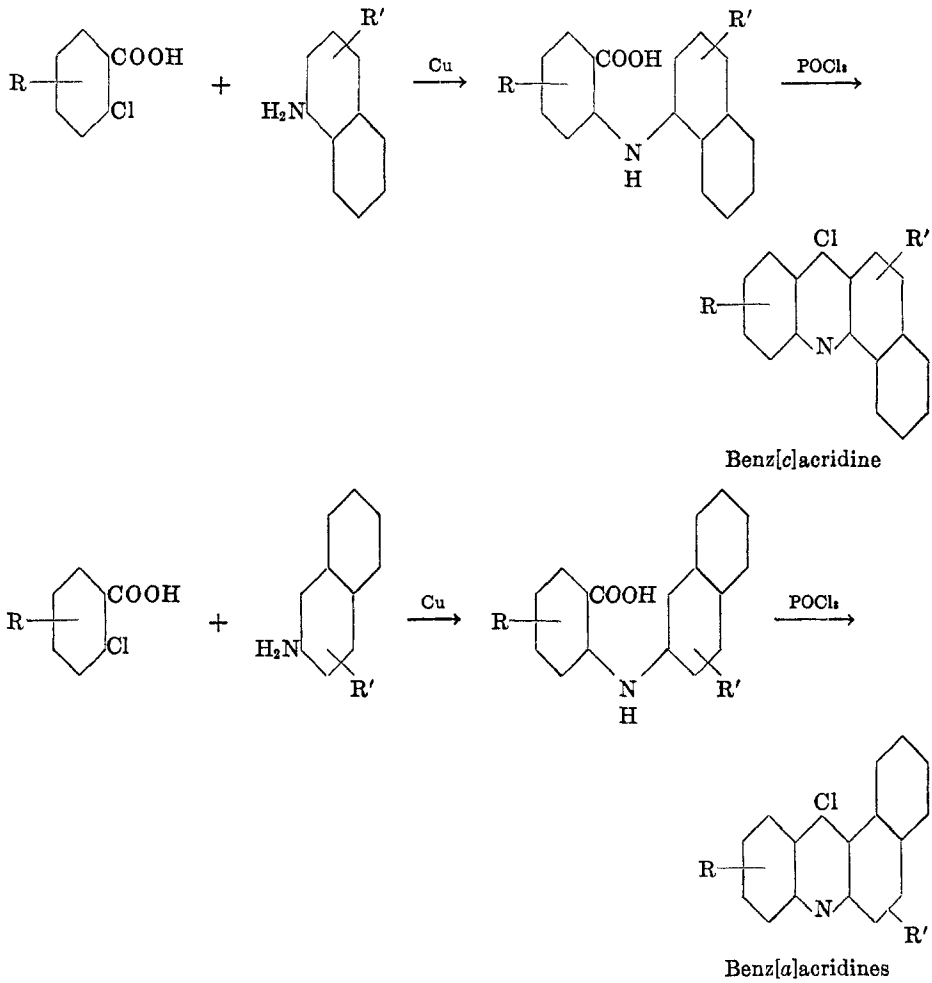
[a] SN refers to the Survey Number designation in reference (7); complete pharmacological data on the antimalarial activities of these compounds will be found in this monograph, pp. 1380–1382. [b] See reference (6), melting point reported 144–145°. [c] NC_4H_8O refers to the 4-morpholinyl (morpholino) radical. [d] NC_5H_{10} refers to the 1-piperidyl (piperidino) radical. [e] *Hydrochloride*, melting point with decomposition.

