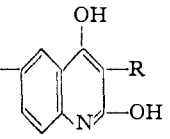
TABLE I

SUBSTITUTED 3-ALKYL-2,4-QUINOLINEDIOLS



R	X	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Cyclohexyl	H	300–305	$C_{15}H_{17}NO_2$	74.0	74.9	6.98	7.33
Cyclohexyl	6-Methoxy	233–234	$C_{16}H_{19}NO_3$	70.4	69.9	6.96	7.19
Cyclohexyl	6-Dimethylamino	[a]	$C_{17}H_{22}N_2O_2$	71.3	70.9	7.67	8.19
3-Cyclohexylpropyl	H	188–189	$C_{18}H_{23}NO_2$	75.9	75.9	8.08	8.24
3-Cyclohexylpropyl	6-Methoxy	197–198	$C_{19}H_{25}NO_3$	72.4	72.3	7.96	8.12
3-Cyclohexylpropyl	6-Dimethylamino	[b]	$C_{20}H_{28}N_2O_2$	73.2	72.9	8.54	8.76

[a] Starts to decompose at 234–235°. [b] Starts to decompose at 250–255°.

Diethyl 3-Cyclohexylpropylmalonate.—3-Cyclohexylpropanol was prepared in 70% yield by hydrogenation of cinnamyl alcohol at 200° and 5000 lb. initial pressure of hydrogen using Raney nickel catalyst. This was converted to the bromide and reacted with sodiomalonic ester.[5]

Diethyl 3-Diethylaminopropylmalonate.—This was prepared in 63% yield from sodiomalonic ester and 3-diethylaminopropyl chloride.[6]

Diethyl Allylmalonate.—This was prepared from allyl bromide and sodiomalonic ester.[7]

3-Cyclohexyl-2,4-quinolinediols.—A solution of 0.11 mole of the malonic ester and 0.10 mole of the aniline in 50 ml. of diphenyl ether was heated under reflux for one hour. The solution was cooled, the product was collected by filtration and washed with hexane. The yield was 95–98% of the theoretical. The 3-cyclohexyl-2,4-quinolinediols were white crystalline solids, slightly soluble in ethanol but very soluble in pyridine, and were recrystallized from pyridine–alcohol solutions. No reaction occurred with malonic ester and *o*-nitroaniline under these conditions.

3-(3-Cyclohexylpropyl)-2,4-quinolinediols.—A solution of 0.11 mole of diethyl 3-cyclohexylpropylmalonate and 0.10 mole of the aniline in 25 ml. of diphenyl ether was heated under reflux for thirty minutes. After cooling, the product was precipitated by adding two volumes of hexane, collected by filtration, and washed with hexane. The 3-(3-cyclohexylpropyl)-2,4-quinolinediols were white crystalline compounds, very soluble in ethanol and were crystallized from an ethanol–water solution. No reaction occurred with 3-cyclohexylpropylmalonic ester and *o*-nitroaniline under these conditions.

Attempted Preparation of 3-(3-Diethylaminopropyl)-2,4-quinolinediols.—No quinolinediol was obtained when diethyl 3-diethylaminopropylmalonate was heated with aniline in diphenyl ether, diamyl ether, mineral oil heated to 250°, or heating in absence of a solvent *in vacuo*. Only intractable tars were obtained from the reaction along with a small amount of 3-diethylaminopropylmalonic acid dianilide, m. p. 163–164°.

Anal. Calcd. for $C_{22}H_{29}N_3O_2$:. N, 11.43. Found: N, 11.73.

Attempted Preparation of 3-Allyl-2,4-quinolinediol.—No crystalline material could be obtained from the reaction of allylmalonic ester with aniline in refluxing diphenyl ether, refluxing diamyl ether, or in mineral oil heated at 250°, 200°, or 180°, nor by heating in absence of a solvent *in vacuo*.

(5) R. Adams and G. Hiers, THIS JOURNAL, **48**, 2385 (1926).

