[CONTRIBUTION FROM THE EXPERIMENTAL BIOLOGY AND MEDICINE INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

STUDIES IN THE ACRIDINE SERIES. VI. THE REACTION OF CERTAIN 9-FORMYLACRIDINES WITH 3-DI-*n*-BUTYL-AMINOPROPYLMAGNESIUM CHLORIDE

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A recent communication (1) from this Laboratory reported the synthesis of a number of acridine amino carbinols, of which three possessed slight activity towards *Plasmodium gallinaceum* (chick infection). It was pointed out at the time that this particular group of substances constituted the first in a series of four new types of acridine amino alcohols prepared for plasmodicidal study. The present paper is concerned with a group of compounds derived from various 9-formylacridines.

Amino alcohols which have proved effective plasmodicides are characterized by a secondary carbinol situated between an aromatic or heterocyclic nucleus and an aliphatic or reduced heterocyclic system (*e.g.* quinine). The amino group occurs on the α- or β-carbon with respect to the carbinol. This type of compound is usually derived, respectively, from the corresponding α-halomethyl ketone by halogen exchange (α), or from the ketone by the Mannich reaction (β), followed by reduction of the resultant amino ketone to the carbinol.

To our knowledge acridine *meso*-amino carbinols (either the α or β type) are, at present, unknown. Since such compounds should be of interest as possible plasmodicides, we have been investigating several possible, alternate routes for their synthesis. One of the more promising methods appears to be the application of some modification of the Grignard reaction. Unfortunately compounds of the type $R_m(CH_2)_xNR_2$, where x is 1 or 2, (R_m being Li or MgX) are unavailable by the usual procedures. However, Marxer (3) has made an excellent study of the preparation of this type of compound in which x is 3 or more. The application of Marxer's technique to our problem has led to a series of three acridine amino alcohols of the butanol type in good yield.

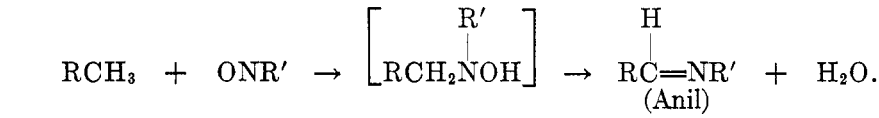
It has been found that, in virtually any series of amino alcohols in which the substituents on the amino group are varied, if plasmodicidal activity is present in *any* member of the series, the dibutylamino homolog will also be active (4). On the basis of this generalization, this investigation has been limited to the 9-dibutylaminobutanol derivatives of three substituted acridines.

9-Methylacridine, the precursor of 9-formylacridine, was prepared from diphenylamine, acetic anhydride, and fused zinc chloride according to Porai-Koshits, *et al.* (5). We were unable to attain their yield of 70%; our average yield was 40%. 9-Methylacridine condensed readily with 4-nitrosodimethylaniline either in boiling ethanol solution (2) or by fusion of the components at 115° in the presence of a little piperidine (6), to give the purported "anil" which was readily cleaved by conc'd hydrochloric acid to 9-formylacridine.

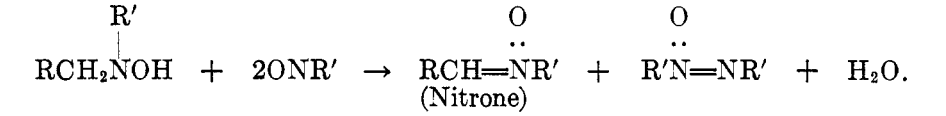
Some interesting observations made in connection with the aforementioned "anil", as well as the two anils to be described later, are worthy of special note. In all three cases low carbon values ranging between 1.2 to 3.2% was the rule.

At first, these discrepancies were attributed to water of crystallization, a view earlier entertained, but never substantiated, by Kaufmann (6). However, when no significant alteration in carbon analysis followed a 6-hour heating-period at 135°/0.3 mm., of one of the anils, we were less inclined to accept the water of crystallization idea. The answer to this dilemma was soon found in two papers by Krohnke (7) on the synthesis and reactions of nitrones. According to Krohnke, aromatic nitroso compounds are capable of interaction with reactive methylene groups in three different ways, two of which are relevant to the present problem. The usual and most common product is an azomethine or anil, which

is probably formed through the intermediate RCH_2NOH as follows:

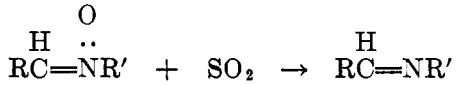


In certain cases, however, a second or third mole of nitroso compound may react with the above intermediate oxidizing it to a *nitrone*, with the concomitant formation of an azoxy body:



The fact that nitrones, like their related anils, are readily hydrolyzed to the same aldehyde by mineral acids, probably accounts for the lack of interest, on the part of earlier workers, in the structure of the intermediate "anils".

