needles were obtained which melted at 220° with sublimation. The yield was 55 mg. corresponding to 96% of the theoretical.

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 69.00; H, 5.75; N, 16.10. Found: C, 69.19; H, 5.89; N, 16.40.

Picrate.—The picrate of this neutral hydrolysis product was obtained by adding a solution of picric acid in benzene to a hot benzene solution of the compound. The picrate separated on cooling as long, deep red needles which melted at 168–170° with decomposition.

Anal. Calcd. for $C_{16}H_{13}N_5O_7$: N, 17.35. Found: N, 17.36.

Iodo Derivative.—The iodo derivative was easily prepared by adding a solution of iodine in potassium iodide to a dilute solution of the compound in 5% aqueous sodium hydroxide. It crystallized in clusters of long colorless needles, m. p. 186°. It was soluble in alcohol and acetone, insoluble in water, and quite stable under ordinary conditions.

Anal. Calcd. for $C_{10}H_9IN_2O$: I, 42.30. Found: I, 42.31.

Hydrolysis of Compound $C_{10}H_{10}N_2O$.—Forty mg. of the product of methanolic alkaline hydrolysis, $C_{10}H_{10}N_2O$ (I), was refluxed for two hours with a 25% aqueous solution of potassium hydroxide. Nitrogen was passed through the solution during the hydrolysis and the volatile base trapped in hydrochloric acid. This base was identified as monomethylamine by preparation of the hydrochloride and the chloroplatinate. From the alkaline solution indole-2-carboxylic acid was isolated in good yield. It melted at 204° and did not depress the melting point of an authentic sample.

Synthesis of Indole-2-carboxylic Acid Methyl Amide (I).—To confirm the identity of the neutral $C_{10}H_{10}N_2O$ product with indole-2-carboxylic acid N-methyl amide this compound was synthesized by the following two methods. 1. Indole-2-carboxylic acid chloride was prepared in the manner previously described[3] and was condensed in benzene solution with methylamine. Long, lustrous needles were obtained on recrystallization from benzene and melted at 219° with sublimation. No depression was observed in a mixed m. p. determination with the neutral product derived from gliotoxin. 2. The methyl amide was also obtained in good yield when indole-2-carboxylic acid ethyl ester reacted with a concentrated alcoholic solution of methylamine. The monomethyl amide of indole-2-carboxylic acid was readily soluble in ethanol, methanol and acetone; less soluble in cold benzene but soluble in hot benzene; it dissolved in hot water and crystallized out on cooling as lustrous, hexagonal platelets. It absorbed bromine in acetic acid solution to yield a crystalline bromo derivative, m. p. 185°. The iodo derivative was described above. The methyl amide coupled in alkaline solution with diazotized sulfanilic acid to form a deep orange-red solution; it gave a positive Ehrlich reaction (*p*-dimethylaminobenzaldehyde and concentrated hydrochloric acid).

Synthesis of the Selenium Degradation Product, $C_{12}H_8N_2O_3$ (II).—Although oxalic acid was not isolated from the hydrolysis products of the selenium sublimate, in view of the structure established for the remainder of the molecule, there was little doubt but that this dicarboxylic acid represented the missing fragment. This assumption was fully justified by the synthesis of the selenium degradation product (II) in the following manner.

Six hundred mg. of indole-2-carboxylic acid methyl amide (I) was dissolved in 10 ml. of dry pyridine and 25 ml. of dry ether added; to this solution was added slowly and with cooling a solution of 600 mg. of ethyl oxalochloride in 25 ml. of anhydrous ether. As the two solutions were mixed, a crystalline precipitate was formed which consisted partially of unchanged amide and partially of pyridine hydrochloride. The mixture was allowed to stand at room temperature for fifteen hours. The crystalline material was removed by filtration and the filtrate evaporated in vacuum. The sirupy residue crystallized upon the addition of ethanol; 115 mg. of pale yellow rhombs was obtained, m. p. 255°. The mother liquors contained some unchanged amide which was recovered and some non-crystalline oil, which probably represented uncyclized condensation products. The synthetic compound was identical in every respect with that isolated from gliotoxin. A mixed m. p. determination showed no depression.

Summary

The degradation of gliotoxin by selenium has been shown to yield 2-methyl-1,3,4-triketotetrahydropyrazino-[1.2-a]-indole. The structure of this substance has been determined by degradation and by synthesis. This formulation is in agreement with the structure of the product of the hydriodic acid reduction of gliotoxin previously published.

