temperature raised to 135° over a period of three to four hours and maintained at 135° for six hours. The water was allowed to escape as formed. The mixture was then poured into 2 liters of water, filtered, the filtrate made basic with ammonium hydroxide, and the refiltered solution acidified with acetic acid. The tar which separated was treated in a similar manner and the dilute acetic acid solution finally concentrated to yield 84 g. (39%) of product crystallized from ethanol; m. p. 205°.

5-Carbonylhydrazidebenzo(f)quinoline (III).—A mixture of II (169 g., 0.71 mole) in methanol (1250 ml.) and 85% hydrazine hydrate (105 g., 1.78 moles) was warmed for fifteen minutes until solid started to separate. The mixture was allowed to stand overnight, the product collected on a filter; yield 160 g. (95%).

5-Hydroxybenzo(f)quinoline (VI).—Crude V (39 g., 0.165 mole) was refluxed for six hours with 200 ml. of 14 *N* sulfuric acid. The mixture was cooled and the orange sulfate salt collected on a filter. The product was dissolved in 300 ml. of hot water, charcoaled and the cooled filtrate made basic with ammonium hydroxide. The yield of crystallized product was 17 g. (53%); m. p. 104–106°. No depression in melting point was observed when mixed with an authentic sample of VI.

5-(4-Diethylamino-1-methylbutylamino)-benzo(f)quinoline (VII).—An amino sulfite solution consisting of 4-diethylamino-1-methylbutylamine (44.3 g., 0.28 mole) in water (100 ml.) containing sulfur dioxide (13 g., 0.2 mole) was refluxed for 216 hours with V (19.6 g., 0.1 mole) under a pressure greater than atmospheric by 20 cm. of mercury. The mixture was poured into 500 ml. of water and the aqueous solution decanted from the separated oil which was then washed with 50 ml. of water. The oil was taken up in 400 ml. of water by the addition of concentrated hydrochloric acid. The solution was made slightly basic to litmus paper with 10% sodium hydroxide solution and the unreacted starting material removed by filtration. The filtrate was made strongly basic to litmus paper with 10% sodium hydroxide solution, and the oil which separated was taken up in ether. The dried ether solution was fractionally distilled at reduced pressure to yield 10 g. (23%) of yellow viscous oil; b. p. 172–173° (0.04 mm.).

Anal. Calcd.[9] for $C_{22}H_{29}N_3$: C, 78.76; H, 8.71. Found: C, 78.70, 78.81; H, 8.70, 8.78.

Summary

1. 5-Carboxybenzo(f)quinoline was prepared by a new modification of the Skraup reaction.

2. 5-Hydroxybenzo(f)quinoline was prepared in 52% yield by the hydrolytic replacement of the 5-amino group in 5-acetaminobenzo(f)quinoline.

3. 4-Diethylamino-1-methylbutylamine was condensed with 5-hydroxybenzo(f)quinoline by the Bucherer reaction.

(9) Analyses by R. E. Benson of this Laboratory.

LINCOLN, NEBRASKA RECEIVED APRIL 19, 1946

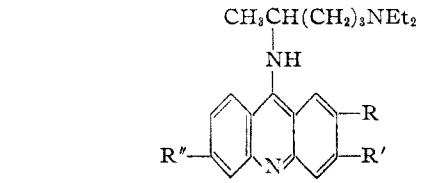
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Heterocyclic Basic Compounds. IX. 3,6-Dichloro-9-(1-methyl-4-diethylaminobutyl)-aminoacridine

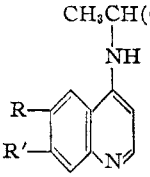
BY DAVID P. SPALDING,[1] GEORGE W. MOERSCH,[1,2] HARRY S. MOSHER AND F. C. WHITMORE

The effect of various nuclear substituents upon the antimalarial activity of acridine derivatives such as Atabrine (I) has been extensively investigated. Apparently the 6-chloro substituent is a greater contributing factor to the activity of this nucleus than the 2-methoxy group; for although "demethoxyatabrine" (II)[3] is reported to be almost as active as Atabrine itself, "dechloroatabrine" (III)[4] is reported to have only slight activity against avian malarial infections. The importance of the 6-chloro substituent in Atabrine is substantiated by a consideration of the corresponding quinoline compounds V and VI in which the 7-chloro-4-aminoquinoline derivative V is reported to be a very potent antimalarial[5] while the 6-methoxy-4-aminoquinoline derivative, VI,[6] possesses only moderate activity in similar tests.