(6) O. Magidson and I. Strukov, *Arch. Pharm. Ber. dtsch. pharmaz. Ges.*, **271**, 569 (1933); *Chem. Zentr.*, **105**, I, 2286 (1934).

(7) M. Conrad and C. Bischoff, *Ann.*, **204**, 168 (1880).

Summary

1. The syntheses of 3-cyclohexyl- and 3-(3-cyclohexylpropyl)-2,4-quinolinediols and their 6-methoxy and 6-dimethylamino derivatives have been described.

2. The diethyl ester and the dianilide of 3-cyclohexylpropylmalonic acid are also described.

EVANSTON, ILLINOIS RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

Antimalarials. The Synthesis of 2,4,7-Trichloroquinoline[1]

BY ROBERT E. LUTZ, GILBERT ASHBURN, JAMES A. FREEK, ROBERT H. JORDAN,[2] NORMAN H. LEAKE, TELLIS A. MARTIN, RUSSELL J. ROWLETT, JR.,[3] AND JAMES W. WILSON, III

2,4,7-Trichloroquinoline (VII) was required and made in quantity as an intermediate in the synthesis of several types of dialkylaminoalkylaminoquinolines which were desired for testing against malaria. This compound was expected to be (and is) a versatile one because of the reactive 2- and 4-chlorine-atoms, and it was hoped that the difference in the reactivities of these two (chlorine atoms) would be sufficient to permit selective displacement.[4]

In the synthesis of this compound the use of *m*-chloroaniline and malonic ester in a quinoline ring closure according to the procedure of Baumgarten and Kärgel,[5] who used aniline itself, seemed certain to lead to mixtures of the isomeric 5- and 7-

(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 the University of Virginia.

(2) At present, Ensign, U. S. Navy.

(3) Present location, Jackson Laboratory, E. I. du Pont de Nemours and Co., Wilmington, Del.

(4) *Cf.* the 2,4-dichloroquinolines of Buchmann and Hamilton, THIS JOURNAL, **64**, 1357 (1942).

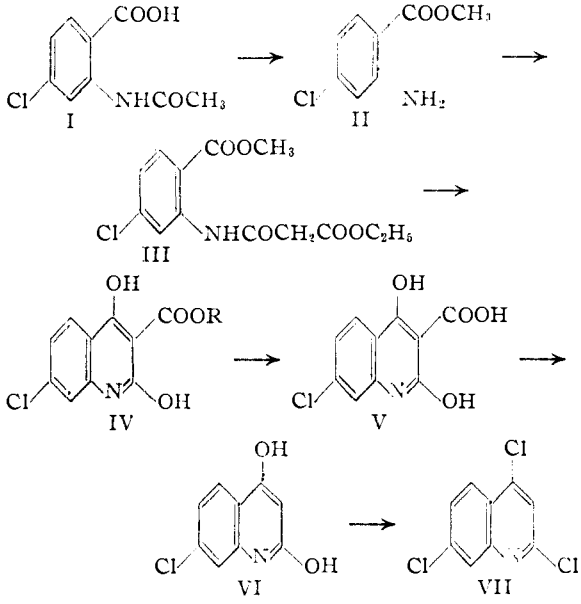
(5) Baumgarten and Kärgel, *Ber.*, **60B**, 832 (1927).

chloroquinolines, as happens in the Skraup synthesis.[6] In fact, the application of this method to the preparation of the 3-acetylquinolines has been reported recently and isomers actually appear to be involved.[7]

The logical starting material for a straightforward and unequivocal synthesis therefore appeared to be 4-chloroanthranilic acid[8] although it should be noted that with the present ready availability of 4,7-dichloroquinoline a simple approach might be possible through the N-methylcarbostyril.[9]

Using the acetyl derivative of 4-chloroanthranilic acid (I), two methods of quinoline ring closure, which are described in the literature for analogs without chlorine, were tried. First, the sodium salt was heated with dry alkali[10] but without success. Second, and successfully to a degree, the ester (of I) was treated with sodium in toluene, paralleling the method of Ashley, Perkin and Robinson[11]; this gave 7-chloro-4-hydroxycarbostyril (VI), although in lower yield than the 28–31%[12,4] reported for this method when applied to acetanthranilic ester itself.