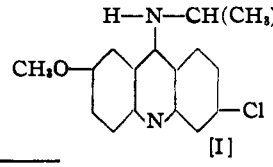
ITHACA, N. Y. RECEIVED JANUARY 20, 1944

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

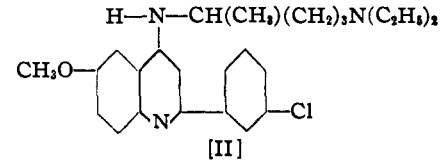
Some Quinolines Patterned as "Open Models" of Atabrine

BY HENRY GILMAN AND SYDNEY M. SPATZ[1]

It seemed of interest to prepare some so-called open models of atabrine [I] in connection with studies on attempted correlations of constitution with antimalarial action. One of these models is 6-methoxy-2-(3′-chlorophenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]-quinoline [II]. This compound has a chlorophenyl group in place of the fused chlorobenzo group in atabrine.



[I]



[II]

Compound [II] was synthesized by the sequence of reactions shown beyond.

The over-all yield is quite satisfactory. *m*-Chlorophenyllithium was prepared in 70% yield

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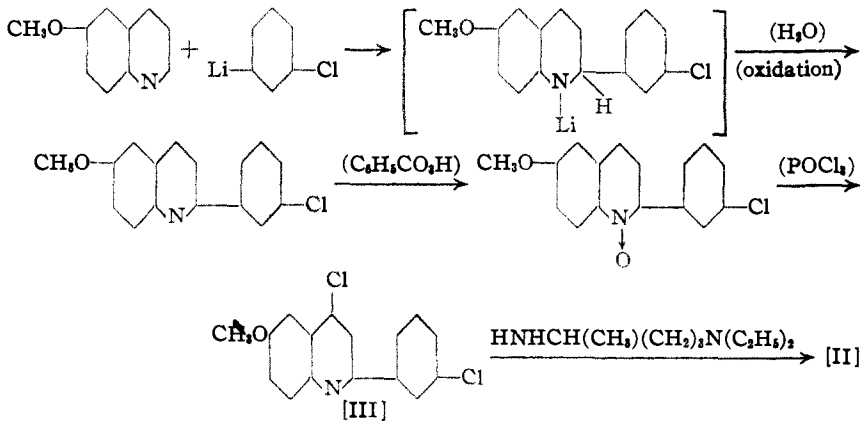


by the following halogen-metal interconversion reaction, which recent[2] related studies show to be of broad applicability for the preparation of a wide variety of substituted aryllithium compounds.

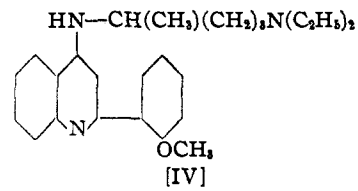
$$m\text{-}ClC_6H_4Br + n\text{-}C_4H_9Li \longrightarrow m\text{-}ClC_6H_4Li + n\text{-}C_4H_9Br$$

4 - Chloro - 6 - methoxy - 2 - (3′ - chlorophenyl)-quinoline [III] was also prepared from 4-chloro-6-methoxyquinoline and *m*-chlorophenyllithium, thereby establishing the position of N-oxide halogenation. It is interesting to note in connection with this reaction that the γ-quinolyl chlorine which is sufficiently reactive to undergo condensation with 1-diethylamino-4-aminopentane, but relatively unreactive toward the RLi compound, does not show any deactivating effect on the anil linkage.[3] The use of substituted RLi compounds provides, in general, a better approach than other more involved procedures hitherto used for the preparation of variously substituted aryl-quinolines.

Although a shift of the chlorine from the 6-position to the 7-position in atabrine extinguishes the antimalarial action,[4a] there was no basis for predicting the effect of a compound in which the *m*-chlorophenyl group of [II] was replaced by a *p*-chlorophenyl group. It is known that 6-chloro-8-dialkylaminoalkylaminoquinolines are weakly active in avian malaria, but a shift of the chlorine atom to the 7-position confers increased activity upon the molecule. Accordingly, 6-methoxy-2-(4′-chlorophenyl) - 4 - [(α - methyl - δ - diethylaminobutyl) - amino] - quinoline was prepared by a sequence of reactions like that used for [II], *p*-chlorophenyllithium being used in place of *m*-chlorophenyllithium. This compound, as well as [II], showed *antimalarial* activity.