This correlation between the activities of the quinoline and acridine antimalarials is not surprising when we consider "demethoxyatabrine" (II) as the benzo[*b*]quinoline derivative of V and "dechloroatabrine" (III) as the benzo[*b*]quinoline derivative of VI.



I R = —OCH_3, R′ = —H, R″ = —Cl
II R and R′ = —H, R″ = —Cl
III R′ and R″ = —H, R = —OCH_3
IV R′ and R″ = —Cl, R = —H



V R = —H, R′ = —Cl
VI R = —OCH_3, R′ = —H

Thus Atabrine itself may be considered a hypothetical fusion product between the two quinoline compounds V and VI.

The above evidence prompted us to attempt the synthesis of 3,6-dichloro-9-(1-methyl-4-diethylaminobutyl)-amino-acridine (IV) which may similarily be considered a hypothetical fusion product

(1) Parke, Davis and Co. fellow, 1945–1946.

(2) Present address, Parke, Davis and Co., Detroit, Michigan.

(3) Mauss and Mietzsch, British Patent 363,392 (Dec. 18, 1931).

(4) Cherntsov and Drozdov, *J. Gen. Chem. U. S. S. R.*, **9**, 1435–1440 (1939); *C. A.*, **34**, 1667 (1940).

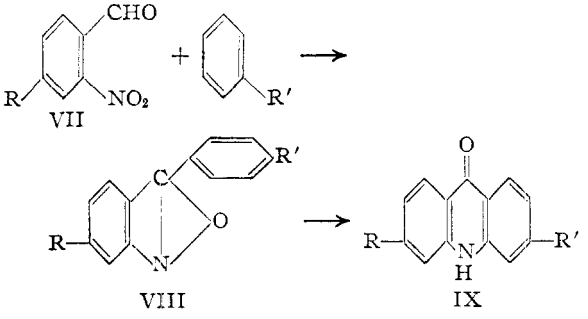
(5) Andersag, Breitner and Jung, U. S. Patent 2,233,970 (March 4, 1941); *C. A.*, **35**, 3771 (1941).

(6) Magidson and Rubtsov, *J. Gen. Chem. U. S. S. R.*, **7**, 1896–1908 (1937); *C. A.*, **32**, 564 (1938); Hal'perin, *Med. Parasitol. Parasitic Disease, U. S. S. R.*, **9**, No. 1–2, 44–53 (1940); *C. A.*, **36**, **1674** (1942).

of two molecules of V. If the above analogies hold, the two chlorine atoms in this compound should occupy the most advantageous positions from the standpoint of antimalarial activity. The synthesis of IV was first attempted by the conventional Ullmann procedure using 2,4-dichlorobenzoic acid and *m*-chloroaniline. Although the product, N-(3′-chlorophenyl)-4-chloroanthranilic acid, was obtained, the yield was very poor and treatment with phosphorus oxychloride failed to give a pure acridine derivative because of the formation of the two isomers 3,6,9-trichloroacridine (X) and 1,6,9-trichloroacridine. This approach was therefore abandoned.

A second attempt through the reductive cyclization of 4,4′-dichloro-2,2′-dinitrobenzophenone was likewise unsuccessful. Meanwhile an investigation was undertaken of the Lehmstedt–Tanasescu reaction between 2-nitro-4-chlorobenzaldehyde and chlorobenzene.

