pared by Dr. Mosher[8] from the product of the reaction of trimethylenediamine and 8-(3-chloropropylamino)-6-methoxyquinoline.

The small forerun obtained in the molecular distillation of III, as described above, was redistilled; 1.2 g. of distillate was converted into 1.1 g. of solid hydrochloride salt, m. p. 224–225°. Elementary analyses suggested that this solid was a mixture of approximately 30% of III trihydrochloride and 70% of 6-methoxy-8-aminoquinoline monohydrochloride. Recrystallization of the mixture from hot alcohol gave the latter compound in nearly pure state, m. p. 226–227°, not depressed by mixture with an authentic sample.

Reaction of 8-(3-Aminopropylamino)-6-methoxyquinoline (I) and Acrylonitrile in 95% Ethanol.—Two grams (0.0066 mole) of 8-(3-aminopropylamino)-6-methoxyquinoline dihydrochloride and 1 g. (0.019 mole) of potassium hydroxide were dissolved in 25 ml. of 95% alcohol, 0.33 g. (0.0062 mole) of acrylonitrile was added, and the mixture was boiled under reflux for two hours. The odor of ammonia was detected. The mixture was cooled, 150 ml. of water was added, and the product extracted with chloroform. Addition of the chloroform extracts to a solution of picric acid in absolute alcohol resulted in the formation of 4.0 g. of a yellow picrate, m. p. 196–197° (dec.) with preliminary darkening at 185°. Several recrystallizations from alcohol raised the melting point only to 197–198° (dec.) with preliminary darkening at 185°.

Anal. Calcd. for $C_{16}H_{22}N_4O_2 \cdot 2C_6H_3N_3O_7$: C, 44.22; H, 3.71; N, 18.42. Found[13]: C, 44.42, 44.14; H, 3.86, 3.83; N, 18.30, 18.49. Picric acid determination: calcd., 60.3; found, 60.9.

A portion of the dipicrate was reconverted into the base and then to the hydrochloride, but the latter proved to be too hygroscopic to isolate in pure condition.

An attempt to add the base I to acrylonitrile in absolute alcohol, using potassium hydroxide as catalyst, yielded only a small amount of the product IV, and most of the starting amine was recovered unchanged.

Summary

8-[3-(3'-Aminopropylamino)-propylamino]-6-methoxyquinoline was prepared by a new procedure for tests of its antimalarial activity. The compound appears to be the same as Robinson's R-120.

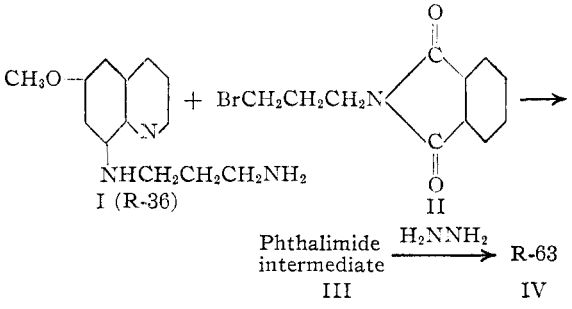
PHILADELPHIA, PENNSYLVANIA RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Heterocyclic Basic Compounds. VIII. 8-[3-(3'-Aminopropylamino)-propylamino]-6-methoxyquinoline

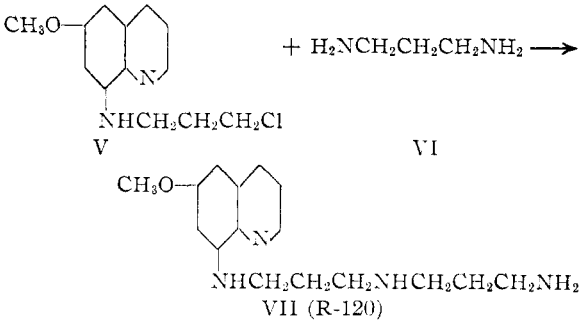
BY HARRY S. MOSHER

One of the most active antimalarial substances reported by Robinson and co-workers in their extensive studies is R-63.[1] This material, whose structure has not been definitely established, was prepared by the following indicated series of reactions



which would be expected to produce the compound whose structure is indicated by formula VII. This compound (VII), which has since been prepared by Crum and Robinson[2] according to the procedure indicated below, was assigned the number R-120. It was completely different in chemical properties and antimalarial activity from R-63.