Having once obtained and characterized the pure aldehydes, we considered it of interest, in view of the indeterminate nature of the precursory anils, to determine whether chemically pure anils would be formed by condensing the aldehydes with 4-aminodimethylaniline under the conditions previously employed. With all three aldehydes, the resulting anils not only proved to be chemically homogeneous, but each differed from the corresponding anil originally prepared from the 9-methyl derivative, in crystalline form, m.p., X-ray powder pattern and absorption spectrum in the visible range.



We have now secured evidence which appears to support Krohnke's view regarding the N-oxide configuration for the nitrones. Just as N-oxides are reduced to the parent amine by SO_2, so treatment of our anil-nitrone mixture with SO_2 resulted in reduction of the nitrone fraction to give the homogeneous anil. The latter now not only gave correct carbon and hydrogen values but had the same crystalline form as the anil derived from 9-formylacridine; no depression in mixture melting point was observed.

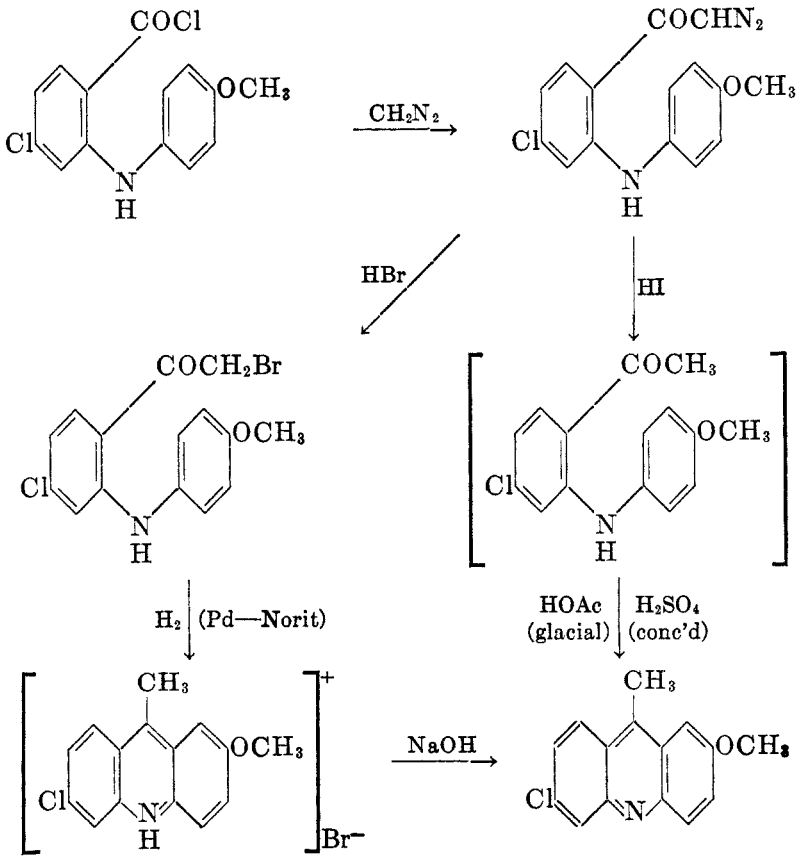
Initial attempts to prepare 2-methoxy-9-methylacridine involved the treatment of 2-methoxyacridone with methylmagnesium iodide. This approach was patterned after the work of Semon and Craig (8) who found that acridone and

methylmagnesium iodide react to give a mixture of 9-methylacridine and 9,9-dimethylacridane in approximately 2:1 ratio. 2-Methoxyacridone was found to react with methylmagnesium iodide, but the method was abandoned because of the poor yield of 2-methoxy-9-methylacridine (10–15%).

Acridone is known to react with phenyllithium to give 9-phenylacridine in 90% yield (9). We were unable, however, to isolate any 2-methoxy-9-methylacridine from the reaction of 2-methoxyacridone with methyllithium under a variety of conditions.

The method ultimately adopted for the large scale preparation of 2-methoxy-9-methylacridine consisted of condensing *o*-aminoacetophenone (10) with 4-bromoanisole followed by cyclization of the resulting substituted diphenylamine according to Jensen (11). The 2-methoxy anil or, more properly, "anil–nitrone" mixture, prepared by fusion of 2-methoxy-9-methylacridine with 4-nitrosodimethylaniline afforded the desired aldehyde on hydrolysis with conc'd hydrochloric acid.