A much more successful method of quinoline ring closure was then developed starting from 4-chloroacetanthranilic ester (II) and proceeding through the malonomonoanthranilate (III) (not isolated) to the 3-carbomethoxy-7-chloro-4-hydroxycarbostyril (IV) as outlined in the diagram.



This synthesis parallels the similar synthesis of 4-hydroxycarbostyril from anthranilic ester by Koller.[13] The resulting quinoline carboxylic ester (IV) was then hydrolyzed and decarboxylated by means of either acid or base to 7-chloro-4-hydroxycarbostyril (VI). The over-all yield in this synthesis starting from the acetanthranilic ester (II), in spite of the extra steps involved, was on the order of 70%, which is far better than the yields obtained in the direct cyclization of acetanthranilic ester by the application of the method of Ashley, Perkin and Robinson.[11] The greater ease of the ring closure in this method, and probably also the better yield, is explainable in terms of the highly reactive malonic type methylene group which is involved.

The hydroxycarbostyril (VI) was converted in excellent yield into the 2,4,7-trichloroquinoline by means of phosphorus oxychloride. The over-all yield of this compound from acetanthranilic acid was 60–65%.

Experimental[14]

4-Chloroanthranilic acid has been made in three ways, (a) by reduction of 4-chloro-2-nitrotoluene, acylation and oxidation,[8] (b) by oxidation of 4-chloro-2-nitrotoluene[15a] followed by reduction,[15b] and (c) by partial ammonolysis of 2,4-dichlorobenzoic acid.[16] Of the two commercially available starting materials we chose 4-chloro-2-nitrotoluene, for use in either of the first two of these preparations, (a) or (b). The direct permanganate oxidation to 4-chloro-2-nitrobenzoic acid (b), gave inferior yields under the usual conditions, and we therefore turned to the procedure used by Magidson and Travin (a).[8b]

2-Amino-4-chlorotoluene has been made by reduction of the chloronitrotoluene using iron[8b]; we used the more convenient stannous chloride. Three hundred and fifteen grams (1.84 moles) of 4-chloro-2-nitrotoluene was added to a solution of 1290 g. of stannous chloride dihydrate in 1720 ml. of concentrated hydrochloric acid under vigorous stirring, with initial warming to promote the reaction, followed by cooling in ice as needed to check the rapid and excessive temperature rise, and finally application of external heat to maintain an approximately constant mixture temperature of 95–100° for three hours. The resulting complex salt which precipitated was filtered, hydrolyzed by means of a mixture of 850 ml. of 35% sodium hydroxide and 300 g. of ice, and extracted with 700 ml. of ether. The ether extract was washed with 10% sodium hydroxide and saturated sodium chloride solution, and cooled. Addition of concentrated hydrochloric acid until acid to congo red (about 140 ml.) gave the colorless crystalline **hydrochloride**, which was filtered and used in the next step without drying. The yields in this step were not usually determined; white prisms, m. p. 265–267°.[17]

2-Acetylamino-4-chlorotoluene[8b] was made directly from the still wet filter cake of 2-amino-4-chlorotoluene hydrochloride by adding it to 140 ml. of water, cooling in ice, liberating the base by addition of 430 ml. of 16% sodium hydroxide, cooling and allowing the base to crystallize, filtering and washing in cold water, suspending in 800 ml. of water, cooling in an ice-bath, and treatment with

(6) La Coste, *Ber.*, **18**, 2940 (1885); Fourneau, Tréfouel, Tréfouel and Wancolle, *Bull. soc. chim.*, [4] **47**, 749 (1930).