We have repeated the synthesis of R-120 (VII) essentially as reported and obtained an 80% yield of distilled base and a 45% yield of re-



crystallized, non-hygroscopic trihydrochloride monohydrate melting with bubbling at 232° (reported by Crum and Robinson,[2] 225° dec.). Kissinger, Von and Carmack[3] have prepared 8-[3-(3'-aminopropylamino)-propylamino]-6-methoxyquinoline hydrochloride (R-120) by a completely independent method and the melting point of the above product was undepressed when mixed with the material kindly furnished by Dr. Carmack.

We have also repeated the Robinson synthesis of R-63 (IV). From the reaction of R-36 (I) with N-3-bromopropylphthalimide (II), after a tedious fractional crystallization, there were obtained unreacted starting materials and two different crystalline products; one of these, m. p. 215–216° (obtained in 19% yield), analyzed for, and corresponded to, the expected phthalimide intermediate (III).[1b] This phthalimide inter-

(1) (a) Robinson and Tomlinson, *J. Chem. Soc.*, 1524 (1943); (b) Quin and Robinson, *ibid.*, 555 (1943); (c) Glen and Robinson, *ibid*, 557 (1934).

(2) Crum and Robinson, *ibid.*, 561 (1943).

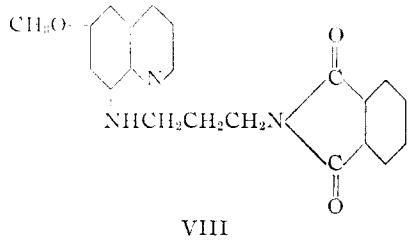
(3) Kissinger, Von and Carmack, THIS JOURNAL, **68**, 1563 (1946).

mediate was converted into the corresponding amino compound by heating with hydrazine in ethanol solution, followed by treatment with sodium hydroxide and ether extraction. The product was converted to the hydrochloride and shown to be identical with the hydrochloride of R-120 as prepared by us and also the compound furnished by Dr. Carmack.[3] In addition, the picrates of the two preparations were compared and shown to be identical.

A consideration of this evidence, along with that already presented by Robinson and co-workers and by Carmack, leaves no doubt that the material melting at 232° dec. corresponding to R-120, is 8-[3-(3′-aminopropylamino)-propylamino]-6-methoxyquinoline (VII), the product expected from (1).

The product designated by Robinson as R-63 certainly contains a fair amount of substance VII. The minimum amount indicated from our experiments is about 20% and probably twice this much is present in the crude reaction mixture. Since Robinson and co-workers have reported that R-120 (VII) is substantially inactive in the same antimalarial tests used with R-63, considerable question still exists as to the component of the R-63 mixture which was responsible for its great potency.

In the condensation of I with II a second compound of a more insoluble nature has been separated in small amounts (4%) and identified as **8-(3-phthalimidopropylamino)-6-methoxyquinoline (VIII)**. Just how this arose is not known, but it is unlikely that it came from 8-amino-6-



VIII

methoxyquinoline as an impurity in the starting material, since the starting material used gave a negative test for an aromatic amine when treated with nitrous acid and β-naphthol. In addition to the above compound, it has been shown that the mother liquors from the purification of the phthalimide intermediate (III) and from the purification of the crude R-63 (IV) contain considerable R-36 (I). Since hydrolysis of VIII will give R-36 (I), it would seem that the crude R-63 preparation of Robinson was predominantly a mixture of R-120 (VII) and R-36 (I). No indication of another impurity in any appreciable amount has been found in our investigations of the above reaction mixture.

Incidental to these studies, the "hydrazine hydrolysis" for substituted phthalimide compounds discovered by Manske, Perkin and Robinson[4a] and more generally developed by Ing and Manske[4b] has been studied and a useful modification has been developed. The preliminary evidence indicates that this reaction is not a hydrolysis in the usual sense and that the accepted procedure of boiling with hydrochloric acid is unnecessary and accounts for much of the difficulty encountered in purifying R-36 which has been prepared according to the conventional method. These studies on the "hydrazine hydrolysis" of substituted phthalimides will be reported in a subsequent paper.

Acknowledgment.—The author is grateful to Dean Frank C. Whitmore for his interest and encouragement, to Dr. George Moersch for his suggestions and advice and to Parke, Davis and Company for their support.

