sodium bicarbonate (2.36 g., 0.028 mole), was treated with hydroxylamine hydrochloride (1.5 g., 0.022 mole) in 25 ml. of water. The precipitated solid was redissolved by the addition of solid sodium bicarbonate and the solution warmed for two hours. An additional 2 g. of sodium bicarbonate was added and the heating continued for two more hours. The reaction mixture was acidified to congo red paper with hydrochloric acid, filtered, and the solid washed with water, ethanol, and ether. Crystallization was effected from aqueous ethanol; yield 2.5 g.

Other isoxazolones were prepared by similar procedures.

## Summary

1. Several aminobenzenearsonic acids have been diazotized and coupled with ethyl acetoacetate.

2. The products from (I) have been treated with hydrazine or hydroxylamine in the presence of base to give the corresponding 4-(arsonophenylazo)-3-methyl-5-pyrazolones or 5-isoxazolones.

3. The barium hydroxide hydrolysis of ethyl $\alpha$-acetoglyoxylate-4-arsonophenylhydrazone produced normal ester hydrolysis rather than the expected acetoacetic ketonic hydrolysis.

LINCOLN, NEBRASKA RECEIVED SEPTEMBER 6, 1946

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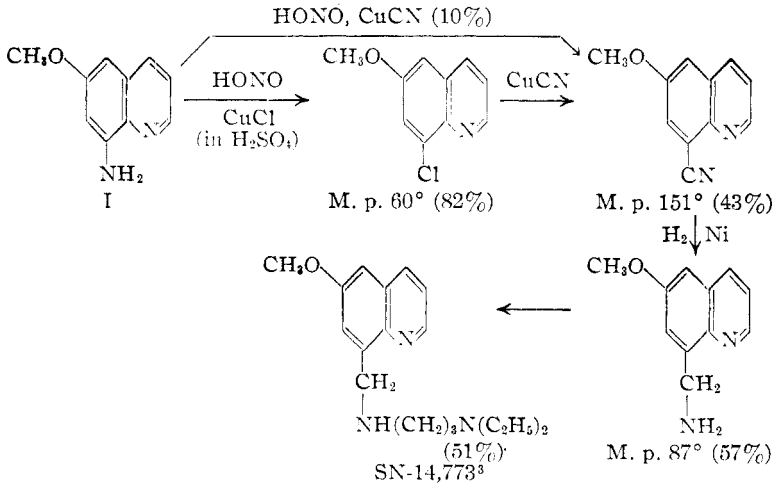
[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# Methylene and *p*-Phenylene Analogs of Plasmocid[1]

BY CHARLES C. PRICE,[2] H. R. SNYDER AND EARLE M. VAN HEYNINGEN

In order to evaluate the effect of interposing a methylene or phenylene residue between the amino side chain and the nucleus in the 8-aminoquinoline series, two analogs of 6-methoxy-8-(diethylaminopropylamino)-quinoline, sometimes referred to as Plasmocid, have been prepared.

The synthesis of both compounds started from 6-methoxy-8-aminoquinoline. The methylene analog was prepared by replacement of the amino group with cyano, preferably through the chloro compound by treatment with cuprous cyanide. The 8-cyano compound was reduced catalytically and then treated with 3-diethylaminopropyl chloride.




The *p*-phenylene analog was prepared by three similar procedures: (1) The amino group of I was diazotized and the product coupled directly with nitrobenzene. (2) The amino group was acetylated, nitrosated and coupled with nitrobenzene. (3) The salt of diazotized I with 1,5-naphthalenedisulfonic acid was isolated and coupled with nitrobenzene. The last was the most convenient procedure.