(7) Vaughan, THIS JOURNAL, **68**, 324 (1946).

(8) (a) Cohn, *Monatsh.*, **22**, 473 (1901). (b) Magidson and Travin, *J. Gen. Chem.* (U. S. S. R.), **7**, 842 (1937) (*Chem. Zentr.*, **110**, I, 1366 (1939).

(9) This latter approach, however, is subject to some difficulties which will be considered in a later paper.

(10) *Cf.* German Patent 117,107 (*Chem. Zentr.*, **72**, I, 236 (1901)).

(11) Ashley, Perkin and Robinson, *J. Chem. Soc.*, 382 (1930).

(12) Brooker and Smith, THIS JOURNAL, **59**, 72 (1937).

(13) (a) Koller, *Ber.*, **60B**, 1108 (1927); (b) *cf.* also Bischoff, *ibid.*, **22**, 386 (1889).

(14) All melting points are corrected. Microanalyses were by Philip S. Bailey, Curtis S. Floyd and Miss Geraldine Alley.

(15) (a) Green and Lawson, *J. Chem. Soc.*, **59**, 1019 (1891); (b) Hunn, THIS JOURNAL, **45**, 1028 (1923).

(16) Sumant, *Ber.*, **75B**, 1008 (1942).

(17) Guldschmidt and Hönig prepared this hydrochloride but failed to report its melting point; *ibid*, **19**, 2441 (1886).

280 g. of acetic anhydride, added all at once in order to dissolve the amine quickly before the acetyl derivative began to crystallize. After the acetyl derivative was completely precipitated it was filtered, slurried three times in a total of 1.3 liters of water, filtered and dried; yield 245 g. (73% from the 4-chloro-2-nitrotoluene); m. p. 129–130° (Magidson and Travin, 72%; 128–130°). This product was usually used directly in the next step without drying.

4-Chloroacetanthranilic acid[8b] (I) was obtained in greatly improved yield by the following modified procedure. Potassium permanganate (782 g.) was added with rapid stirring to a suspension of 300 g. (1.63 moles) of 2-acetylamino-4-chlorotoluene in 10 liters of water containing 652 g. of magnesium sulfate heptahydrate at a temperature of 70°. The temperature rose slowly and was held at 85° for two hours first by the addition of ice and later on as became necessary by external heating. The excess of permanganate and the manganese dioxide were then destroyed and the product precipitated by means of sulfur dioxide. After cooling, the precipitate was filtered, washed and dried; m. p. 208–211° (Cohn,[8a] 214°); yield 344 g. The product contained some inorganic salts, however, and was on the average about 90% pure; the yield on this basis was 89% of actual product calculated from the 2-acetamino-4-chlorotoluene (Magidson and Travin,[8b] 57%). The over-all yield from 4-chloro-2-nitrotoluene was 65%.

Methyl 4-chloroanthranilate (II) was first prepared by Hunn[15b] by esterification of the acid. Adapting this method to larger scale work, 4-chloroacetanthranilic acid (I) was simultaneously hydrolyzed and esterified by suspending 1.4 moles in 4 liters of methanol and bubbling hydrogen chloride into the mixture (without cooling) for four hours; two-thirds of the acid esterified during this time, and by refluxing overnight the conversion was brought to about 80%. By making a second and a third addition of hydrogen chloride, each followed by an overnight period of refluxing, the conversion was raised to 95%. It was noticed that an inflammable gas (presumed to be dimethyl ether) escaped in large quantities along with hydrogen chloride during the refluxing. The mixture was poured into 6 liters of ice water and the hydrochloride crystallized; the free ester was liberated by means of sodium bicarbonate, collected on a filter and recrystallized from 1.5 liters of ligroin (b. p. 65–110°); yield of white needles, 94%, allowing for about 5% of unesterified 4-chloroanthranilic acid which was recovered by acidifying the filtrate; m. p. of the ester 65–66° (Hunn,[15b] 68.5°).