TABLE III

BENZ[*a*]ACRIDINES

SN No.[a]	SUBSTITUENTS	YIELD, %	M.P., °C.	DERIVATIVE M.P., °C.	FORMULA	ANALYSIS					
						Calc'd			Found		
						C	H	N	C	H	N
	12-Cl	80	157		$C_{17}H_{10}ClN$	[c]					
	12-Cl, *9*-Cl	74	168–169		$C_{17}H_9Cl_2N$	68.46	3.40		68.58	3.20	
	12-Cl, *5*-Cl, *9*-OCH_3	74	199–200		$C_{18}H_{11}Cl_2NO$	65.79	3.38		65.95	3.61	
8,011	*12*-$NH(CH_2)_3NC_4H_8O$[b]	71	74		$C_{24}H_{25}N_3O$			11.31			11.10
8,014	*12*-$NH(CH_2)_3N(C_2H_5)_2$	67		260[d]	$C_{24}H_{27}N_3 \cdot 2HCl$			9.76			9.66
	12-$NH\text{-}CH(CH_3)(CH_2)_3N(C_2H_5)_2$,*5*-Cl,*9*-$OCH_3$	9.4		295[d]	$C_{27}H_{32}ClON_3 \cdot 2HCl \cdot H_2O$	61.23	6.49		61.12	6.75	
11,650	*12*-NHC_6H_3-*3'*-$CH_2N(C_2H_5)_2$-*4'*-OH	15		224–226[e]	$C_{28}H_{21}N_3O \cdot 2HCl \cdot 1\frac{1}{2}H_2O$	64.48	6.18		64.38	6.31	
11,651	*12*-NHC_6H_3-*3'*-$CH_2N(C_2H_5)_2$-*4'*-OH,*9*-Cl	40		215–219[e]	$C_{28}H_{27}ClN_3O \cdot 2HCl \cdot H_2O$	61.38	5.70		61.59	5.79	

[a] SN refers to the Survey Number designation in Ref. (7); complete pharmacological data on the antimalarial activity of these compounds will be found in this source, pp. 1380–1382. [b] NC_4H_8O refers to the 4-morpholinyl radical. [c] See reference (6), m.p. reported 158°. [d] *Hydrochloride*, melting point with decomposition. This compound reported in reference (6), melting point "by instantaneous method" 250–252°. [e] *Hydrochloride*, m.p. with decomposition.



in the final reaction to give the products listed in Tables I and II varied, depending upon the nucleus and side-chain amine employed.

Various attempts were made to prepare 2-chloro-5-methoxybenzoic acid from the available 2-chloro-5-methoxytoluene. Of the oxidation experiments using sodium dichromate, nitric acid, chromic oxide, and potassium permanganate, only the latter produced any of the desired acid and then in only minor amounts. The 2-chloro-5-methoxybenzoic acid was prepared from the commercially available 2-chloro-5-nitrobenzoic acid by a three-step process. Hydrogenation in the presence of Adams' catalyst converted the nitro group to the amino group in 78% yield.[6] The amine group was converted to the hydroxy group in fair yield by diazotization according to the method of Minaev

[6] Hübner [*Ann.*, **222**, 198 (1884)] reduced this compound with zinc and hydrochloric acid and Nereshkin [*Ukrainskii Khem. Zur.*, **4**, Sci. Pt., 525–530 (1929); *Chem. Abstr.*, **24**, 5741 (1930)] claimed a 90–94% yield by zinc dust-acetic acid reduction.

(10). The hydroxyl group was methylated in the final step with dimethyl sulfate. This was a more direct approach and gave a higher over-all yield than that used by Bachman and Picha (6) in which 5-methoxyisatin was prepared and oxidized to 5-methoxyanthranilic acid which was then converted by the Sandmeyer reaction into the desired 2-chloro- or 2-bromo-5-methoxybenzoic acid.

The 4-methoxy-1-naphthylamine used in these studies was prepared by nitrating 1-methoxynaphthalene essentially according to the method of Hodgson and Smith (11) followed by reduction of the resulting 4-nitro-1-methoxynaphthalene. The yield of the purified 4-isomer in the nitration was only 48% but the direct approach compensated for the better yields obtained in the more circuitous route utilized by Bachman and Wetzel (4).

Hodgson and co-workers (12–14) have described the preparation of 4-chloro-2-naphthylamine from 1-acetylaminonaphthalene by a process involving nitration, separation of isomers, chlorination, hydrolysis, deamination, and reduction. This method proved impractical as a synthetic route because of the low yields on the nitration and chlorination steps and because of the difficulty encountered in the separation of the 4-nitro-1-acetaminonaphthalene from the 2-nitro isomer. Reversing the sequence of nitration and chlorination steps theoretically should lead to a more favorable process and this indeed proved to be the case. The most favorable conditions for the chlorination were found to be a modification of those employed by Reverdin and Crépieux (15) using sodium chlorate, concentrated hydrochloric acid, and a ferric chloride catalyst. The separation of 4-chloro-1-acetylaminonaphthalene from the 2-chloro isomer in a good state of purity was a simple process as compared to the separation of the analogous mixture of nitro compounds.