## Experimental[4]

**8-Cyano-6-methoxyquinoline by the Sandmeyer Reaction.**—To 3 g. (0.017 mole) of 8-amino-6-methoxyquinoline was added a solution of 1.1 ml. (0.02 mole) of concentrated sulfuric acid (sp. gr. 1.84) in 50 ml. of water. The mixture was heated to dissolve the yellow sulfate that formed, and then cooled rapidly an in ice-bath to reprecipitate the sulfate in fine needles. The cooled suspension was diluted with a solution of 3.3 ml. (0.06 mole) of sulfuric acid in 50 ml. of water and then diazotized at a temperature below 5° with a 5 *N* sodium nitrite solution to a starch-iodide end-point. A deep red solid formed during the course of the diazotization and this was filtered from the diazotization mixture. The filtrate was made neutral to red litmus paper with cold 30% sodium hydroxide by gradual addition such that the temperature of the mixture did not rise above 5°. A pink precipitate formed. This neutral suspension was poured slowly with stirring into 23 ml. of 1 *N* sodium cuprous cyanide cooled in an ice-bath. No visible change occurred so the mixture was stirred overnight, thus slowly coming to room temperature. Then the solid in the mixture was collected and extracted with 50 ml. of boiling 95% ethanol. The alcohol extract was evaporated to dryness on a steam-bath and the dark residue dissolved by heating in a minimum amount of 20% acetic acid. The hot acetic acid solution was treated with a small amount of Darco and filtered. The white crystals that formed on cooling were 8-cyano-6-methoxyquinoline, m. p. 147–150° (9.5%).

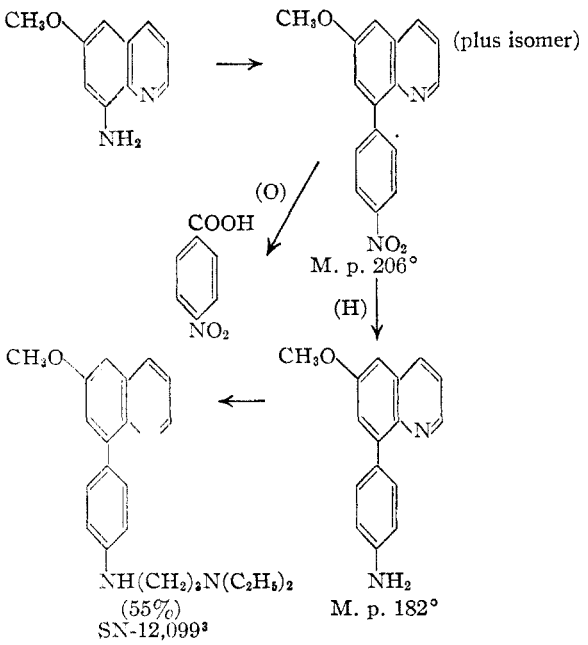
Replacing the sulfuric acid by phosphoric or hydrochloric acid did not change the yield. Addition of the acidic diazonium solution to a solution of sodium cuprous cyanide and excess sodium cyanide at either 50 or 100° gave none of the desired 8-cyano-6-methoxyquinoline.

(1) The work reported was carried out under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

(2) Present address: University of Notre Dame, Notre Dame, Indiana.

(3) The Survey Number, designated SN-, refers to the number assigned by the Survey of Antimalarial Drugs. The activity of such compounds will be compiled in a forthcoming monograph.

(4) Analyses were performed by Misses T. Spoor and L. Hruda.




**8-Chloro-6-methoxyquinoline.**—Nineteen grams (0.27 mole) of sodium nitrite was added in small portions to 120 ml. of concentrated sulfuric acid at temperatures below 10°. When addition was complete, the sulfuric acid–sodium nitrite mixture was heated at 70° to effect complete solution of the sodium nitrite. Then the solution was again cooled to 10° and 40 g. (0.23 mole) of 8-amino-6-methoxyquinoline in 150 ml. of glacial acetic acid was added from a dropping funnel. The addition was at such a rate that the temperature was maintained at 18–20°.[5] Simultaneously, a solution of 0.24 mole of cuprous chloride in 166 ml. of concentrated hydrochloric acid was prepared according to the method of Marvel and McElvain.[6] When the addition of the amine was complete and stirring had been continued for ten minutes, the diazotization mixture was poured with shaking into the cuprous chloride solution. Since the reaction was strongly exothermic, the flask was cooled beneath a water tap during the addition. To ensure complete reaction, the flask was heated on a steam-bath overnight.