Experimental

Reaction of Trimethylenediamine and 8-(3-Chloropropylamino)-6-methoxyquinoline.—A mixture of 15 g. of 8-(3-chloropropylamino)-6-methoxyquinoline hydrochloride[2,5] and 29 ml. of trimethylenediamine[6] was heated at 140° for seven hours in a sealed tube. The crystals of trimethylenediamine monohydrochloride were filtered from the reaction, wt. 6.5 g., and the filtrate was stirred with 20 g. of powdered sodium hydroxide, filtered through a sintered-glass funnel, and distilled to give 19 g. of recovered trimethylenediamine, b. p. 74° (1 mm.), and 12.1 g. (80%) of light yellow liquid, b. p. 190° (0.5 mm.). The latter was dissolved in dry ether and cooled to −60°; a white crystalline product was obtained which would not redissolve readily in ether, 10.5 g., m. p. 80–85°. A small sample was crystallized from ether and a little alcohol, m. p. 95–96°. This base was not very stable in air and was hygroscopic.

The crude, crystalline base melting at 80–85°, 9.5 g., was dissolved in an absolute ether-alcohol solution and 25 ml. of 3.74 *N* alcoholic hydrogen chloride added. The sticky salt which separated, solidified on standing, was filtered and dried, wt. 12.2 g., m. p. 145–155° dec. This was treated with Norit in 185 ml. of 93% ethanol, filtered and cooled slowly to give 9.5 g. of crystals m. p. 224–226° dec. A further crystallization raised the melting point to 227–229°.

Anal. Calcd. for $C_{16}H_{24}ON_4 \cdot 3HCl \cdot H_2O$: C, 46.3; H, 7.0; N, 13.4. Found: C, 46.5; H, 7.0; N, 12.9.

After two further recrystallizations the product melts at 232° dec.; mixed melting point with the product furnished by Dr. Carmack[3] 232° dec.

A picrate derivative was prepared in 90% ethanol solution and recrystallized from a large volume of absolute ethanol, m. p. 164–165°.

Anal. Calcd. for $C_{16}H_{24}ON_4 \cdot 3C_6H_3O_7N_3$: C, 41.0; H, 3.4. Found: C, 41.0; H, 3.7.

The following preparation of R-36 is repeated here in spite of its previous description in the literature. The preparation of R-36 according to the methods of Robinson has given very erratic results in our laboratories and the final product has often decomposed on attempted distillation. In contrast, the following procedure gives a product which distills undecomposed with no appreciable forecut or residue.

8-(3-Phthalimidopropylamino)-6-methoxyquinoline.—To a refluxing mixture of 174 g. of 8-amino-6-methoxyquinoline, 500 ml. of *n*-propanol and 200 ml. of methyl "Cellosolve" (boiling point of the mixture was 108°), was added

(4) (a) Manske, Perkin and Robinson, *J. Chem. Soc.*, 1 (1927); (b) Ing and Manske, *ibid.*, 2348 (1926).

(5) Yanko, Mosher and Whitmore, THIS JOURNAL, **67**, 664 (1945).

(6) Kindly furnished by Sharples Chemical Company.

270 g. of N-3-bromopropylphthalimide over a four-hour period. After addition was complete, the mixture was refluxed six hours and cooled overnight. The crystals were filtered, washed twice with ethanol and once with ether, yielding 196 g. of yellow orange product m. p. 200–205°. An additional 125 g. of crystals, m. p. 200–205° was obtained by adding 100 ml. of 33% hydrobromic acid to the filtrate, boiling the precipitate with 300 ml. of absolute ethanol and washing with alcohol and ether. The total yield of very crude dry hydrobromide was 312 g. (70%). The 312 g. of crude hydrobromide was suspended in 2 liters of 95% ethanol and made basic with ammonium hydroxide. The solution deposited crystals of the base which on treatment with Norit and recrystallization from methanol gave 153 g. (42.5%) of the pure 8-(3-phthalimidopropylamino)-6-methoxyquinoline base, m. p. 101–102°.

