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

# Heterocyclic Basic Compounds. XI.[1,1a] Derivatives of 8-(3-Aminopropylamino)-6-methoxyquinoline

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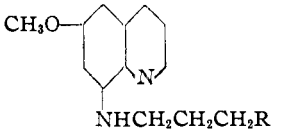
In the course of our work on the derivatives of 8-amino-6-methoxyquinoline[4] we had occasion to reinvestigate the compound 8-(3-aminopropylamino)-6-methoxy-quinoline (I) which had previously been made by Robinson and co-workers.[5] The hydrochloride of this compound was designated by them as R-36. Our sample of this compound[6] has been tested by Dr. R. J. Porter[7,8] and he reported that it was among the most active 8-aminoquinoline derivatives he had tested. Since this compound has a terminal primary amino group on the side chain, it offered an opportunity for the synthesis of many chemical variations not possible with the derivatives of 8-amino-6-methoxyquinoline having a terminal tertiary amine group such as found in Plasmochin. We therefore undertook the synthesis of a group of compounds which may be considered derivatives of 8-(3-aminopropylamino)-6-methoxyquinoline (I); some of these, in which the terminal amine was replaced with a heterocyclic basic radical, have already been reported,[4] others, in which the primary amine has been protected with various groups such as acetyl (II), carbamyl (III), methylol (IV), sodium methylene sulfonate (V), and glucosido (VI), are now described. This group of compounds contains derivatives of I which are known to be hydrolyzed with relative ease. It was hoped that some such variation would effect a reduction in toxicity even as the toxicity of arsphenamine is reduced by treatment with sodium formaldehyde sulfoxylate or that of aniline is lowered by acetylation. Although some of the compounds showed considerable activity, all of the variations resulted in products with less activity than the parent antimalarial (I).

With the exception of a glucose sodium bisulfite reaction product, all of the compounds were obtained in a demonstrable state of purity and were non-hygroscopic in nature. The acetyl derivative was especially easy to purify, giving large colorless plates. Much difficulty was experienced initially with the purification of the glucoside (VI). Attempted crystallization always produced a colored, impure product. It was found that the purity of the product was greatly dependent upon the purity of the starting material and the absence of air during the reaction. When freshly distilled I was boiled with *d*-glucose, ammonium chloride, and absolute ethanol with the rigid exclusion of air, a white glucoside precipitated from the reaction mixture; this could be purified by stirring with 95% ethanol in which it was relatively insoluble. It was likewise insoluble in water but rapidly dissolved with hydrolysis in dilute acid solutions. The high activity of this glucoside (Table I, Q = 40) warranted toxicity studies; Dr. M. H. Seevers'[9] studies on this compound indicated that the toxicity is that which would be expected by the hydrolysis of this substance to the parent amine (I) after ingestion.

In addition to the compounds listed above, the acetylbutyrolactone derivative of I was prepared according to a patent[10] but attempts to crystallize the hydrochloride resulted in hydrolysis to the parent amine (I). The sodium methylene sulfinate was also prepared by treatment of I with sodium formaldehyde sulfoxylate in an inert atmosphere.

TABLE I



| | R = | SN[8] | Activity[7] |
|---|---|---|---|
| I, | $-NH_2$ | 14,524 | 50 Q |
| II, | $-NHCOCH_3$ | 11,643 | 3 |
| III, | $-NHCONH_2$ | 13,166 | 1 |
| IV, | $-NHCH_2OH$ | .... | 15 |
| V, | $-NHCH_2SO_3Na$ | 13,393 | 20 |
| VI, | $-NHCH\text{—}(CHOH)_3CHCH_2OH$ (O-bridged) | 11,279 | 40 |
| VII, | 5-methoxy derivative of I | 11,645 | 35 |

(1) Previous paper in this series, THIS JOURNAL, **69**, 303 (1947).

(1a) It is with the deepest gratitude and appreciation that we herewith express our indebtedness to the late Dean Frank C. Whitmore whose inspiration and leadership are responsible for this work and in whose laboratories these studies were conducted.

