As, 22.50. Calcd. for $C_{10}H_9BrNAsO_4$: N, 3.78; As, 20.69. Found: N, 3.62; As, 20.48. Calcd. for $C_{10}H_9ClNAsO_4$: As, 23.59. Found: As, 23.60.

Summary

1. 2-Acetamido-5-bromotoluene and 2-acetamido-5-chlorotoluene were converted by means of the Skraup reaction into 6-bromo-8-methylquinoline (77% yield) and 6-chloro-8-methylquinoline (67% yield), respectively. Each of these 6-halo-8-methylquinolines nitrated chiefly in the 5-position as was indicated by the fact that 2-acetamido-5-halo-4-nitrotoluenes yielded the same nitroquinolines when subjected to Skraup ring-closure conditions. The samples of 2-acetamido-5-halo-4-nitrotoluenes used were shown to be authentic ones by employing well characterized reactions to change them into substances possessing established structures. A picrate of 6-chloro-8-methylquinoline was prepared and analyzed.

2. 6-Bromo-2-chloro-8-methylquinoline and 2,6-dichloro-8-methylquinoline were synthesized from the corresponding 1-methyl-2-quinolones that were in turn obtained from 6-bromo-8-methylquinoline and 6-chloro-8-methylquinoline, respectively. Hydrolysis of these 2-chloroquinolines in an autoclave gave 2-hydroxyquinolines. Nitration of the 2-chloroquinolines gave 2-chloro-5-nitroquinolines; these same 2-chloro-5-nitroquinolines were also produced from the 6-halo-8-methyl-5-nitroquinolines *via* the 1-methyl-2-quinolones. Although 6-chloro-2-hydroxy-8-methylquinoline gave upon nitration some of the same substance as resulted from the hydrolysis of 2,6-dichloro-8-methyl-5-nitroquinoline, no 6-bromo-2-hydroxy-8-methyl-5-nitroquinoline was isolated after nitrating 6-bromo-2-hydroxy-8-methylquinoline; hydrolysis of 6-bromo-2-chloro-8-methyl-5-nitroquinoline did yield 6-bromo-2-hydroxy-8-methyl-5-nitroquinoline.

3. 6-Bromo-8-methyl-5-nitroquinoline, 6-chloro-8-methyl-5-nitroquinoline, 2-chloro derivatives, and 2-hydroxy derivatives of these nitroquinolines were reduced in presence of Raney nickel to amines. Pressures as high as 500 pounds per square inch at 80° were resorted to during some of these reductions. Acetamido and benzamido derivatives of the amines were prepared. The amines were also converted by means of the Bart reaction into arsonic acids.

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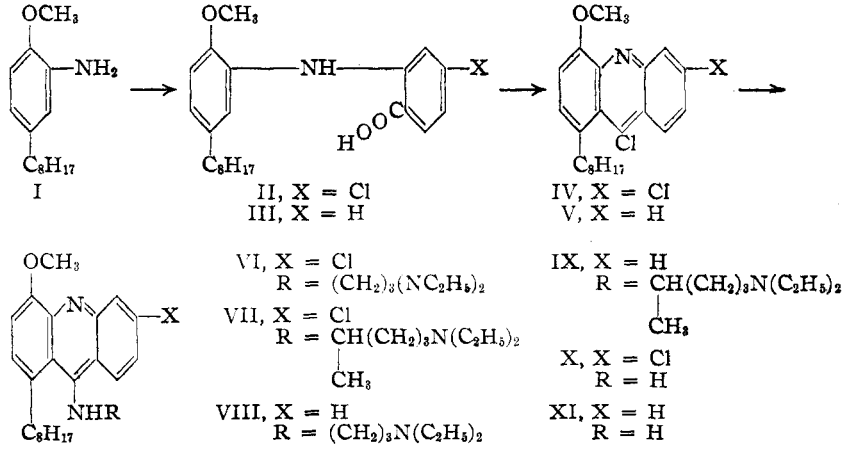
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NEW YORK UNIVERSITY]

Acridines Derived from *p*-(1,1,3,3-Tetramethyl)-butylphenol[1]

BY JOSEPH B. NIEDERL AND MURRAY B. HUNDERT[2]

Ehrlich's accidental discovery of the therapeutic properties of acridine initiated a vigorous search for other active derivatives which culminated in the production of many synthetic antimalarials, the most widely known of which is 3-chloro-7-methoxy-9-(5-diethylamino-2-pentylamino)-acridine dihydrochloride, more commonly known as "Atabrine." In an effort to find substances of enhanced activity, the possibility that alkyl substituted acridines containing the bactericidal 1,1,3,3-tetramethylbutyl[3] group would result in more effective antimalarial and bactericidal compounds was investigated.



