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Carbinolamines Derived from N-Acetyl-9-ω-bromoacetyl-9,10-dihydroacridine. Rearrangement of the Halomethyl Ketone[1]

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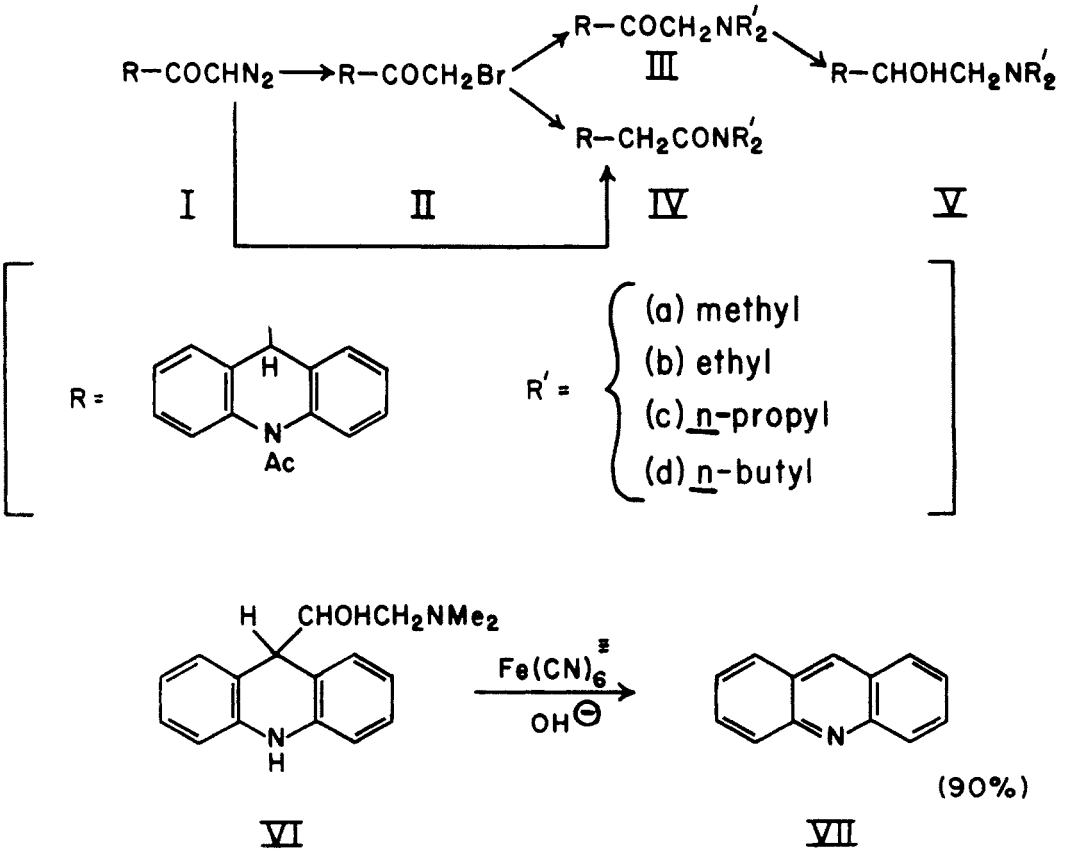
A series of 9-substituted dihydroacridine carbinolamines of the type R—CHOH—CH_2NR_2' has been synthesized and found to be devoid of plasmodicidal activity. The rearrangement of the intermediate halomethyl ketones—in significant yield—, in the presence of secondary amines, to N',N'-disubstituted amides has been observed. Mild oxidation (ferricyanide) of a representative N-desacetylcarbinolamine resulted in complete cleavage of the side chain with the formation of acridine in high yield.

In extending a study of the effect, upon plasmodicidal activity, of altering the position of the carbinolamine chain in the acridine system, N-acetyl-9-ω-bromoacetyl-9,10-dihydroacridine was synthesized and condensed with a number of secondary amines. The resulting amino ketones then were reduced to the corresponding amino carbinols in the manner described earlier.[2]

Acridan-9-carboxylic acid, the precursor of the desired halomethylketone, was prepared according to Burtner and Cusic[3] and N-acetylated with acetyl chloride. The conversion of the N-acetyl acid to the acid chloride occurred smoothly with phosphorus pentachloride; thionyl chloride, on the other hand, led to a difficultly separable mixture of products. The acid chloride gave, with diazomethane, in the usual manner, a crystalline diazoketone which was transformed to the ω-bromoketone by treatment with 48% hydrobromic acid.[4]