The method of Jensen (11) proved superior, too, for the synthesis of 2-methoxy-6-chloro-9-methylacridine from 2-amino-4-chloroacetophenone (10) and 4-bromoanisole. The same acridine derivative was obtained in two other ways, albeit in low yield, from N-(4′-methoxyphenyl)-4-chloroanthraniloyl chloride (12) according to the following sequence of reactions:



The concomitant dehydrobromination of the bromoketone and cyclization of the intermediate to the substituted 9-methylacridine is noteworthy, despite the low yield obtained.

Fusion of 2-methoxy-6-chloro-9-methylacridine with 4-nitrosodimethylaniline followed by acid hydrolysis of the intermediate "anil–nitrone" mixture afforded the desired aldehyde.

The three drugs described here exhibited strong plasmodicidal activity towards *P. gallinaceum* (chick infection). The respective quinine equivalents were: 0.3 for the unsubstituted acridine amino butanol; 0.5 for the 2-methoxy homolog, and 0.8 for the 2-methoxy-6-chloro homolog (13).

Acknowledgment. The microanalyses are by C. A. Kinser and Betty Mount, both formerly of this Laboratory.

EXPERIMENTAL

Melting points are uncorrected.

9-Methylacridine. The synthesis of this substance from diphenylamine, acetic anhydride, and fused zinc chloride was effected according to Porai-Koshits (5). 9-Methylacridine may also be prepared from *o*-aminoacetophenone and bromobenzene (10, 11).

α-9-Acridyl-N-(4-dimethylaminophenyl)nitrone. (From 9-methylacridine). Eisleb's directions (2) for condensing 9-methylacridine with 4-nitrosodimethylaniline in ethanol solution afforded the anil-nitrone mixture in 66% yield. After two crystallizations from ethanol, dark red prisms, m.p. 247–248° (d).

Anal. Calc'd for $C_{22}H_{19}N_3O$: C, 77.4; H, 5.61; N, 12.31.
Found: C, 78.4, 78.3, 78.5, 78.04, 78.13.
H, 5.87, 5.99, 5.85, 6.02, 5.91; N, 11.93.

The constancy of the above analytical values suggests the formation of a double compound consisting of 3 moles of nitrone and 1 mole of anil. This discrepancy in the analysis of nitrones has been noted previously (7)[1].

Another route to the nitrone lies in the fusion of the components at 115° in the presence of a trace of piperidine (6).

9-Formylacridine. The acid hydrolysis of the above nitrone to the aldehyde was effected in 75% yield according to Eisleb (2). Crystallization from methanol–water gave golden-yellow needles, m.p. 149.5–151°.

9-(4-Dimethylaminophenyliminomethyl)acridine. (From 9-formylacridine). A mixture of 0.5 g. of acridine-9-aldehyde, 0.35 g. (1.1 equiv.) of *p*-aminodimethylaniline,[2] and 2 drops of piperidine was heated at 115–120° (oil-bath) for 30 minutes. The dark melt was triturated with a few ml. of cold ethanol, diluted with ether, and filtered; yield 0.45 g. The *anil* crystallized in garnet rhombs from ethanol. After three crystallizations, m.p. 257.5–259°.

Anal. Calc'd for $C_{22}H_{19}N_3$: C, 81.2; H, 5.89.
Found: C, 81.2; H, 6.04.

Regeneration of the aldehyde. A small amount of the above anil was hydrolyzed with dilute HCl in the usual way and the product crystallized from methanol–water; bright yellow needles, m.p. 149–150°, alone or in mixture with 9-formylacridine.

Reduction of the nitrone to the anil. A cooled suspension of 0.5 g. of nitrone in 25 ml. of anhydrous tetrahydrofuran was treated with 25 ml. of a cold, saturated solution of dry

[1] Since the submission of our communication, the paper of Chardonnens and Heinrich, *Helv. Chim. Acta*, **32**, 656 (1949), appeared, in which this *nitrone*, after recrystallization from chlorobenzene, gave a correct analysis. The reported m. p. was 243° as compared with our m. p. of 247–248°.

