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SYNTHETIC POLIOMYELITICIDALS

By

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Thesis submitted to the Faculty of the Graduate School of the University of Maryland in partial fulfillment of the requirements for the degree of Doctor of Philosophy

1953

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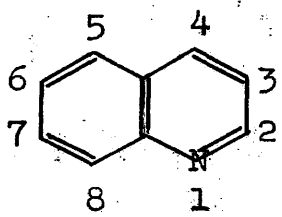
INTRODUCTION

General Discussion

The numbering of the quinoline ring system, used in this thesis, is shown in the following formula:



In general discussions, groups on the benzene ring are referred to as Bz-derivatives, and groups on the pyridine ring as Py-derivatives. Specific compounds are named as derivatives of the parent compound listed in Chemical Abstracts. For example, substituted 2-hydroxyquinolines are named as derivatives of carbostyril.

This thesis is organized in numbered sections. These sections are initiated by a schematic preparative chart, which indicates the basic reactions considered for the preparation of the desired compounds. A solid arrow signifies a completed reaction, for which the experimental procedure is given in the experimental part of the section. A broken arrow indicates a reaction attempted, from which the desired compound was not obtained. Attempted syntheses may be discussed in the sections, but none are included in the experimental directions. The schematic preparative charts do not show all the compounds included in this work nor alternate reagents used in accomplishing a particular step.

The 2-substituted-8-(3-diethylaminopropylamino)-quinolines synthesized in this work were prepared for testing as poliomyelitiocidals. The nature of the testing procedure required one hundred grams of the final drug. This requirement posed, from a practical standpoint, the necessity of working out in detail the preparation of intermediate compounds in high yields, and from a research aspect on a relatively large scale. Thus optimum reaction conditions were important for each step of the synthesis and also reactions which would be applicable to large scale operations were of prime consideration. These factors, in conjunction with a desire to minimize chances for failure, suggested attempting more than one synthetic route to a final drug, and, in particular, stressed the development aspect of the problem.

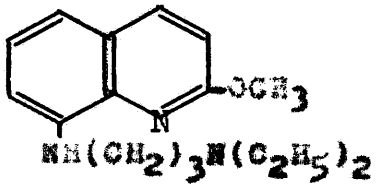
To be able to prepare any particular compound was not sufficient. Various methods and /or changes in reaction conditions were resorted to in attempts to attain optimum reaction conditions for high yields on large scales. An example, which illustrates these factors, is the preparation of 8-amino-2-chloroquinoline. Four reduction systems were used in preparing this compound, and eleven runs were made under various conditions, utilizing the most promising of the four reduction systems.

This development work, with optimum conditions of preparation, strongly suggested recording experimental details

after the manner used in "Organic Syntheses". As an idealistic aim and for consistency, it would have been most satisfactory to record all experimental work in this manner. Wherever possible, this method has been used. The preparation of 1 g. of 8-(3-diethylaminopropylamino)-2-methoxyquinoline dihydriodide points out the impractability of recording, in all instances experimental work using the style employed in "Organic Syntheses". In any event, details have been recorded with the aim of giving as much aid as possible to the experimental chemist, who might have occasion to use the procedures.

All calculations in this manuscript have been made with a slide rule except per cent composition of compounds and the concentrations of solutions used to obtain ultraviolet absorption data. The ultraviolet absorption curves are qualitative, and in all cases the compounds investigated were assumed to be pure. The molar extinction coefficient is defined on page 69. Melting points are corrected.

The investigation of the poliomyeliticidal properties of quinoline type derivatives was first stimulated by the observation of A. B. Sabin[1], that 8-(3-diethylaminopropylamino)-2-methoxyquinoline, SW13050, Isoplasmocid,



[1]Unpublished results- A. B. Sabin, Childrens Hospital Research Foundation, Cincinnati 29, Ohio.

restrained the invasion stage of poliomyelitis. Under the auspices of the National Foundation for Infantile Paralysis, a coordinated program for the investigation of certain quinoline compounds as poliomyeliticidals was instigated.