This suggested an examination of a chlorine-free type, because some quinoline antimalarials are known to retain their biologic effect without the presence of a chlorine. 6 - Methoxy - 2 - phenyl - 4 - [(α - methyl - δ - diethylaminobutyl) - amino]-quinoline was synthesized, and found to be active in experimental malaria.

Although the positions of the chlorine in the new compounds previously mentioned are without appreciable effect, the position of the methoxy group is important. A chlorine-free compound having the methoxy group in the phenyl and not in the quinolyl nucleus was prepared. This 2-(2′ - methoxyphenyl) - 4 - [(α - methyl - δ - diethylaminobutyl) - amino] - quinoline [IV] was found to be inactive.



[IV]

Experimental

***m*-Chlorophenyllithium.**—To a vigorously stirred, clear filtered solution of 0.2 mole of *n*-butyllithium in 250 cc. of ether, cooled to −35°, was added 38.3 g. (0.2 mole) of *m*-chlorobromobenzene in 50 cc. of ether. Fifty-cc. aliquots were withdrawn at three-minute intervals and carbonated with finely powdered dry-ice. The yields of *m*-chlorobenzoic acid were: 50.3% (3 min.); 66% (6 min.); 69.7% (9 min.); 67.7% (12 min.); and 48.4% (16 min.). Therefore, the optimal yield of this RLi compound at −35° is obtained over a range of six to twelve minutes. From a related experiment at room temperature and for a twelve minute period, the yield of crude *m*-chlorobenzoic acid was 29.4%. Mr. Wright Langham obtained 50% of crude acid (m. p. 145–149°) or 42% of purer acid (m. p. 149–151°) by the rapid addition at room temperature of 0.03 mole of *n*-butyllithium to 0.02 mole of *m*-chlorobromobenzene, with carbonation being carried out at the end of two minutes.

Temperature Effect on Addition of *m*-Chlorophenyllithium to 6-Methoxyquinoline.—These addition reactions were carried out as an index to the more favorable temperature of addition of the RLi compound to some of the quinolines. The yields of anil addition product (2-*m*-chlorophenyl-6-methoxyquinoline) were: 11.1% (−35°); 29.6% (−7 to −5°); 49–54% (0°); and 16.7% (36°).

6-Methoxy-2-(3′-chlorophenyl)-quinoline.—To a solution of *m*-chlorophenyllithium (prepared from 0.2 mole of *m*-chlorobromobenzene) was added, with vigorous stirring and in a dry nitrogen atmosphere, 15.9 g. (0.1 mole) of 6-methoxyquinoline in 100 cc. of ether. The ice-bath was removed, and stirring was continued for ten minutes. After hydrolyzing by pouring the entire reaction mixture into ice water, the ether layer was separated, concentrated

(2) Gilman, Langham and Moore, THIS JOURNAL, **62**, 2327 (1940); Langham, Brewster and Gilman, *ibid.*, **63**, 545 (1941); Gilman, Langham and Jacoby, *ibid.*, **61**, 106 (1939); Gilman and Jacoby, *J. Org. Chem.*, **3**, 108 (1938); see, also, pp. 538–539 in Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y. (1943) for some newer illustrations.

(3) Gilman and Spatz, THIS JOURNAL, **62**, 446 (1940), and *ibid.*, **63**,1553 (1941).

(4) (a) Krichevskii, Shternberg and Halperin, *J. Microbiol. Epidemiol., Immunbiol.*, (U. S. S. R.), **14**, 642 (1935) [*C. A.*, **30**, 4218 (1936)]; Magidson and Grigorovskii, *Ber.*, **69B**, 396 (1936); Feldman and Kopeliovich, *Org. Chem. Ind.*, (U. S. S. R.), **1**, 31 (1936) [*C. A.*, **30**, 3821 (1936)]; (b) Magidson and Bobyshev, *J. Gen. Chem.* (U. S. S. R.), **8**, 899 (1938) [*C. A.*, **33**, 1827 (1939)].

to about one-half the volume, and to this solution was added a hot alcoholic solution of 27 g. of picric acid. The picrate was filtered off (after chilling the solution in an ice box overnight), dried, and decomposed by boiling with dilute alkali. The crude red-brown product was dissolved in hot benzene–petroleum ether (b. p. 60–70°) mixture and separated from an insoluble dark-colored gum by filtration. On cooling, there was obtained 11.9 g. of almost colorless crystals of 6-methoxy-2-(3′-chlorophenyl)-quinoline melting at 110–111°. An additional 1.4 g. from the filtrate gave a total yield of 49.3%. From a duplicate experiment, the yield was 53%. When the synthesis was carried out at −35°, the yield was only 11.1%; and a preparation at room temperature gave 16.7%.