In the subsequent reactions of N-acetyl-9-ω-bromoacetyl-9,10-dihydroacridine with secondary aliphatic amines, varying amounts of *neutral* material were isolated along with the expected amino ketones. The latter underwent smooth hydrogena-



(1) Studies in the Acridine Series IX.
(2) Sargent and Small, *J. Org. Chem.*, **13**, 447 (1948).
(3) Burtner and Cusic, *J. Am. Chem. Soc.*, **65**, 1583 (1943).
(4) For a review of this reaction, *cf.* Bachmann and Struve, *Org. Reactions*, **1**, 38 (1942).

tion to the corresponding amino carbinols. The *neutral* fractions, arbitrarily purified in two of the four exchange reactions that were carried out proved to be the N′,N′-dialkylacetamides isomeric with the corresponding amino ketones. Their identity was established through comparison with their synthetic counterparts prepared (*via* the Arndt-Eistert technique[4]) from the above-mentioned diazoketone and the appropriate amine.

It is interesting to note that these rearrangements parallel those observed by May and Mosettig in their studies with dihydroanthryl halomethyl ketones,[5] and apparently should be classified as further examples of the Favorskiĭ reaction, the mechanism of which was so elegantly deduced recently by Loftfield,[6] and studied in another sense by Dauben and collaborators.[7]

In order to ascertain the effect of a fully aromatic amino carbinol upon plasmodicidal activity, an attempt was made to oxidize 9-(2-dimethylamino-1-hydroxyethyl)-9,10-dihydroacridine *via* alkaline potassium ferricyanide. However, instead of the expected 9-substituted acridine amino carbinol, the only isolable product was acridine (90% yield). It would be idle to speculate on a mechanism for this observation since no attempt was made to study the kinetics of the oxidation.

Albert[8] has reviewed the various methods that are available for the conversion of acridanes into acridines, and alkaline ferricyanide appears heretofore not to have been used. In view of our observations, this reagent should be added to Albert's list of oxidants.

The various amino carbinols described herein were ineffective toward blood innoculated (*gallinaceum*) chick infections.[9]

EXPERIMENTAL[10]

N-Acetyl-9,10-dihydroacridine-9-carboxylic acid. A mixture of 13.3 g. of 9,10-dihydroacridine-9-carboxylic acid[3] and 32 ml. of acetyl chloride was heated on the steam-bath (reflux) for 30 minutes. After treatment with crushed ice, the crude product was collected, thoroughly washed with cold water,[11] and air-dried—yield 15.2 g. The latter was dissolved in 125 ml. of hot methanol and clarified with Norit. Concentration of the solution and refrigeration (12 hours) gave 11.6 g. of colorless prisms, m.p. 216–218° (dec.). After two further recrystallizations, m.p. 219–221° (dec.).

Anal. Calc'd for $C_{16}H_{13}NO_3$: C, 71.9; H, 4.90. Found: C, 72.07; H, 4.94.

The acid chloride. The above acid (8 g., powdered) was heated with 8 g. of powdered phosphorus pentachloride in 120 ml. of dry petroleum ether (b.p. 30–60°) for 2.5 hours (steam-bath). The product was collected and recrystallized from benzene-petroleum ether (b.p. 30–60°); pale-yellow prisms, 7.8 g., m.p. 169–171° (dec.).

The diazoketone (I). To a mechanically stirred and cooled (0–5°) solution of diazomethane (from 15.8 g. of N-nitroso-N-methylurea) in 280 ml. of ether, 7.8 g. of the powdered acid chloride was added during 45 minutes. After stirring for 1.5 hours longer (at 0°) and standing for 15 hours (at 5°) the nearly colorless, crystalline diazoketone was collected and air-dried—7.2 g., m.p. 151–153° (dec.).

9-(ω-Bromoacetyl)-N-acetyl-9,10-dihydroacridine (II). A solution of 7 ml. of 48% hydrobromic acid in 7.5 ml. of dry ether (containing a few drops of absolute ethanol) was gradually added during 30 minutes to a stirred and cooled (10–15°) suspension of 7.2 g. of the above diazoketone in 225 ml. of dry ether; the suspension gradually dissolved. Stirring was continued for 30 minutes longer, during which interval the bromo ketone began to separate. After diluting the system with 500 ml. of ether the clear solution was successively washed with saturated sodium bicarbonate, water, then dried; concentration (*in vacuo*) gave 7.3 g. of product. Recrystallization from dry ether yielded 6.8 g. of virtually colorless prisms, m.p. 132–133.5°. A sample was recrystallized twice again from benzene-petroleum ether (b.p. 28–38°)—m.p. 133–134.5°.