The cooled mixture was then carefully neutralized with concentrated ammonium hydroxide. When the mixture became basic, it was cooled and the sticky, black tar that remained was filtered off, washed with ammonium hydroxide and then with water. The tar was extracted with ten 100-ml. portions of ether, then the combined extracts were treated once with Darco, filtered, and dried over anhydrous magnesium sulfate. Evaporation of the ether left 36.6 g. (82%) of crude, gray 8-chloro-6-methoxyquinoline, m. p. 50–54°. The quinoline was recrystallized from aqueous methyl alcohol to yield a white crystalline compound, m. p. 58–60°.

*Anal.* Calcd. for $C_{10}H_8NOCl$: C, 62.02; H, 4.17. Found: C, 61.94; H, 4.28.

In other preparations using this method yields varying between 70 and 80% were obtained. The crude product was found to be of sufficient purity to be used in the succeeding reaction; however, it could be distilled to give a white product of slightly higher melting point than the crude. Purification of the reaction product by distillation of the unextracted reaction mixture was unsuccessful; a yellow compound distilled in small amount and much charring occurred in the flask. The material recrystallized from 95% ethanol in yellow plates, m. p. 167–169°.

*Anal.* Found: C, 57.54; H, 5.35; N, 11.49.

No structure has been assigned to this compound but the analysis corresponds to the formula $C_{23}H_{26}N_4OCl_3$.

*Anal.* Calcd. for $C_{23}H_{26}N_4OCl_3$: C, 57.50; H, 5.45; N, 11.65.

**8-Cyano-6-methoxyquinoline.**—Seventeen grams (0.19 mole) of cuprous cyanide was placed in a 100-ml. distilling flask with 24.5 g. (0.127 mole) of 8-chloro-6-methoxyquinoline. The flask was connected for vacuum distillation and then heated directly with a small, smoky flame until the contents of the flask fused to a black liquid. The water pump was then connected to the flask and the black mixture heated for a short time so the chloroquinoline did not distil. Then the flask was allowed to cool slightly and connected to an oil pump. Distillation was effected by heating with a smoky flame and continued until no more distillate came over. The distillate was then redistilled from a Claisen flask under 2–3 mm. pressure. Two fractions were collected, the first from 140–165° and then the remainder distilling mostly at 205–210°. The first fraction was extracted with ether (the cyanoquinoline is relatively insoluble in ether) and recrystallized once from ethanol, m. p. 138–140°. The second fraction was recrystallized directly from ethanol, m. p. 140–143°. The weight of the combined portions of crude 8-cyano-6-methoxyquinoline was 10 g. (43%). Repeated recrystallizations of this crude material from 95% ethanol, with evaporation of filtrates and recrystallization of the solids so obtained, gave about an 80% recovery, m. p. 148–150°.

The ether extract of the first fraction above and the final combined ethanol filtrates on evaporation gave a mixture of the chloro- and cyanoquinolines which could be used again in the nitrile synthesis.

The compound was recrystallized from 20% acetic acid as long, white needles, m. p. 150–151°.

*Anal.* Calcd. for $C_{11}H_8ON_2$: C, 71.72; H, 4.38. Found: C, 71.80; H, 4.36.

**8-Aminomethyl-6-methoxyquinoline.**—A glass liner to a 270-ml. high-pressure bomb was cooled in a Dry Ice–alcohol-bath. In it was placed a suspension of 17.5 g. of 8-cyano-6-methoxyquinoline in 75 ml. of absolute methanol and 6 g. of Raney nickel. To the cold mixture, 50 ml. of liquid ammonia was added and the liner was sealed in the bomb. The reduction was conducted at an initial hydrogen pressure of 2500 lb. per sq. in. at a temperature of 75° for a period of five hours. After the reduction, the catalyst was removed by filtration and the methanol solution was evaporated to dryness on a steam-bath. The sticky, brown residue was extracted repeatedly with Skellysolve B (100 ml.); the solution being cooled after each extraction, the product filtered, and the filtrate used in a succeeding extraction with additional solvent to give 100 ml. Recrystallization of the product from Skellysolve B gave 10.3 g. (57%) of 8-aminomethyl-6-methoxyquinoline, m. p. 85–87°. A small sample distilled for analysis boiled at 148° (2 mm.).

