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CARBINOLAMINES OF THE TYPE R-CHOH-CH_2NR_2 DERIVED FROM 7- AND 8-ACETYL-1,2,3,4-TETRAHYDROACRIDINES AS PLASMODICIDES[1]

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The introduction of certain amino carbinol systems at various positions of the acridine nucleus, with the view to studying their effect on plasmodicidal activity, was the subject of a series of recent investigations in this laboratory. Although only slight activity was elicited by several bz-substituted amino carbinols derived from 9,10-dihydroacridine (1), the corresponding derivatives prepared from 9-formylacridine were found to be fairly active plasmodicides (2). In extending this study it was of interest to determine the influence, on activity, of partial saturation of the acridine molecule, and this paper describes two groups of amino carbinols synthesized from 7- and 8-acetyl-1,2,3,4-tetrahydroacridines by way of the respective bromo ketones as was done previously (1).

Petrow (3) has described the only known bz-acetyl-1,2,3,4-tetrahydroacridine which was synthesized from formylcyclohexanone and *m*-aminoacetophenone as shown in Figure 1. Owing to the possibility of isomer formation (depending upon the direction of ring closure in the second step) the position of the acetyl group was tentatively assigned to either the 6- or 8-position of the resulting tetrahydroacridine system, but the structure was not established.

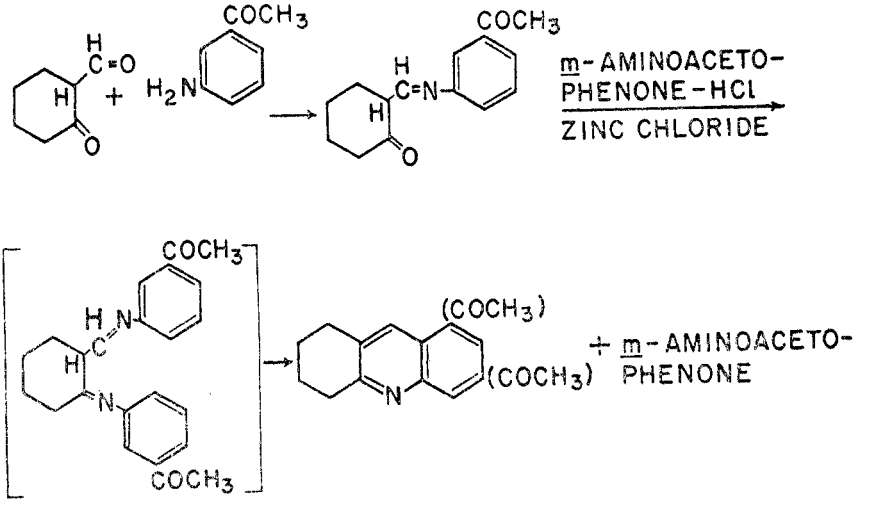

FIG. 1.

We have repeated Petrow's experiments and have been able to demonstrate that his 6- or 8-acetyltetrahydroacridine is, in fact, the 8-acetyl derivative.

[1] Studies in the Acridine Series VIII.

Wolff-Kishner reduction of Petrow's substance gave an ethyl-1,2,3,4-tetrahydroacridine which was dehydrogenated (palladium-charcoal) to an ethylacridine identical with 1-ethylacridine synthesized by an unequivocal route (4). The possibility of ethyl group migration or elimination during dehydrogenation was tested and shown not to occur in this as well as in related instances[2]. Because the 1- and 8-positions in acridine are equivalent, it follows that Petrow's derivative must have been 8-substituted.

It is of interest to note that these observations are at variance with those made by Petrow with the homologous methyltetrahydroacridine (obtained from formylcyclohexanone and *m*-toluidine), in that he reports obtaining 6-methyltetrahydroacridine. It is possible that the decidedly different activating influences operative in these two instances (*viz.*, the effect of the methyl group on the reactivity of the various positions in the aromatic moiety of the *m*-toluidine-derived *anil* on the one hand, and the corresponding effect of the acetyl group in the *anil* prepared from *m*-aminoacetophenone on the other) may well account for the different directions taken in the respective intramolecular cyclizations.

