were obtained from certain condensates. These studies presented evidence for the ionization of fluorene into a fluoryl ion and a proton.

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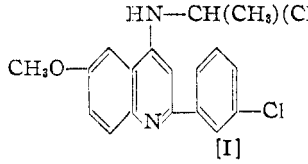
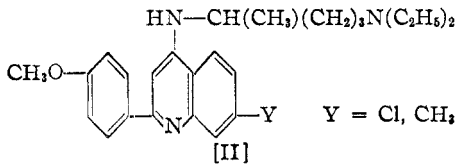
Some Methylquinolines Patterned as "Open Models" of Atebrin

BY HENRY GILMAN, J. LEWIS TOWLE AND SYDNEY M. SPATZ[1]

The initial[2,3] series of so-called open models of atebrin, designed primarily to incorporate the gametocidal activity of certain quinolines as well as the schizonticidal activity of certain acridines, was focused chiefly on 6-methoxy-2-(3'-chlorophenyl) - 4 - [(α - methyl - δ - diethylaminobutyl)-amino]-quinoline [I]. In [I] the chlorophenyl



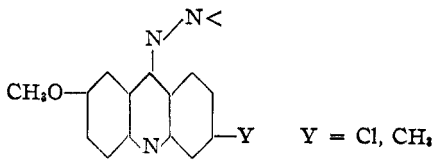
[I]



[II]

group replaces the fused chlorobenzo group of atebrin.

The acridine nucleus of atebrin may be "opened" at three other positions to yield quinolines of interest in antimalarial studies. For example, a consideration of atebrin as a methoxybenzo derivative of 7-chloro-4-substituted-aminoquinoline suggests the synthesis of [II] where Y is chlorine. Because of the relative inaccessibility of 7-chloroquinoline when this study was commenced a few years ago,[4] the synthesis of [II] where Y is the methyl group was attempted instead. In connection with the replacement of the chlorine atom by the methyl group, it should be noted that Mietzsch and Mauss[5] demonstrated the importance of either a chlorine atom or a methyl group in the 6-position of 2-methoxy-9-basically substituted acridines [III]. These findings, first demonstrated in malaria infected canaries,[6] were confirmed by other studies[7] on the sparrow. Later,



[III]

a series of active quinolines with a dialkylaminoalkylamino chain in the 4-position and either a methyl group or preferably a chlorine atom in the 7-position was reported in the patent literature.[8]

The synthesis of the isomeric 6-methyl-2-(4'-methoxyphenyl) - 4 - ([α-methyl - δ - diethylaminobutyl)-amino]-quinoline was carried out to study further[2,3] the effect of position isomerism on the thereapeutic activity of the open models. The first step in the two syntheses, involving the addition of the *p*-anisyllithium to the —N=C< linkage of the 6- and 7-methylquinolines, yielded, subsequent to hydrolysis, both the 1,2-dihydro compound and the dehydrogenated derivative. The syntheses are summarized in the equations presented below.

An unsuccessful attempt to prepare the isomer of [II] with the methyl group in the 8-position was due to the failure of the 8-methyl-2-(4'-methoxyphenyl)-quinoline to undergo N-oxidation. A similar phenomenon, possibly steric in origin, was observed in the case of the 8-methyl-2-(4'-chlorophenyl)-quinoline.[3]

The 2-(*p*-dimethylaminophenyl)-quinolines listed in Table I were prepared by the azomethine-addition reaction of *p*-dimethylaminophenyllithium with quinoline, 6-methyl-, 7-methyl-, 8-methyl-, 8-hydroxy- and 8-methoxyquinoline, respectively.

Of the several compounds described in this report, the only one which showed any activity in experimental avian malaria was 8-methyl-2-(*p*-dimethylaminophenyl)-quinoline.

Experimental

6-, 7- and 8-Methyl-2-(4'-methoxyphenyl)-quinolines and 6-, 7-Methyl-1,2-dihydro-2-(4'-methoxyphenyl)-quinolines.—Two-tenths of a mole[9] of *n*-butyllithium and 46.8 g. (0.25 mole) of *p*-bromoanisole in 350 cc. of ether were stirred at 0° for fifteen minutes. Without delay, a solution of 28.6 g. (0.2 mole) of the methylquinoline in 50 cc. of ether was added at 0° over a three-minute interval to the

(1) Present address: National Aniline Division, Allied Chemical and Dye Corp., Buffalo, N. Y.

(2) Gilman and Spatz, THIS JOURNAL, **66**, 621 (1944).