Accordingly, the dihydrochlorides of 1-(1,1,3,3-tetramethyl) - butyl - 4 - methoxy - 6 - chloro - 9-(3-diethylaminopropylamino)-acridine (VI), 1-(1,1,3,3 - tetramethyl) - butyl - 4 - methoxy - 6 - chloro - 9 - (5 - diethylamino - 2 - pentylamino)-acridine (VII), 1-(1,1,3,3,-tetramethyl)-butyl-4-methoxy-9-(3-diethylaminopropylamino)-acridine (VIII), and 1-(1,1,3,3-tetramethyl)-butyl-4-methoxy - 9 - (5 - diethylamino - 2 - pentylamino) - acridine (IX) were synthesized from *p*-(1,1,3,3-tetramethyl)-butylphenol through the anisidino[4]

(1) Presented before the Division of Organic Chemistry at the Atlantic City meeting of the American Chemical Society, September, 1949.

(2) Abstracted from the thesis presented by M. B. Hundert to the Graduate School of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, November, 1949.

(3) J. B. Niederl, *Ind. Eng. Chem.*, **30**, 1269 (1938).

(4) J. B. Niederl and M. I. Dexter, THIS JOURNAL, **63**, 1475 (1941).

derivative by reaction with either 2,4-dichlorobenzoic acid or *o*-bromo(or chloro)-benzoic acid to yield the substituted anthranilic acids (II) and (III). Cyclization of the anthranilic acids with phosphorus oxychloride and condensation of the resulting 9-chloroacridines (IV) and (V) with dialkylaminoalkylamines gave the above listed "Atabrine"-type compounds which combine the bactericidal 1,1,3,3-tetramethylbutyl group with known antiplasmodial structures. Preliminary tests indicate that these are inactive against *P. lophurae* when tested in ducks. By treating the chloroacridines (IV) and (V) with ammonium carbonate, the corresponding 9-aminoacridines (X) and (XI) were obtained. These compounds show bactericidal activity (*cf.* Table I). The various reactions involved are illustrated.

TABLE I

BACTERIOLOGICAL REPORTS

	Bactericidal concentration, gamma/ml.		Bacteriostatic concentration,[a] gamma/ml.	
	Staph. aureus P 209	*Strep. hemolyticus* NY 5	*Staph. aureus* P 209	*Strep. hemolyticus* NY5
Phenol	5630	2825		
1-(1,1,3,3-Tetramethyl)-butyl-4-methoxy-6-chloro-9-aminoacridine (XIII)[b]	62.5	7.8	7.8	1.95
1-(1,1,3,3-Tetramethyl)-butyl-4-methoxy-9-aminoacridine (XIV)[b]	31.25	15.62	15.62	3.9

[a] After eight hours. [b] Tested as the hydrochlorides.

Experimental

2-[*p*-(1,1,3,3-Tetramethyl)-butylanisidino]-4-chlorobenzoic acid (II).—A mixture of 13.6 g. (0.05 mole) of 4-(1,1,3,3-tetramethyl)-butylanisidine hydrochloride,[4,5] 19.2 g. (0.10 mole) of 2,4-dichlorobenzoic acid, 22 g. of anhydrous potassium carbonate, 0.05 g. of copper powder, and 55 cc. of isoamyl alcohol (Eastman Kodak Co.) was placed in a three-neck flask fitted with a stirrer and air condenser. The contents were stirred and refluxed for three hours permitting some loss of water and alcohol to occur. Water was then added and the amyl alcohol steam distilled. Addition of solid sodium bicarbonate to the aqueous solution gave a filterable solid. The precipitate was twice suspended in 10% aqueous sodium bicarbonate, once in dilute hydrochloric acid, and filtered. After air drying, the purple solid was washed with petroleum ether. Recrystallization from ethanol gave a product which melted at 173–174°.

Anal. Calcd. for $C_{22}H_{28}ClNO_3$: C, 67.78; H, 7.2; N, 3.60. Found: C, 67.36; H, 7.45; N, 3.34.

In a similar manner, reaction with *o*-chloro(or *o*-bromo)-benzoic acid resulted in the corresponding substituted benzoic acid, 2-[*p*-(1,1,3,3-tetramethyl)-butylanisidino]-benzoic acid (III), m. p. 161°.

Anal. Calcd. for $C_{22}H_{29}NO_3$: C, 74.41; H, 8.17; N, 3.94. Found: C, 74.64; H, 8.41; N, 3.93.