A further, albeit indirect, demonstration that the acetyl group in the tetrahydroacridine in question is not 6-substituted was effected as follows. 6-Formyl-3-ethylcyclohexanone was condensed with aniline and the resulting *anil* was treated further with aniline hydrochloride in the presence of zinc chloride to arrive at 3-ethyl-1,2,3,4-tetrahydroacridine. Dehydrogenation of this afforded an ethylacridine which *differed* from that obtained from Petrow's substance but was identical with synthetic 3-ethylacridine prepared by unambiguous means (4). 6-Acetyl-1,2,3,4-tetrahydroacridine would have afforded 6-ethylacridine (equivalent to 3-ethylacridine). This series of reactions, taken with the demonstration of non-rearrangement during dehydrogenation, serves also to establish the structure of the hitherto unknown 6-formyl-3-ethylcyclohexanone. Formylation of 3-ethylcychlohexanone conceivably could have led either to 2-formyl-3-ethyl- (A in Figure 2) or to 6-formyl-3-ethyl-cyclohexanone (B in Figure 2) thereby influencing the structure of the substituted acridine ultimately formed.

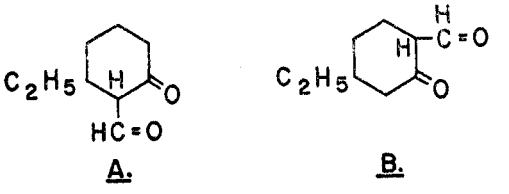

FIG. 2.

Bromination of 8-acetyl-1,2,3,4-tetrahydroacridine in 48% HBr solution yielded the ω-bromo ketone. Condensation of this with a series of secondary amines afforded the intermediate amino ketones which were then reduced to the corresponding amino carbinols shown in Table I.

[2] The retention and/or non-rearrangement of a side-chain ethyl group during dehydrogenation with palladium-charcoal is not unusual; [*cf.* Cocker, *et al.*, *J. Chem. Soc.*, 72 (1952)].