[2] Prepared by high-pressure reduction (135 atms.) of 4-nitrosodimethylaniline over Raney nickel at room temperature.

sulfur dioxide in tetrahydrofuran. After standing for 15 hours (at 20°), with the exclusion of moisture, the solution was filtered from a small amount of solid material, concentrated to *ca.* 10 ml. and basified with excess 2.5 *N* Na_2CO_3 solution. The resultant precipitate was washed with water and dried (0.36 g.). Recrystallization from ethanol afforded 0.11 g. of garnet rhombs, m.p. 255–257°. A mixture m.p. with the pure *anil* (derived from 9-formylacridine) showed no depression.

Anal. Calc'd for $C_{22}H_{19}N_3$: C, 81.2; H, 5.89.
Found: C, 81.2; H, 6.09.

3-Di-n-butylaminopropylmagnesium chloride. This preparation is a modification of the excellent general procedure developed by Marxer for preparing this and other amino Grignard reagents (3). It is essential that the apparatus and solvents used be absolutely dry. While some moisture may be tolerated once the reaction between the amino halide and the magnesium has been initiated, the presence of moisture at the outset makes it quite difficult to start the reaction. If the apparatus is not disassembled, but is only opened to the extent necessary to remove the Grignard reagent at the end of the reaction, the subsequent preparation of a new batch is much facilitated. The ether used as solvent in the first phase of the reaction should be dried with a Grignard reagent, such as EtMgBr, and distilled directly into the reaction flask. The use of an inert atmosphere is recommended and we have successfully employed dry hydrogen or helium; nitrogen is somewhat less suitable.

Ethyl (or methyl) halide is used to activate the magnesium. In small runs it may be desirable to remove most of this alkylmagnesium halide and this may be accomplished if a stopcock is sealed into the bottom of the flask. In larger runs, this small amount of extraneous RMgX is usually inconsequential.

It is important to keep the reaction going continuously. This is best accomplished by using a minimum of ether, adding the halide as rapidly as possible, and employing an ether–benzene solvent mixture (the latter seems to prevent the formation of a surface coating on the magnesium).

The following is a *typical run*: 60 g. of magnesium turnings was covered with dry ether and activated by the addition of 3 ml. of ethyl bromide. As soon as the reaction had subsided, another ml. of ethyl bromide was added and, as this reaction approached its peak, 50 ml. of 3-di-*n*-butylaminopropyl chloride was introduced during the next few minutes. When the reaction was well under way, a solution of 224 g. of 3-di-*n*-butylaminopropyl chloride in a mixture of 125 ml. of dry ether and 250 ml. of dry benzene was added at the rate of 15 ml. per minute. At the end of the spontaneous reaction, the solution was refluxed for 30 minutes, separated from excess magnesium and diluted to one liter. Typical electrometric titration values indicated the solution to be 0.82 *molar* with respect to magnesium and 1.09 *molar* in amine. This represented a yield of 70% of amino Grignard reagent and 100% recovery of amine.

9-(4-Di-n-butylamino-1-hydroxybutyl)acridine. A stirred solution of 6.8 g. (0.0328 mole) of 9-formylacridine in 250 ml. of dry benzene was gradually treated with 90 ml. (0.0738 mole) of a warm 0.82 *M* solution of 3-di-*n*-butylaminopropylmagnesium chloride in benzene. After refluxing for 15 mins. the Michler's ketone test was only faintly positive. The complex was decomposed with aqueous NH_4Cl, the organic layer separated and thoroughly extracted with 1.0 *N* HCl. Upon basifying with NH_4OH, an oil separated which soon crystallized, m.p. 98–103°; yield 10 g. After three recrystallizations from 70% ethanol, from which the base separates in stout prisms, the m.p. was 96–102°; yield 5.9 g. The substance apparently contains one mole of water of crystallization which is easily lost by drying in a vacuum-desiccator. The base becomes gummy and resolidifies as the hydrate when exposed to the atmosphere.

Anal. Calc'd for $C_{25}H_{34}N_2O \cdot H_2O$: C, 75.7; H, 9.15.
Found: C, 75.9; H, 9.26.

The *dihydrochloride*, prepared in acetone with the calculated amount of conc'd HCl, crystallized in bright-yellow needle rosettes from absol. ethanol; m.p. 168–170° d.

Anal. Calc'd for $C_{25}H_{36}Cl_2N_2O$: C, 66.5; H, 8.04.
Found: C, 66.2; H, 7.90.

