5-Nitro-8-methoxyquinoline[5] was prepared by first adding 50 g. of concd. sulfuric acid to 15.9 g. (0.1 mole) of 8-methoxyquinoline[6] at 0°; then the concd. nitric acid was added dropwise, keeping the temperature below 0°. The subsequent operations were like those described for the preparation of 5-nitro-6-methoxyquinoline and the yield of product melting at 151–153° was 16 g. (80%). The reduction was carried out by the procedure of Balaban.[5b]

6-Nitro-2-methoxyquinoline[7] was prepared by adding 5 g. (0.0314 mole) of 2-methoxyquinoline dropwise to 25 cc. of fuming nitric acid cooled to 0°, then 40 g. of concd. sulfuric acid was added at a rate not to increase the temperature above 0°. After stirring for two hours the mixture was poured upon crushed ice, allowed to stand overnight, filtered, and crystallized from benzene to give 6 g. (93%) of product melting at 187°. Koenigs[7] reported a melting point of 181°, but gave no yield. No yield was given by Friedlaender[8] for the preparation of 2-methoxyquinoline. We prepared this ether in 98% yield by adding 30 g. (0.184 mole) of 2-chloroquinoline in 30 cc. of methanol to a solution of sodium methoxide made by dissolving 9 g. (0.391 g. atom) of sodium in 20 cc. of methanol. The solution was refluxed for one hour, and then 15 cc. of 1:1 hydrochloric acid was added, the methanol was removed under reduced pressure, and the residue was extracted with ether and sodium hydroxide solution. The dried ether extracts were distilled to give 28.5 g. (98%) of 2-methoxyquinoline. 6-Nitro-8-methoxyquinoline was prepared in accordance with the procedure of Fourneau and co-workers[9] by a Skraup reaction with 2-amino-5-nitroanisole in a yield of 67.5%. Our melting point agreed with theirs, but they gave no yield. The nitro compound was reduced to the corresponding amine by means of stannous chloride and hydrochloric acid.[5b,9]

8-Nitro-7-methoxyquinoline was prepared by first adding, with cooling, 50 g. of conc. sulfuric acid to 10 g. (0.063 mole) of 7-methoxyquinoline[10]; then 30 g. of concd. nitric acid was added dropwise, keeping the temperature below 0°. The mixture was stirred for one hour, during which time the temperature was allowed to rise to that of the room. The yellow precipitate obtained after pouring upon crushed ice was filtered after first neutralizing with ammonium hydroxide. Crystallization from chloroform gave 8.5 g. (66.2%) of product melting at 177–178°. Balaban[5b] reported a melting point of 178° and a yield of 33%. The reduction of 8-nitro-7-methoxyquinoline was carried out by the procedure of Fieser and Hershberg.[11] A suspension of 8.6 g. (0.042 mole) of the nitro compound and 0.085 g. of Adams catalyst in 50 cc. of ethyl acetate and 10 cc. of absolute ethanol was reduced at a pressure of 43 pounds for three hours at 100°. The yield of 8-amino-7-methoxyquinoline, melting at 118° after recrystallization from ethanol, was 6.3 g. (86.2%). Balaban[5b] reported a yield of 32% using the method of Jacobs and Heidelberger,[4b] and a melting point of 108°. We carried out a reduction of 8.5 g. (0.042 mole) of 8-nitro-7-methoxyquinoline by this[4b] method and obtained 2.5 g. (34%) of 8-amino-7-methoxyquinoline which melted at 108° after recrystallization from 50% ethanol.

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

Five isomers of the known, active 6-methoxy-8-(2,5-dimethylpyrryl-1)-quinoline have been prepared in connection with studies on experimental avian malaria. Only 8-methoxy-6-(2,5-dimethylpyrryl-1)-quinoline was active, but the activity was appreciably less than the isomer in which the two substituents were transposed.

(5) (a) Vis, *J. prakt. Chem.*, [2] **48**, 26 (1893); (b) Balaban, *J. Chem. Soc.*, 2624 (1932).

(6) The 8-methoxyquinoline was prepared by the Skraup [*Monatsh.*, **3**, 544 (1882)] reaction using the modification of Strukov, *Org. Chem. Ind., U. S. S. R.*, **4**, 523 (1937) [*C. A.*, **32**, 4987 (1938)].