TABLE I

SUBSTITUTED 1,2,3,4-TETRAHYDROACRIDINE DIHYDROCHLORIDES

Compound	Appearance	Formula	M. p., °C.	Analyses			
				Calc'd		Found	
				C	H	C	H
7-(2-Dimethylamino-1-hydroxyethyl)-	Needles[a]	$C_{17}H_{24}Cl_2N_2O$	237–239 d.	59.5	7.05	59.8	7.47
7-(2-Diethylamino-1-hydroxyethyl)-	Rosettes[b]	$C_{19}H_{28}Cl_2N_2O$	246–248 d.	61.5	7.60	61.4	7.60
7-(2-Di-*n*-propylamino-1-hydroxyethyl)-	Needles[a]	$C_{21}H_{32}Cl_2N_2O$	255–257 d.	63.1	8.08	62.8	7.87
7-(2-Di-*n*-butylamino-1-hydroxyethyl)-	Flat needles[a]	$C_{23}H_{36}Cl_2N_2O$	240–242 d.	64.6	8.49	64.4	8.44
7-(2-Di-*n*-amylamino-1-hydroxyethyl)-	Plates[a]	$C_{25}H_{40}Cl_2N_2O$	220–222 d.	65.9	8.86	66.3	8.75
7-(2-Di-*n*-hexylamino-1-hydroxyethyl)-	Plates[a]	$C_{27}H_{44}Cl_2N_2O$	198–199 d.	67.1	9.17	66.8	9.18
7-(2-Di-*n*-heptylamino-1-hydroxyethyl)-	Plates[a]	$C_{29}H_{48}Cl_2N_2O$	195–197 d.	68.1	9.46	67.7	9.51
7-(2-Di-*n*-octylamino-1-hydroxyethyl)-	Plates[a]	$C_{31}H_{52}Cl_2N_2O$	201–203 d.	69.0	9.71	68.7	9.37
7-(2-Di-*n*-nonylamino-1-hydroxyethyl)-	Barrel-shaped plates[a]	$C_{33}H_{56}Cl_2N_2O$	207–209 d.	69.8	9.94	69.4	9.73
7-(2-Di-*n*-decylamino-1-hydroxyethyl)-	Irregular plates[a]	$C_{35}H_{60}Cl_2N_2O$	207–209 d.	70.6	10.2	70.2	10.5
8-(2-Diethylamino-1-hydroxyethyl)-	Needles[b]	$C_{19}H_{28}Cl_2N_2O$	260–261 d.	61.5	7.60	61.7	7.53
8-(2-Di-*n*-propylamino-1-hydroxyethyl)-	Plates[a]	$C_{21}H_{32}Cl_2N_2O$	250–252 d.	63.1	8.08	62.7	8.07
8-(2-Di-*n*-butylamino-1-hydroxyethyl)-	Plates[a]	$C_{23}H_{36}Cl_2N_2O$	225–227 d.	64.6	8.49	64.4	8.36
8-(2-Di-*n*-amylamino-1-hydroxyethyl)-	Prisms[a]	$C_{25}H_{40}Cl_2N_2O$	209–210 d.	65.9	8.86	65.8	8.71
8-(2-Di-*n*-heptylamino-1-hydroxyethyl)-	Plates[c]	$C_{29}H_{48}Cl_2N_2O$	185–187	68.1	9.46	67.8	9.56
8-(2-Di-*n*-octylamino-1-hydroxyethyl)-	Plates[a]	$C_{31}H_{52}Cl_2N_2O$	190–192 d.	69.0	9.71	68.8	9.85
8-(2-Di-*n*-nonylamino-1-hydroxyethyl)-	Crystalline crusts[d]	$C_{33}H_{56}Cl_2N_2O$	168–170	69.8	9.94	69.4	9.68
8-(2-Di-*n*-decylamino-1-hydroxyethyl)-	Crystalline crusts[c]	$C_{35}H_{60}Cl_2N_2O$	145–147	70.6	10.2	70.7	9.9

[a] Acetone, absol. alcohol plus ether. [b] Absol. alcohol plus ether. [c] Acetone. [d] Acetone plus ether.

7-Acetyl-1,2,3,4-tetrahydroacridine has been synthesized for the first time from formylcyclohexanone and *p*-aminoacetophenone and transformed through analogous reactions to a series of amino carbinols listed in Table I. It is clear that, in this instance, the acetyl group can occupy only the 7-position regardless of which direction intramolecular cyclization of the intermediate *anil* takes.

Representative condensations of each bromo ketone with a secondary amine are described below, and it will be noted that either anhydrous ether or dry chloroform may serve as reaction solvent. In general however, chloroform, because it made for homogeneous systems, proved superior.

With regard to their effect on *Plasmodium gallinaceum* (chick infection), all of the 8-substituted amino carbinols were found to be moderately active, whereas the 7-substituted analogs were inactive (5).

EXPERIMENTAL[3]

2-(m-Acetylphenyliminomethyl) cyclohexanone.[4] The condensation of 76 g. (0.6 mole) of freshly distilled formylcyclohexanone (3) with 81.6 g. (0.6 mole) of *m*-aminoacetophenone (6) in 275 ml. of absolute ethanol (steam-bath, 2 hrs.) and subsequent cooling, yielded 139 g. of light-yellow crystals, m.p. 137–138°. [Lit. (3) m.p. 139–140°].