Anal. Calcd. for $C_{16}H_{12}ONCl$: N, 5.20. Found: N, 5.28.

The **picrate,** prepared in a customary manner, as glistening yellow crystals, melted at 196–197°.

Anal. Calcd. for $C_{22}H_{15}O_8N_4Cl$: N, 11.24. Found: N, 11.35.

6-Methoxy-2-(3′-chlorophenyl)-quinoline-N-oxide.—A 700 cc. chloroform solution of 32.5 g. (0.12 mole) of 6-methoxy-2-(3′-chlorophenyl)-quinoline and 32 g. (0.23 mole) of perbenzoic acid was kept in an ice box for three days. The ruby red solution was concentrated to a volume of about 250 cc., diluted with 100 cc. of ethanol, brought to a boil and then added with stirring to a hot concentrated alcoholic solution of 32 g. of hydrated picric acid. On cooling, the yellow crystalline picrate (m. p. 155–158°) precipitated. The unrecrystallized picrate was dried and then decomposed by dilute alkali to yield 25 g. (73%) of the crude N-oxide (m. p. 147–149°). Recrystallization from a 1:1 alcohol–benzene mixture gave 23 g. (67%) of N-oxide melting at 153–154°.

Anal. Calcd. for $C_{16}H_{12}O_2NCl$: N, 4.91. Found: N, 4.99.

The **picrate,** prepared in hot alcohol solution from the N-oxide, separated on cooling as pale yellow rosets melting at 158.5–159°.

Anal. Calcd. for $C_{22}H_{15}O_9N_4Cl$: N, 10.89. Found: N, 10.96.

4-Chloro-6-methoxy-2-(3′-chlorophenyl)-quinoline.—Ten grams (0.035 mole) of 6-methoxy-2-(3′-chlorophenyl)-quinoline-N-oxide was treated with 43 g. (0.28 mole) of phosphorus oxychloride. Reaction was instantaneous, and the mixture was heated, first on a water-bath for ten minutes, and then gently over asbestos for twenty minutes. The mixture was then poured upon 300 g. of chopped ice, and the crude chlorination product filtered off. An additional quantity was obtained by making the filtrate alkaline. Crystallization from a 3:1 ethanol–pyridine mixture gave a product melting at 153–154°. The yield was 6.7 g. (63.2%). A mixed m. p. with the parent N-oxide (which melts at the same temperature) was 129–133°. From a second preparation, the yield was 63.8%.

Anal. Calcd. for $C_{16}H_{11}ONCl_2$: N, 4.61. Found: N, 4.77.

The same compound (mixed m. p.) was obtained by interaction of 1.1 g. (0.0057 mole) of 4-chloro-6-methoxyquinoline and *m*-chlorophenyllithium in ether in a yield of 34.7%.

6-Methoxy-2-(3′-chlorophenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]-quinoline.—Four grams of 4-chloro-6-methoxy-2-(3′-chlorophenyl)-quinoline and 5.0 g. (2.4 equivalents) of 1-diethylamino-4-aminopentane were heated at 200–205° for 100 hours. The melt was worked up in the manner described later for the preparation of the 4′-chlorophenyl isomer. The 6-methoxy-2-(3′-chlorophenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]-quinoline was obtained as a yellow, amorphous powder in a yield of 3.4 g. (60.7%).

Anal. Calcd. for $C_{26}H_{32}ON_3Cl$: N, 9.87. Found: N, 9.63.

The compound is soluble in cold ethanol, forming a brown solution with a marked greenish fluorescence. It is also soluble in cold acetone and in cold benzene with red-blue fluorescence, but difficultly soluble in ether.

6-Methoxy-2-(4′-chlorophenyl)-quinoline.—To an ether solution of *p*-chlorophenyllithium (prepared from 0.2 mole of *p*-chlorobromobenzene) was added a solution of 27 g. (0.18 mole) of 6-methoxyquinoline in 30 cc. of ether. The addition was over a two-minute period, and stirring was continued for an additional five minutes. The orange colored, crystalline intermediate N-lithium compound settled out immediately. After hydrolysis, the ether layer was dried; and removal of the ether left an oily residue which crystallized on cooling to long needles melting at 194–195°. Recrystallization from an ethanol–pyridine mixture did not raise the melting point. The yield was 23 g. (50.2%).