Condensation with Malonic Ester.—Extensive study of the condensation with malonic ester led to a procedure that differed in two respects from Koller's[13a] as applied to anthranilic ester itself. A large excess of malonic ester was used to suppress the formation of the malono-di-anthranilide; and the ring closure step with sodium alkoxide was carried out in ether at refluxing temperature rather than at the 140–150° used by Koller.[13a]

A solution of 186 g. (1 mole) of methyl 4-chloroanthranilate (II) in 900 g. (5.6 moles) of diethyl malonate was heated rapidly to 165°, and then gradually on up to 195° over a period of ninety minutes, and was kept at 195–198° (refluxing) for one hour longer. During this time about one mole of ethanol distilled through a partial reflux condenser. Most of the excess of diethyl malonate (about 740 g.) was then distilled under reduced pressure and continual stirring (the stirrer shaft passed through a lubricated heavy rubber sleeve). On cooling, a solid precipitated which largely dissolved upon addition of 1 liter of absolute ether. The resulting ether solution of the monoanthranilide was used directly in the cyclization step below.

Ethyl malono-4-chloroanthranilide methyl ester (III) was isolated in one run from a small sample of this ether solution by evaporating the solvent; recrystallization from ethanol and then from ligroin gave plates which melted at 78–79°.

Anal. Calcd. for $C_{13}H_{14}ClNO_5$: N, 4.67. Found: N, 4.89.

Malono-di-(4-chloroanthranilide Methyl Ester).[18]—The crystals which failed to dissolve in the ether were recrystallized repeatedly from ethanol, rod-shaped crystals, m. p. 186–187°.

Anal. Calcd. for $C_{19}H_{16}Cl_2N_2O_6$: C, 51.95; H, 3.67; N, 6.38. Found: C, 51.68; H, 3.27; N, 6.58.

Cyclization.—A solution of 27 g. of sodium in 500 ml. of absolute alcohol was added dropwise to the stirred and refluxing ether solution of crude mono-anthranilide (III) (from the preceding operation) over a period of two and one-half hours. The resulting thick suspension was allowed to stand overnight. The ether was evaporated (during this operation 1.2 liters of water was added portionwise in order to prevent the mixture from becoming excessively viscous).

Hydrolysis was carried out without isolating the ester (IV) by adding 300 g. of 40% sodium hydroxide to the mixture and heating at 60–70° for one hour.

Decarboxylation.—The acid (V), without being isolated, was decarboxylated under either basic[13a] (procedure A) or acid[13b] conditions (procedure B); the latter method was longer but involved a minimum of the troublesome frothing that accompanied alkaline decarboxylation. (Koller,[13a] in his analogous work, had employed 60% alkali.)

Procedure A.—The temperature of the warm alkaline solution of V (from the preceding step) was raised from 70 to 95° over a period of three and one-half hours; alcohol distilled out slowly and frothing was excessive although controllable. After cooling to 70° the alkali-insoluble material was filtered, slurried in 400 ml. of 10% sodium hydroxide at 70°, refiltered, and washed with hot water; 20 g.; white powder; m. p. 220–250° dec. (not identified). The 7-chloro-4-hydroxycarbostyril (VI) was precipitated from the combined alkaline filtrates by acidifying to *p*H 3. The resulting gelatinous precipitate was filtered, washed by slurrying three times in a total of 14 liters of 5% sodium bicarbonate (mechanical stirring), refiltered and dried in an oven. The yield of nearly white product was 141 g. (72%); m. p. 320–350° dec. Acidification of the sodium bicarbonate solutions precipitated 20.5 g. of material believed to be largely the undecarboxylated quinoline acid (V).

7-Chloro-4-hydroxycarbostyril (VI).—An analytical sample was made by recrystallization from quinoline and then from ethanol; plates, m. p. 430–433° (in vac.).