8-Acetyl-1,2,3,4-tetrahydroacridine.[4] Fifty grams (0.21 mole) of the above described *anil* was heated for 12 hrs. (steam-bath) with 50 g. (0.29 mole) of *m*-aminoacetophenone hydrochloride and 28 g. (0.21 mole) of fused zinc chloride in 750 ml. of absolute ethanol. The reaction mixture was concentrated (*vacuo*) to about one-third its original volume, diluted with 1 l. of water, basified with 25% NaOH, and extracted with ether. The latter solvent yielded a dark oil which was dissolved in 50 ml. of ethanol and treated with a hot solution of 75 g. (excess) of picric acid in 450 ml. of ethanol. After keeping at 5° for 15 hrs., the picrate was collected, washed with a little cold ethanol, and dried; 100 g. Decomposition of this with 2 *N* NaOH and ether yielded 21.5 g. of crude, 8-acetyltetrahydroacridine (a weight which was equalled in several runs). Distillation of the ketone from a sabre-flask at 180–195°/0.3 mm. (metal-bath) gave a colorless solid contaminated with *m*-aminoacetophenone. By dissolving 79 g. of the distillate in 525 ml. of boiling 40% (v/v) ethanol and allowing the solution to cool slowly to room temperature, pure 8-acetyltetrahydroacridine (64 g.) crystallized in colorless needles, m.p. 130–131.5°. The residue remaining in the distilling flask was sublimed at 140°/0.3 mm. and yielded, after recrystallization, another 6 g. of ketone, m.p. 129–131°.

The *oxime*, leaflets from 40% (v/v) ethanol, m.p. 172–174°.

Anal. Calc'd for $C_{15}H_{16}N_2O$: C, 75.0; H, 6.71.
Found: C, 74.8; H, 7.17.

The *semicarbazone*, plates from dioxane, m.p. 253–255° dec.

Anal. Calc'd for $C_{16}H_{18}N_4O$: C, 68.1; H, 6.43.
Found: C, 67.6; H, 6.68.

The *hydrochloride*, flat needles from ethanol-ether, m.p. 205–207°.

Anal. Calc'd for $C_{15}H_{16}ClNO$: C, 68.8; H, 6.16.
Found: C, 68.8; H, 6.59.

8-(ω-Bromoacetyl)-1,2,3,4-tetrahydroacridine. The following is an adaptation of a procedure used by Nandi (7) for brominating 3-quinolyl methyl ketone. A stirred solution of 10 g. of 8-acetyl-1,2,3,4-tetrahydroacridine in 50 ml. of 48% HBr, maintained at 45–50°, was treated during 25 mins. with a solution of 2.4 ml. (2.02 atoms) of bromine in 20 ml. of 48% HBr. After stirring and warming for 15 mins. longer, the system was cooled and poured

[3] Melting points and boiling points are uncorrected. Analyses are by E. A. Garlock and Betty Mount, both, formerly of this laboratory.

[4] Petrow (ref. 3) prepared this substance on a small scale.

into 300 ml. of an ice-water slurry. Neutralization with solid Na_2CO_3 precipitated the bromo ketone as a gum which crystallized when rubbed. The product was filtered, triturated with cold 2 *N* Na_2CO_3, collected, washed with water, and dried in a vacuum desiccator over $CaCl_2$. Recrystallization of the bromo ketone (13 g.) from a concentrated solution in acetone gave 10 g. of nearly colorless prisms, a specimen of which was recrystallized once again; m.p. 175.5–177°.

Anal. Calc'd for $C_{15}H_{14}BrNO$: C, 59.2; H, 4.64.
Found: C, 59.5; H, 4.80.

2-(p-Acetylphenyliminomethyl) cyclohexanone. Formylcyclohexanone (74 g., 0.6 mole) was condensed with an equivalent amount of *p*-aminoacetophenone (79.5 g., 0.6 mole) in 375 ml. of absolute ethanol (2 hrs., steam-bath). The cooled, pale-yellow product was collected and dried; 143 g. The *anil* crystallizes in light-yellow plates from ethanol, m.p. 201–202.5°.

Anal. Calc'd for $C_{15}H_{17}NO_2$: C, 74.0; H, 7.04.
Found: C, 73.7; H, 7.12.