*Anal.* Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43. Found: C, 70.40; H, 6.54.

A **picrate** was prepared in 95% ethanol. After repeated recrystallization, it darkened at 210° and melted at 223°.

*Anal.* Calcd. for $C_{17}H_{15}N_5O_8$: C, 48.92; H, 3.62. Found: C, 48.95; H, 3.75.

**8-(3-Diethylaminopropylaminomethyl)-6-methoxyquinoline.**—A mixture of 10.2 g. (0.0542 mole) of 8-aminomethyl-6-methoxyquinoline and 8.1 g. (0.0542 mole) of 3-diethylaminopropyl chloride was stirred and heated in an oil-bath at 140° for one and one-quarter hours. The viscous mass that was obtained on cooling was treated with 25 ml. of 20% potassium hydroxide with gentle warming. The cooled mixture was then extracted with 200 ml. of ether in 50-ml. portions. A small amount of black, ether-insoluble oil remained with the basic water layer and it was discarded. The combined ether extracts were treated once with Darco, filtered, and dried over anhydrous sodium

(5) The diazotization was carried out according to general directions of Hodgson and Walker, *J. Chem. Soc.*, 1620 (1933).

(6) Marvel and McElvain, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, New York N. Y., 1941, p. 170.

carbonate overnight. The ether was evaporated and the residue distilled at 0.01 to 0.005 mm. pressure. Two fractions were collected; the first, boiling from 135–155°, consisted principally of unchanged aminomethylquinoline; the second, boiling from 155–165° and mainly at 163–165° was a light yellow, viscous liquid. The latter weighed 8.4 g. (61%). A small sample taken midway in the distillation of the final fraction had the composition of 8-(3-diethylaminopropylaminomethyl)-6-methoxyquinoline.

*Anal.* Calcd. for $C_{18}H_{27}N_3O$: C, 71.72; H, 9.03. Found: C, 71.96; H, 9.34.

**A picrate** was prepared by dissolving the amine in ethanol and heating with a saturated ethanolic solution of picric acid. Recrystallization several times from ethanol yielded the picrate in yellow plates, m. p. 156–159°.

*Anal.* Calcd. for $C_{30}H_{33}N_9O_{15}$: C, 47.43; H, 4.38. Found: C, 47.51; H, 4.44.

**6-Methoxy-8-*p*-nitrophenylquinoline through 6-Methoxyquinoline-8-diazonium 1,5-Naphthalenedisulfonate.**—To 118 g. (0.62 mole) of freshly distilled 8-amino-6-methoxyquinoline was added a solution of 218 ml. of hydrochloric acid in 2 liters of water. The yellow hydrochloride that immediately precipitated was dissolved by heating the mixture to about 70° and then reprecipitated by cooling in ice while stirring. This slurry of hydrochloride was then cooled in a Dry Ice–ethanol-bath to about −1 to −3° with careful mechanical stirring so that the water did not freeze on the sides of the beaker. It was then diazotized with approximately 160 ml. of 5 *N* sodium nitrite to a starch–iodide end-point, the nitrite being added from a dropping funnel as fast as the solution would consume it. At the end of the diazotization small crystals of ice formed in the red diazotization mixture. This cold diazonium solution was filtered to remove a small amount of red solid and 142 g. (0.378 mole) of 75% 1,5-naphthalenedisulfonic acid was added with stirring. A tan precipitate immediately formed; nevertheless, the mixture was stirred for one-half hour to insure complete precipitation. The solid was removed by filtration and washed first with 200 ml. of ethanol and then 200 ml. of ether. It still retained a large amount of moisture so that it was dried in the air for several days and then ground to a fine powder. The yield of tan-yellow 6-methoxyquinoline-8-diazonium 1,5-naphthalenedisulfonate was 203.6 g. (0.309 mole), a quantitative yield. The salt could not be purified by recrystallization because it decomposed in hot solvents. The crude material was still solid at 300°.