Quinoline derivatives of the type described in this thesis are screened by toxicity tests, then when warranted are tested as antimalarial drugs. The antimalarial program has been adequately surveyed by several authors. Early work specifically concerning 8-aminoquinoline derivatives has been reviewed in detail by Goldman.[2] The entire field has been covered up to 1946 by Wiselogle.[3]

The rhesus monkey has been used for determining the toxicity of these drugs. This particular genus of monkey reacts much the same as man does to drugs which affect the central nervous system. Since the poliomyelitis virus involves the central nervous system these animals are probably the most suitable for conducting screening tests. Complicating factors have been the scarcity and cost of these animals. Until 1940, the monkey was the only experimental animal in which it was possible to reproduce poliomyelitis.[4]

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[2] L. Goldman, "Synthetic Antimalarials", Ph.D. Thesis, University of Maryland, 1944.

[3] F. Y. Wiselogle, "Survey of Antimalarial Drugs 1941-1945": J. E. Edward, Ann Arbor Michigan 1946 (3 volumes).

[4] Annual Report, The National Foundation for Infantile Paralysis. New York, 1940.

N-ALKYL DERIVATIVES OF 8-AMINOQUINOLINES

There are three general methods for preparing N-alkyl derivatives of 8-aminoquinoline.[5] One consists of condensing an 8-iodoquinoline with an alkylamino compound. A second method involves using the Skraup reaction on an appropriately substituted benzene. The third method which has been investigated in some detail, particularly during the antimalarial program of the second world war, appears to be of a more general application. This method utilizes an 8-aminoquinoline which is alkylated, usually, by an alkyl halide. Common usage has evolved the term "nucleus" for the 8-aminoquinoline entity and "side chain" for the alkylating agent. There are several modifications of the details in the third general method. Five schemes which have been used in a number of cases, involve the coupling conditions shown.

Scheme A: 1 mole "nucleus", 1.1 mole "side chain", 60 ml. absolute alcohol.

Scheme B: 1 mole "nucleus", 1 mole "side chain" as salt, small amount of water.

Scheme C: 1 mole "nucleus", .2 mole sodium acetate, 5 moles "side chain", 50% ethyl alcohol.

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[5] Specific examples with references, illustrating these type reactions are summarized in Van Nook, "A Study of the Preparation and Properties of 8-(5-iso-propylaminoamylamino)-6-methoxyquinoline and some of its Salts", Ph. D. Thesis University of Maryland 1946.

Scheme D: 1 mole "nucleus", 1 mole "side chain", Na_2HPO_4-citric acid, buffer pH 4.8.

Scheme E: 1 mole "nucleus", 2.5 moles "side chain".

The method of isolating the desired product from the reaction mixture varies considerably, but in many cases depends on adjusting the pH in such a manner that "nucleus" and "side chain" may be precipitated or extracted from the condensation product which may then be converted to a salt and recrystallized. Fractional and molecular distillation at low pressures have been used extensively for separation and partial purification.

The problem may be arbitrarily resolved into five steps.

1- A suitable synthesis of the substituted 8-amino-quinoline.

2- Preparation of the alkylating agent.

3- A workable method of coupling "nucleus" and "side chain".

4- The isolation and purification procedure for the condensed compound.

5- The formation of a solid salt and estimation of the purity.

POLIOMYELITIS

Poliomyelitis is defined as an acute specific infectious disease.[6] It is believed to be caused by only three types of filterable virus.[7] The disease manifests itself in a majority of cases by early symptoms referable to the respiratory or gastro-intestinal systems, and subsequent attack on the central nervous system. The advanced stages frequently result in paralysis and occasionally in death. Despite a tremendous amount of study, the disease remains one of the most baffling as well as interesting communicable diseases. Many essential facts remain obscure.

Transmission. In general the disease is spread by way of the upper respiratory passages or from the gastro-intestinal tract. Direct contact from one person to another, probably through nasal secretions is a favorable possibility. Indirect transmission through water, milk or other foods which have been contaminated with excreta from the intestinal tracts of patients with the disease is a possibility, since it has been demonstrated that the virus is present in stools of individuals suffering from mildest forms of the disease. There is little evidence that such factors as insect hosts or diets have any part in transmission of the disease.