Mannino and Didonato (16) reported the formation of an x-nitro-x-chloro-1-acetylaminonaphthalene, m.p. 219°, by the action of *aqua regia* on 1-acetylaminonaphthalene in a one-step process. Since this is the same melting point found for 1-acetylamino-2-nitro-4-chloronaphthalene, their work was repeated in the hope that the two compounds would prove to be identical. The melting point reported by Mannino and Didonato was confirmed but a mixture of this compound with authentic 1-acetylamino-2-nitro-4-chloronaphthalene melted at 212–215°; their non-identity was substantiated by the preparation of derivatives.

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EXPERIMENTAL[7]

2-Chloro-5-methoxybenzoic acid. Technical 2-chloro-5-nitrobenzoic acid (1 kg., m.p. 146–153°) was thoroughly stirred with one liter of cold ethanol, filtered, and the process repeated on the crystals with 500 ml. of cold ethanol; 750 g. of purified product, m.p. 162.0–163.5° was obtained. The melting point was not raised by a further crystallization from ethanol. This purified product (65 g.) was dissolved in 500 ml. of absolute ethanol in a one-

[7] All melting points are uncorrected.

liter hydrogenation bottle and was reduced in the presence of 0.1 g. of Adams' catalyst at 2–3 atmospheres pressure. The hydrogenation took place very rapidly and the temperature rose to 53°. It would be preferable to use less catalyst or to cool the hydrogenation mixture. About 3.5 g. of insoluble material was filtered from the warm reduction mixture, the solution was concentrated to 300 ml., and the crystals which separated on cooling were filtered to give 43 g. (78%) (m.p. 180.5–182°) of 2-chloro-5-aminobenzoic acid. More product is recoverable from the filtrate.

The 2-chloro-5-aminobenzoic acid (300 g.) was diazotized in sulfuric acid and the diazonium compound was decomposed in hot water according to the method reported by Minaev (10). The product was purified by crystallization from a toluene solution containing 5% absolute ethanol to give 130.5 g. (43.5%), m.p. 174–176°.

2-Chloro-5-hydroxybenzoic acid (126 g.), dissolved in 700 ml. of a 10% sodium hydroxide solution, was methylated with dimethyl sulfate (70 ml.) by warming for two hours. The resulting solution was cooled, acidified with hydrochloric acid, and the resultant tan solid filtered. The crude product, when dried, weighed 100 g. (73%), m.p. 159–166°; it was purified by Norit treatment and recrystallization from 250 ml. of ethanol to give 64.5 g. (47%), m.p. 170–171°. This product showed no depression of melting point when mixed with the acid obtained by permanganate oxidation of 2-chloro-4-methoxytoluene (17).

1-Methoxy-4-nitronaphthalene (11). A nitrating mixture composed of 366 ml. of concentrated nitric acid which had been added to 732 ml. of acetic anhydride with cooling and then diluted with 732 ml. of acetic anhydride was added with stirring over a six-hour period to a solution of 732 g. of 1-methoxynaphthalene dissolved in 1500 ml. of acetic anhydride at a temperature of 0–8°. After stirring 20 hours the mixture was diluted with five liters of cold water, stirred for five hours, and the red solid which separated was filtered and dried; weight, 937 g. The crude product was recrystallized twice from ethanol to give 460 g. (48.3%) m.p. 81–82°, of purified 1-methoxy-4-nitronaphthalene.

4-Methoxy-1-naphthylamine. Catalytic reduction of the above nitro compound was carried out in four 50-g. portions each dissolved in 500 ml. of absolute ethanol using Adams' catalyst and 2 to 3 atmospheres pressure in a one-liter hydrogenation bottle; the theoretical pressure drop occurred in two hours. Evaporation of the solvent and distillation of the residue gave 125 g. (72.5% yield), b.p. 165° (7 mm.). A *picrate*, m.p. 177°, and acetate, m.p. 178–179°, were prepared.

4-Chloro-β-naphthylamine. 1-Acetylaminonaphthalene (746 g.) was dissolved in 7.5 l. of glacial acetic acid and 1.5 l. of conc'd hydrochloric acid; 15 g. of ferric chloride was added. The solution was cooled to 8° and maintained at 8–10° while a solution of 142 g. of sodium chlorate in 1120 ml. of water was added dropwise over a period of 3.5 hours. The reaction mixture was diluted with 6 l. of water and the solid which separated was filtered, washed with water, then with 400 ml. of ethanol, filtered, and dried; 370 g., m.p. 171–180°. This was crystallized from 4 l. of ethanol to give a total of 273 g. (31% purified yield), m.p. 186.5–187.5°.