2-Methoxy-9-methylacridine. A stirred mixture of 26 g. (0.192 mole) of *o*-aminoacetophenone (10), 43.5 g. (0.23 mole) of redistilled *p*-bromoanisole, 43 g. (0.405 mole) of anhydrous Na_2CO_3 (dried at 120°), 1.55 g. of copper powder, and 200 ml. of dry nitrobenzene was gradually heated to 185° (oil-bath temp.) where slight foaming occurred. The temperature was cautiously raised to 205–210°; excessive foaming being effectively controlled by intermittent withdrawal of the source of heat. After 3 hours heating the nitrobenzene and excess bromoanisole were steam-distilled off, the residual oil taken up in ether, dried and concentrated (*vacuo*); the yield was 42 g. This oil was cyclized by dissolving it in 105 ml. of glacial acetic acid, carefully treating with 21 ml. of conc'd H_2SO_4 and heating on the steam-bath for 6 minutes. The crystalline acridine salt which separated as a thick sludge was cooled and dispersed in 500 ml. of ice-cold water. The cooled suspension was basified (conc'd NH_4OH) and the dark brown precipitate washed with water and dried; yield 33 g. Although the procedure was slow, the product was best purified by sublimation at 140–145°/0.4 mm. In order to prevent caking, it was found advantageous to mix the crude material with a little clean sand before sublimation. Yield, 17.7 g. (44%, based on *o*-aminoacetophenone used). Recrystallization from ether–petroleum ether (30–60°) afforded 15.3 g. of pale yellow needles. An analytical sample was sublimed twice again, m.p. 140–141.5°.

Anal. Calc'd for $C_{15}H_{13}NO$: C, 80.7; H, 5.87.
Found: C, 80.9; H, 5.88.

α-(2-Methoxy-9-acridyl)-N-(4-dimethylaminophenyl)nitrone. (From 2-methoxy-9-methylacridine). An intimate mixture of 8 g. (0.0358 mole)of 2-methoxy-9-methylacridine, 10.8 g. (0.072 mole) of *p*-nitrosodimethylaniline, and 6 drops of piperidine was gradually heated to 95° (oil-bath). When the initial exothermic reaction subsided, the temperature was raised and maintained at 120° for 30 minutes. The cooled melt was triturated with 10 ml. of ethanol, diluted with 150 ml. of ether, and filtered; yield 10.8 g. (82%). From ethanol (Norit), long, yellow rectangular plates; after four crystallizations, m.p. 225–227° dec. The analytical sample was dried for 2 hours at 97° (*in vacuo*).

Anal. Calc'd for $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70.
Found: C, 74.6; H, 5.69.

2-Methoxy-9-formylacridine. A suspension of 12 g. of the above nitrone in a mixture of 22 ml. of conc'd HCl and 38 ml. of water was heated on the steam-bath for 10 minutes. The resulting crystalline, orange magma of the formylacridine hydrochloride was washed with 125 ml. of cold (1:3) saturated NaCl-2 *N* HCl mixture. Digestion of the hydrochloride with a concentrated aqueous solution of sodium acetate (5 minutes at 100°) afforded the crude aldehyde. A clarified (Norit) solution of the latter in 350 ml. of methanol was concentrated to *ca.* 150 ml. and diluted with an equal volume of water. The bright yellow precipitate weighed 4.5 g. (57%), m.p. 145–147°. It was purified by sublimation at 145°/0.4 mm., yellow prisms, m.p. 146.5–148°.

Anal. Calc'd for $C_{15}H_{11}NO_2$: C, 75.9; H, 4.67.
Found: C, 76.2; H, 4.86.

The *oxime*, prepared in the usual way, crystallized in yellow needles (ethanol), m.p. 236–238° dec.

Anal. Calc'd for $C_{15}H_{12}N_2O_2$: C, 71.4; H, 4.80.
Found: C, 71.5; H, 5.07.

2-Methoxy-9-(4-dimethylaminophenyliminomethyl)acridine. (From 2-methoxy-9-formylacridine). The condensation of 0.5 g. of 2-methoxy-9-formylacridine with 0.35 g. (1.2 equiv.) of *p*-aminodimethylaniline using 2 drops of piperidine as catalyst was carried out as outlined above. Recrystallization of the crude anil (0.42 g.) from ethanol (Norit) afforded amber plates mixed with a small quantity of bright red needles. Mechanically separated, the amber plates showed the m.p. 184–185.5°, while the red needles melted at 183.5–185°; on mixing the two, the m.p. was 184–185.5°. Although the two crystalline

modifications are readily interconvertible, the red needles appear to be more stable since repeated recrystallization of a mixture gradually leads to the red-needle form exclusively. A mixture of either crystalline form with the anil derived from 2-methoxy-9-methylacridine (m.p. 225–227° dec.) melted at 177.5–179° dec.