(7) Koenigs, *Ber.*, **18**, 2397 (1885). We prepared the corresponding amine in a 66% yield by his procedure.

(8) Friedlaender, *ibid.*, **15**, 336 (1882).

(9) Fourneau and co-workers, *Ann. inst. Pasteur*, **44**, 748 (1930) [C. A., **26**, 1592 (1932)].

(10) Späth and Brumer, *Ber.*, **57**, 1243 (1924).

(11) Fieser and Hershberg, THIS JOURNAL, **62**, 1640 (1940).

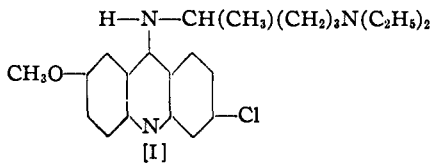
AMES, IOWA RECEIVED JANUARY 22, 1946

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

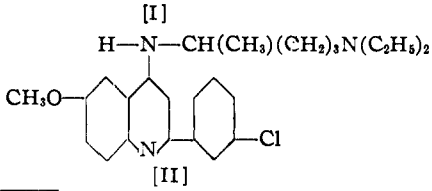
Some Quinolines Patterned as "Open Models" of a Modified Atebrin

BY HENRY GILMAN, ROBERT V. CHRISTIAN AND SYDNEY M. SPATZ[1]

It was shown recently[2] that there was a correlation of some so-called open quinoline models of atebrin [I] with the fundamental acridine type.



[I]



[II]

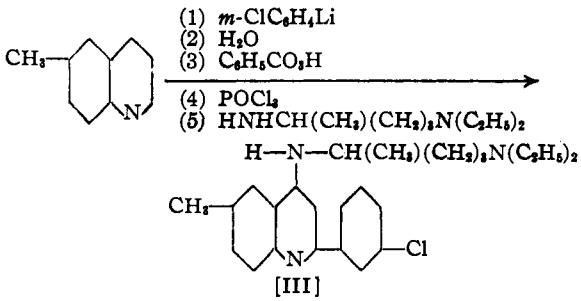
One of the quinolines then reported which bears a formal relationship to atebrin, and which was active in experimental avian malaria, was 2-(3′-chlorophenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]-6-methoxyquinoline [II]. This compound has a chlorophenyl group in place of the fused chlorobenzo group in atebrin.

In view of the partial replaceability of the methoxyl group in atebrin by a methyl group,[3] it seemed of interest to prepare some open quinoline models having a methyl group in place of the methoxyl group. One of these is 2-(3′-chlorophenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]-6-methylquinoline [III] which was prepared by the following sequence of reactions.

(1) Present address: National Aniline Division, Buffalo, N. Y.

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

(3) Magidson and Grigorowsky, *Ber.*, **69**, 396 (1936).



[III]

This compound was active but the following two isomers were inactive: 2-(4'-chlorophenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]-6-methylquinoline and 2-(4'-chlorophenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]-7-methylquinoline.

Experimental

2-(3'-Chlorophenyl)-6-methylquinoline.—A solution of 0.139 mole[4] of *n*-butyllithium in 250 cc. of dry ether was cooled in an ice-bath and stirred vigorously while 26.6 g. (0.139 mole) of *m*-chlorobromobenzene dissolved in 60 cc. of ether was added during a three-minute period. The resulting solution of *m*-chlorophenyllithium was stirred for five minutes; then 10 g. (0.07 mole) of 6-methylquinoline in 70 cc. of ether was added during four minutes and stirring was continued for ten minutes. All of the above operations were carried out in an atmosphere of dry nitrogen.

After hydrolysis, by pouring the mixture into ice-water, the ether layer was separated, dried over sodium sulfate, and evaporated under reduced pressure to give 29.7 g. of a yellow oil. This was dissolved in 95% ethanol, heated to boiling, and added to a hot ethanol solution of 34.8 g. of picric acid. The picrate, which separated on cooling, was filtered, and then washed with ethanol to give 26 g. of orange crystals. The yield of brownish crystals obtained after refluxing the picrate for forty minutes with 7.5% sodium hydroxide solution and then digesting twice with hot water was 13.7 g. (77%). Crystallization from petroleum ether (b. p., 85–115°) gave 10.1 g. (57%) of pale tan leaflets melting at 103–104°. Recrystallization from 95% ethanol gave colorless leaflets melting at 104–105°.