Anal. Calc'd for $C_{17}H_{14}BrNO_2$: C, 59.31; H, 4.10. Found: C, 59.56; H, 4.28.

9-(2-Diethylamino-1-hydroxyethyl)-N-acetyl-9,10-dihydroacridine (Vb). To a cooled solution of 9-(ω-bromoacetyl)-N-acetyl-9,10-dihydroacridine (5 g.) in a mixture of 30 ml. of acetone and 100 ml. of alcohol-free ether, 3.35 ml. (2.2 equivs.) of diethylamine was added. After keeping at 5° overnight, the precipitated diethylamine hydrobromide (2 g., 90% recovery) was collected. Concentration of the filtrate (*in vacuo*) yielded a sirup which was taken up in 100 ml. of dry ether (a further, small amount of amine hydrobromide was removed) and concentrated again to give 5.8 g. of amber sirup. The latter, in 30 ml. of acetone, was treated at 0° with gaseous hydrogen chloride to Congo Red acidity. Dilution with dry ether precipitated the amino ketone hydrochloride. This substance was collected (filtrate retained) and triturated three times with fresh ether (washings combined with main filtrate). The hydrochloride afforded 3.2 g. of oily amino ketone. A solution of this in 50 ml. of methanol with 0.15 g. of platinum oxide absorbed 0.96 mole of hydrogen in 17 hours and gave 2.9 g. of sirupy amino alcohol which crystallized slowly. The crude product was dissolved in 25 ml. of methanol, filtered, and concentrated to about half the original volume. Careful dilution with water to faint, permanent turbidity and seeding gave (after 48 hours) 2.3 g. of virtually colorless prisms, m.p. 108–110°.

The analytical sample was recrystallized twice again (methanol-water) and dried in a high vacuum at 78°; m.p. 115–116°.

Anal. Calc'd for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74. Found: C, 74.13; H, 7.50.

The *perchlorate* was prepared in absolute ethanol with 1.0 *N* ethanolic perchloric acid, and recrystallized thrice from acetone-ether; slender prisms, m.p. 217–218.5°.

Anal. Calc'd for $C_{21}H_{27}ClN_2O_6$: C, 57.47; H, 6.20. Found: C, 57.41; H, 6.18.

9-(α-[N′,N′-diethylacetamido])-N-acetyl-9,10-dihydroacridine (IVb). The combined ether washings of the crude amino ketone (above) were extracted several times with 25-ml. portions of 0.5 *N* hydrochloric acid, and then were washed with water. After drying and concentration (*in vacuo*) there remained 1.8 g. of an amber sirup which crystallized overnight. After two recrystallizations from 50% aqueous meth-

(5) May and Mosettig, *J. Am. Chem. Soc.*, **70**, 1077 (1948).

(6) Loftfield, *J. Am. Chem. Soc.*, **73**, 4707 (1951).

(7) Dauben, Hiskey, and Muhs, *J. Am. Chem. Soc.*, **74**, 2082 (1952).

(8) Albert, *The Acridines*, Arnold & Co., London, 1951, p. 6.

(9) Coatney and Cooper, N. I. H., unpublished results.

(10) Analyses are by the Analytical Service laboratory of this Institute, under the supervision of Dr. W. C. Alford. Melting points are uncorrected.

(11) It is essential that the product be free of mineral acid, otherwise esterification occurs to a considerable extent during methanol recrystallization.

anol, 0.9 g. of pale yellow prisms was obtained. A sample was sublimed twice at 130°/0.04 m.m., colorless prisms, m.p. 135–137°.

Anal. Calc'd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19. Found: C, 74.95; H, 7.04.

Synthesis of 9-(α-[N',N'-diethylacetamido])-N-acetyl-9,10-dihydroacridine (IVb). The diazoketone (I) (0.5 g.) in 5 ml. of dioxane was treated with a mixture of 0.65 ml. of diethylamine, 0.6 ml. of water, and 0.8 ml. of 10% silver nitrate.[4] After heating for 20 mins. (steam-bath), filtration gave a light yellow solution. Dilution with water and scratching caused the separation of a flocculent, tan precipitate which was collected and air-dried; 0.35 g., m.p. 125°. After being twice sublimed at 130°/0.04 m.m., colorless prisms, m.p. 135–137° were obtained; the melting point was undepressed when mixed with the amide described above.