Three recrystallizations from ethanol did not raise the m.p. (183.5–185°) of the *red-needle form*.

Anal. Calc'd for: $C_{23}H_{21}N_3O$: C, 77.7; H, 5.96.
Found: C, 77.8; H, 6.19.

Hydrolysis of a small amount of the crude 2-methoxy anil with dil. HCl afforded a bright yellow substance, m.p. 147–148°, identical with 2-methoxy-9-formylacridine.

2-Methoxy-9-(4-di-n-butylamino-1-hydroxybutyl)acridine. One hundred fifty-five ml. (0.127 mole) of 0.82 *M* 3-di-n-butylaminopropylmagnesium chloride in benzene was gradually added to a stirred benzene solution of 6.7 g. (0.0283 mole) of 2-methoxy-9-formylacridine. The reaction mixture was refluxed for 15 minutes and then worked up as described above. The resulting gummy base was conveniently purified by dissolving it in a little absolute ethanol and adding a solution of 20 g. (excess) of 85% phosphoric acid in 80 ml. of absolute ethanol. The sparingly soluble phosphate that separated was thoroughly washed with absolute ethanol, dried, and converted to the free base (NH_4OH–ether); yield 8.8 g., m.p. 95–105°. The latter crystallized in thick prisms from ethanol, 6.8 g., m.p. 103.6–105°. Two further recrystallizations gave m.p. 105–6°.

Anal. Calc'd for $C_{26}H_{36}N_2O_2$: C, 76.4; H, 8.88.
Found: C, 76.6; H, 8.94.

The *dihydrochloride*, prepared in acetone with conc'd HCl, crystallized in yellow needles from absol. ethanol–ether; m.p. 179–180.5° d.

Anal. Calc'd for: $C_{26}H_{38}Cl_2N_2O_2$: C, 64.8; H, 7.96.
Found: C, 64.4; H, 7.82.

The compound formed with *perchloric acid* sintered at 98° and melted at 181–3° (aq. ethanol); the compound formed with *phosphoric acid* crystallized as small rosettes from aqueous ethanol.

2-Nitro-4-chloroacetophenone was prepared according to the method of Leonard and Boyd (10). The final product, obtained in 72% yield (lit. 61%), melted at 54–56°; 10° higher than that reported (10).

The *oxime* crystallized in white needles from aqueous ethanol; m.p. 95°.

Anal. Calc'd for $C_8H_7ClN_2O_3$: C, 44.8; H, 3.29.
Found: C, 45.0; H, 3.33.

The *semicarbazone*, cream colored, hair-like needles or stout prisms from ethanol; m.p. 229–231° (sinters at 224°).

Anal. Calc'd for $C_9H_9ClN_4O_3$: C, 42.1; H, 3.54.
Found: C, 42.2; H, 3.84.

2-Amino-4-chloroacetophenone. The selective, catalytic reduction of the nitro group in 2-nitro-4-chloroacetophenone proceeded smoothly (PtO_2–ethanol) (10).

2-Methoxy-6-chloro-9-methylacridine. A. From 2-amino-4-chloroacetophenone. The condensation of 7.8 g. (0.046 mole) of 2-amino-4-chloroacetophenone with 13 g. (0.0695 mole) of redistilled *p*-bromoanisole in 60 ml. of nitrobenzene in the presence of 13 g. of anhydrous sodium carbonate, 0.5 g. of copper powder, and 2 drops of water was carried out as previously described under 2-methoxy-9-methylacridine. The crude, oily product was cyclized with a mixture of 25 ml. of glacial acetic acid and 5 ml. of conc'd H_2SO_4 by warming on the steam-bath for 5 minutes. The resulting acridine salt was washed well with glacial acetic acid, then with ether; yield 10.7 g. The salt was best crystallized from glacial acetic acid; m.p. 220–230° dec.

The *base*, regenerated from the purified sulfate, weighed 4.3 g. (37%), m.p. 169–170°. It could be sublimed at 160°/0.4 mm.; m.p. 170°.

Anal. Calc'd for $C_{15}H_{12}ClNO$: C, 69.9; H, 4.70.
Found: C, 70.2; H, 4.79.