The mother liquors from the filtration and washing of the 312 g. of crude hydrobromide deposited 105 g. of brick red solid on standing for approximately one month. Upon decolorization and crystallization from methanol several times there was obtained 32 g. (13% recovery) of N-3-bromopropylphthalimide, m. p. 73–74°. The filtrate on concentration gave 20 g. of a tan crystalline compound which was quite insoluble although it had been the last substance to crystallize from the mother liquors. Conversion to the base by boiling in alcoholic ammonium hydroxide gave 13 g. (2.7% yield based on 8-amino-6-methoxyquinoline), m. p. 166–168°, which corresponded to the 8-[*bis*-(3-phthalimidopropyl)-amino]-6-methoxyquinoline described by Robinson and co-workers and showed an undepressed melting point when mixed with a sample obtained previously in a similar manner which had analyzed as follows:

Anal. Calcd. for $C_{32}H_{28}O_5N_4$: C, 70.0; H, 5.1; N, 10.2. Found: C, 69.7; H, 5.2; N, 10.3.

The combined mother liquors from all of the crystallizations were made basic, diluted with water, extracted with ether and distilled to give 39 g. (22%) of recovered 8-amino-6-methoxyquinoline.

A similar run in which methyl "Cellosolve" alone was used as the solvent (refluxed four hours at 125°) resulted in a 47% yield of the main product and 3.6% yield of the *bis* compound.

8-(3-Aminopropylamino)-6-methoxyquinoline, R-36, I.—In a three-liter flask was refluxed for two and one-half hours a mixture of 186 g. of 8-(3-phthalimidopropylamino)-6-methoxyquinoline, 1000 ml. of 95% ethanol and 35.0 g. of 85% hydrazine hydrate. The granular white precipitate[7] was filtered and the filtrate concentrated under vacuum to about 300 ml. The concentrate and the white precipitate were both suspended in one liter of ether contained in a separatory funnel; this was shaken with 280 g. of a 30% potassium hydroxide solution. The ether was decanted from the semi-solid precipitate and the extraction repeated twice. The ether extracts were dried over potassium carbonate and distilled to give 109 g. (91.4%) of distillate, b. p. 183–190° (0.2–0.3 mm.). This distillate gives a negative test for an aromatic amine when treated with nitrous acid and added to β-naphthol solution.

8-[*bis*-(3-Aminopropyl)-amino]-6-methoxyquinoline.—8-[*bis*-(3-Phthalimidopropyl)-amino]-6-methoxyquinoline, 23 g., was boiled with 5.2 g. of 85% hydrazine hydrate in 50 ml. of absolute ethanol for two hours. Most of the solvent was removed under vacuum and the residue was suspended in 300 ml. of ether and shaken with 40 g. of 50% potassium hydroxide solution; five additional 200-ml. portions of ether were used for the extraction. The ether extracts, after drying and distilling, gave 10.0 g. of a viscous yellow liquid, b. p. 210–214° (1 mm.). This was converted to the salt by bubbling dry hydrogen chloride into its ethereal solution. The product was a light tan, non-hygroscopic, crystalline powder, 8.0 g., m. p. 165–170°. The melting point was raised to 168–170° on recrystallization from alcohol and ether.

Anal. Calcd. for $C_{16}H_{24}ON_4 \cdot 3HCl$: C, 48.3; H, 6.8; N, 14.1. Found: C, 48.1; H, 7.2; N, 13.7.

Reaction of 8-(3-Aminopropylamino)-6-methoxyquinoline (I) and N-3-Bromopropylphthalimide.—A mixture of 20 g. of distilled 8-(3-aminopropylamino)-6-methoxyquinoline (I) and 24 g. of N-3-bromopropylphthalimide (II), m. p. 73–74°, was stirred and heated with a little ethanol under an inert atmosphere. During the first one and one-half hours, the temperature was slowly and uniformly raised from 90 to 106°. The reaction mixture became quite thick and was diluted with 20 ml. of methyl "Cellosolve" and the temperature slowly raised to 125° where it was maintained for four hours. The reaction was diluted with a warm mixture of 300 ml. of ethanol and 20 ml. of 34% hydrobromic acid solution. After cooling, 30.0 g. of orange yellow crystals melting at 155–180° separated from the solution. This solid was submitted to a systematic eight-stage fractional crystallization from 80% ethanol to give 9.5 g. of brick-red crystals melting at 215–216° dec.

Anal. Calcd. for $C_{24}H_{26}O_3N_4 \cdot 2HBr$: C, 49.6; H, 4.8; N, 9.6. Found: C, 49.3; H, 5.2; N, 9.3.