Anal. Calcd. for $C_9H_6ClNO_2$: C, 55.26; H, 3.09; N, 7.16. Found: C, 55.28; H, 3.08; N, 7.29.

Procedure B.—The alkaline solution of the carboxylic acid was cooled to 30–40° and acidified to *p*H 3 by means of hydrochloric acid. The white precipitate (largely the quinoline acid, V) was filtered and while still wet was placed in a 4-liter beaker with 1 liter of concentrated hydrochloric acid. The resulting suspension was boiled slowly for six hours, during which time about two-thirds of the liquid evaporated. Two liters of water was added and after cooling the *p*H was raised to 4 with sodium hydroxide. The impure 7-chloro-4-hydroxycarbostyril (VI) which precipitated was collected on a filter, suspended in 2 l. of water, treated with 100 g. excess of sodium bicarbonate to neutralize and to dissolve any material which had escaped the decarboxylation, stirred thoroughly at room temperature, and again filtered (at a higher temperature the sodium bicarbonate appeared to dissolve considerable amounts of the carbostyril). The filtrate upon acidification to *p*H 3 yielded 3 g. of material believed to be largely the quinoline acid (V).

The wet filter cake of carbostyril was digested for one hour at 60–70° with 2.5 liters of 10% sodium hydroxide; most of it dissolved. The mixture was filtered while still warm, and the residue was digested again with 1.5 liters of warm 10% alkali, filtered and washed (24 g., unidentified). The filtrates and washings were acidified to *p*H 4 by means of hydrochloric acid, and the precipitated carbostyril (VI) was filtered, washed by slurrying in 2 to

(18) *Cf.* Chattaway and Olmsted, *J. Chem. Soc.*, **97**, 938 (1910).

3 liters of water, refiltered, washed, and oven dried; cream colored powder; yield 141 g. (72%).

2,4,7-Trichloroquinoline (VII).—This procedure approximates standard practice.[4] A suspension of 100 g. (0.51 mole) of powdered 7-chloro-4-hydroxycarbostyril in 650 ml. of phosphorus oxychloride was refluxed with vigorous stirring until solution was complete (thirty minutes) and for thirty minutes thereafter. The mixture was cooled to room temperature, poured over 8 liters of crushed ice with vigorous stirring, and allowed to stand overnight. The resulting mixture was made alkaline (under cooling) using about 6.5 liters of 20% sodium hydroxide. The suspension of trichloroquinoline (VII) was then filtered and washed thoroughly with warm water until the washings came through alkali-free; yield, 116 g. (98%); m. p. 102–106°. This product was further purified by recrystallizing (with norite treatment) from absolute ethanol; yield 100 g. (84%) white needles; m. p. 104.5–106°. Repeated recrystallizations raised the melting point to 106.5–107.5°.

Anal. Calcd. for $C_9H_4Cl_3N$: C, 46.49; H, 1.73. Found: C, 46.25; H, 1.83.

Summary

2,4,7-Trichloroquinoline has been synthesized by an unequivocal path from 4-chloroanthranilic acid by condensation of the ester with malonic ester, cyclization to 3-carbomethoxy-7-chloro-4-hydroxycarbostyril, hydrolysis, decarboxylation and hydrochlorination. Conditions have been developed to produce the compound in an over-all yield of 60–65%.

CHARLOTTESVILLE, VIRGINIA RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

Antimalarials. Hydrolysis and Methanolysis of 2,4,7-Trichloroquinoline[1]

BY RUSSELL J. ROWLETT, JR.,[2] AND ROBERT E. LUTZ

4,7-Dichlorocarbostyril (III) and 4,7-dichloro-2-methoxyquinoline (VI) were needed as intermediates in the program[1] of synthesis of a variety of substituted 4 - (dialkylaminoalkylamino) - quinolines[3] for testing as possible antimalarials.

