C^{14} (V). Dehydration of V with phosphorus pentoxide was accompanied by a Wagner rearrangement to form the desired phenanthrene-9-C^{14} (VI). The over-all yields of VI, based on barium carbonate, were 50–55%.

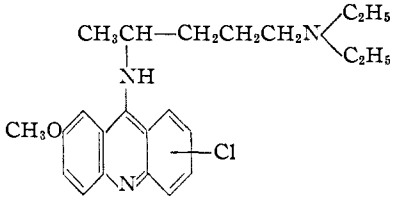
OAK RIDGE, TENNESSEE RECEIVED FEBRUARY 6, 1948

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Synthesis of Nuclear Isomers of Quinacrine

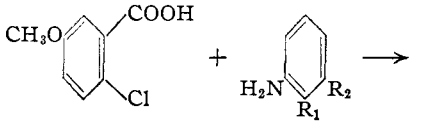
BY WILLIAM G. DAUBEN[1]

During the past few years much work has been done on the synthesis of compounds related to Quinacrine. However, of the four possible isomers of this compound which have the methoxyl

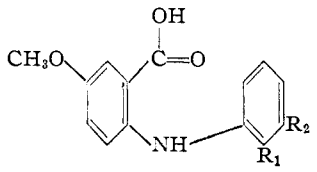


group in position two of the acridine nucleus and the chlorine atom in the opposite, nitrogen-free ring, only two have been reported. They are the 2-methoxy-6-chloro-9-substituted-aminoacridine[2] (Quinacrine) and the related 7-chloro isomer.[3] The present paper is concerned with the synthesis of the 5-chloro and the 8-chloro isomers.[4]

Following the observations of Ullmann and Kipper[5] that 2-chloro-5-methoxybenzoic acid[6] (I) can be used in the Ullmann condensation to prepare substituted N-phenylanthranilic acids (III), this compound (I) was utilized as the precursor of the desired methoxyl-substituted ring of the acridine. When the above acid (I) was allowed to react with *m*-chloroaniline (IIa) in the presence of anhydrous potassium carbonate and copper powder in boiling isoamyl alcohol, N-(3′-chlorophenyl)-5-methoxyanthranilic acid (IIIa) was formed in a yield of 19.9% and the majority of the starting acid (I) was recovered. Likewise, when acid I was allowed to react with *o*-chloroaniline (IIb), N-(2′-chlorophenyl)-5-methoxyanthranilic acid (IIIb) was isolated in a yield of only



I IIa (R_1 = H, R_2 = Cl)
IIb (R_1 = Cl, R_2 = H)

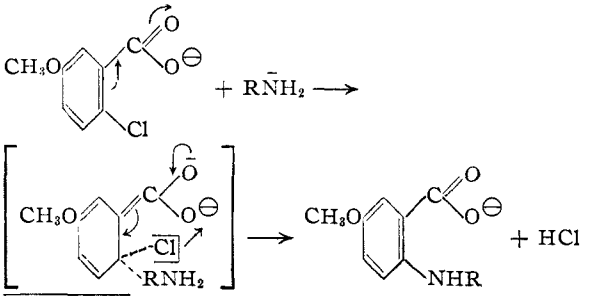


III (R_1 = R_2 = H)
IIIa (R_1 = H, R_2 = Cl)
IIIb (R_1 = Cl, R_2 = H)

11.4% and again the majority of the starting acid was recovered. It was found that the use of solvents with different boiling points, as *n*-butanol, *n*-pentanol, *n*-hexanol and cyclohexanol, gave still lower yields and that when the reaction was conducted in boiling nitrobenzene extensive decomposition occurred.

The small quantity of the desired materials (IIIa and IIIb) was not easily separated from the large amount of starting acid by fractional crystallization. However, this mixture was easily separated by partial acidification of a solution of their potassium salts since a substituted-anthranilic acid is a much weaker acid than a substituted benzoic acid. Crude product was precipitated when the *p*H was adjusted to seven and the starting acid was deposited from solution at a *p*H of five.

In view of the poor yields obtained in the above condensations, it is interesting to note that Ullmann and Kipper[5] have reported that the same acid (I) reacts with aniline to give N-phenyl-5-methoxyanthranilic acid (III) in a yield of 80% and that Lehmstedt and Schrader[7] have reported



(1) Present address: Department of Chemistry, University of California, Berkeley 4, California.