Anal. Calcd. for $C_{16}H_{12}ONCl$: N, 5.20; Cl, 13.15. Found: N, 5.35; Cl, 12.99.

The **picrate,** prepared from a hot glacial acetic acid solution of the quinoline compound and a hot ethanolic solution of picric acid, formed yellow glistening crystals which melted at 205°.

Anal. Calcd. for $C_{22}H_{15}O_8N_4Cl$: N, 11.24. Found: N, 11.30.

6-Methoxy-2-(4′-chlorophenyl)-quinoline-N-oxide.—A tetrachloroethane solution of 19 g. (0.07 mole) of 6-methoxy-2-(4′-chlorophenyl)-quinoline was added slowly with shaking to an ice-cold solution of 18.4 g. (0.13 mole) of perbenzoic acid in 500 cc. of chloroform. Oxidation proceeded slowly as indicated by the gradual conversion of the difficultly soluble parent compound to the more soluble N-oxide. At the end of one week, the red solution was concentrated to a volume of about 400 cc.; and extracted with dilute alkali. After drying and further concentration, the oil was dissolved in ethanol and treated with a slight excess of picric acid in hot alcohol to give 27 g. (73%) of the picrate (m. p. 171–172°). From the picrate and alkali was obtained the N-oxide which after crystallization from ethanol softened at 164° and melted at 166–168°. The yield of pure N-oxide was 11 g. (55%).

Anal. Calcd. for $C_{16}H_{12}O_2NCl$: N, 4.91; Cl, 12.42. Found: N, 4.74; Cl, 12.22.

4-Chloro-6-methoxy-2-(4′-chlorophenyl)-quinoline.—Seven grams (0.025 mole) of 6-methoxy-2-(4′-chlorophenyl) quinoline-N-oxide was treated with 40 g. (0.26 mole) of phosphorus oxychloride in the manner described for the other chlorination. After hydrolysis, the gummy material solidified to an amorphous body, which after crystallization from hot methanol melted at 163.5–164°. The yield was 5.7 g. (76.5%).

Anal. Calcd. for $C_{16}H_{11}ONCl_2$: N, 4.61; Cl, 23.33. Found: N, 4.72; Cl, 23.06.

A mixed m. p. with a specimen prepared from 6-methoxy-4-chloroquinoline and *p*-chlorophenyllithium in 48% yield showed no depression. A mixed m. p. with the parent N-oxide was 138–145°.

6-Methoxy-2-(4′-chlorophenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]-quinoline.—Two and one-half grams of 4-chloro-6-methoxy-2-(4′-chlorophenyl)-quinoline and 2.85 g. (2.2 mole equivalents) of 1-diethylamino-4-aminopentane were heated at 200° for 72 hours. The melt was dissolved in warm ethanol, and added to a slight excess of dilute alkali. The gummy product was dissolved in warm ethanol and precipitated as a yellow amorphous product by the slow addition of water. The yield of dry powdery product was 2.4 g. (69%). The compound is soluble in cold ethanol, forming a brown solution which has a blue-green fluorescence.

Anal. Calcd. for $C_{26}H_{32}ON_3Cl$: N, 9.87. Found: N, 9.72.

2-(2′-Methoxyphenyl)-quinoline.—To an ether solution of *o*-methoxyphenyllithium (prepared by a halogen-metal interconversion starting with 0.26 mole of *o*-bromoanisole, in a three-minute reaction with *n*-butyllithium) was added 28.5 g. (0.22 mole) of freshly distilled quinoline in 30 cc. of ether. The reaction was carried out at −14° over a period

of about twelve minutes, and hydrolysis was effected by ice water. The picrate, formed from the hydrolyzate, was decomposed by boiling with 5% sodium hydroxide. After distilling off the benzene used to extract the oil, the largest fraction was a heavy yellow oil distilling at 201–204° (2 mm.) (chiefly at 203.5°). The yield was 24 g. (41.2%).

Anal. Calcd. for $C_{16}H_{13}ON$: N, 5.96. Found: N, 6.11.

In two subsequent preparations, approximately the same yields were obtained, an 18% recovery of quinoline was effected, and no *n*-butylquinoline was isolated. Accordingly, it appears that an improved yield might be had by a longer period of reaction of the RLi compound and quinoline at the temperature used.