(2) Parke, Davis and Company Post-Doctorate Fellow, 1944–1945.

(3) (a) Present address: Parke, Davis and Co., Detroit, Michigan; (b) Stanford University, Dept. of Chemistry, Stanford Univ., Calif.

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

(5) Robinson and Tomlinson, *J. Chem. Soc.*, 1624 (1934); Glen and Robinson, *ibid.*, 557 (1934); Baldwin, *ibid.*, 2959 (1929).

(6) Mosher, THIS JOURNAL, **68**, 1567 (1946).

(7) All of the activities reported in Table I are quinine equivalents determined therapeutically on *P. gallinaceum* in chicks. We are greatly indebted to Dr. R. J. Porter of the University of Michigan for these results.

(8) The details of the pharmacological tests on these compounds will be found in the monograph "A Survey of Antimalarial Drugs 1941–1945," F. Y. Wiselogle, Edward Brothers, Ann Arbor, Mich., 1947. The SN numbers refer to the designations in this monograph.

(9) Dr. M. H. Seevers reported in a private communication that "The toxicity values for SN 11,279 (VII) and Plasmochin were almost identical. Orally in dogs a dose equivalent to 77 mg./kg. of SN 11,279 base produced 15% methemoglobin after twenty-five hours and death after twenty-nine hours, while a dose equivalent to 85 mg. of Plasmochin base produced 17% methemoglobin after twenty-four hours and death in twenty-eight hours. There was no advantage of this compound over Plasmochin."

(10) Andersag, U. S. Patent 2,187,847 (Jan. 23, 1940).

The product, however, was a non-crystalline powder with indefinite decomposition point and underwent change on standing in air so that satisfactory analysis could not be obtained.

On the basis of the report by Schönhöfer[11] that the 5,6-dimethoxy-8-aminoquinoline derivatives were less toxic than the corresponding 6-methoxy-8-aminoquinoline derivatives, we undertook the synthesis of the 5,6-dimethoxy analog (VIII) of I.[12] This synthesis was achieved by following the same route employed by Lauer through the initial bromination of *p*-acetylanisidine[13] followed by nitration and a Skraup reaction.

The 5-bromo-6-methoxy-8-nitroquinoline was converted in 96% yield to the 5,6-dimethoxy derivative, by refluxing with sodium methoxide in methanol.[14]

The direct bromination of the available 6-methoxy-8-nitroquinoline would have been a much simpler synthesis but four attempted brominations using (1) acetic acid solvent, (2) carbon tetrachloride solvent and reduced iron catalyst, (3) acetic acid solvent and pyridine catalyst, and (4) propionic acid with pyridine catalyst gave only recovered 6-methoxy-8-nitroquinoline.

**Acknowledgment.**—We wish to thank Dr. M. H. Seevers and Dr. R. J. Porter for allowing us to quote some of their pharmacological results, Mr. R. N. Walter for many of the analyses reported herein, and Parke, Davis and Company whose generous support made these studies possible.

## Experimental

**8-(3-Acetylaminopropylamino)-6-methoxyquinoline** (R = —NHCOCH$_3$).—Distilled 8-(3-aminopropylamino)-6-methoxyquinoline[6] (I), 17 g., was refluxed one hour with 20 ml. of acetic acid and 9 g. of acetic anhydride. After this time, the acetic acid was distilled under vacuum on the steam-bath and the residue extracted with ether from a saturated potassium carbonate solution. The product crystallized from the ether on concentration and was dissolved in warm ethanol (150 ml.), treated with Norit, and cooled; 16.0 g., (79.5%), m. p. 107–108°.

*Anal.* Calcd. for $C_{15}H_{19}O_2N_3$: C, 65.93; H, 6.96; N, 15.68. Found: C, 65.88; H, 7.35; N, 15.30.