The finely powdered diazonium salt was mixed with 1400 ml. of nitrobenzene. Then 48 g. (0.585 mole) of anhydrous sodium acetate and 17 g. (0.167 mole) of acetic anhydride were added and the mixture stirred at room temperature for eleven days. The mixture was filtered through a Buchner funnel and the brown solid residue washed once with 50 ml. of nitrobenzene and then discarded. The nitrobenzene was removed by distillation under high vacuum. A black, sticky tar which remained in the flask was removed by extracting with four successive 150-ml. portions of chloroform and then with 200-ml. portions of boiling *n*-butyl ether. After each extraction, the extract was cooled, the red solid that precipitated removed by filtration, and the filtrate again used with fresh solvent in a subsequent extraction. This process was continued until no more precipitate formed on cooling the extract. The red solid was dissolved in 200 ml. of glacial acetic acid, the solution treated with Darco at its boiling point, filtered, and diluted with water until no more precipitation occurred. This was repeated once to give a tan-brown product, m. p. 180–200°. When dry it weighed 27.2 g. (15.7%).

In similar preparations under the same conditions as above except that the stabilized diazonium salt was stirred with the nitrobenzene for periods of fifty and one hundred hours, yields of crude product of 12.2 and 24.7% respectively, were obtained. The long period of stirring seems to improve the yield.

When a small sample of the crude product was recrystallized from glacial acetic acid without dilution, a pure isomer was isolated. This pure yellow compound melted at 205–6° and was shown to be **6-methoxy-8-*p*-nitrophenylquinoline**.

*Anal.* Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.58; H, 4.32. Found: C, 68.40; H, 4.33.

The method of Doebner–von Miller[7] for the oxidation of pyridine rings was used to establish the structure of the 6-methoxy-8-*p*-nitrophenylquinoline. A suspension of 0.135 g. of the compound (m. p. 205–206°) in 20 ml. of water was heated to boiling. Then sufficient 6 *N* sulfuric acid was added to give complete solution. The solution was then cooled to 40–50° and maintained at this temperature for a period of one-half hour while a solution of 0.6 g. of potassium permanganate in 20 ml. of water was added drop by drop. After complete addition the mixture was allowed to digest at 40° for an additional one-half hour before cooling and filtering. The filtrate on neutralization with concentrated ammonium hydroxide became only faintly cloudy, indicating complete oxidation of the pyridine ring. The residue was heated to boiling in 10 ml. of 10% sodium carbonate and the mixture filtered. This was repeated. The combined filtrates on acidification gave a flocculent, yellow precipitate. This solid, filtered from the solution and dried, weighed 0.025 g. It was recrystallized by heating in 10 ml. of water, treating with Darco, filtering, and cooling to give white plates, m. p. 228–230°. The melting point of an authentic sample of *p*-nitrobenzoic acid was 230–231° (uncor.) and a mixed melting point was 225–227°.

### Alternate Preparations of 6-Methoxy-8-*p*-nitrophenylquinoline

**(a) Nitrosoacetamide. (1) 6-Methoxy-8-nitrosoacetamidoquinoline.**—A mixture of 71.5 g. (0.316 mole) of 8-acetamido-6-methoxyquinoline (m. p. 124–125°), 28.7 g. (0.35 mole) of sodium acetate, and 3 g. of phosphorus pentoxide in 190 ml. of acetic anhydride and 375 ml. of acetic acid was stirred while 25 g. (0.38 mole) of nitrosyl chloride in 75 ml. of cold acetic anhydride was added over a period of one hour. The mixture was then added to 800 ml. of water and ice, about 200 g. of sodium carbonate was added and the precipitate that formed was filtered and dried between clay plates. The weight of green nitroso compound was 36.1 g. (51%).