It has been shown[7] that *o*-nitrobenzaldehydes with benzene and concentrated sulfuric acid give 3-phenylanthranils which have been assigned structure VIII. These on strong heating or treatment with nitrous acid at room temperature rearrange to acridones (IX). The reported yields have been rather poor.



The identity of the acridones obtained by this method have been verified in several cases by comparison with the product obtained by the ring closure of the Ullmann condensation product.

In the present work, 4-chloro-2-nitrobenzaldehyde (VII, R = −Cl)[8] was obtained in 48% crude yield by the oxidation of 4-chloro-2-nitrotoluene with chromic anhydride in acetic anhydride followed by hydrolysis of the resulting aldehyde diacetate. The aldehyde was then condensed with chlorobenzene in concentrated sulfuric acid containing some sodium nitrite, to give 3,6-dichloroacridone (IX, R,R′ = −Cl) in a maximum yield of 53%. The acridone was converted to the 3,6,9-trichloroacridine (X) by treatment with phosphorus oxychloride. The structure of this product (X) was confirmed by independent synthesis from 3,6-diaminoacridone[9] by way of the Sandmeyer reaction and subsequent treatment with phosphorus oxychloride.

The 3,6,9-trichloroacridine was converted into 3,6-dichloro-9-(1-methyl-4-diethylaminobutyl)-aminoacridine (IV) by treatment with excess 1-diethylamino-4-aminopentane in phenol at 95–100° for one hour.

Dr. R. J. Porter reports that this compound has a quinine equivalent of 5.0 when tested therapeutically against *P. gallinaceum* infections in chicks.[10] Atabrine in the same tests has a quinine equivalent of 1.3.

Acknowledgment.—We are greatly indebted to Dr. R. J. Porter of the University of Michigan for the privilege of quoting the results of his antimalarial tests and to Parke, Davis and Company for the grant which made this work possible.

Experimental

Attempted Synthesis of 3,6,9-Trichloroacridine (X) *via* the Ullmann Condensation.—The sodium salt of 2,4-dichlorobenzoic acid, 43 g., was condensed with *m*-chloroaniline, 52 g., by refluxing for two hours in commercial methylcyclohexanol (Barrett) containing 11 g. of anhydrous sodium carbonate and 1 g. of cupric oxide. The residue from the steam distillation of the reaction mixture was filtered, acidified and the yellow solid crystallized twice from benzene and once from acetone to give 3.2 g. (5.8%), m. p. 196–198°. *Anal.* Equivalent weight calcd. for $C_{13}H_9O_2NCl_2$: 282. Found: 284.

When this product was treated with refluxing phosphorus oxychloride and the mixture decomposed in cold water, the only material isolated charred at about 140° but did not melt completely below 250°.

Attempted Synthesis of 3,6,9-Trichloroacridine (X) by the Reductive Cyclization of 4,4′-Dichloro-2,2′-dinitrobenzophenone.—4,4′-Diaminodiphenylmethane was nitrated according to the method of Schnitzspahn[11] to give a 71.5% yield of 4,4′-diamino-2,2′-dinitrodiphenylmethane, m. p. 206–207°. This was converted in 34.6% yield by the Sandmeyer reaction into 4,4′-dichloro-2,2′-dinitrodiphenylmethane, m. p. 117–119°. Mascarelli[12] reports a melting point of 121–122°.

4,4′-Dichloro-2,2′-dinitrodiphenylmethane, 20 g., was oxidized by dissolving it in 400 ml. of acetic acid and gradually adding 32 g. of chromic anhydride to the refluxing solution over a forty-five minute period. After refluxing an additional two and one-half hours, the mixture was filtered and diluted with cold water. The pink solid which separated was filtered, treated with Norit, crystallized and recrystallized from a mixture of acetone and ethanol to give a total of 12.3 g. (59%) of the desired 4,4′-dichloro-2,2′-dinitrobenzophenone, m. p. 160–162°.

Anal. Calcd. for $C_{13}H_6O_5N_2Cl_2$: C, 45.77; H, 1.77. Found: C, 45.92; H, 2.08.