9-(2-Dimethylamino-1-hydroxyethyl)-N-acetyl-9,10-dihydroacridine (Va). This substance was prepared in essentially the manner outlined above for the diethyl-analog. From 5 g. of bromo ketone in 25 ml. of acetone and 2.7 g. of dimethylamine in 100 ml. of dry ether there resulted, after catalytic reduction of the intermediate amino ketone, 3.6 g. of a yellow glass. Recrystallization of the latter from dilute methanol gave 3.1 g. of light tan prisms, m.p. 124–127°. After two further recrystallizations, the substance had m.p. 134–136°.

Anal. Calc'd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.15. Found: C, 73.47; H, 7.03.

The *perchlorate*, formed prisms from absolute ethanol-ether; m.p. 241–243° dec.

Anal. Calc'd for $C_{19}H_{23}ClN_2O_6$: C, 55.54; H, 5.64. Found: C, 55.43; H, 5.61.

A small quantity of *neutral* material (0.8 g.) presumed to be the dialkylamide also was isolated. Recrystallization from dilute methanol afforded prisms, m.p. 148–150°.

9-(2-Dimethylamino-1-hydroxyethyl)-9,10-dihydroacridine (VI). A solution of 0.5 g. of the above N-acetylamino carbinol in 4 ml. of 95% ethanol was heated with 4 ml. of 10% ethanolic potassium hydroxide for two hours (steam bath). Dilution of the cooled solution with 100 ml. of 15% aq. sodium chloride precipitated a cream-colored solid which was taken up in ether and dried. The latter gave 0.35 g. of tan crystals. After three recrystallizations from dilute methanol, colorless prisms, m.p. 163–165°, resulted.

Anal. Calc'd for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51. Found: C, 76.15; H, 7.43.

Ferricyanide oxidation of 9-(2-dimethylamino-1-hydroxyethyl)-9, 10-dihydroacridine to acridine (VII). To a stirred suspension of 0.5 g. of VI in 25 ml. of water, 5 ml. of 30% aq. KOH was added and the system was treated (during 10 mins.) with a solution of 2.6 g. (2 equivs. of oxygen) of potassium ferricyanide in 20 ml. of water. After stirring for an additional hour, the pale yellow suspension was collected, washed with water and air-dried; 0.3 g. (90%), m.p. 104–107°. It gave no depression in m.p. when mixed with an authentic specimen of acridine. Both the picrate and the perchlorate of the oxidation product were identical with the corresponding salts of acridine.

9-(2-Di-n-propylamino-1-hydroxyethyl)-N-acetyl-9,10-dihydroacridine (Vc). Treatment of 5 g. of bromo ketone in 30 ml. of acetone with a solution of 3.1 g. of di-*n*-propylamine in 100 ml. of dry ether gave, after the usual work-up and catalytic hydrogenation, 2.8 g. of sirupy amino carbinol which crystallized in rectangular plates from dilute methanol; yield 2 g., m.p. 107–109°.

The *perchlorate* crystallized in prisms from acetone-ether, m.p. 177–179°.

Anal. Calc'd for $C_{23}H_{31}ClN_2O_6$: C, 59.16; H, 6.69. Found: C, 58.98; H, 6.75.

9-(α-[N',N'-di-n-propylacetamido])-N-acetyl-9,10-dihydroacridine (IVc). The *neutral* fraction, in this case, amounted to 1.5 g. of oily crystals which, after three crystallizations from dilute methanol, gave 0.6 g. of light yellow prisms, m.p. 120–122°.

Anal. Calc'd for $C_{23}H_{28}N_2O_2$: C, 75.8; H, 7.74. Found: C, 75.93; H, 7.49.

This amide was identical with its synthetic counterpart prepared from the diazoketone and di-*n*-propylamine as described above for the diethyl analog.

9-(2-Di-n-butylamino-1-hydroxyethyl)-N-acetyl-9,10-dihydroacridine perchlorate (Vd). In a manner analogous to that described above, the reaction of 1.5 g. of bromo ketone in 8 ml. of acetone with 1.2 g. of di-*n*-butylamine in 25 ml. of dry ether, afforded 0.5 g. of sirupy amino carbinol. This was converted to the *perchlorate* in the usual way, and was recrystallized from acetone-ether; colorless prisms, m.p. 186–188°.

Anal. Calc'd for $C_{25}H_{35}ClN_2O_6$: C, 60.71; H, 7.13. Found: C, 60.57; H, 6.96.

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