The nitroso derivative was mixed with 600 ml. of nitrobenzene and stirred for forty-five hours in a water-bath at 35°. The product was worked up in the same manner as in the stabilized diazonium salt preparation described above. The yield of red, crude product was 14.1 g. (31% based on the nitrosoacetamide, 16% based on the acetamide), m. p. 183–200°.

**(b) Gomberg–Bachmann Synthesis.**[8]—A mixture of 60 ml. of concentrated hydrochloric acid, 175 ml. of water and 43.3 g. (0.25 mole) of 8-amino-6-methoxyquinoline was diazotized with 30% sodium nitrite. The solution was first filtered from an appreciable amount of solid and then mixed with 400 ml. of nitrobenzene cooled to 5°. With stirring, 7.6 g. of sodium hydroxide in 58 ml. of water was added dropwise over an hour's time. The mixture was then allowed to come to room temperature while stirring an additional two hours. After standing overnight, the solid was removed by filtration and extracted with *n*-butyl ether in a Soxhlet extractor. From the extract 3.6 g. of crude product was obtained, a yield of 5.2%.

**(c) Ullmann Reaction.**—An Ullmann reaction was attempted with 8-iodo-6-methoxyquinoline (prepared in 31% yield by the method of Dains and Eberly,[9] m. p. 105–108°) and *p*-chloronitrobenzene. From the reaction conducted after the method of Adams and Stoughton[10] only 0.9 g. of product soluble in ethanol could be isolated. Recrystallized from ethanol, it melted at 276–278°. It

(7) Doebner and von Miller, *Ber.*, **19**, 1195 (1886).

(8) Bachmann and Hofmann, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 224.

(9) Dains and Eberly, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1944, p. 355.

(10) Adams and Stoughton, THIS JOURNAL, **54**, 4426 (1932).

was soluble in acid and contained no halogen (Beilstein test). It evidently was 6,6′-dimethoxy-8,8′-biquinolyl.

*Anal.* Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10. Found: C, 76.05; H, 5.10.

**8-*p*-Aminophenyl-6-methoxyquinoline.**—To 27.2 g. (0.097 mole) of crude tan-colored 6-methoxy-8-nitrophenylquinolines was added 145 ml. of 6 *N* hydrochloric acid and 88 g. (0.389 mole) of stannous chloride dihydrate. This mixture was heated under reflux on a steam-bath for forty minutes and the clear red solution which formed was allowed to cool to room temperature. A brown precipitate, probably the stannic chloride salt of the higher melting amine, formed in the solution. This salt was filtered and decomposed with an excess of 40% sodium hydroxide to give a tan, alkali-insoluble solid. After this solid was filtered and washed free of sodium hydroxide, it was recrystallized from 400 ml. of 95% ethanol, the boiling solution being treated with Darco. On cooling the amine crystallized in light yellow prisms, m. p. 181–182°. The filtrates were evaporated and the solids obtained fractionally recrystallized. The total weight of amine so obtained was 6.6 g. (27.2%). Recrystallized for analysis, the aminophenylmethoxyquinoline melted at 180–182°.

*Anal.* Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.20. Found: C, 76.66; H, 5.84; N, 11.41.

It was found that when the purified sample of 6-methoxy-8-*p*-nitrophenylquinoline melting at 206° was reduced it gave a product identical with this amine, establishing its structure as 8-*p*-aminophenyl-6-methoxyquinoline.

The filtrate from removal of the tin salt was made alkaline with excess 40% sodium hydroxide to give a red-brown solid. This solid was washed with water and then dissolved in 100 ml. of 95% ethanol. Cooling in an ice-bath for an hour gave only a trace of brown crystals. An equal volume of water was added to the filtrate and the milky solution so produced was again cooled. A dark brown precipitate separated. This precipitate was again dissolved in ethanol, and the solution was diluted with water to cloudiness. The solution was heated, treated with Darco, filtered and cooled to give a white solid. This procedure was repeated until the solid fused at 130–132°, although the melt was not clear until 140°. The weight of dry material so obtained was 5.5 g. (23%).

A portion of this fraction was recrystallized repeatedly from 75% ethanol. After five recrystallizations, the product melted constantly at 148–149° and had the composition of an aminophenylmethoxyquinoline.