7-Acetyl-1,2,3,4-tetrahydroacridine. Condensation of 50 g. (0.21 mole) of the immediately above *anil* with 50 g. (0.29 mole) of *p*-aminoacetophenone hydrochloride in the presence of 28 g. (0.21 mole) of fused zinc chloride was effected in 750 ml. of absolute ethanol (12 hrs. steam-bath). The reaction mixture was worked up, and treated as described for the 8-isomer, yielding 75 g. of 7-acetyl-1,2,3,4-tetrahydroacridine picrate which, in turn, gave 20.6 g. of crude ketone. The latter, purified by distillation at 0.5 mm. (sabre-flask, metal-bath at 207–210°) was obtained as a virtually colorless solid, 18.5 g. A sample was sublimed at 100°/0.3 mm., m.p. 104.5–106°.

Anal. Calc'd for $C_{15}H_{15}NO$: C, 80.0; H, 6.71.
Found: C, 80.1; H, 6.59.

The *oxime*, small prisms (absolute ethanol), m.p. 225–227°.

Anal. Calc'd for $C_{15}H_{16}N_2O$: C, 75.0; H, 6.71.
Found: C, 75.1; H, 6.62.

The *semicarbazone*, fine needles (absolute ethanol), m.p. 251–253° dec.

Anal. Calc'd for $C_{16}H_{18}N_4O$: C, 68.1; H, 6.43.
Found: C, 68.0; H, 6.41.

The *picrate*, flat prisms (ethanol), m.p. 207–208° dec.

Anal. Calc'd for $C_{21}H_{18}N_4O_8$: C, 55.5; H, 3.99.
Found: C, 55.7; H, 4.05.

The *hydrochloride*, needles (absolute ethanol), m.p. 287–289° dec.

Anal. Calc'd for $C_{15}H_{16}ClNO$: C, 68.8; H, 6.16.
Found: C, 68.7; H, 6.26.

7-(ω-Bromoacetyl)-1,2,3,4-tetrahydroacridine. Bromination of 36 g. of 7-acetyl-1,2,3,4-tetrahydroacridine in 250 ml. of 48% HBr with a solution of 8.7 ml. (2.02 atoms) of bromine in 54 ml. of 48% HBr was carried out as above. Addition of a few ml. of water to the ice-cooled system caused the separation of the crystalline bromo ketone hydrobromide. This was collected (sintered glass funnel), suspended in cold 2 *N* Na_2CO_3, and the bromo ketone was taken up in ether. The latter was washed with water, dried, concentrated to small volume (*vacuo*), and the residue kept at 5° for 15 hrs. After decanting the mother liquor, the solid was recrystallized from alcohol-free ether[5] and gave 29.9 g. of pale-yellow prisms, m.p. 94–95°. Reworking the combined mother liquors yielded another 1.7 g. of bromo ketone, m.p. 92–94°. A sample was recrystallized twice again from anhydrous ether; m.p. 94–95°.

Anal. Calc'd for $C_{15}H_{14}BrNO$: C, 59.2; H, 4.64.
Found: C, 59.1; H, 4.58.

7-(2-Di-n-butylamino-1-hydroxyethyl)-1,2,3,4-tetrahydroacridine dihydrochloride. A cold

[5] Crystallization from U. S. P. ether yielded a lower-melting, presumably alcohol-solvated, form of m.p. 77–79°. Recrystallization from anhydrous ether raised the m.p. to 94–95°.