The starting material for the preparation of these two compounds was 2,4,7-trichloroquinoline (II) which has been described in the preceding paper.[4] The 2-chlorine was expected and found to be more reactive than the 4-chlorine,[5] sufficiently so as to be smoothly replaced by hydroxyl upon acid hydrolysis[6]; 4,7-dichlorocarbostyril (III) was thus obtained in good yield. Methanolysis with sodium methoxide, however, was not as specific for the 2-chlorine as was hydrolysis; and a mixture of 4,7-dichloro-2-methoxy- (VI), 2,7-dichloro-4-methoxy- (V) and 7-chloro-2,4-dimethoxyquinolines (IV) was obtained with the relative quantities of these products dependent on the reaction time and temperature. The accompanying diagram illustrates these syntheses and some of the interrelationships which serve as proof of structures of the products.

The required and rigorous proof that hydrolysis of 2,4,7-trichloroquinoline (II) had actually replaced the 2-chlorine and not the 4-chlorine, was obtained by conversion of the product into carbostyril by catalytic hydrogenolysis of the 4,7-chlorines using Raney nickel in the presence of an excess of alkali.

The attempt to make the 2-methoxy compound (VI) from the carbostyril (III) by methylation, although it furnished additional proof of the location of the hydroxyl, led to the unexpected results, namely, N-methylation in the main instead of the hoped for oxygen-methylation. Both methyl iodide and alkali, and diazomethane yielded chiefly 4,7-dichloro-1-methylcarbostyril (VII) which was synthesized in an entirely different and unequivocal fashion from 4-chloro-N-methylanthranilic acid.[7]

The reaction between diazomethane and the amide system of the carbostyril (III), which gave 70% of N-methylation as compared with the 10% yield of the oxygen-methylation product, is to be contrasted with the methylation by diazomethane of carbostyril itself which gives exclusively 2-methoxyquinoline[8] and the diazomethylations of 2- and 4-hydroxypyridines[8,9] where the major products are the methoxy pyridines and where N-methylation occurs only to a very minor extent. However, N-methylation by means of diazomethane occurs in considerable proportion in other cases. It is the dominant reaction in the diazomethylation of cyanuric[10] and 6-hydroxynicotinic acids.[8] It also occurs to a minor extent in the diazomethylation of vitamin B-6,[11a] although the lactone of 2-methyl-3-hydroxy-4-hydroxymethyl-5-carboxypyridine[11b] and 3-hydroxypyri-

(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 the University of Virginia.

(2) Present location: Jackson Laboratory, E. I. du Pont de Nemours and Co., Wilmington, Del.

(3) The attachment of the dialkylaminoalkylamino side chains to these two chloroquinolines was carried out by Dr. N. L. Drake at the University of Maryland.

(4) Lutz, *et al.*, THIS JOURNAL, **68**, 1285 (1946).

(5) *Cf.* Buchmann and Hamilton, *ibid.*, **64**, 1357 (1942).

(6) This reaction was patterned on the hydrolysis of 2-chloroquinolines by (a) Kaufmann and de Petherd, *Ber.*, **50**, 336 (1917), and (b) Ing, *J. Chem. Soc.*, 2202 (1931).

(7) *Cf.* Lutz and co-workers, results to be published.

(8) Meyer, *Monatsh.*, **26**, 1317 (1905).

(9) Pechmann, *Ber.*, **28**, 1625 (1895).

(10) Degering, "Organic Nitrogen Compounds," University Lithoprinters, Ypsilanti, Mich., 1945, p. 354.

(11) (a) Itiba and Miti, *Sci. Papers Inst. Phys. Chem. Research* (Tokyo), **35**, 73 (1938); **36**, 1 (1939); *cf.* also Rosenberg, "Chemistry and Physiology of the Vitamins," Interscience Pub., Inc., New York, N. Y., 1942, p. 201; (b) Harris, Stiller and Folkers, THIS JOURNAL, **61**, 1244 (1939).