*Anal.* Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.20. Found: C, 76.55; H, 5.70; N, 11.36.

**8-(*p*-3-Diethylaminopropylaminophenyl)-6-methoxyquinoline.**—A mixture of 11.24 g. (0.045 mole) of 8-*p*-aminophenyl-6-methoxyquinoline and 7.0 g. (0.047 mole) of 3-diethylaminopropyl chloride was heated in an oil-bath at 130° for seven hours. The reaction mixture was cooled, the hard, glassy hydrochloride was treated with a solution of 6 g. of sodium hydroxide in 50 ml. of water and the mixture was extracted with ether. Quite a large amount of the reaction mixture was insoluble in ether and it was discarded. The ether solution was dried, the ether removed and the product distilled with a mercury vapor pump. The fraction boiling at 200–208°, a viscous, yellow liquid, was collected. It weighed 9.0 g. (0.0248 mole) representing a yield of 55%.

*Anal.*[11] Calcd. for $C_{23}H_{29}N_3O$: C, 76.00; H, 8.04. Found: C, 76.29; H, 8.20.

Attempts to isolate a crystalline hydrobromide were unsuccessful, since even very slight exposure to moist air caused it to turn into a red, semi-solid mass. The picrate was prepared in ethyl alcohol. It initially formed as a liquid but recrystallization gave a red solid, m. p. 157–158°.

*Anal.* Calcd. for $C_{35}H_{39}N_9O_{15}$: C, 51.16; H, 4.29. Found: C, 50.92; H, 4.34.

## Summary

8-(3-Diethylaminopropylaminomethyl)-6-methoxyquinoline and 8-(*p*-3-diethylaminopropylaminophenyl)-6-methoxyquinoline have been synthesized and submitted for testing as potential antimalarial drugs.

(11) Analysis by Mr. H. L. Clark.

NOTRE DAME, INDIANA RECEIVED AUGUST 19, 1946

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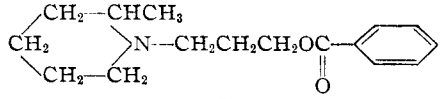
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

# Piperidine Derivatives. XVII. Local Anesthetics Derived from Substituted Piperidinoalcohols

BY S. M. McELVAIN AND THOMAS P. CARNEY[1]

The favorable pharmacological properties of the hydrochloride of γ-(2-methylpiperidino)-propyl benzoate[2] (I) (Metycaine) have led to its rather extensive clinical adoption for both topical and infiltration local anesthesia. More recently it has been used and recommended for continuous caudal analgesia.[3] This compound has the additional clinical advantage of not showing the antagonism to the sulfa drugs that is characteristic of such *p*-aminobenzoate esters as procaine.[4] The general usefulness of I as a local anesthetic suggested a systematic study of the effects of variations of its structure on the pharmacological properties of the resulting compounds, in the hope that even more satisfactory local anesthetics might be discovered.



I

For the purposes of this work, the structure of I was considered as composed of three structural

(1) Eli Lilly and Company Post-doctorate Fellow, 1943–1944; present address: The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana.

(2) McElvain, THIS JOURNAL, **49**, 2835 (1927).

(3) Edwards and Hingson, *Am. J. Surg.*, **57**, 459 (1942); Hingson and Southworth, *ibid.*, **58**, 93 (1943); Hingson and Edwards, *Anesthesia and Analgesia*, **21**, 301 (1942); *J. Am. Med. Assoc.*, **121**, 225 (1943); *ibid.*, **123**, 538 (1943); Southworth, Edwards and Hingson, *Ann. Surg.*, **117**, 321 (1943); Southworth and Hingson, *ibid.*, **118**, 945 (1943).

(4) *Cf. inter alia*, Keltch, Baker, Krahl and Clowes, *Proc. Soc. Exp. Biol. Med.*, **47**, 533 (1941); Pfeiffer and Grant, *Anesthesiology*, **5**, 605 (1945); Peterson and Finland, *Am. J. Med. Sci.*, **207**, 166 (1944).