When 3 g. of this benzophenone derivative was heated at 80° for one hour with 15 g. of stannous chloride in 15 ml. of concentrated hydrochloric acid, the yellow crystalline product which was recovered (2.4 g.) melted at 136–137°, gave a positive diazo test for an aromatic amino group and obviously was not the desired acridone (IX, R,R′ = −Cl). Similarly, catalytic reduction of 3 g. of the 4,4′-dichloro-2,2′-dinitrobenzophenone with Raney nickel catalyst under

(7) Kliegl, *Ber.*, **41**, 1845–1851 (1908); **42**, 591–594 (1909); Bamberger, *ibid.*, **42**, 1706–1723 (1909); Bradbury and Linnell, *J. Chem. Soc.*, 377–381 (1942); Tanasescu, *Bull. soc. chim.*, **41**, 528–537 (1927); Lehmstedt, *Ber.*, **65B**, 834–839, 999–1005 (1932).

(8) German Patent 128,727 (Jan. 13, 1902); Van der Lee, *Rec. trav. chim.*, **45**, 681–683 (1926); Sachs and Kempf, *Ber.*, **56**, 3299–3303 (1903).

(9) Matsumura, THIS JOURNAL, **51**, 816–820 (1929).

(10) The details of the pharmacological tests on this compound will be published subsequently in the monograph entitled "A Survey of Antimalarial Drugs 1941–1945," F. Y. Wiselogle, Editor.

(11) Schnitzspahn, *J. prakt. Chem.*, [2] **65**, 315–345 (1902).

(12) Mascarelli, Toschi and Zambonini, *Gazz. chim. ital.*, **42**, I, 75–82 (1912).

three atmospheres pressure gave 1 g. of a product melting at 240–243° which likewise gave a positive diazo test for an aromatic amino group and could not have been the desired acridone. On the assumption that this compound was the 2,2′-diamino-4,4′-dichlorobenzophenone, it was treated with hot concentrated hydrochloric acid, hydrochloric acid and zinc chloride, and hot concentrated sulfuric acid but the product was recovered unchanged in each case.

Preparation of 3,6,9-Trichloroacridine (X) by the Lehmstedt–Tanasescu Method. 2-Nitro-4-chlorobenzaldehyde (VII, R = Cl).[8]—To a mixture of 370 g. (2.16 moles) of 2-nitro-4-chlorotoluene (Eastman Kodak Co. practical), 3420 ml. of glacial acetic acid and 3390 ml. of acetic anhydride in a 12-liter flask, was added 510 ml. of concentrated sulfuric acid with stirring and cooling. The temperature of the mixture was held between 5 and 10° while 600 g. of chromic anhydride was added over an eight-hour period. The mixture thickened near the end of the addition and was stirred for an additional hour. The reaction mixture, including a black tarry precipitate, was poured with stirring into 36 l. of ice water and allowed to stand overnight. The white solid was separated by filtration, washed with water, stirred with 2 liters of sodium carbonate solution for three hours, filtered, and the filter cake refluxed with 1 liter of petroleum ether, cooled, filtered, and the filter cake refluxed with 1 liter of petroleum ether, cooled, filtered and dried; weight 280 g., m. p. 116°. Concentration of the petroleum ether extracts gave 36 g. of recovered 2-nitro-4-chlorotoluene. No acid was precipitated by acidification of the carbonate wash solution.

The 280 g. of the aldehyde diacetate was heated on the steam-bath with 2100 ml. of water, 1280 ml. of concentrated hydrochloric acid and 400 ml. of ethanol for six hours. The mixture was cooled, filtered, and the resulting 196 g. of crude aldehyde (48% yield) was crystallized from a mixture of 800 ml. of ether and 800 ml. of petroleum ether. A first crop of 100 g., m. p. 58° was obtained; by concentration and cooling a second crop, 19 g., m. p. 58° and a third crop, 35 g., m. p. 50° were obtained. This material was impure and contained some of the unhydrolyzed aldehyde diacetate. By recrystallization and steam distillation, the melting point was raised to 67–68°, that reported in the literature.[8]