Anal. Calcd. for $C_{16}H_{12}NCl$: N, 5.52. Found: N, 5.68.

2-(3'-Chlorophenyl)-6-methylquinoline-N-oxide.—An ice-cold solution of 25.8 g. (0.102 mole) of 2-(3'-chlorophenyl)-6-methylquinoline in 150 cc. of chloroform was added slowly and with shaking to a cold solution of 0.159 mole of perbenzoic acid in 300 cc. of chloroform. The clear, pale yellow solution was allowed to stand in a refrigerator for ten days. The reddish brown solution was concentrated under reduced pressure to 200 cc., extracted three times with 80-cc. portions of 5% sodium hydroxide solution, and washed with water. Then the chloroform solution was evaporated to dryness under reduced pressure to yield 25.5 g. (93%) of tan crystals melting at 121–126°. Recrystallization from a mixture of petroleum ether (b. p., 85–115°) and absolute ethanol gave 20.7 g. (76%) of light tan leaflets melting at 132–134°.

Anal. Calcd. for $C_{16}H_{12}ONCl$: N, 5.18. Found: N, 5.26.

2-(3'-Chlorophenyl)-4-chloro-6-methylquinoline.—Using conventional procedures,[2] 7 g. (0.026 mole) of 2-(3'-chlorophenyl)-6-methylquinoline-N-oxide was treated with 40 g. (0.26 mole) of phosphorus oxychloride. The reaction mixture was hydrolyzed and the resulting oil was triturated under water until it solidified. After making the resulting mixture slightly basic with concd. ammonium hydroxide it was filtered, washed several times by decantation with water, filtered and dried to yield 5.5 g. (78%) of a cream colored powder melting at 105–110°. Recrystallization, for analysis, from an ethanol–pyridine mixture gave small colorless crystals melting at 115–116°.

Anal. Calcd. for $C_{16}H_{11}NCl_2$: N, 4.86. Found: N, 4.94.

2-(4'-Chlorophenyl)-6-methylquinoline.—To a solution of *p*-chlorophenyllithium prepared from 33.4 g. (0.175 mole) of *p*-chlorobromobenzene and 0.165 mole of *n*-butyllithium was added a solution of 22.2 g. (0.155 mole) of 6-methylquinoline in 30 cc. of ether. Subsequent to hydrolysis and recrystallization from 95% ethanol containing a little pyridine there was obtained 11.5 g. (30%) of product melting at 167–167.5°.

Anal. Calcd. for $C_{16}H_{12}NCl$: N, 5.52. Found: N, 5.77.

The **picrate** of **2-(4'-chlorophenyl)-6-methylquinoline** was obtained as bright yellow leaflets melting at 214–215°.

Anal. Calcd. for $C_{22}H_{15}O_7N_4Cl$: N, 11.60. Found: N, 11.66.

2-(4'-Chlorophenyl)-6-methylquinoline-N-oxide.—From 25.4 g. (0.1 mole) of 2-(4'-chlorophenyl)-6-methylquinoline in 500 cc. of chloroform and 0.163 mole of perbenzoic acid in 300 cc. of chloroform was obtained, after standing in a refrigerator for one week, 21.1 g. (78%) of light brown crystals. Recrystallization from a mixture of 95% ethanol and chloroform gave 15.7 g. (58%) of pale tan crystals melting at 188–189°, with softening at 184°. After another crystallization, for an analytical sample, the compound melted at 189°.

Anal. Calcd. for $C_{16}H_{12}ONCl$: N, 5.18. Found: N, 5.24.

2-(4'-Chlorophenyl)-4-chloro-6-methylquinoline.—From 7 g. (0.026 mole) of 2-(4'-chlorophenyl)-6-methylquinoline-N-oxide and 38.4 g. (0.25 mole) of phosphorus oxychloride was obtained, subsequent to hydrolysis, 8 g. of a white, amorphous powder. Recrystallization from ethanol containing a little pyridine gave 3.5 g. (47%) of fine colorless crystals which melted at 139°, after subliming slightly above 121°.