**8-(3-Carbamylaminopropylamino)-6-methoxyquinoline** (R = —NHCONH$_2$).—A mixture of 21 g. (0.09 mole) of distilled I and 20 g. (0.3 mole) of urea was heated at 128°; the evolved ammonia was absorbed in standard acid, 0.03 equivalent being evolved in the first twenty minutes, 0.08 equivalent in the first forty-five minutes, and 0.09 equivalent after one hour. The reaction cake which resulted on cooling was boiled with water, filtered, triturated with water, dried *in vacuo* over phosphorus pentoxide; 22.4 g. (94%), white powder m. p. 171–172°.

*Anal.* Calcd. for $C_{14}H_{18}O_2N_4$: C, 61.28; H, 6.62; N, 20.41. Found: C, 61.21; H, 6.54; N, 20.78.

**Reaction of 8-(3-Aminopropylamino)-6-methoxyquinoline, Sodium Bisulfite and *d*-Glucose.**—To a solution of 11.2 g. (0.109 mole) of sodium bisulfite and 22.75 g. (0.127 mole) of *d*-glucose in 175 ml. of water was added 29.75 g. (0.037 mole) of 8-(3-aminopropylamino)-6-methoxyquinoline (I). A clear orange-colored solution was formed which upon heating for one-half hour on the steam-bath deposited a red oil. The solution was decanted from the oil and the residue washed with water to remove any excess sodium bisulfite or glucose. All attempts to crystallize this oil were unsuccessful. The oil was heated under one mm. pressure on a water-bath to give a light tan powder, 34 g. with indefinite melting point around 80°.

*Anal.* Found: C, 56.1; H, 6.22; N, 12.50; S, 2.31; insol. residue, 1.54.

**Glucoside of 8-(Aminopropylamino)-6-methoxyquinoline** (R = —NH—CH(—O—)—(CHOH)$_3$—CH—CH$_2$OH).—A solution of 24 g. of *freshly distilled* I in 100 ml. of absolute ethanol was placed in a 250-ml. Erlenmeyer flask equipped with a reflux condenser and which had been thoroughly flushed with hydrogen gas. An equimolar quantity of *d*-glucose, 18.25 g., and 0.25 g. of ammonium chloride in 25 ml. of anhydrous ethanol was added and the solution refluxed for two hours. The precipitated white solid was filtered, twice stirred with 75-ml. portions of 95% ethanol, filtered and vacuum dried to give 23 g. (56%), m. p. 126°.

*Anal.* Calcd. for $C_{19}H_{27}O_8N_3$: C, 57.99; H, 6.92; N, 10.69. Found: C, 57.67; H, 6.92; N, 10.75.

**8-(3-Methylolaminopropylamino)-6-methoxyquinoline** (R = —NHCH$_2$OH).—To a solution of 2.3 g. of I in 25 ml. of 50% methanol was added 2.3 ml. of 37% formaldehyde solution; an oil precipitated immediately. The mixture was heated for fifteen minutes on the steam-bath and the liquid decanted from the insoluble oil which was then taken up in warm aqueous alcoholic hydrogen chloride solution. On cooling, brilliant red micro crystals separated, 2.45 g. (70%), m. p. 220–230° dec., depending upon the rate of heating. A white solid, apparently paraformaldehyde, collected in the cool portion of the melting point tube during the decomposition. Recrystallization from 98% alcohol did not alter the melting point.

*Anal.* Calcd. for $C_{14}H_{19}O_2N_3 \cdot 2HCl \cdot H_2O$: N, 11.92. Found: N, 11.89, 11.87.

**8-(3-Methylenesulfonate-aminopropylamino)-6-methoxyquinoline, Sodium Salt** (R = —NHCH$_2$SO$_3$Na).—Sodium formaldehyde sulfonate solution was prepared by bubbling sulfur dioxide into a solution of 5.3 g. of sodium carbonate in 15 ml. of water. This solution was aerated one minute on the steam-bath and 7.5 ml. of 40% formaldehyde solution added. After heating ten minutes, this was poured with stirring into a solution of 21.1 g. of distilled I in 50 ml. of 50% methanol. After heating on the steam-bath one hour, the solution was treated with Norit, filtered and the filtrate diluted with 600 ml. of warm methanol and cooled; 12.8 g. (50%), m. p. 237–238° after softening at approximately 180°.