3,6-Dichloroacridone (IX, R,R′ = Cl).—The following is a description of the best of four runs. Crude 2-nitro-4-chlorobenzaldehyde, 18.5 g. (0.1 mole), chlorobenzene, 78.7 g. (0.7 mole), concentrated sulfuric acid, 37.5 ml., and sodium nitrite, 0.35 g., were treated for six days to alternate nine hours shaking and fifteen hours standing. At the end of each two-day period (except the last) 10 ml. of concentrated sulfuric acid containing 0.1 g. of sodium nitrite was added to the reaction mixture. The mixture was poured into 500 ml. of water and steam distilled until no further aldehyde solidified in the condenser. The residue from the steam distillation was filtered and digested twice with benzene, leaving 14 g. (53%) of dark yellow solid which did not melt below 315°.

3,6,9-Trichloroacridine (X).—The above acridone, 14 g., was refluxed for one hour with 25 ml. of phosphorus oxychloride, cooled and decomposed with ammoniacal ice water. The precipitate was filtered and extracted with benzene in a Soxhlet apparatus. On concentrating the benzene solution 4 g. (27%) of product melting at 223–225° was obtained. Recrystallization of a sample raised the melting point to 224–225°. Similar phosphorus oxychloride treatment of the acridone from another run in which a five-fold weight excess of phosphorus oxychloride was employed resulted in a 49% yield of the 3,6,9-trichloroacridine.

Anal. Calcd. for $C_{13}H_6NCl_3$: C, 55.26; H, 2.14; Cl, 37.64. Found: C, 55.20; H, 2.21; Cl, 36.84.

Preparation of 3,6,9-Trichloroacridine (X) from 3,6-Diaminoacridone.—3,6-Diaminoacridone,[9] 4 g., was diazotized in a solution of 40 ml. of water and 14 ml. of concentrated hydrochloric at 0° by adding to the suspension 2 g. of sodium nitrite in 6 ml. of water. This diazo solution was then added to a solution of 2.6 g. of freshly prepared cuprous chloride in 30 ml. of *N* hydrochloric acid; after the initial vigorous evolution of nitrogen had subsided, the mixture was heated on the steam-bath. The tan, solid product was filtered and stirred with 20 ml. of boiling acetone; a residue of 1.5 g. (32%) of 3,6-dichloroacridone (IX, R,R′ = Cl), m. p. above 325° remained.

This acridone on treatment with phosphorus oxychloride as previously described gave a 62% yield of 3,6,9-trichloroacridine, m. p. 224–225°, mixed melting point with product obtained by the Lehmstedt–Tanasescu method, 224–225°.

3,6-Dichloro-9-(1-methyl-4-diethylaminobutyl)-aminoacridine (IV).—To a mixture of 25 ml. of phenol and 8.7 g. of 1-diethylamino-4-aminopentane was added 15 g. of 3,6,9-trichloroacridine. The mixture was heated to 95–100° in an oil-bath for one hour, cooled and a solution of 25 ml. of concentrated hydrochloric acid in 250 ml. of acetone was added with stirring. The yellow precipitate, 19 g., which separated on cooling overnight, and an additional 6 g. obtained by further dilution with acetone, were dissolved in 600 ml. of water and filtered; 25 ml. of concentrated hydrochloric acid was added and the solution cooled. The product after drying in a vacuum desiccator over solid potassium hydroxide weighed 20 g. (77%), m. p. 235°.

Anal. Calcd. for $C_{22}H_{27}N_3Cl_2 \cdot 2HCl$: C, 51.47; H, 6.48; N, 8.19. Found: C, 51.29; H, 6.74; N, 8.20.

Summary

1. The structure of 3,6,9-trichloroacridine has been confirmed by its synthesis according to two independent procedures.

2. The 3,6,9-trichloroacridine has been converted into the antimalarial 3,6-dichloro-9-(1-methyl-4-diethylaminobutyl)-aminoacridine.

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