(3) Gilman, Christian and Spatz, *ibid.*, **67**, 979 (1945).

(4) Syntheses of such types by R. A. Benkeser, starting with 4,7-dichloroquinoline, will be reported later.

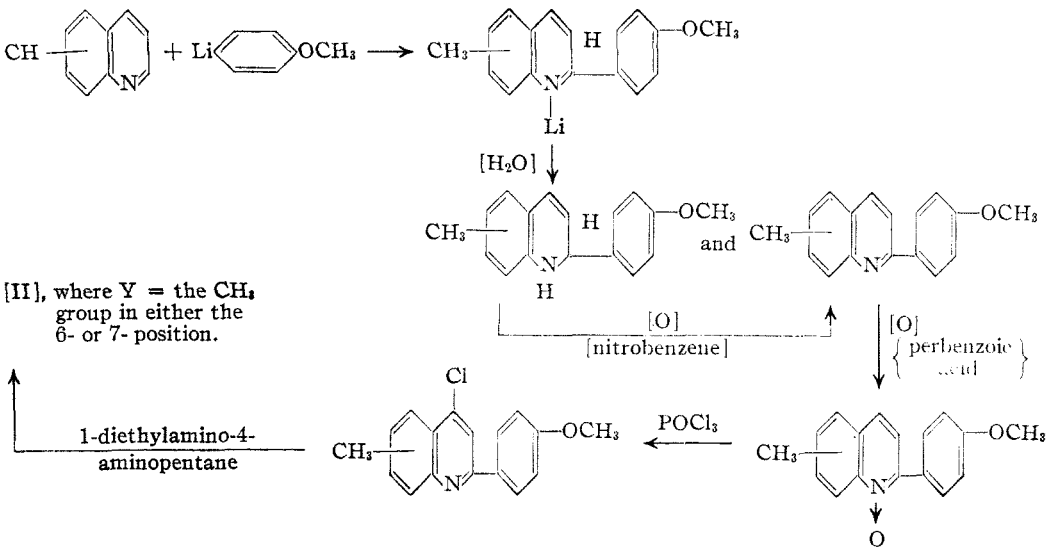
(5) Mietzsch and Mauss, *Klin. Wochschr.*, **12**, 1276 (1933); German Patent 553,072 (1930) [*Chem. Zentr.*, **103**, II, 1201 (1932)], German Patent 571,449 (1930) [*Chem. Zentr.*, **104**, I, 3969 (1933)]; *Angew. Chem.*, **47**, 633 (1934); *Ber.*, **69B**, 641 (1936); U. S. Patent 2,077,249 (1937) [*C. A.*, **31**, 4060 (1937)].

(6) Mietzsch, in "Medicine in its Chemical Aspects," Vol. III, "Bayer," Germany, 1936.

(7) Feldman and Kopeliovich, *Arch. Pharm.*, **273**, 488 (1935).

(8) Andersag, Breitner and Jung, U. S. Patent 2,233,970 (1941) [*C. A.*, **35**, 3771 (1941)].

(9) Estimated by the procedure of Gilman and Haubein, THIS JOURNAL, **66**, 1515 (1944).



freshly prepared solution of *p*-anisyllithium. After an additional ten minutes of stirring at the same temperature, the reaction mixture was hydrolyzed in ice-water. The ether layer was added to a hot, alcoholic solution of 50 g. of hydrated picric acid. The picrate was filtered off and decomposed by boiling with dilute sodium hydroxide to yield, as in the case of the 7-methylquinoline adduct, a crude mixture of 7-methyl-2-(4'-methoxyphenyl)-quinoline and the corresponding 1,2-dihydro product. The two compounds were separated by fractional crystallization from a 1:1 solution of benzene and ligroin (b. p., 85–108°). The dehydrogenated product crystallized out upon cooling and the lower melting 1,2-dihydro compound separated out after concentrating the mother liquor. The latter compound was quantitatively converted to the major product of the reaction by oxidizing it with boiling nitrobenzene for ten to fifteen minutes, and then removing the nitrobenzene by steam distillation.

The 6-methyl isomer was isolated by concentrating and cooling the dried ethereal solution. The crystalline material which separated out was a mixture of the dehydrogenated product and the 1,2-dihydro derivative. These components were separated by fractional crystallization as described above and the 1,2-dihydro compound converted to the desired product with nitrobenzene.

The 8-methyl derivative was isolated as a picrate. A 1,2-dihydro compound was not obtained with this isomer.