(2) Mauss, German Patents 553,072, 565,411.

(3) Feldman and Kopeliowitsch, *Arch. Pharm.*, **273**, 488 (1935).

(4) Since this paper was submitted for publication, Grigorovskii and Terent'eva (*J. Gen. Chem.* (*U. S. S. R.*), **17**, 517 (1947)) have reported the synthesis of the 5-chloro isomer and the attempted preparation of the 8-chloro isomer. The 2-methoxy-5,9-dichloroacridine (IV), prepared from 2,3-dichlorobenzoic acid and *p*-anisidine through the intermediate N-(4′-methoxyphenyl)-3-chloroanthranilic acid, had identical physical properties with the compound reported in this work. They, likewise, were unable to obtain a crystalline hydrochloride of the Quinacrine analog but they did obtain a solid oxalate. The 5-chloro isomer showed no anti-malarial activity. Their attempted synthesis of the 8-chloro isomer from 2,6-dichlorobenzoic acid and *p*-anisidine failed and the product isolated from the Ullmann reaction was *m*-bis-(*p*-methoxyanilino)-benzene.

(5) Ullmann and Kipper, *Ber.*, **38**, 2120 (1905).

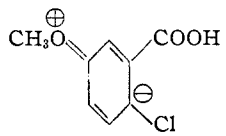
(6) Peratoner and Condorelli, *Gazz. chim. ital.*, **28**, I, 213 (1898).

(7) Lehmstedt and Schrader, *Ber.*, **70**, 838 (1937).

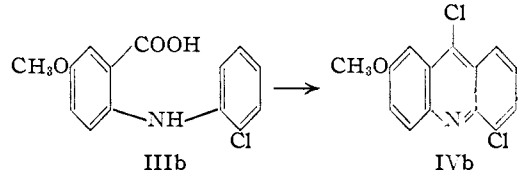
that *m*-chloroaniline (IIa) reacts with *o*-chlorobenzoic acid to give N-(3′-chlorophenyl)-anthranilic acid in 53% yield. If the mechanism of the Ullmann condensation is considered as a nucleophilic displacement of the chlorine atom by the amine, it can be seen that not only is the electrophilic strength of the *o*-chlorobenzoic acid important but also the nucleophilic strength of the reacting amine.[8] For example, Hertel and Luhrmann[9] have shown in a similar type of displacement reaction that the rate of the reaction decreases as the strength of the base decreases. From this work it would appear that the dissociation constant of the amine is a measure of its nucleophilic reactivity. This same correlation is qualitatively observed when the basic strengths[10] of the amines used in the above condensations are

Amine	$K_B \times 10^{10}$	Yield, %
Aniline	126	80
m-Chloroaniline	8.5	20
o-Chloroaniline	1.4	11

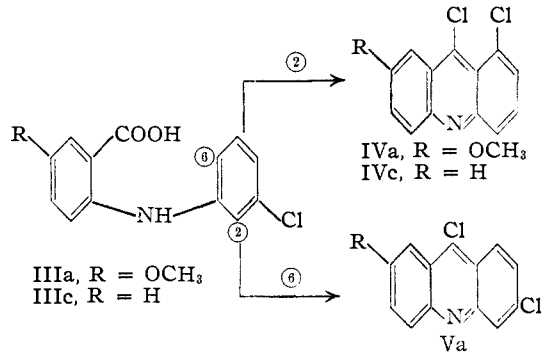
considered. Also, Tuttle[11] has shown that the presence of an electronegative group *para* to the chlorine atom of an *o*-chlorobenzoic acid greatly increases the reactivity of the chlorine toward nucleophilic displacement. In the case of 2-chloro-5-methoxybenzoic acid (I), the presence of an electropositive group, a methoxyl, in the *para* position to the chlorine atom would be expected to lessen the tendency of this chlorine atom to be displaced by a nucleophilic reagent (that is decrease the electrophilic tendency of the carbon atom holding the chlorine).