suspension of 7 g. of 7-ω-bromoacetyltetrahydroacridine in 200 ml. of anhydrous ether was mechanically shaken with 6.25 g. (2.1 equivs.) of di-*n*-butylamine for 15 hrs. at 20°. After cooling and removal of di-*n*-butylamine hydrobromide, concentration of the filtrate (*vacuo*, 30°) yielded 8.6 g. of syrupy amino ketone which was reduced with 24 ml. of 3 *N* aluminum isopropoxide (8)[6] during 50–60 mins. (steam-bath). Propanol-2 was distilled (*vacuo*) and the cooled residue was shaken into ether in the presence of excess 2 *N* NaOH. The water-washed and dried ether solution afforded 7.3 g. of a syrup, a cold acetone (20 ml.) solution of which was treated with a small excess (Congo Red) of alcoholic-HCl. Separation of the amino carbinol dihydrochloride was slow. After 15 mins., 75 ml. of anhydrous ether was slowly added, the system was refrigerated for 3 hrs., and the pink salt was collected. A suspension of the latter in 100 ml. of boiling acetone was brought into solution by the addition of 60 ml. of absolute ethanol (Norit). Addition of anhydrous ether to the filtered solution (to light turbidity) induced crystallization. After 2 hrs. at 5°, the yield of light-pink needles was 6.5 g. The analytical sample was recrystallized twice again.

8-(2-Di-n-amylamino-1-hydroxyethyl)-1,2,3,4-tetrahydroacridine dihydrochloride. To a cooled solution of 8-ω-bromoacetyltetrahydroacridine (7 g.) in 75 ml. of dry $CHCl_3$, 7.3 g. (2 equivs.) of di-*n*-amylamine was added and the clear solution was kept at room temperature for 2.5 hrs. Following concentration (*vacuo*, 30°), the residue was triturated at 0° with 75 ml. of anhydrous ether and the di-*n*-amylamine hydrobromide was collected. The filtrate gave 10 g. of sirupy amino ketone and this was reduced with 35 ml. of 3 *N* aluminum isopropoxide (8)[6] during 60 mins. After the usual work-up the product, in 10 ml. of acetone, was treated at 0° with anhydrous hydrogen chloride to Congo Red acidity; rubbing induced the separation of the dihydrochloride as a crystalline magma which was diluted with a mixture of 10 ml. of acetone and 50 ml. of anhydrous ether and kept at 5° for 2 hrs. The yield of pink-colored salt (vacuum-dried over $CaCl_2$) was 5.8 g. This was dissolved in a hot mixture of 75 ml. of acetone and 10 ml. of absolute ethanol and was digested with Norit. Dilution of the filtered solution with 300 ml. of anhydrous ether, seeding and keeping at 5° for 12 hrs. gave 3.9 g. of faintly-pink prisms, m.p. 203–205°.

2-(Phenyliminomethyl)-5-ethylcyclohexanone. Following Petrow's procedure for the preparation of the homologous methylformylcyclohexanone (3), the condensation of 26 g. (0.206 mole) of 3-ethylcyclohexanone (9) with 24.4 g. (0.208 mole) of isoamyl formate in the presence of 4.75 g. (0.206 mole) of sodium wire in 150 ml. anhydrous ether gave 14.3 g. of *2-formyl-5-ethylcyclohexanone*, b.p. 118.5–120°/22 mm., n_D^{23} 1.5007. This product (13.8 g.) in 85 ml. of absolute ethanol was heated for 2 hrs. with 8.35 g. (1 equiv.) of redistilled aniline (steam-bath, reflux). The light-yellow *anil* was collected, rinsed with a little cold methanol, and dried. Recrystallization from absolute ethanol afforded 16.4 g. of colorless plates, m.p. 166–167.5°.

Anal. Calc'd for $C_{15}H_{19}NO$: C, 78.6; H, 8.35.
Found: C, 78.6; H, 8.31.

3-Ethyl-1,2,3,4-tetrahydroacridine. A mixture of the above *anil* (15 g.) with 8.5 g. (1 equiv.) of aniline hydrochloride and 8.9 g. (1 equiv.) of fused zinc chloride in 300 ml. of absolute ethanol was heated on the steam-bath (reflux) for 15 hrs., and worked up as outlined above. Treatment of the crude product with a solution of 25 g. of picric acid in 150 ml. of ethanol gave an orange precipitate which was collected (after 1 hr. at 5°), washed with a little cold ethanol, and dried. Decomposition of the picrate (2 *N* NaOH-ether) yielded 5.5 g. of a light-brown, tacky solid which was chromatographed on alumina (light petroleum ether-benzene) to give 4.5 g. of nearly colorless prisms. A specimen was sublimed at 135°/0.3 mm., m.p. 46–47.5°.