6- and 7-Methyl-2-(4'-methoxyphenyl)-quinoline-N-oxides.—A solution of 18.0 g. (0.072 mole) of 6-methyl-2-(4'-methoxyphenyl)-quinoline and 20.2 g. (0.147 mole) of perbenzoic acid in 450 cc. of chloroform was kept tightly stoppered in the refrigerator for nine days, during which time the solution turned cherry red. After extracting the benzoic acid with 200 cc. of 10% sodium hydroxide, the chloroform was removed by distillation under reduced pressure at room temperature. The N-oxide residue, which melted at 160°, weighed 17.0 g. (88%). Recrystallization from a benzene–petroleum ether (b. p., 60–68°) mixture raised the melting point to 163°.

Anal. Calcd. for $C_{17}H_{15}O_2N$: N, 5.28. Found: N, 5.00.

The 7-methyl isomer was isolated from the concentrated chloroform solution as the picrate. Subsequent decomposition with dilute alkali gave, after two recrystallizations from 40% ethanol, the pure compound melting at 145° in 75% yield.

Anal. Calcd. for $C_{17}H_{15}O_2N$: N, 5.28. Found: N, 5.49.

A mixed melting point of the parent compound with the N-oxide melted at 120–125°.

The 8-methyl compound treated in the same manner as the 6- and 7-methyl isomers failed to yield the desired N-oxide. The unoxidized material was recovered in almost quantitative yield.

6- and 7-Methyl-4-chloro-2-(4'-methoxyphenyl)-quinolines.—Forty g. (0.26 mole) of phosphorus oxychloride was added in one portion through the condenser exit to 7.0 g. (0.027 mole) of 6-methyl-2-(4'-methoxyphenyl)-quinoline-N-oxide. The reaction flask was immersed in an ice-bath. After the vigorous reaction subsided, the mixture was heated at 90° (external temperature) for forty-five minutes. The resulting solution was poured into an excess of ice-water to yield a gummy precipitate which gradually solidified. The crude material was filtered off and purified by trituration with dilute sodium carbonate, followed by crystallization from methanol. The product, obtained in a yield of 75%, melted at 107–109°.

Anal. Calcd. for $C_{17}H_{14}ONCl$: N, 4.94. Found: N, 5.12.

The 7-methyl-4-chloro-2-(4'-methoxyphenyl)-quinoline, prepared by the method described above, melted at 91° (76.5%).

Anal. Calcd. for $C_{17}H_{14}ONCl$: N, 4.94. Found: N, 5.00.

6-Methyl-2-(4'-methoxyphenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]-quinoline.—A mixture of 5 g. (0.018

TABLE I

2-(4'-METHOXYPHENYL)-QUINOLINES

Addition product, (4'-methoxyphenyl)-	M. p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Yield,[b] %	Picrate m. p., °C.	1,2-Dihydro-compound, m. p., °C.[c]
6-Methyl-2-[a]	136–137	$C_{17}H_{15}ON$	5.62	5.84	46.2	210	90–95
7-Methyl-2-[a]	141–142	$C_{17}H_{15}ON$	5.62	5.74	61	205–207	106–110
8-Methyl-2-[d]	85.5–87	$C_{17}H_{15}ON$	5.62	5.89	30.5	185–186	

[a] Recrystallized from a benzene solution followed by dilution with an equal volume of petroleum ether (b. p., 60–68°). [b] Based on the *n*-butyllithium used. [c] Recrystallization failed to raise the melting points, due perhaps to instability of the molecule. [d] Recrystallized from ethanol.

mole) of 4-chloro-6-methyl-2-(4'-methoxyphenyl)-quinoline and 6.54 g. (0.041 mole) of 1-diethylamino-4-aminopentane was heated at each of the following temperature ranges for twenty-four hours: 175–180, 180–200, 200–210 and 210–220°. The cooled melt was dissolved in ethanol and the solution filtered from 1.7 g. of an insoluble substance. The filtrate was evaporated and the residue triturated with 5% sodium hydroxide solution. The crude product was purified by dissolving in a small amount of ethanol and diluting the solution with water. From this solution the condensation product was precipitated by the addition of small amounts of sodium chloride and sodium bicarbonate. The condensation product came down as a fine, amorphous, yellow powder. It was insoluble in water, and soluble in acetone, alcohol and benzene. It exhibited a bluish fluorescence in alcohol and benzene.