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[6] Poliomyelitis is also referred to as Infantile Paralysis or Heine-Medin disease.

[7] "Today's Health", American Medical Association, April 1932, p. 15.

Epidemiology. Poliomyelitis has a very low attack rate. Even in large families, where direct contact is favored, usually only one child is attacked. This unusual feature has been explained on a basis of difficult communicability. However a more plausible explanation is that the majority of individuals build protection or immunity by coming into contact with small doses of the virus. These small doses of virus are adequate to stimulate the development of immunity but are insufficient to produce easily recognizable symptoms. One attack generally produces life-long immunity, however a few authentic cases of second attacks have been reported. The majority of cases occur in the first ten years of life, under one year is unusual, but there is an increasing tendency for the disease to strike older age groups. Males are more susceptible than females. No race is completely immune but the negro appears the most resistant. The incidence of the disease strikes a peak in the hottest weather, generally July and August and declines quickly with onset of cool weather. Infantile paralysis also appears to be primarily a temperate zone disease.

Dissemination. At one time it was thought that the virus spread by way of the lymphatics and the blood, eventually reaching the central nervous system. Experimental evidence was then presented which indicated that only the central nervous system was responsible for the dissemination in the body. This led to the "axonal transmission" theory

which held that the virus had an affinity only for nerve tissue, entered the nose, thence along the nerve axones of the olefactory bulb to the posterior and anterior horn cells of the spinal cord. The latest evidence independently determined by D. Bodian and D. M. Horstmann and presented to the American Association of Immunologists during April 1952, in New York City indicates that the virus is in the blood stream at some phase of the disease.

Pathology. Originally it was thought that poliomyelitis was confined strictly to the central nervous system, the most striking clinical feature being the well known paralysis resulting from destruction of anterior horn cells of the spinal cord. At the present time, it has been shown that other portions of the nervous system such as the posterior horn cells of the cord, cerebrum and other parts of the brain may be involved. It also appears certain that the entire body is involved to a certain extent in the attack of the virus. For example, marked changes in the gastro-intestinal tract may occur, from hemorrhages of the stomach, extensive multiplication of tissue elements resulting in increased size, to congestion of the lymphoid tissues of the lower intestinal tract. The lymphoid structures of the spleen, thymus and tonsil are also affected. The visceral vessels as well as the meninges and central nervous system show marked congestions, which at times may be sufficient to cause hemorrhages into the tissues.

The two most conspicuous findings in the central nervous system are edema and collection of large numbers of lymphocytes outside the capillary walls. Destruction of the nerve cell itself is probably the direct result of the virus, but a complicating factor is the interference of the blood supply resulting from the edemic condition. The degree of paralysis depends upon the extent to which the nerve cell has been destroyed, whereas in many cases nerve cells whose function has been interfered with because of lack of blood supply will regain their function after edema has subsided and thus paralysis will disappear.

Symptomatology. The clinical manifestations of polioencephalitis may be divided into three parts: 1- invasion, 2- involvement of the central nervous system and 3- paralysis.

1- Invasion: The onset of the disease is not always uniform. A majority of cases start with a relatively low fever which is accompanied with symptoms such as upset stomach, cold in the head, bronchitis and general lassitude. In a certain percentage of cases, these first symptoms may disappear and then reappear after two or three days along with symptoms described under involvement of the central nervous system. In many cases the temperature continues throughout the incubation stage, or the initial stage of invasion may be absent with a sudden temperature and attack on the central nervous system. Examination of the spinal fluid during any of these type invasions will give a

normal cell count. It is this uncharacteristic invasive stage which makes absolute diagnosis impossible. If an epidemic is present and there is an unquestionable history of exposure, and the initial symptoms entirely subside then the case is generally designated as "abortive".

2- Involvement of Central Nervous System: The second stage of the disease appears as a stiffness of the neck and spine. Pain and soreness are evident on attempting to move the patient. Sometimes pain on movement of the spine will be evident in the extremities which is indicative of possible paralysis of those parts. In general there is a tendency for hypersensitiveness of the skin of the entire body. Drowsiness, twitchings and tremors are not unusual and reflexes are generally affected in some manner. The temperature is usually moderate but the pulse rate is rapid. The spinal fluid will now reveal an increase in protein and cells, the majority being lymphocytes. At this point there has been no paralysis and this stage has sometimes been called the preparalytic stage. If after two or three weeks there is no paralysis, generally the disease is of the non-paralytic type, never progressing to the third stage.