2-(2′-Methoxyphenyl)-quinoline hydrochloride was prepared in quantitative yield by treating a dry ether solution of the quinoline compound with hydrogen chloride. The hydrochloride is precipitated from an ethanolic solution by dry ether, as cream colored, fine crystals which melt at 184.5–185° with decomposition. The salt is easily hydrolyzed to the free base.

Anal. Calcd. for $C_{16}H_{14}ONCl$: N, 5.16; Cl, 13.06. Found: N, 5.17; Cl, 12.74.

2-(2′-Methoxyphenyl)-quinoline picrate, prepared from either the free base or the hydrochloride, melts at 177–178°.

Anal. Calcd. for $C_{22}H_{16}O_8N_4$: N, 12.07. Found: N, 12.01.

2-(2′-Methoxyphenyl)-quinoline-N-oxide.—A one-liter chloroform solution of 46.4 g. (0.2 mole) of 2-(2′-methoxyphenyl)-quinoline and two equivalents of perbenzoic acid were kept in a refrigerator for two days. The solution was concentrated to a volume of about 300 cc., and to it was added a hot solution of 52 g. of picric acid in 300 cc. of ethanol. The crude picrate, decomposed by dilute alkali, gave a dark tan product. Crystallization from ethanol-water gave 34 g. (68.6%) of large, glassy, tan-colored crystals melting at 178–178.5°.

An alternate procedure for isolating the N-oxide is to concentrate the chloroform solution to one-third its volume; extract with dilute alkali to remove the benzoic acid; dry the chloroform solution over sodium sulfate, and then recrystallize the 16.2 g. of crude residue (after removing the chloroform) from ethanol. The yield was 11.7 g. (64%) of product melting at 178–178.5°.

Anal. Calcd. for $C_{16}H_{13}O_2N$: N, 5.58. Found: N, 5.76.

The **picrate** of 2-(2′-methoxyphenyl)-quinoline-N-oxide melts at 133.5–134°.

Anal. Calcd. for $C_{22}H_{16}O_9N_4$: N, 11.67. Found: N, 11.66.

4-Chloro-2-(2′-methoxyphenyl)-quinoline.—From a reaction between 5.8 g. (0.023 mole) of 2-(2′-methoxyphenyl)-quinoline-N-oxide and 21.5 g. (0.14 mole) of phosphorus oxychloride was obtained 3.5 g. (56.5%) of the 4-chloro compound as pale yellow needles melting at 96–98° after crystallization from petroleum ether (b. p. 60–68°). The compound is very soluble in ethyl ether, hot methanol, and hot ethanol. A mixed m. p. determination with a specimen prepared from *o*-methoxyphenyllithium and 4-chloroquinoline showed no depression.

Anal. Calcd. for $C_{16}H_{12}ONCl$: N, 5.20; Cl, 13.15. Found: N, 5.37; Cl, 12.91.

The **picrate** of 4-chloro-2-(2′-methoxyphenyl)-quinoline melts at 200–201°.

Anal. Calcd. for $C_{22}H_{15}O_8N_4Cl$: N, 11.24. Found: N, 11.19.

Quinoline-N-oxide hydrochloride was prepared with some modifications of the procedure of Meisenheimer.[5] The yield, in the following typical experiment, was practically quantitative. A 600-cc. chloroform solution of 25.2 g. (0.2 mole) of quinoline and 32.2 g. (0.23 mole) of perbenzoic acid was kept in an ice box for thirty-six hours. After concentrating to a volume of about 400 cc., the solution was extracted with 10% hydrochloric acid, and the extract washed with chloroform. The extract was evaporated to dryness under reduced pressure, and the residue was crystallized by dissolving in hot absolute ethanol followed by the addition of anhydrous ether. The product was filtered, after cooling, and dried *in vacuo* over calcium chloride. The hydrochloride melted at 130–132°, and the picrate at 142–143°. The 4-chloroquinoline was prepared from the N-oxide by Meisenheimer's[5] procedure, with the yield and m. p. reported by him.

2-(2′-Methoxyphenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]-quinoline.—Four grams of 4-chloro-2-(2′-methoxyphenyl)-quinoline and 5.15 g. (2.2 mole equivalents) of 1-diethylamino-4-aminopentane were heated at 190–200° for seventy-five hours. The product was purified by distillation (b. p. 248–255° (0.025 mm.)). The yellow oil cooled at room temperature to a glass-like, transparent substance, and the yield was 4 g. (69%).