B. From N-(4-methoxyphenyl)-4-chloroanthraniloyl chloride. The diazoketone. To a stirred, ice-cooled, ethereal solution of diazomethane (from 3.1 g. of nitrosomethylurea), a solution of 2 g. of N-(4-methoxyphenyl)-4-chloroanthraniloyl chloride (12) in 50 ml. of dry ether was added during 20 minutes. After 12 hours at 5°, concentration (*vacuo*) at 25–35° afforded 1.9 g. of bright yellow, nacreous plates, m.p. 106–107.5° (gas evolution). A mixture of this with the original acid chloride (m.p. 108–110°) melted at 85°.

The bromoketone. A stirred solution of the diazoketone (1.9 g.) in 65 ml. of dry ether was treated, at 0°, with a mixture of 1.75 ml. (2.2 equiv.) of 48% HBr, 10 ml. of ether, and a few drops of absolute ethanol to ensure homogeneity. The ice-bath was removed and stirring continued for 45 minutes. After washing with water and dil. $NaHCO_3$, the ether solution was digested with Norit, filtered, and concentrated to a small volume. The addition of 4 volumes of petroleum ether (30–60°) and a seed crystal afforded, after 15 hours, 1.2 g. of slender orange prisms, m.p. 102–103.5°; unchanged after two more recrystallizations from ether–petroleum ether.

Anal. Calc'd for $C_{15}H_{13}BrClNO_2$: C, 50.8; H, 3.69.
Found: C, 51.1; H, 3.73.

Debromination. A solution of 1 g. of the above recrystallized bromoketone in 90 ml. of absolute ethanol was shaken in hydrogen with 0.6 g. of palladium-Norit catalyst (5% Pd); 84 ml. (1.1 moles) of H_2 was absorbed in 1 hour. Concentration (*vacuo*) yielded 0.7 g. of yellow needles mixed with a little oil. After two triturations with 3-ml. portions of cold methanol, the needles were crystallized from methanol; 0.15 g., m.p. 279–281° dec. Two more recrystallizations raised the m.p. to 281–282.5° dec.

Anal. Calc'd for $C_{15}H_{13}BrClNO$: C, 53.2; H, 3.87.
Found: C, 53.3; H, 3.66.

The oily fraction was not examined.

By suspending the crystalline fraction (finely powdered) in 2 *N* NaOH and extracting with ether, a light yellow solid was obtained, m.p. 167–169°. Sublimation at 150°/0.4 mm. gave pale yellow prisms, m.p. 170–171.5°, not depressed when mixed with 2-methoxy-6-chloro-9-methylacridine (above).

C. From N-(4-methoxyphenyl)-4-chloroanthraniloyl chloride, via the diazoketone and hydriodic acid. Employing the technique described by Wolfram (14), 6 ml. of 47% HI (by dilution of freshly distilled 57% acid) was added, all at once, to a solution of 2 g. of the above-described diazoketone in 15 ml. of chloroform. Gas evolution accompanied the ensuing, mildly exothermic reaction. After shaking for 5 minutes, a little water was added, the $CHCl_3$ layer separated and washed successively with water, sodium thiosulfate, water, and then dried. The $CHCl_3$ solution gave 1.8 g. of a dark brown syrup.

Cyclization. One and two-tenths grams of the above syrup dissolved in 4 ml. of glacial acetic acid was treated with 1 ml. of conc'd H_2SO_4 and heated on the steam-bath for 6 minutes. The dark brown solution was poured into 50 ml. of ice-water, basified with conc'd ammonia and the greenish-yellow precipitate dried (0.9 g.). A clarified (Norit) ethereal solution of the latter was concentrated to incipient crystallization. The cooled, crystalline suspension was freed of mother liquor and the yellow prisms rinsed with petroleum ether (30–60°); m.p. 164–168°. After two sublimations at 150°/0.4 mm., the m.p. was 170.5–172°. A mixture m.p. with 2-methoxy-6-chloro-9-methylacridine (see above) showed no depression.

α-(2-Methoxy-6-chloro-9-acridyl)-N-(4-dimethylaminophenyl)nitrone. (From 2-methoxy-6-chloro-9-methylacridine). An intimate mixture of 8.4 g. (0.032 mole) of 2-methoxy-6-chloro-9-methylacridine, 9.8 g. (0.065 mole) of *p*-nitrosodimethylaniline, and 8 drops of piperidine was carefully heated, with frequent stirring, in an oil-bath (115–120°) for 30 minutes. The cooled reaction product was processed as before (see 2-methoxy analog). Recrystallization of the crude material (12.5 g.) from ethanol (Norit) yielded 8.6 g. of a mixture of garnet colored prisms and dark red needles. Both forms melted at 196–198° dec.; no depression on mixture. The red needles reverted to the garnet prisms on repeated

recrystallizations; after three recrystallizations, m.p. 198–200° dec. The analytical sample was dried for 2 hours at 78°/0.4 mm.