Quin and Robinson[1b] found a melting point of 222–223° dec. for this compound prepared by a different method. This indicates that our material was contaminated with a difficultly separable impurity. This compound was converted to the free base by treatment with ammoniacal methanol and recrystallized from methanol, m. p. 173–174°.

A second compound more insoluble than the expected product was separated, 2.1 g., m. p. 215–216°, mixed melting point with the hydrobromide of the expected product, 206–210°. This was converted to the base with ammonium hydroxide and recrystallized from ethanol, m. p. 102–103°; a mixture with an authentic sample of 8-(3-phthalimidopropylamino)-6-methoxyquinoline showed no depression in its melting point.

Anal. Calcd. for $C_{21}H_{21}O_3N_3$: C, 69.8; H, 5.3; N, 11.6. Found: C, 69.7; H, 5.5; N, 11.9.

The mother liquors from all of the crystallizations were combined, made basic, and the precipitated sticky solid taken up in absolute alcohol and refluxed for three hours with 5 g. of 85% hydrazine hydrate. The solvent was removed under vacuum on the steam-bath and the residual sirup and white solid were suspended in ether and shaken with 15 ml. of a 40% potassium hydroxide solution. The ether extraction was repeated three times. Upon drying the ether and bubbling in dry hydrogen chloride gas, an orange-red, hygroscopic hydrochloride precipitated; wt., 9.2 g., m. p. 120–130°. It was readily crystallized from absolute ethanol but the melting point was essentially unchanged. A dilute alcoholic solution of the above hydrochloride deposited a crystalline picrate which melted without recrystallization at 202–203°. Further recrystallization did not change this melting point. Mixed with an authentic sample of the picrate of R-36 (I) the melting point was still 202–203°. From this it is apparent that there is considerable unreacted starting material in the final product. It was also possible to separate, in a similar manner, the picrate of R-36 (I) from the mother liquors of the original reaction mixture prior to its hydrazine treatment.

Hydrazine Hydrolysis of 8-[3-(3'-Phthalimidopropylamino)-propylamino]-6-methoxyquinoline.—The 8-[3-(3'-phthalimidopropylamino)-propylamino]-6-methoxyquinoline, m. p. 215–216°, 9.0 g., was refluxed for two hours on the steam-bath with 60 ml. of absolute ethanol and 3.0 g. of 85% hydrazine hydrate. The reaction mixture was concentrated under vacuum, the residue suspended in ether and shaken with 10 ml. of 40% potassium hydroxide in the cold. The extraction was repeated four times and the extracts dried with potassium carbonate, shaken with Norit, filtered, and dry hydrogen chloride bubbled into the solution. The bright yellow precipitated salt was filtered

(7) Most of the R-36 is contained in this white precipitate since one molar equivalent of hydrazine hydrate was employed. If, however, two molar equivalents of hydrazine are used, the precipitate is the hydrazine salt of phthalylhydrazide and all of the R-36 is present as the free amine in the filtrate.

and dried to give 4.2 g. (64%). A single crystallization brought the melting point up to 217–219°. This material contained a persistent impurity, presumably R-36, and only after seven crystallizations was the melting point raised to 232° dec., mixed melting point with the previous preparation (R-120) from trimethylene diamine and 8-(3-chloropropylamino)-6-methoxyquinoline was 232°. Similarly a mixed melting point with sample furnished by Dr. Carmack was 232° dec. A picrate prepared from the above material melted at 164–165° and its melting point was undepressed when mixed with the picrate from our R-120 preparation.

Summary

1. The synthesis of Crum and Robinson's R-120, 8-[3-(3′-aminopropylamino)-propylamino]-6-methoxyquinoline, has been repeated and the structure of the product confirmed.

2. It has been demonstrated that a purified preparation made approximately according to the method utilized by Baldwin and Robinson for the synthesis of R-63, has the same structure as R-120.

3. In addition it has been indicated that probably the major impurity in Baldwin and Robinson's R-63 preparation is the unreacted starting material, R-36.