Anal. Calcd. for $C_{25}H_{33}ON_3$: N, 10.74. Found: N, 10.56.

6-Methoxy-2-phenylquinoline.—From 12.7 g. (0.08 mole) of 6-methoxyquinoline and 0.1 mole of phenyllithium was obtained 12.4 g. (66%) of pure product, melting at 132–133°. (The m. p. of the picrate was 205°.) These constants agree with those reported by Döbner,[6] who prepared 6-methoxy-2-phenylquinoline by decarboxylation of α-phenylquininic acid; the latter was prepared in an 18% yield from *p*-anisidine, pyruvic acid and benzaldehyde.

6-Methoxy-2-phenylquinoline-N-oxide.—From a reaction between 22.9 g. (0.17 mole) of perbenzoic acid in 400 cc. of chloroform and 26.5 g. (0.11 mole) of 6-methoxy-2-phenylquinoline was obtained, through the picrate, 6-methoxy-2-phenylquinoline-N-oxide as thick, lustrous crystals melting at 170–171° after crystallization from ethanol. The yields were in the range of 55–65%.

Anal. Calcd. for $C_{16}H_{13}O_2N$: N, 5.58. Found: N, 5.66.

4-Chloro-6-methoxy-2-phenylquinoline.—From 15.7 g. (0.063 mole) of 6-methoxy-2-phenylquinoline-N-oxide and 76.5 g. (0.5 mole) of phosphorus oxychloride was obtained 13.7 g. (81%) of 4-chloro-6-methoxy-2-phenylquinoline as long needles melting at 110–111° after crystallization from ethanol. In smaller-sized preparations using 1–5 g. of the N-oxide, the yields were in the range of 88–91%. Incidentally, the over-all yield by our three-stage procedure starting with 6-methoxyquinoline is larger than that obtained by the longer method of John and Lukas.[7]

The same compound (mixed m. p.) was obtained (in 61.5% yield) by the reaction of 4-chloro-6-methoxyquinoline with phenyllithium. The 4-chloro-6-methoxyquinoline, together, coincidentally, with 2-chloro-6-methoxyquinoline, was prepared by the method of Magidson and Rubtsov.[8] The yield of the 4-chloro isomer was 35.5%, and that of the 2-chloro isomer was 58.4%. The necessary precursor, 6-methoxyquinoline-N-oxide hydrochloride, was obtained in 87.5% yield; m. p., 192–194°, and the m. p. of the picrate was 173–174°.[8]

6-Methoxy-2-phenyl-4-[(α-methyl-δ-diethylaminobutyl)-amino]-quinoline.—Four grams of 4-chloro-6-methoxy-2-phenylquinoline and 5.15 g. (2.2 mole equivalents) of 1-diethylamino-4-aminopentane were heated at 135° for twenty-four hours, at 175–180° for twenty-four hours and then at 210° for twenty-four hours. From the glassy melt was obtained (after solution in ethanol and treatment with 2% sodium hydroxide) 4 g. (69%) of a pale tan, amorphous powder, insoluble in water, and soluble in ethanol acetone and benzene. In the latter two solvents the compound exhibits a weak bluish fluorescence.

Anal. Calcd. for $C_{25}H_{33}ON_3$: N, 10.74. Found: N, 10.60.

(5) Meisenheimer, *Ber.*, **59**, 1848 (1926); Meisenheimer and Stotz, *ibid.*, **58**, 2335 (1925).

(6) Döbner, *Ann.*, **249**, 106 (1888).

(7) John and Lukas, *J. prakt. Chem.*, [2] **130**, 328 (1931).

(8) Magidson and Rubtsov, *J. Gen. Chem.* (U. S. S. R.), **7**, 1896 (1937) [*C. A.*, **32**, 564 (1938)].

Acknowledgments.—The authors are grateful to Parke Davis and Company for arranging for the biological tests, the results of which will be reported in detail elsewhere. In addition to the general results mentioned previously, the following data include some of the intermediates examined for antimalarial activity in avian infections: 4-chloro-6-methoxy-2-phenylquinoline, 2-(2′-methoxyphenyl)-quinoline hydrochloride, 6-methoxy-2-(4′-chlorophenyl)-quinoline, 6-methoxy-2-(4′-chlorophenyl)-quinoline-N-oxide, 4-chloro-6-methoxy-2-(4′-chlorophenyl)-quinoline, 6-methoxy-2-(3′-chlorophenyl)-quinoline, 6-methoxy-2-(3′-chlorophenyl)-quinoline-N-oxide, and 4-chloro-6-methoxy-2-(3′-chlorophenyl)-quinoline were inactive; and 4-chloro-2-(2′-methoxyphenyl)-quinoline was of doubtful activity.