It is well-known that when a N-phenylanthranilic acid is allowed to react with phosphorus oxychloride a 9-chloroacridine is formed; that is, a ring closure and a subsequent chlorination occur. When the above anthranilic acids (IIIa and IIIb) were allowed to react with boiling phosphorus oxychloride only the corresponding 9-acridones were isolated. However, when chlorobenzene was used as a solvent and the reaction temperature was raised to 140°, good yields of the 9-chloroacridines were isolated. Starting with acid IIIb, 2-methoxy-5,9-dichloroacridine (IVb) was formed in a yield of 83.3%.



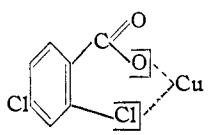
In the case of acid IIIa, two possible isomers (IVa and Va) can be formed.



Lehmstedt and Schrader[7] have studied in detail ring closures of this type. They have found in the case of N-(3-chlorophenyl)-anthranilic acid (IIIc) that reaction occurs mainly at the carbon two position to give the 8-chloro isomer (IVc). Linnell[12] also has reported similar results with compounds of this type. When acid IIIa was allowed to react with phosphorus oxychloride, only one pure dichloro compound could be obtained. After eight fractional crystallizations from benzene, 2-methoxy-8,9-dichloroacridine (IVa) was isolated in 24% yield. However, after this work was completed, Nargund and co-workers reported[13] that this same acid (IIIa) upon treatment with phosphorus oxychloride gave 2-methoxy-6,9-dichloroacridine (Va) as the only product of the reaction. These workers have published no experimental detail and no physical properties of their product so it is not possible to fully evaluate their work at this time. The 8-chloro structure was assigned to our compound IVa since it melts at 182° as compared to a melting point of 162° for the 6-chloro compound (Va), and a mixture of the two isomers melts from 145–158°. Also, the Quinacrine analog (VI) differs from Quinacrine in melting point, solubility and biological activity. The structure IVa is likewise in agreement with the results of Lehmstedt and Schrader[7] and of Linnell.[12]

The desired amino-side chain was attached to the acridine nucleus by allowing 2-methoxy-8,9-dichloroacridine (IVa) to react with 1-diethylamino-4-aminopentane in molten phenol. 2-

(8) In view of the specific reactivity of the *o*-halogen in this reaction, the role of the copper powder may be to aid in a simultaneous back and front side attack in the displacement reaction (see Swain, THIS JOURNAL, **70**, 1119 (1948)), by forming a weak, intramolecular coördinate bond between the halogen atom and the carboxylate anion.



(9) Hertel and Luhrmann, *Z. Elektrochem.*, **45**, 405 (1939); Branch and Calvin, "The Theory of Organic Chemistry," p. 426, Prentice-Hall, New York, N. Y., 1941.

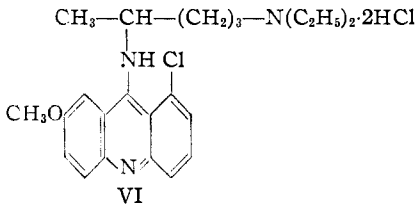
(10) Bennett, Brooks and Glasstone, *J. Chem. Soc.*, 1821 (1935).

(11) Tuttle, THIS JOURNAL, **45**, 1906 (1923).

(12) Bradbury and Linnell, *J. Chem. Soc.*, 377 (1942), and earlier papers.

(13) Shah, Kshatriga, Patel and Nargund, *J. Univ. Bombay*, Sect. A, **15**, pt. 3 (Science No. 20), 42 (1946).

Methoxy-8-chloro-9-[(4-diethylamino-2-amyl)-amino]-acridine (VI) was isolated as the dihydrochloride hydrate in a yield of 58%.



VI

When 2-methoxy-5,9-dichloroacridine (IVb) was treated in a similar manner, no crystalline amino product could be isolated. However, 2-methoxy-5-chloro-9-phenoxyacridine was obtained in 41% yield.

Dr. J. H. Bauer of the Rockefeller Foundation has investigated the antimalarial activity of the 8-chloro-isomer (VI). It was found that when it was used in 50-mg. amounts per day per 65 g. chick, it was non-toxic and had a very definite effect in prolonging the incubation period of the infection. Quinacrine, when assayed under the same conditions, was found to be effective in 8-mg. doses.

The author wishes to express his appreciation to Professor L. F. Fieser for his advice during the course of this investigation.