4. An improved synthesis for the starting material, R-36, has been described.

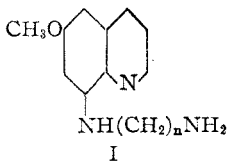
STATE COLLEGE, PA. RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

Aminoalkylamino Derivatives of 8-Aminoquinoline[1]

BY ROBERT C. ELDERFIELD, WALTER J. GENSLER, THOMAS H. BEMBRY, FREDERICK BRODY, LOUIS WIEDERHOLD III AND BERNICE NEWMAN

Derivatives of 6-methoxy-8-aminoquinoline of the type Formula I



I

have been described previously in the cases where n = 1–5.[2-7] The series does not appear to have been extended to longer side chains. As part of a program dealing with the systematic investigation of the 8-aminoquinolines as antimalarials, compounds of type I in the cases where n = 6, 8 and 10 have been prepared. Further, in order to take advantage of the reputed effectiveness of the 5,6-dimethoxy-8-aminoquinoline nucleus[8] 5,6-dimethoxy-8-(3′-aminopropylamino)-quinoline has been prepared.

The mode of synthesis used followed closely that used by previous workers and involved condensation of the appropriate 8-aminoquinoline with an ω-bromoalkylphthalimide followed by cleavage of the phthalimido group. In the course of the work, several new bromoalkylphthalimides were prepared.

(1) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

(2) Baldwin, *J. Chem. Soc.*, 2959 (1929).

(3) Bramachari and Bhattacharjee, *J. Indian Chem. Soc.*, **8**, 571 (1931).

(4) Fourneau, *et al.*, *Ann. Inst. Pasteur*, **50**, 731 (1933).

(5) Robinson and Tomlinson, *J. Chem. Soc.*, 1524 (1934).

(6) Beer, *J. Gen. Chem.* (U. S. S. R.), **9**, 2158 (1936).

(7) Magidson and Bobyshev, *ibid.*, **8**, 899 (1938).

(8) Elderfield, *et al.*, THIS JOURNAL, **68**, 1584 (1946).

Experimental[9,10]

8-Bromooctylphthalimide.—This was prepared according to the method of Muller and Kraus[11] by heating 4 moles of 1,8-dibromoöctane with 1 mole of potassium phthalimide at 140–145° for six hours. The substance formed white needles from alcohol and melted at 54–55°.

Anal. Calcd. for $C_{16}H_{20}BrO_2N$: C, 56.8; H, 5.9. Found: C, 57.0; H, 6.0.

10-Bromodecylphthalimide.—This was prepared exactly as was the octyl compound. It crystallized as needles from alcohol and melted at 62–63°.

Anal. Calcd. for $C_{18}H_{24}BrNO_2$: C, 59.0; H, 6.6. Found: C, 59.1; H, 6.7.

6-Methoxy-8-(ω-phthalimidoalkylamino)-quinolines.—These were prepared by a modification of the method of Ing and Manske[12] of which the preparation of 6-methoxy-8-(6′-phthalimidohexylamino)-quinoline is representative. A solution of 85 g. of 6-bromohexylphthalimide and 73 g. of 6-methoxy-8-aminoquinoline in 150 ml. of isopropyl alcohol was heated in an open round-bottom flask in an oil-bath at an initial temperature of 80°. The temperature was raised to 125° over thirty minutes and then held at 125–130° for an additional hour and a half. During the course of the heating, the isopropyl alcohol evaporated and the residual solid was broken up occasionally with a stout stirring rod. To the warm melt 500 ml. of benzene was added and the mixture was digested on the steam-bath for ten minutes. Insoluble 6-methoxy-8-aminoquinoline hydrobromide was filtered off, and the filtrate was concentrated. On cooling, 6-methoxy-8-(6′-phthalimidohexylamino)-quinoline crystallized. After recrystallization from acetone, it melted at 126–127°. The yield was 60 g. or 70% based on the 6-methoxy-8-aminoquinoline available for the reaction.

Anal. Calcd. for $C_{24}H_{25}N_3O_3$: C, 71.4; H, 6.3. Found: C, 71.5; H, 6.5.

6-Methoxy-8-(8′-phthalimidoöctylamino)-quinoline.—This was prepared as was the hexyl compound, except that the free base crystallized only after being rubbed up in acetone–alcohol. It melted at 88–89°. The yield was 72%.

(9) All melting points are corrected.

(10) Microanalyses by the Misses Lois May and Lathrope Baker.

(11) Muller and Kraus, *Monatsh.*, **61**, 219 (1932).

(12) Ing and Manske, *J. Chem. Soc.*, 2348 (1926).