Anal. Calcd. for $C_{16}H_{11}NCl_2$: N, 4.86. Found: N, 4.97.

The **picrate** of **2-(4'-chlorophenyl)-4-chloro-6-methylquinoline** melted at 154–156° after recrystallization from 95% ethanol and acetic acid.

Anal. Calcd. for $C_{22}H_{14}O_7N_4Cl_2$: N, 10.83. Found: N, 11.03.

2-(4'-Chlorophenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]-6-methylquinoline.—A mixture of 4 g. (0.014 mole) of 2-(4'-chlorophenyl)-4-chloro-6-methylquinoline and 5.26 g. (0.033 mole) of 1-diethylamino-4-aminopentane was heated under reflux for fifty hours at 190–200° and then for twenty hours at 220–230°. Subsequent to hydrolysis, the product, which distilled over from 225 to 245° at a pressure of less than 10^{-4} mm., was obtained as an amber glass exhibiting blue-green fluoresence. The yield was 3.8 g. (60%).

Anal. Calcd. for $C_{25}H_{33}N_3Cl$: N, 10.25. Found: N, 10.07.

2-(3'-Chlorophenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]-6-methylquinoline.—A mixture of 5.46 g. of crude 2-(3'-chlorophenyl)-4-chloro-6-methylquinoline (m. p. 105–110°) and 7.2 g. of 1-diethylamino-4-aminopentane was heated under reflux for twenty-four hours at 180–190°, then for twenty-four hours at 200°, and finally for forty hours at 210°. The resulting brown oil was treated with 10% sodium hydroxide solution, and the ether extract of this was dried over potassium carbonate. Subsequent to removal of the ether on a steam-bath, the product was distilled at 200–220° (0.4 mm.). The yield of yellow, viscous oil which showed a blue-green fluoresecence was 4.9 g. (63%).

(4) The titer of the *n*-butyllithium solution was determined by the procedure of Gilman and Haubein, THIS JOURNAL, **66**, 1515 (1944).

Anal. Calcd. for $C_{25}H_{32}N_3Cl$: N, 10.25. Found: N, 10.27.

2-(4'-Chlorophenyl)-7-methylquinoline.—*p*-Chlorophenyllithium was prepared by the dropwise addition of 33.4 g. (0.175 mole) of *p*-chlorobromobenzene dissolved in 50 cc. of ether to an ice-cold, stirred solution of 0.165 mole of *n*-butyllithium in 250 cc. of ether. A solution of 22.2 g. (0.155 mole) of 7-methylquinoline in 30 cc. of ether was then added with stirring. The reaction mixture was hydrolyzed and worked up as usual.

Evaporation of the dried ether solution gave a pale brown oil which showed little tendency to crystallize. The oil was dissolved in 95% ethanol, and the solution was allowed to stand in the refrigerator for several days. The solid which separated was filtered, and on drying there was obtained 22.3 g. (57%) of pale yellow, waxy crystals melting over the range of 85–125°. Two crystallizations from 95% ethanol containing a few drops of pyridine gave 9.7 g. (25%) of colorless crystals melting at 142–143°. The sample prepared for analysis melted at 143–144°.

Anal. Calcd. for $C_{16}H_{12}NCl$: N, 5.52. Found: N, 5.56.

The low yield was due to the difficulty of removing the yellow impurity which may have been the 1,2-dihydroquinoline derivative. If this were the case, then oxidation by treatment with nitrobenzene should improve the yield.

Picrate of 2-(4'-Chlorophenyl)-7-methylquinoline.—The picrate, prepared in 95% ethanol solution, was obtained as small, yellow rhombic crystals melting at 202–203°.

Anal. Calcd. for $C_{22}H_{15}O_7N_4Cl$: N, 11.60. Found: N, 11.59.

2-(4'-Chlorophenyl)-7-methylquinoline-N-oxide.—From 27.3 g. (0.107 mole) of 2-(4'-chlorophenyl)-7-methylquinoline and 0.165 mole of perbenzoic acid was obtained, by customary procedures, 27.5 g. (95%) of a pale brown solid melting at 193–197°. Recrystallization from 95% ethanol containing a little chloroform yielded 15.5 g. (54%) of tan needles melting at 198–199°.