3- Paralysis: Paralysis is generally grouped into two major types, spinal and bulbar. In spinal paralysis the anterior horn cells of the cord are affected, and the bulbar type resulting from damage to the cranial nerve nuclei.

A combination of these two may produce a facial or voice paralysis along with paralysis of one or more limbs. Almost any combination of paralysis may occur.

The spinal type is the most common, the legs the most frequently paralysed with the arms the next most usual site. Paralysis of the back or abdomen muscles is rare but when the diaphragm or respiratory muscles are affected breathing may become impossible and thus the mechanical "iron lung" resorted to.

The bulbar type affects the facial nerves most frequently which by itself is not serious. Paralysis of the pharynx muscles is dangerous because the patient cannot swallow and the end result may be aspiration pneumonia. The tongue, eyes and larnyx are other parts of the body which may be affected.

A combination of these two types may paralyze the legs, back and abdominal muscles, arms, neck, bulbocranial nerves and the respiratory center, resulting in death.

Prophylaxis. Two methods of active immunization against the disease have been tried. One used a killed virus and the other a live virus. The killed virus proved to be useless while the live virus proved to be too dangerous for use on human beings. Various drugs have been claimed to exert some action either in preventing or modifying the attack. Potassium tartrate, mercurochrome, hexylresorcinol, vitamin C, antimony and p-aminophenyl

stibonic acid are among some of the chemical agents which modify the infection. In general the sulfonamides have been ineffective.

Chemical Agents. Many chemicals have been used in attempts to find an agent which would cure or modify the effects of the poliomyelitis virus. von Rooyen and Rhodes* indicate that such chemicals as urea, formalin, copper sulfate, potassium permangenate, boric acid and methanol destroyed the virus, vitamin D and ascorbic acid inactivated the virus, whereas the virus was resistant to the action of ether and glycerol. The picture is complicated since a uniform test was not used throughout, most of the tests were conducted in vitro and virus from several different experimental animals were used. It is believed the virus strains from one animal group may be somewhat different from those of another group.[6]

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[6] The foregoing review of poliomyelitis has been summarized from the following sources.

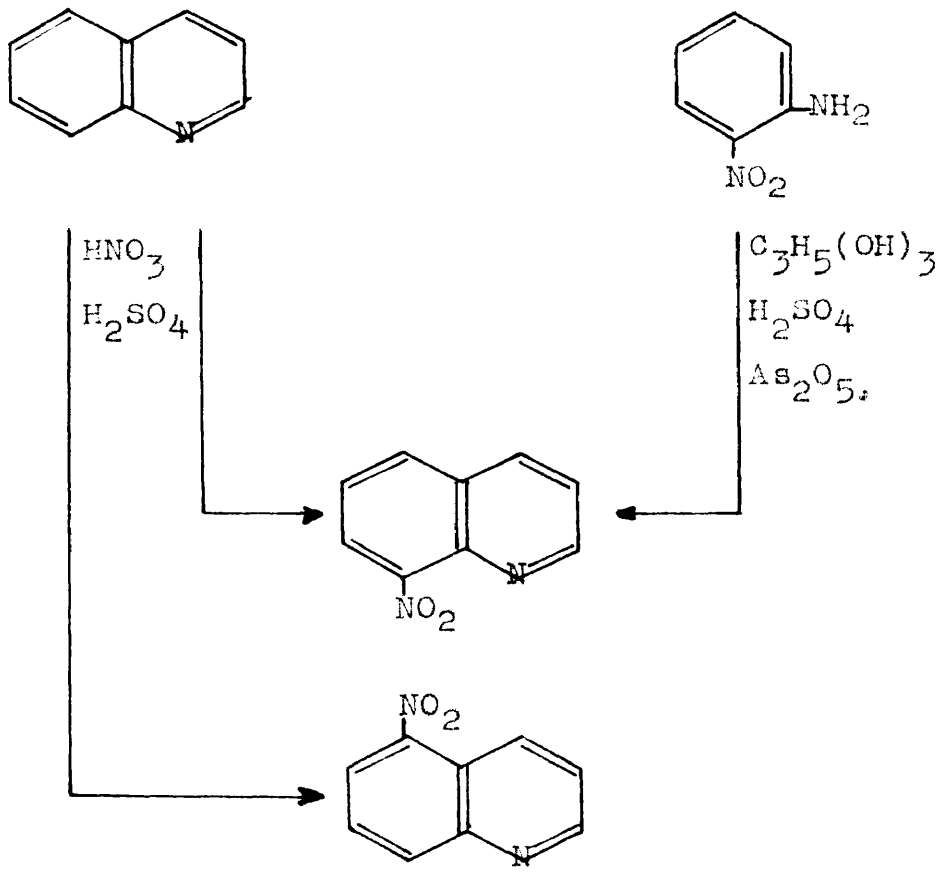
J.P.C. Top, "Handbook of Communicable Diseases", C.V. Mosby Co., St. Louis: 1941 Chapt. 26