Anal. Calc'd for $C_{23}H_{20}ClN_3O_2$: C, 68.06; H, 4.97.
Found: C, 69.7, 69.5; H, 5.18, 5.01.

2-Methoxy-6-chloro-9-formylacridine. The hydrolysis of 10.4 g. of the above nitrone with a mixture of 19 ml. of conc'd HCl and 33 ml. of water was effected as outlined under 2-methoxy-9-formylacridine. The crude aldehyde was purified by dissolving it in 125 ml. of boiling dioxane (Norit) and diluting the cooled filtrate with 2 volumes of methanol. The yellow crystals were washed with ether; 4.6 (64%), m.p. 185–186°. Yellow prisms, m.p. 185–186°, were obtained by subliming a sample at 165–170°/0.3 mm.

Anal. Calc'd for $C_{15}H_{10}ClNO_2$: C, 66.3; H, 3.71.
Found: C, 66.1; H, 3.77.

The *oxime* crystallized in yellow needles (ethanol), m.p. 240–241° dec.

Anal. Calc'd for $C_{15}H_{11}ClN_2O_2$: C, 62.8; H, 3.87.
Found: C, 63.1; H, 3.87.

2-Methoxy-6-chloro-9-(4-dimethylaminophenyliminomethyl)acridine. (From 2-methoxy-6-chloro-9-formylacridine). One-half gram of 2-methoxy-6-chloro-9-formylacridine was condensed at 115° with 0.3 g. (1.2 equiv.) of *p*-aminodimethylaniline in the presence of 2 drops of piperidine and the product isolated as usual. The anil (0.44 g.) crystallized from ethanol in fine, dark red needles, m.p. 196°.

Anal. Calc'd for $C_{23}H_{20}ClN_3O$: C, 70.9; H, 5.17.
Found: C, 70.9; H, 5.28.

A mixture of this anil with the nitrone obtained from 2-methoxy-6-chloro-9-methylacridine (m.p. 198–200° dec.) melted at 194–195° dec. The hydrolysis (dil. HCl) of a small amount of this anil yielded a bright yellow solid, m.p. 184–185°, not depressed by 2-methoxy-6-chloro-9-formylacridine.

2-Methoxy-6-chloro-9-(4-di-n-butylamino-1-hydroxybutyl)acridine. A stirred solution of 5 g. (0.0184 mole) of 2-methoxy-6-chloro-9-formylacridine in 130 ml. of dry benzene was treated with 48 ml. (0.0393 mole) of a warm 0.82 *N* solution of 3-di-n-butylaminopropylmagnesium chloride in benzene. The system was gently refluxed for 50 minutes, cooled and decomposed with cold aqueous NH_4Cl. The aqueous layer was extracted once with benzene and the combined benzene solutions were diluted with ether and dried over sodium sulfate. The resulting syrupy carbinol (10 g.) was cooled in ice and treated dropwise with 20% ethanolic H_3PO_4 (to Congo Red acidity); scratching induced crystallization. After 12 hours at 5° the bright yellow phosphate was washed with a little cold absolute ethanol; yield 10.2 g., m.p. 196–198° dec.

The free base, regenerated from the salt (NH_4OH–ether) appeared as an amber syrup (6.1 g.). On rubbing this with a little petroleum ether (28–38°) slow crystallization occurred. Repeated recrystallization from petroleum ether gave small, pale yellow rhombs, m.p. 87–88.5°.

Anal. Calc'd for $C_{26}H_{35}ClN_2O_2$: C, 70.5; H, 7.96.
Found: C, 70.2; H, 8.00.

The *dihydrochloride* was prepared in acetone with the calculated amount of conc'd HCl, and recrystallized from a concentrated absolute ethanol solution; minute, yellow needles, m.p. 195–197° dec.

Anal. Calc'd for $C_{26}H_{37}Cl_3N_2O_2$: C, 60.5; H, 7.23.
Found: C, 60.2; H, 7.34.

SUMMARY

1. The synthesis of three new amino carbinols possessing strong plasmodicidal activity, and derived from various 9-formylacridines is described.

2. The formation of nitrones through the condensation of aromatic nitroso compounds with reactive methylene groups has been confirmed.

3. The reduction, by sulfur dioxide, of a nitrone to the corresponding anil suggests an N-oxide configuration in the former.

4. The synthesis of two new acridine-9-aldehydes is reported.

BETHESDA 14, MD.

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