Anal. Calc'd for $C_{15}H_{17}N$: C, 85.3; H, 8.11.
Found: C, 85.3; H, 8.10.

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[6] These reductions were carried out shortly before lithium aluminum hydride became generally available. It is very likely that better yields would result through the use of this versatile reducing agent.

A mixture of this with the isomeric 8-ethyl-1,2,3,4-tetrahydroacridine (m.p. 38.5–40°; see below) was liquid at 25°.

The *picrate* (from ethanol) first separated as yellow needles which gradually gave way to thick, yellow prisms on keeping, m.p. 174–176°.

Anal. Calc'd for $C_{21}H_{20}N_4O_7$: C, 57.3; H, 4.58.

Found: C, 57.2; H, 4.80.

3-Ethylacridine by dehydrogenation of 3-ethyl-1,2,3,4-tetrahydroacridine[2]. A mixture of 0.55 g. of 3-ethyl-1,2,3,4-tetrahydroacridine, 1.0 g. of 5% palladium-charcoal catalyst, and 8.0 g. of diphenyl was heated at 250–260° (metal-bath) for 2.5 hrs. The cooled mass was taken up in 100 ml. of ether, filtered, and extracted with 10-ml. portions of 0.2 *N* HCl until the extracts were colorless. After washing the combined extracts with ether, the basic material was recovered (NH_4OH-ether) as a syrup, and was converted to the *picrate* (alcoholic picric acid); 0.49 g. bright-yellow needles, m.p. 225–227°. From 0.4 g. of the latter (using 1 *N* NaOH-ether) an oil was obtained, a benzene solution of which was chromatographed on alumina, employing benzene-ether (9:1) for elution. The resulting pale-yellow oil (0.26 g.) crystallized spontaneously. After sublimation at 115–120°/0.4 mm., very pale-yellow prisms, m.p. 87.5–89° were obtained.

Anal. Calc'd for $C_{15}H_{13}N$: C, 86.9; H, 6.32.

Found: C, 87.0; H, 6.23.

The melting point of this substance was not depressed when mixed with authentic 3-ethylacridine, m.p. 90–91.5° (4). Moreover, the perchlorate of this base (from methanol-ether, m.p. 181–182°) was identical with 3-ethylacridine perchlorate, m.p. 184–185° (4).

8-Ethyl-1,2,3,4-tetrahydroacridine. 8-Acetyl-1,2,3,4-tetrahydroacridine (2 g.) was heated for 3.5 hrs. with a mixture of 2 g. of KOH and 2 ml. of 85% hydrazine hydrate in 20 ml. of triethylene glycol according to Huang-Minlon (10). Evaporative distillation of the product at 120–125°/0.3 mm. gave a yellow oil (1.44 g.) which crystallized when chilled in dry-ice and scratched. Sublimation at 115–120°/0.3 mm. gave an oil which crystallized in pale-yellow prisms, m.p. 38.5–40°.

Anal. Calc'd for $C_{15}H_{17}N$: C, 85.3; H, 8.11.

Found: C, 85.2; H, 8.17.

The *picrate*, yellow prisms from methanol, m.p. 160–162°.

Anal. Calc'd for $C_{21}H_{20}N_4O_7$: C, 57.3; H, 4.58.

Found: C, 57.1; H, 4.72.

8-Ethylacridine from 8-ethyl-1,2,3,4-tetrahydroacridine[2]. Dehydrogenation of 8-ethyl-1,2,3,4-tetrahydroacridine (0.55 g.) was carried out as outlined above (*cf.* 3-ethylacridine). The crude crystalline product (0.32 g.) was purified by chromatography (alumina) to yield 0.28 g. of a pale-yellow solid, m.p. 87–89°. The analytical sample was sublimed at 115–120°/0.4 mm., faintly-yellow prisms, m.p. 89–90.5°.