H.C. Gage and J.P. Landon, "Communicable Diseases", F.A. Davis Co., Philadelphia: 1944 Chapt. 26

*von Rooyen and Rhodes, "Virus Diseases of Man", Nelson Co., New York: 1948 Chapts. 121 through 138

CHART I

8-NITROQUINOLINE



SECTION I

8-NITROQUINOLINE

Discussion

In the course of this problem it became necessary to investigate in some detail the production of 8-nitroquinoline. Three important factors made this investigation advisable: an extended delay in obtaining a supply from commercial sources, the considerable amounts required, and the high cost of the substance ($50.00 per pound).

8-Nitroquinoline has been prepared in three ways:- by the direct nitration of quinoline, by some modification of the Skraup reaction, and by heating 8-nitro-2-quinolinecarboxylic acid.

Beathorn and Ibele[9] nitrated 2-quinolinecarboxylic acid, separated the 5- and 8-nitroquinaldinic acids through the solubility of their barium salts, and regenerated the free acids; heating 8-nitro-2-quinolinecarboxylic acid to the melting point formed the desired 8-nitroquinoline by elimination of carbon dioxide. This method appeared least promising of the three methods and was not attempted.

The direct nitration of quinoline has been carried out by several workers. A survey of these procedures indicated

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[9]Beathorn and Ibele, Ber., 39 2333 (1906)

that it was possible to vary the amounts of isomers and position of the entering nitro group by suitable modification of the nitrating conditions and reagents.

Bacharach, Haut and Caroline[10] used metallic nitrates with acetic anhydride as a nitrating medium. They found nitrates of heavy metals unsatisfactory, however, use of aluminum and lithium nitrates in the presence of cupric nitrate, resulted in the production of 7-nitroquinoline, previously available only through a Skraup reaction. Scherigin and Toptschiev[11] nitrated quinoline using nitrogen tetraoxide and obtained a low yield of 7-nitroquinoline.

Königs[12] treated quinoline nitrate with a mixture of fuming nitric acid and concentrated sulfuric acid. Claus and Kramer[13] studied Königs method and separated two mono nitroquinolines and a dinitroquinoline. Claus and Küttner[14] nitrated quinoline sulfate with concentrated nitric acid in a sealed tube at 160°. Koelting and Trautmann[15] treated quin-

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[10]Bacharach, Haut and Caroline, Rec. trav. chim., 52 413-19 (1933)

[11]Scherigin and Toptschiev, Ber., 69 1874-7 (1936)

[12]Königs, ibid 12 449 (1879)

[13]Claus and Kramer, ibid 18 1243 (1885)

[14]Claus and Küttner, ibid 19 2885 (1886)

[15]Koelting and Trautmann, ibid 23 3655 (1890)

oline sulfate with a mixture of fuming nitric acid and concentrated sulfuric acid. The experimental details for all these procedures are rather limited and in no case was a yield of any pure isomer reported. Moelting and Trautmann[16] indicated that the temperature during nitration affected the proportion of 5- and 8- nitroquinolines. Larger amounts of the 5-nitroquinoline were formed at lower temperatures.