Experimental[14]

2-Chloro-5-methoxytoluene.[6]—2-Chloro-5-hydroxytoluene (71.5 g., 0.5 mole, m. p. 65°) was methylated in the usual manner with dimethyl sulfate (126 g., 1 mole) and 10% aqueous sodium hydroxide (200 cc.). The methyl ether distils at 77–78° (3 mm.), yield 71.5 g. (91.5%), $n^{23}D$ 1.5348.

2-Chloro-5-methoxybenzoic Acid.[6]—A mixture of 2-chloro-5-methoxytoluene (30 g., 0.192 mole), potassium permanganate (91.2 g., 0.577 mole) and water (9 liters) was refluxed, with stirring, for seven hours. The unreacted toluene compound was removed by steam distillation, the manganese dioxide filtered, and the clear, colorless filtrate acidified. The acid was obtained as white needles, yield 23.0 g. (64.3%), m. p. 172–173°. When the manganese dioxide was dissolved by bubbling-in sulfur dioxide, the same yield of acid was obtained.

N-(3'-Chlorophenyl)-5-methoxyanthranilic Acid (IIIa).—A mixture of 2-chloro-5-methoxybenzoic acid (25 g., 0.134 mole), *m*-chloroaniline (25 g., 0.196 mole), anhydrous potassium carbonate (25 g., 0.181 mole), copper powder (0.6 g.), and isoamyl alcohol (100 cc.) was heated under reflux with stirring for a period of twenty-four hours. The reaction mixture was diluted with water, the isoamyl alcohol and the unreacted amine removed by steam distillation, and the solution decolorized with Norit. The cooled filtrate then was acidified with dilute hydrochloric acid to a *p*H of 7. The yellow precipitate was removed by filtration and the filtrate was acidified to a *p*H of 5. A voluminous white precipitate of the starting acid was deposited. Upon making the latter filtrate acid to congo red, a mixture of the white solid and a brown oil was formed.

Recrystallization of the yellow precipitate from aqueous ethanol yielded N-(3-chlorophenyl)-5-methoxyanthranilic acid as yellow, feather-like needles, yield 7.4 g. (19.9%, 49.7% allowing for recovered acid), m. p. 190–191°.

Anal. Calcd. for $C_{14}H_{12}O_3NCl$: C, 60.54; H, 4.36; N, 5.04; Cl, 12.76. Found: C, 60.44; H, 4.28; N, 5.30; Cl, 12.75.

The white solids upon recrystallization from aqueous ethanol gave 15 g. of starting acid. The brown sirup partially crystallized on standing and the solid which separated was starting acid. The remaining sirup was acidic but its composition was not investigated.

2-Methoxy-8,9-dichloroacridine (IVa).—The ring closure and subsequent chlorination was accomplished by heating a solution of N-(3-chlorophenyl)-5-methoxyanthranilic acid (12.6 g., 0.045 mole), phosphorus oxychloride (100 cc.), and chlorobenzene (250 cc.) at a temperature of 140° for a period of five hours. The reaction mixture was concentrated to dryness in a vacuum at 80°. The brown, sirupy residue upon the addition of dilute aqueous ammonia hardened to a yellow crystalline mass. The solid was filtered, washed with water until the washings were neutral, and then dried. The crude product was dissolved in excess dry benzene, the solution was decolorized with Norit, and the solvent was distilled until crystals began to appear. A small volume of dry benzene then was added and the solution cooled. This procedure was repeated seven times in order to obtain pure 2-methoxy-8,9-dichloroacridine. The product is light-yellow plates melting at 181–182°; the yield was 3.1 g. (24%).

Anal. Calcd. for $C_{14}H_9ONCl_2$: C, 60.45; H, 3.26; N, 5.04; Cl, 25.50. Found: C, 60.45; H, 3.24; N, 5.40; Cl, 25.72.

2-Methoxy-6,9-dichloroacridine melts at 161–162° and a mixture of these two isomers melts from 145–158°.

The mother liquors from the above fractional crystallization on concentration deposited 4.0 g. of a yellow compound which melts over a large range and was entirely melted by 138°. When this solid was treated in the above manner no change in its composition appeared to occur.