(5) Nitration of the free phenol followed by methylation was found to be preferable to nitration of the methyl ether in the preparation of this substance.

1-(1,1,3,3-Tetramethyl)-butyl-4-methoxy-6,9-dichloroacridine (IV).—The appropriately substituted anthranilic acid was refluxed with ten times its weight of phosphorus oxychloride for three hours, after which time approximately half of the phosphorus oxychloride was distilled under reduced pressure. The residue was poured into a water–ice mixture containing an excess of concentrated ammonium hydroxide. A yellow crystalline product was obtained. Recrystallization from alcohol–water yielded the pure product. A small amount of ammonia was found to aid in the recrystallization; m. p. 168.5–169.5°.

Anal. Calcd. for $C_{22}H_{28}Cl_2NO$: C, 67.82; H, 6.42; N, 3.57. Found: C, 68.22; H, 6.30; N, 3.67.

The corresponding 1-(1,1,3,3-tetramethyl)-butyl-4-methoxy-9-chloroacridine (V) melted at 123–125°.

Anal. Calcd. for $C_{22}H_{28}ClNO$: C, 74.26; H, 7.31; N, 3.94. Found: C, 74.59; H, 6.59; N, 4.16.

Preparation of "Atabrine"-type Compounds (VI–IX).—The following general procedure was used for the preparation of all of these compounds: The required 9-chloroacridine (0.005 mole) together with 6 g. of phenol were heated to 70°, and then 0.01 mole of the appropriate dialkylaminoalkylamine was added. After heating for two hours at 120–130°, with occasional stirring, the mixture was made alkaline, extracted with ether and the ether washed with water until the wash water was no longer alkaline. After drying over magnesium sulfate, treatment with anhydrous hydrogen chloride precipitated a gummy dihydrochloride. The freed base was then reprecipitated as the hydrochloride from anhydrous ether. On standing in a desiccator over sulfuric acid, the gummy material solidified; yields ranged from 40–50%.

1-(1,1,3,3-Tetramethyl)-butyl-4-methoxy-6-chloro-9-(3-diethylaminopropylamino)-acridine dihydrochloride (VI), m. p. 119–122°: *Anal.* Calcd. for $C_{29}H_{44}Cl_3N_3O$: N, 7.55. Found: N, 7.61.

1-(1,1,3,3-Tetramethyl)-butyl-4-methoxy-6-chloro-9-(5-diethylamino-2-pentylamino)-acridine dihydrochloride (VII), m. p. 136–138°: *Anal.* Calcd. for $C_{31}H_{48}Cl_3N_3O$: N, 7.18. Found: N, 7.18.

1-(1,1,3,3-Tetramethyl)-butyl-4-methoxy-9-(3-diethylaminopropylamino)-acridine dihydrochloride (VIII), m. p. 153-156°: *Anal.* Calcd. for $C_{29}H_{46}Cl_2N_3O$: N, 8.05. Found: N, 8.19.

1-(1,1,3,3-Tetramethyl)-butyl-4-methoxy-9-(5-diethylamino-2-pentylamino)-acridine dihydrochloride (IX), m. p. 155–158°: *Anal.* Calcd. for $C_{31}H_{49}Cl_2N_3O$: N, 7.63. Found: N, 7.44.

All four compounds melted with fizzing.

Preparation of Aminoacridines (X) and (XI).—These compounds were prepared in a manner similar to that described above for the preparation of the antimalarials, except that ammonium carbonate (minimum assay 30% NH_3), powdered just prior to use, was added to the chloroacridines dissolved in phenol.

1-(1,1,3,3-Tetramethy)-butyl-4-methoxy-6-chloro-9-aminoacridine hydrochloride (X), m. p. 146–147.5°: *Anal.* Calcd. for $C_{22}H_{28}Cl_2N_2O$: N, 6.90. Found: N, 6.67.

1-(1,1,3,3-Tetramethyl)-butyl-4-methoxy-9-aminoacridine hydrochloride (XI), m. p. 218–219°: *Anal.* Calcd. for $C_{22}H_{29}ClN_2O$: N, 7.55. Found: N, 7.81.

Both of these compounds melted with fizzing.

Acknowledgment.—The authors are indebted to Dr. Frank E. Stirn of Lederle Laboratories for the bacteriological and animal tests.

Summary

p-(1,1,3,3-Tetramethyl)-butylphenol has been used as the starting point in the synthesis of 1,1,3,3-tetramethylbutyl substituted acridines.

Two 9-aminoacridines containing the 1,1,3,3-tetramethylbutyl group have been shown to be active bactericides.

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