*Anal.* Calcd. for $C_{14}H_{18}O_4N_3SNa$: C, 47.45; H, 5.23; N, 12.10; Na, 6.65. Found: C, 47.28; H, 5.58; N, 12.36; Na, 6.90.

**5,6-Dimethoxy-8-nitroquinoline.**—The reaction of 5-bromo-6-methoxy-8-nitroquinoline with sodium methylate can be carried out rapidly under pressure at temperatures above the atmospheric boiling point of methanol or more slowly at reflux temperatures, but in either case a large excess of methanol is essential for good yields.

Sodium, 8.1 g., (0.3 mole) was dissolved in 3 liters of methanol, 50 g. (0.176 mole) of 5-bromo-6-methoxy-8-nitroquinoline added, and the solution refluxed for four days on the steam-bath. One-half of the methanol was removed by distillation and the residue poured into an equal volume of water to give 91–96% yields of 5,6-dimethoxy-8-nitroquinoline, m. p. 116–119°. On recrystallization from ether, the melting point was 119–120° and showed no depression when mixed with a sample

(11) Schönhöfer, *Z. physiol. Chem.*, **274**, 1 (1942).

(12) Other recent publications on the derivatives of 8-amino-5,6-dimethoxyquinoline are: (a) Drake, *et al.*, THIS JOURNAL, **68**, 1536–1543 (1946); (b) Lauer, *et al.*, *ibid.*, 1546–1548; (c) Campbell, *et al.*, *ibid.*, 1559–1562; (d) Elderfield, *et al.*, *ibid.*, 1584–1587.

(13) Berkenheim and Antik, *J. Gen. Chem.* (*U. S. S. R.*), **11**, 537–540 (1941); *Chem. Zentr.*, **113, I**, 2002 (1942). See also Bures and Nedelkova, *C. A.*, **23**, 3675 (1929).

(14) Schönhöfer, German Patent 531,083, (Feb. 18, 1030).

of 5,6-dimethoxy-8-nitroquinoline prepared by the Skraup reaction on 4-amino-5-nitroveratrole.[15]

**8-Amino-5,6-dimethoxyquinoline.**—The above 5,6-dimethoxy-8-nitroquinoline was reduced to the amine with iron and hydrochloric acid (70–80%), m. p. 145–147°. Recrystallization from ether gave a product melting at 147.5°, reported previously, 148°,[11] 148–149°.[12d]

**8-(3-Aminopropylamino)-5,6-dimethoxyquinoline.**—This was made by the method of Robinson and Tomlinson[4] with some slight modifications.[5] The 8-amino-5,6-dimethoxyquinoline, 13.5 g., was coupled with 3-bromopropylphthalimide by refluxing (125°) for four hours in methyl Cellosolve. The 5,6-dimethoxy-8-(3-phthalimidopropylamino)-quinoline was obtained by diluting the reaction mixture with water, neutralizing with sodium hydroxide, saturating with sodium carbonate, extracting with ether, and converting to the hydrochloride. This was purified by crystallization from methanol; m. p. 170–171°, 6.1 g. (22%). The use of *n*-propanol solvent or the absence of solvent failed to materially alter the purified yield.

*Anal.* Calcd. for $C_{22}H_{21}O_4N_3$: N, 10.77. Found: N, 10.98.

The phthalimide group was removed by refluxing the purified base with one equivalent of hydrazine hydrate in absolute ethanol for two hours, removing the solvent under vacuum, and shaking the residue in ether with excess 50% sodium hydroxide. The product was obtained as the hydrochloride by treating the ether extracts with Norit, drying with potassium carbonate and bubbling in dry hydrogen chloride; m. p. 205–206°. This was further purified by recrystallizing from methanol, m. p 207°, 66% yield.

*Anal.* Calcd. for $C_{14}H_{19}O_2N_3.2HCl$: N, 12.57. Found: N, 12.46.