2-Methoxy-8-chloro-9-[(4-diethylamino-2-amyl)-amino]-acridine-(VI).—1-Diethylamino-4-aminopentane (2.9 g., 0.018 mole) was added dropwise to a well-stirred mixture of 2-methoxy-8,9-dichloroacridine (3.65 g., 0.0131 mole) and phenol (18.4 g.) over a period of thirty minutes. The entire addition was conducted at steam-bath temperature. The reaction mixture was heated for an additional two hours and then diluted with warm 10% sodium hydroxide (80 cc.). A brown oil separated which floated on the alkaline solution. The entire mixture was cooled and extracted with a 1:1 mixture of benzene–ether. The extract was washed with water, dried over sodium sulfate, and the solvent was removed at reduced pressure at room temperature. The brown sirupy residue which was contaminated with a small amount of the yellow acridone was dissolved in acetone leaving the insoluble acridone. The acetone solution was acidified with dry hydrogen chloride at 0° and a small amount of the solvent was removed by means of a stream of dry air. The cooled solution set to a solid mass which yielded 5.1 g. (82.3%) of the yellow crystalline hydrochloride.

The hydrochloride was dissolved in distilled water (150 cc.) at room temperature, filtered, and the free amine generated by the addition of 50 cc. of one normal sodium hydroxide. The yellow milky solution was extracted twice with 100-cc. portions of ether, the ethereal extract dried, and the solvent removed at reduced pressure at room temperature. The brown residual oil was dissolved in 125 cc. of dry acetone; dry hydrogen chloride was added at 0°. At first, the solution became milky colored and a sirup came out of solution but upon continued addition of the gas, the sirup finally redissolved. The solution was cooled to 0° for twenty-four hours and the precipitate removed by filtration. The air-dried material melts from 135–140°. After drying at 80° at a pressure of 1 mm., the acridine melts at 197.5–199° (dec.), yield 3.75 g. (58%). Quinacrine dihydrochloride melts from 248–250°.

Anal. Calcd. for $C_{23}H_{30}ON_3Cl\cdot 2HCl\cdot H_2O$: C, 56.27; H, 6.98; N, 8.58; Cl, 21.68. Found: C, 56.40; H, 7.16; N, 8.89; Cl, 21.60.

A much less convenient method of crystallization was to dissolve the amine in dilute aqueous hydrochloric acid and

(14) All melting points are corrected. Microcombustions by Miss E. Werble.

allow the solution to stand in a vacuum desiccator over sulfuric acid at 0°. After a few days a yellow solid, identical with the above, appeared.

N-(2'-Chlorophenyl)-5-methoxyanthranilic Acid (IIIb).—A mixture of 50 g. (0.268 mole) of 2-chloro-5-methoxybenzoic acid, 50 g. (0.392 mole) of *o*-chloroaniline, 50 g. (0.362 mole) of anhydrous potassium carbonate, 1 g. of copper powder,[15] and 250 cc. of isoamyl alcohol was condensed and processed as described above. The yellow precipitate obtained by acidification to a *p*H of 7 was recrystallized twice from aqueous ethanol. The yield was 8.5 g. (11.4%, 28.5% allowing for recovered acid), m. p. 189–190°.

Anal. Calcd. for $C_{14}H_{12}O_3NCl$: C, 60.54; H, 4.36; N, 5.04; Cl, 12.76. Found: C, 60.63; H, 4.32; N, 5.34; Cl, 12.92.

The white precipitate obtained at a *p*H of 5 yielded 30 g. of the starting acid. Further acidification of the mother liquor gave only a brown oil.

2-Methoxy-5,9-dichloroacridine (IVb).—The ring closure was conducted as described above employing 7.4 g. (0.027 mole) of N-(2-chlorophenyl)-5-methoxyanthranilic acid. The yield of pure product was 6.2 g. (83.8%), m. p. 157–158° (benzene).

Anal. Calcd. for $C_{14}H_9ONCl_2$: C, 60.45; H, 3.26; N, 5.04; Cl, 25.50. Found: C, 60.55; H, 3.28; N, 4.77; Cl, 26.01.

2-Methoxy-5-chloro-9-[(4-diethylamino-2-amyl)-amino]-acridine.—The condensation was carried out and worked up as described above using 1.1 g. (0.004 mole) of 2-methoxy-5,9-dichloroacridine. Upon removal of the ether, a mixture of a yellow solid and a brown sirup was obtained. The yellow solid was removed and recrystallized from benzene. The compound was 2-methoxy-5-chloro-9-phenoxyacridine, m. p. 189–190°, yield 0.55 g. (41%).