Dufton[17] had need for considerable amounts of 8-nitroquinoline and established in detail a nitration procedure based on fifty grams of quinoline. He used this procedure successfully with as much as three hundred grams of quinoline. The method involved preparation of solid quinoline nitrate using fuming nitric acid and the addition of this salt in portions to concentrated sulfuric acid. A small quantity of fuming sulfuric acid was added after each portion of quinoline nitrate to prevent excessive dilution of the nitrating mixture. The temperature was controlled using an ice bath and by careful addition of the quinoline salt. The reaction mixture was poured into water and a small amount of dinitrohydroxyquinoline removed by filtration. The crude 5- and 8-nitroquinolines were precipitated with base and then dissolved in a large quantity of dilute nitric acid. On cooling,

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[16] Moelting and Trautmann, loc. cit.

[17] Dufton, J. Chem. Soc., 61 782 (1892)

the 5-nitroquinoline salt separated in almost pure form. The mother liquor was neutralized and the crude 8-nitroquinoline crystallized once from alcohol. This method starting with three hundred grams of quinoline, gave one hundred fifty grams (37.1%) of 8-nitroquinoline which melted at 89°.

Melgen[18] treated quinoline sulfate with a mixture of fuming nitric acid and fuming sulfuric acid (40% anhydride), keeping the temperature at -20°. The 5- and 8- nitroquinolines were separated through the nitrate salts using Dufton's method. Sixty five grams of 8-nitroquinoline (46.3%) were obtained from one hundred grams of quinoline. Melting points were not reported for the nitroquinolines obtained by Melgen.

LeFevre and LeFevre[19] using essentially Dufton's method, obtained nine grams of 8-nitroquinoline (13.4%) from fifty grams of quinoline. The compound melted at 88-89°. Bennett and Drove[20] repeated Dufton's work. Details were not given on the yield and quality of the 8-nitroquinoline obtained.

Elkshoorn[21] prepared twenty three grams (34.1%) of 8-nitroquinoline, by using as a basis, the work of Melgen.

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[18] Melgen, J. prakt. Chem. 2 *II* 473 (1938)

[19] LeFevre and LeFevre, J. Chem. Soc., 1472 (1935)

[20] Bennett and Drove, ibid, 376-80 (1945)

[21] Elkshoorn, Rec. trav. chim., 48 147 (1929)

Fieser and Hershberg[22] nitrated synthetic quinoline sulfate at 15-20° by dissolving the salt in 65% "oleum" and then adding fuming nitric acid. The 5- and 8- nitroquinolines were separated through the solubility of the nitrate salts. In this manner, Fieser and Hershberg obtained eighty seven grams (64.6%) of crude 8-nitroquinoline which melted from 77 to 87°. The yield of pure 8-nitroquinoline was not reported.

La Coste[23] prepared 8-nitroquinoline using 2-nitroaniline and glycerin in a modification of the Skraup reaction. The product melted at 89°, but the yield was not given. Knueppel[24] applied a modification of the Skraup reaction, starting with fifty grams of 2-nitroaniline and obtained thirty six grams (57.2%) of 8-nitroquinoline. Bradley and Robinson[25] simplified Knueppel's procedure by extracting the crude 8-nitroquinoline with benzene and recrystallizing from light petroleum ether. The product melted at 87-88°, but the yield was not reported. LeFevre and LeFevre[26] used Knueppel's directions, simplified the purification scheme and reported forty five grams (71.4%) of 8-nitroquinoline

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[22] Fieser and Hershberg, J. Am. Chem. Soc., 62 1640-5 (1940)

[23] La Coste, Ber., 16 673 (1883)

[24] Knueppel, Ibid, 29 704 (1896)

[25] Bradley and Robinson, J. Chem. Soc., 125-63 (1932)

[26] LeFevre and LeFevre, loc. cit.

which melted at 88-89°. Smith and Getz[27], using Knueppels directions as a basis, worked out in detail a procedure for the preparation of 8-nitroquinoline based on two pounds of 2-nitroaniline. The crude material which they obtained, was used directly in a reduction reaction for the preparation of 8-aminoquinoline. The overall yield for both reactions was reported as 50%.