Anal. Calcd. for $C_{26}H_{35}ON_3$: N, 10.37. Found: N, 10.34.

7-Methyl-2-(4'-methoxyphenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]-quinoline.—Five grams (0.018 mole) of the 4-chloro-7-methyl-2-(4'-methoxyphenyl)-quinoline and 6.54 g. (0.041 mole) of 1-diethylamino-4-aminopentane reacted in the manner described for the preparation of the 6-methyl isomer. The melt was processed in a customary manner to give the condensation product which was isolated as a yellow, amorphous powder. In this form it was insoluble in water, and soluble in acetone, alcohol and benzene. It exhibited weak bluish fluorescence in the latter two solvents.

Anal. Calcd. for $C_{26}H_{35}ON_3$: N, 10.37. Found: N, 10.35.

2-*p*-Dimethylaminophenylquinolines.—The six 2-*p*-dimethylaminophenylquinolines, listed with their melting points and nitrogen analyses in Table II, were prepared by the addition of *p*-dimethylaminophenyllithium to the azomethine linkage of the given quinoline. Experimentally, the procedure involved the gradual (5–11 minutes) addition of an ethereal solution of the quinoline compound to a slight excess of the *p*-dimethylaminophenyllithium,[10] in ether. The reaction was carried out at 0° in an atmosphere of nitrogen. After all of the quinoline had been added, the reaction mixture was stirred for an additional fifteen to forty minutes: in some cases, a yellow crystalline precipitate of the N-lithio-1,2-dihydro product separated out. The reaction mixture was hydrolyzed by pouring gradually into ice-water. The ether layer was separated and dried over Drierite; the drying agent was filtered off; and the solvent removed by distillation to yield either a crystalline residue or a viscous oil. In either case the residue was dissolved in the minimum amount of a hot organic solvent, from which the dehydrogenated azomethine addition product separated out on cooling. Solvents found suitable for this purpose were ethanol, ethanol and water, benzene, and benzene and petroleum ether (b. p., 60–68°). The products were recrystallized to constant melting point. Generally, the yields were of the order of 50–65%.

In the reaction with 8-hydroxyquinoline, two equivalents of the RLi reactant were used, one of them being needed for reaction with the hydrogen of the hydroxy group.

An alternate method for purifying the crude azomethine adduct involves conversion to the picrate, as described for the isolation of the 7-methyl-2-(4'-methoxyphenyl)-quinoline and other products.[3]

(10) Gilman, Zoellner and Selby, THIS JOURNAL, **55**, 1252 (1933).

TABLE II

2-*p*-DIMETHYLAMINOPHENYLQUINOLINES

Addition product, -quinoline	M. p., °C.	Formula	Nitrogen, % Calcd.	Found
2-*p*-Dimethylaminophenyl-[a,d]	173–175	$C_{17}H_{16}N_2$	11.28	11.36
2-*p*-Dimethylaminophenyl-6-methyl-[a,e]	185–186	$C_{18}H_{18}N_2$	10.69	11.01
2-*p*-Dimethylaminophenyl-7-methyl-[a,f]	187–189	$C_{18}H_{18}N_2$	10.69	11.00
2-*p*-Dimethylaminophenyl-8-methyl-[a,g]	155	$C_{18}H_{18}N_2$	10.69	10.96
2-*p*-Dimethylaminophenyl-8-hydroxy-[b]	151–152	$C_{17}H_{16}ON_2$	10.61	10.90
2-*p*-Dimethylaminophenyl-8-methoxy-[c]	138	$C_{18}H_{18}ON_2$	10.10	10.00

[a] Recrystallized from ethanol or from a benzene solution followed by dilution with Skelly B (b. p., 60–68°). [b] Recrystallized from aqueous ethanol. [c] Recrystallized from benzene. [d] The picrate melted at 219°. [e] The dipicrate melted at 215–217°. *Anal.* Calcd. for $C_{30}H_{24}O_{14}N_8$: N, 15.55. Found: N, 15.67. [f] The picrate melted at 231–232°. [g] The picrate melted at 195–196°.

Acknowledgment.—The authors are grateful to Drs. R. J. Porter and L. T. Coggeshall, of the University of Michigan, for the antimalarial tests, the results of which will be published elsewhere.

Summary

7-Methyl-2-(4'-methoxyphenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]-quinoline and the isomeric 6-methyl compound were synthesized for study as further variants of "open models" of atebrin.

The syntheses of a series of 2-*p*-dimethylaminophenylquinolines are described.

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