Anal. Calcd. for $C_{20}H_{14}O_2NCl$: C, 71.53; H, 4.20; N, 4.17. Found: C, 71.42; H, 4.22; N, 4.17.

The brown sirup was processed in a manner analogous to that used for the 8-chloro isomer but no crystalline hydrochloride was obtained. Attempts to distil the product led to decomposition.

(15) When copper bronze was used as the catalyst, it was found necessary to dissolve the coating of wax and stearic acid by heating with ethanol.

Summary

2-Methoxy-8,9-dichloroacridine and 2-methoxy-5,9-dichloroacridine have been prepared. The 8-chloro isomer of Quinacrine has been prepared and its antimalarial activity determined. The 5-chloro isomer has been made but was not obtained in a crystalline form.

BERKELEY 4, CALIFORNIA RECEIVED FEBURARY 9, 1948

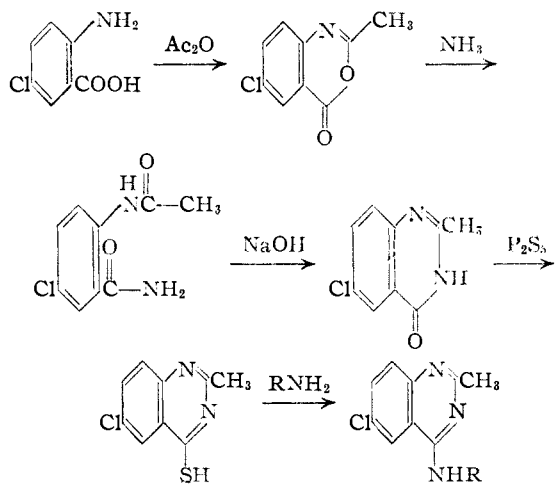
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Quinazolines. VI. Syntheses of Certain 2-Methyl-4-substituted Quinazolines[1]

BY ARTHUR J. TOMISEK AND BERT E. CHRISTENSEN

The study of the quinazoline compounds provides unusual interest, in view of the many novel[2] reactions and unpredictable[3] reaction products. During the course of nitration studies of 2,4-dimethylquinazoline, another unusual reaction was observed; instead of a nitro-2,4-dimethylquinazoline, the reaction product was 2-methyl-6-nitro-4-quinazolone. Even when equimolar quantities of reagents were used the nitrated quinazolone and unreacted quinazoline were the only compounds isolated from the reaction mixture, which fact indicates that the nitration of the quinazolone must have taken precedence over all other reactions. This reaction again illustrates the marked activity of a univalent substituent in the 4-position of the quinazoline nucleus.[4]

Another unpredictable reaction[5] of the quinazolines is illustrated in the chlorination of 2-methyl-4-quinazolone; in this instance benzenoid chlorination occurs along with the replacement of the 4-hydroxyl group. This makes it impossible to prepare 4-alkylaminoquinazolines with a methyl substituent in the 2-position by the usual procedures, *i. e.*, coupling of the 4-chloro derivative with desired amine. Recently Leonard and Curtin[6] have successfully employed the 4-mercaptoquinazolines in place of the usual chloro derivative as intermediates for synthesis of alkylamino compounds. This procedure has now been used to circumvent the problem of benzenoid chlorination in the preparation of 4-alkylamino-2-methylquinazolines; 2-methyl-4-quinazolone and 6-chloro-2-methyl-4-quinazolone were readily converted to the respective 4-mercaptoquinazolines by means of phos-



(1) Published with the approval of the Monographs Publication Committee, Oregon State College, as Research Paper No. 124.

(2) Leonard and Curtin, *J. Org. Chem.*, **11**, 341 (1946).

(3) Tomisek and Christensen, THIS JOURNAL, **70**, 874 (1948).

(4) Tomisek and Christensen, *ibid.*, **67**, 2112 (1945).

(5) Dehoff, *J. prakt. Chem.*, **2, 42**, 352 (1890); Bogert and May, THIS JOURNAL, **31**, 511 (1909).

(6) Leonard and Curtin, *J. Org. Chem.*, **11**, 349 (1946).