(15) We are greatly indebted to Dr. R. B. Taylor of this Laboratory for the purified sample of 5,6-dimethoxy-6-nitroquinoline made by this procedure.

## Summary

1. Five new derivatives of 8-(3-aminopropylamino)-6-methoxyquinoline have been prepared by reactions involving the terminal amino group.

2. The antimalarial activities of all of these derivatives were less than that of the parent compound and in general the toxicities were proportional to the per cent. of the parent compound in combination.

3. The corresponding 8-(3-aminopropylamino)-5,6-dimethoxyquinoline was also prepared.

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(16) Original manuscript received October 21, 1946.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES, GENERAL MILLS, INC.]

# Investigation of the Reserve Carbohydrates of Leguminous Seeds. I. Periodate Oxidation[1]

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The results of the Malaprade[1a] reaction have been successfully employed by various investigators in the elucidation of the linkages present in polymeric carbohydrates. Oxidation by periodate has been applied to naturally occurring polysaccharides, and their derivatives, such as starch,[2a,b] cellulose[3,4,5] and alginic acid.[6] Recently, Lew and Gortner discussed the periodate oxidation of the reserve carbohydrates (so called gums) from the carob bean[7] (*Ceratonia silique*, L.) and the honey locust bean[8] (*Gleditschia tricanthos*, L). The present report concerns an investigation of the periodate oxidation of the reserve polysaccharide from guar seed (*Cyamposis tetragonalaba* (*psoralioides*)). In connection with this work it became necessary to repeat certain parts of the work of Lew and Gortner. Our results lead to conclusions about the structural linkages of these polymeric carbohydrates which are at considerable variance from the conclusions of Lew and Gortner.

These reserve carbohydrates, found in the endosperms of leguminous seeds, are mannogalactans (or galactomannans) since they are composed principally of mannose and galactose units. The ratios of mannose to galactose in the mannogalactans from carob, honey locust and guar are 3.0–4.0:1,[7] 4.4:1[8] and 2:1,[8a] respectively. Lew and Gortner reported the polysaccharide from the carob bean consumed approximately one mole of periodate per hexose unit. Hydrolysis of the polymeric dialdehyde (cleavage product) yielded two aldehydo compounds which were considered by them to be glyceric aldehyde and tartron dialdehyde. These results were construed as indicative of the presence of 1,2 linkages between the anhydro sugar units.

Lew[8] observed that the polysaccharide from the honey locust bean required 2–2.5 moles of periodate per hexose unit. Hydrolysis of the cleavage product (dialdehydo) yielded glyoxal which was identified as the phenylosazone. These results were interpreted by him as indicative either

(1) Paper No. 80, Journal Series, General Mills, Inc., Research Department. Presented at the 111th meeting of the American Chemical Society, Atlantic City, N. J., April 14–18, 1947.

(1a) M. L. Malaprade, *Bull. soc. chim.*, (4) **43**, 683 (1928); *Compt. rend.*, **186**, 382 (1928).

(2) (a) E. L. Jackson and C. S. Hudson, THIS JOURNAL, **59**, 2049 (1937); (b) C. G. Caldwell and R. M. Hixon, *J. Biol. Chem.*, **123**, 595 (1938).

(3) E. L. Jackson and C. S. Hudson, THIS JOURNAL, **60**, 989 (1938).

(4) G. Jayme, M. Saetre and S. Maris, *Naturwissenschaften*, **29**, 768 (1941).

(5) D. H. Grangaard, E. K. Gladding and C. B. Purves, *Paper Trade J.*, **115**, 41 (1942).

(6) H. J. Lucas and W. T. Stewart, THIS JOURNAL, **62**, 1792 (1940).

(7) B. W. Lew and R. A. Gortner, *Arch. Biochem.*, **1**, 325 (1943).

(8) B. W. Lew, Pb. D. Thesis, University of Minnesota, October, 1941.

(8a) Unpublished results of Dr. P. E. Ramstad of this Laboratory.