Anal. Calcd. for $C_{16}H_{12}ONCl$: N, 5.18. Found: N, 5.30.

2-(4'-Chlorophenyl)-4-chloro-7-methylquinoline.—From 7 g. (0.026 mole) of 2-(4'-chlorophenyl)-7-methylquinoline-N-oxide and 40 g. (0.26 mole) of phosphorus oxychloride was obtained, subsequent to crystallization from a mixture of 95% ethanol and pyridine, 3.5 g. (50%) of microscopic needles melting at 135–135.5°, with softening at 134°.

Anal. Calcd. for $C_{16}H_{11}NCl_2$: N, 4.86. Found: N, 4.99.

2-(4'-Chlorophenyl)-4-[α-methyl-δ-diethylaminobutyl)-amino]-7-methylquinoline.—A mixture of 3.34 g. of 2-(4'-chlorophenyl)-4-chloro-7-methylquinoline and 4.4 g. of 1-diethylamino-4-aminopentane was heated under reflux for twenty-four hours at 180°, then for twenty-four hours at 200°, and finally for twenty-four hours at 220°. The product distilled at 225–235° (0.01 mm.) and the yield of golden-orange glass exhibiting strong green fluorescence was 2.34 g. (50%).

Anal. Calcd. for $C_{25}H_{32}N_3Cl$: N, 10.25. Found: N, 10.51.

2-(4'-Chlorophenyl)-8-methylquinoline.—From a reaction of 15.6 g. (0.109 mole) of 8-methylquinoline and the RLi compound prepared from 24.5 g. (0.128 mole) of *p*-chlorobromobenzene by the halogen–metal interconversion reaction was obtained 15 g. (54%) of product distilling at 132° (0.5 mm.). Recrystallization from absolute methanol gave glistening prisms which melted at 79–80°.

Anal. Calcd. for $C_{16}H_{12}NCl$: N, 5.52. Found: N, 5.42.

This quinoline compound was largely recovered after an attempted N-oxidation by perbenzoic acid. It was similarly observed[5] that 2-(4'-methoxyphenyl)-8-methylquinoline failed to undergo N-oxidation with perbenzoic acid under conditions where the 6-methyl and 7-methyl isomers formed the corresponding oxides in good yields. Steric hindrance factors are probably partially responsible.

9-(β-Di-*n*-propylaminoethyl)-carbazole Hydrochloride.—This compound was prepared, incidental to a related study, by heating a mixture of 8 g. (0.035 mole) of 9-β-chloroethylcarbazole[6] and 7.1 g. (0.07 mole) of di-*n*-propylamine under reflux at 110–125° for twenty-four hours, and then at 130° for twenty-four hours. The emulsion formed on treatment with water was made basic with 40% sodium hydroxide, extracted with ether, and the ether extract treated with 5% hydrochloric acid until no more solid separated. Recrystallization of the 9.2 g. (80%) of crude product which melted at 165–175°, from a mixture of ether and absolute ethanol, gave 7.05 g. (61%) of crystals melting at 181–185°.

Anal. Calcd. for $C_{20}H_{27}N_2Cl$: N, 8.46; Cl, 10.7. Found: N, 8.78; Cl, 11.0.

This compound had a doubtful activity in experimental avian malaria.

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

Reactions are described for the synthesis of 2-(3'-chlorophenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]-6-methylquinoline, 2-(4'-chlorophenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]-6-methylquinoline, and the 7-methylquinoline isomer of this compound. These compounds, as well as 9-(β-di-*n*-propylaminoethyl)-carbazole, have been examined in experimental avian malaria.

AMES, IOWA RECEIVED FEBRUARY 11, 1946

(5) Studies by J. L. Towle and S. M. Spatz.

(6) 9-β-Chloroethylcarbazole was prepared in a 46.2% yield essentially by the procedure of Clemo and Perkin, *J. Chem. Soc.*, **125**, 1810 (1924). The product melted at 130–131°, as reported. Although they reported a yield of 25.8% for the crude product (m. p., 125–126°), actually the procedure was found to give a 57.8% yield of crude, crystalline product, melting at 125–127°.