Summary

Four α-aryl-γ-chloroquinolines have been conveniently prepared through a three-step sequence of reactions involving: (1) RLi addition to the anil linkage; (2) N-oxide formation of the anil addition product; and (3) halogenation of the latter with phosphorus oxychloride. Condensation of these variously substituted γ-chloroquinolines with 1-diethylamino-4-aminopentane resulted in a series of compounds having essentially the functional groups of the more highly fused atabrine.

Antimalarial activity in avian malaria was shown by 6-methoxy-2-(3′-chlorophenyl)-4-[(α-methyl - δ - diethylaminobutyl) - amino] - quinoline, and by the isomeric (4′-chlorophenyl) compound. The presence of chlorine is not a necessary condition for activity, for 6-methoxy-2-(phenyl) - 4 - [(α - methyl - δ - diethylaminobutyl) - amine]-quinoline is also active. However, the position of the methoxy group (in the chlorine-free type) is important, because 2-(2′-methoxyphenyl) - 4 - [(α - methyl - δ - diethylaminobutyl)-amino-quinoline, unlike the 6-methoxy isomer, is inactive.

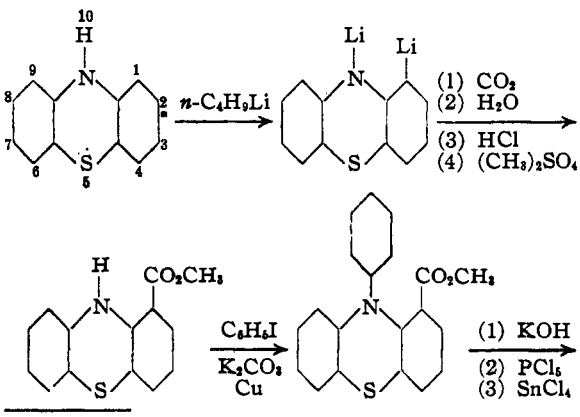
AMES, IOWA RECEIVED JANUARY 3, 1944

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Metalation of Phenothiazine[1]

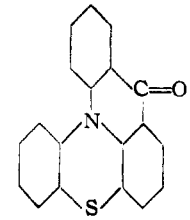
BY HENRY GILMAN, DAVID A. SHIRLEY AND PAUL R. VAN ESS

Phenothiazine is mono-metalated by *n*-butyllithium to give an RLi compound which, subsequent to carbonation, yields a mono-carboxylic acid. On the basis of earlier studies on metalations,[2] it appeared probable that metalation occurred in the 1- or the 4-position. After some unsuccessful attempts to prepare 1-carboxyphenothiazine by ring closure reactions, the acid obtained by metalation was shown to have the carboxyl group in the 1-position by the following indirect proof.



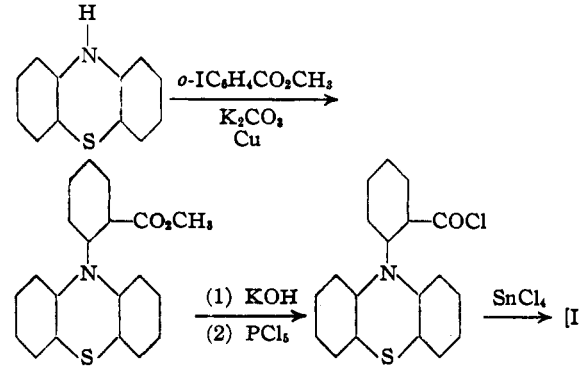
(1) Paper LIV in the series: "The Relative Reactivities of Organometallic Compounds"; the preceding paper is in THIS JOURNAL, 65, 1729 (1943).

(2) See p. 536 of Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943.



[I]

The identity of 9-quino(3,2,1-kl)phenothiazinone [I] prepared by the above sequence of reactions was established by comparison with the product obtained by the following transformations



The metalation of phenothiazine by *n*-butyllithium in the 1-position is of interest for two reasons. First, all previously described nuclear