1-Acetylamino-4-chloronaphthalene (526 g.), was nitrated in 7.7 l. of glacial acetic acid by adding 193 ml. of concentrated nitric acid to the solution over a period of 30 minutes while the reaction mixture was at 65 to 68°. The product rapidly crystallized from the reaction mixture; it was filtered and washed to give 400 g. (68% yield) of product, m.p. 218–219°. This melting point was not lowered by mixing the sample with the product obtained by the chlorination of 1-acetylamino-2-nitronaphthalene (13).

The 4-chloro-2-nitroacetaminonaphthalene (400 g.) was stirred on the steam-bath for four days with 18 lbs. of concentrated sulfuric acid and 10 ml. of octyl alcohol to act as an antifoaming agent. The bright orange product was filtered, washed by stirring with water, potassium carbonate solution, again with water, and finally with 300 ml. of acetone to give 332 g. (98.5% yield) of dried product, m.p. 200–203°. The deamination of this material to 4-chloro-2-nitronaphthalene, m.p. 128–129° was carried out as described by Hodgson and Elliot (13), but the 4-chloro-2-nitronaphthalene was reduced catalytically using Adams' catalyst and ethanol solvent instead of by the action of stannous chloride as reported by

previous workers (13). The product, 4-chloro-β-naphthylamine, m.p. 68–69°, *hydrochloride* m.p. 223–228° dec., was obtained in 60% yield.

Preparation of the N-naphthylanthranilic acids. The synthesis of the unsubstituted N-naphthylanthranilic acids has been described by Ullmann (8), and Bachman and Picha (6). The same methods were used here for the substituted derivatives; the yields were generally low as reported in the latter reference, especially with the α-naphthylamine derivatives. Two examples will be described to illustrate the method.

N-(4'-Chloro-2'-naphthyl)-5-methoxyanthranilic acid. Sodium 2-chloro-4-methoxybenzoate (20 g., 0.096 mole), 2-amino-4-chloronaphthalene (50 g., 0.28 mole), sodium carbonate (10 g.), sodium iodide (1 g.), copper powder (1 g.), and 350 ml. of *n*-amyl alcohol were refluxed with stirring for 18 hours. The reaction mixture was steam-distilled and 30 g. of the starting amine was recovered from 38 l. of distillate. Acidification of the residue gave a dark solid which was treated with Norit and twice crystallized from ethanol to give 7.5 g. (22.9% yield) (m.p. 196–197° dec.) of N-(4'-chloro-2'-naphthyl)-5-methoxyanthranilic acid; equivalent weight calculated: 328; found: 330.

Anal. Calc'd for $C_{18}H_{14}ClNO_3$: C, 65.96; H, 4.31.
Found: C, 66.14; H, 4.43.

N-(2'-Naphthyl)-4-chloroanthranilic acid. Sodium 2,4-dichlorobenzoate (106 g.), β-naphthylamine (150 g.), potassium carbonate (35 g.), cupric oxide powder (1 g.), and 300 ml. of fusel oil were refluxed for 4.5 hours in an oil-bath maintained at 140°. The mixture was diluted with 200 ml. of 2% potassium carbonate solution and steam-distilled. The residue was acidified with conc'd hydrochloric acid and the solid which separated was filtered, washed with water, and crystallized successively from ethanol and acetone to give 62.5 g. (41.6% yield) of purified N-(2'-naphthyl)-4-chloroanthranilic acid, m.p. 230° dec.; equivalent weight calculated: 296; found: 298.

When 1-amino-4-methoxynaphthalene was substituted for the β-naphthylamine in the above preparation, a 1.8% yield of N-(4'-methoxy-1'-naphthyl)-4-chloro anthranilic acid, m.p. 267–268° dec., was obtained; equivalent weight calculated: 329; found: 324.

12-Chlorobenz[a]acridines and 7-chlorobenz[c]acridines. These intermediates were made by the action of phosphorus oxychloride on the appropriate substituted anthranilic acid in the standard manner as described by Bachman and co-workers (4–6). Their properties and yields are reported in Tables I and II.

Substituted 12-aminobenz[a]acridines and 7-aminobenz[c]acridines. The accepted procedure for replacing the active halogen with an aliphatic amino side-chain by heating in phenol was employed. The amines used have been previously described (18). The aromatic amino substituent was prepared and introduced as indicated in the work of Burckhalter, *et al.* (2). The final products with their properties and yields are to be found in Tables I and II.

SUMMARY

Several benz[a]acridines and benz[c]acridines have been prepared and tested as antimalarial agents. The properties and methods of preparation have been described.

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