Anal. Calc'd for $C_{15}H_{13}N$: C, 86.9; H, 6.32.

Found: C, 87.1; H, 6.35.

This substance was indistinguishable from synthetic 1-ethylacridine, m.p. 89-90° (4). Similarly the *perchlorates* of the two substances showed the same m.p. 201–203°; no depression was observed in a mixture melting point.

The *picrate*, yellow prisms from ethanol, m.p. 220–222°. A mixture of this with 3-ethylacridine picrate (m.p. 225–227°) melted at 205°.

Demonstration of non-rearrangement during dehydrogenation experiments. (*a*) *1-Ethylacridine.* A mixture of 50 mg. of synthetic 1-ethylacridine and 100 mg. of 5% palladium-charcoal in 1 g. of diphenyl was heated at 250–260° for 2.5 hrs. and worked up as described above. The resulting crystalline product, 31 mg.,[7] m.p. 85–86°, was identical with 1-ethylacridine. So, too, were the perchlorates of the two substances.

(*b*) *3-Ethylacridine.* The analogous treatment of 0.3 g. of synthetic 3-ethylacridine with 0.6 g. of catalyst in 4.5 g. of diphenyl yielded 0.15 g.[7] of crystalline material, m.p. 82–84°, identical with 3-ethylacridine as such, or when compared through the perchlorates.

[7] Percentage-wise, these yields approximate those obtained in the respective, larger-scale aromatizations.

1,2,3,4-Tetrahydroacridine-8-carboxylic acid.[8] To a solution of 8-acetyl-1,2,3,4-tetrahydroacridine (10 g.) in 100 ml. of pyridine, 36 ml. of freshly prepared, approx. 5 *N* sodium hypochlorite (11) and 14 ml. of water were added and the system was heated under reflux for 45 mins. The reaction mixture was poured into 500 ml. of water containing 100 g. of NaCl and 25 ml. of 10 *N* NaOH and the pyridine was removed by steam-distillation. Acidification of the cooled, residual solution (glacial AcOH) gave a tan precipitate which was dissolved in aqueous $NaHCO_3$ and digested with Norit on the steam-bath. Acidification of the filtered solution gave a cream-colored solid, 4.2 g. Sublimation at 200°/0.4 mm. afforded 3.8 g. of pale-yellow prisms, m.p. 273–274.5°.

Anal. Calc'd for $C_{14}H_{13}NO_2$: C, 74.0; H, 5.77.
Found: C, 73.9; H, 5.85.

1,2,3,4-Tetrahydro-8-hydroxymethylacridine. Reduction of the above acid (4.3 g.) with 37 ml. of 1.8 *N* ethereal $LiAlH_4$ was effected according to the procedure used by Nystrom and Brown (12) for the reduction of anthranilic acid. After 15 hrs., the Soxhlet thimble still contained 1.5 g. of the acid. The crude product obtained from the reaction mixture, in the usual way, was sublimed at 180°/0.3 mm., and the tacky sublimate was leached several times with small portions of boiling ether. The pale-yellow, crystalline residue weighed 1.0 g.; another 0.3 g. of product was recovered from the concentrated ether washings. A sample was sublimed for analysis; colorless prisms, m.p. 189–191°.

Anal. Calc'd for $C_{14}H_{15}NO$: C, 78.8; H, 7.09.
Found: C, 78.7; H, 7.14.

SUMMARY

1. The synthesis of two groups of amino carbinols derived from 7- and 8-acetyl-1,2,3,4-tetrahydroacridine is described.

2. The structure of 8-acetyl-1,2,3,4-tetrahydroacridine has been established.

3. It has been demonstrated that alkyl migration apparently does not occur during Pd-C dehydrogenation of either 3-ethyl-, or 8-ethyl-1,2,3,4-tetrahydroacridine.

4. Moderate plasmodicidal activity was shown by all of the 8-substituted amino carbinols. Members of the 7-series were inactive.

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[8] Petrow (ref. 3) prepared the ethyl ester of this acid by another route.