Time became a very important factor at this point, and a modified Skraup reaction and nitration procedure were investigated concurrently. Dr. T. L. Loo prepared crude 8-nitroquinoline by a Skraup type reaction and a method for the purification of this crude material was determined.[28] This purification is detailed in the experimental part of this section. The yield of 8-nitroquinoline, which melted at 88-89°, was 50-60% of the theory based on 2-nitroaniline.

An attempt was made to nitrate quinoline using the method of Dufton, by adding fuming nitric acid to fifty grams of quinoline and then adding the solid salt in portions to concentrated sulfuric acid. The salt was not well defined and had a tendency to become oily which made it difficult to handle. In an ice bath the addition of 10 ml. of 20-30% fuming sulfuric acid caused the temperature to rise from 10°

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[27]Smith and Getz, Chem. Rev., 16 113-20 (1935)

[28]The writer wishes to thank Dr. T. L. Loo for preparing some six hundred grams of crude 8-nitroquinoline for this problem.

to 110°. A dry ice-chloroform bath was resorted to in order to keep the temperature at 10° ± 5 during the addition of the fuming sulfuric acid. On pouring the reaction mixture into water and neutralizing, only oily quinoline was obtained. A second nitration patterned after that described by Fieser and Hershberg using the sulfate salt of quinoline, 30% fuming sulfuric acid and fuming nitric acid resulted in a 23.8% yield of 8-nitroquinoline which melted at 87-88°. Repeating this work using a higher temperature and longer reaction time resulted in a considerable amount of dark red solid material, which was relatively acid insoluble. This method gave a 24.3% yield of 8-nitroquinoline which melted at 88-89°.

8-Nitroquinoline as supplied by Merck and Company, Inc., was a chocolate brown powder which melted at 88-89.5° to an almost black liquid. The quality of 8-nitroquinoline was not satisfactory for use as a starting material and was purified. Three methods were determined which were suitable as purification processes. The method used depended upon such factors as; the amount of material to be recrystallized, the equipment and solvents available. Purification procedures for the crude 8-nitroquinoline from the Skraup reaction, nitration of quinoline and commercial product are detailed in the experimental part of this section.

In general, using isopropyl ether as a recrystallizing solvent for 8-nitroquinoline resulted in a nearly white product which melted at 88-89°. The recovery was almost

quantitative. The disadvantages of using this solvent are the high volatility, and the low solubility of the 8-nitroquinoline. It is to be recommended for the purification of relative small amounts (less than 150 g.) of 8-nitroquinoline.

Method C, given in the experimental part of this section, using dilute hydrochloric acid and recrystallization from 95% alcohol is to be recommended for the purification of large amounts of 8-nitroquinoline.

EXPERIMENTAL

NITRATION OF QUINOLINE

Procedure

A mixture of 32 ml. of concentrated sulfuric acid and 200 g. of 30% "oleum" was placed in a 1-l. beaker, equipped with a mechanical stirrer nested in a 2-l. stainless steel pan. Chloroform and dry ice were placed in the steel pan (note 1) and 75 g. (.58 mole) of freshly distilled (note 2) quinoline was added dropwise to the acid mixture, with vigorous stirring. The temperature was kept below 40° by regulating the addition of quinoline and by the addition of dry ice to the cooling bath. The homogeneous solution was cooled to 15°, stirred and 110 g. of fuming nitric acid added from a dropping funnel over a 30 minute period. The solution was allowed to stir an additional 30 minutes and then poured into 750 ml. of cold water. Bright red crystals precipitated and were removed by filtration (note 3). The filtrate was then made strongly basic with approximately 12% sodium hydroxide. Brownish-yellow crystals separated and were collected on a Büchner funnel, washed several times with water and pressed as dry as possible. This precipitate was dissolved in 500 ml. of nitric acid, having a specific gravity of 1.12 (21%), by heating on a steam bath. On cooling in an ice bath, bright orange crystals of the nitrate salt of 5-nitroquinoline precipitated and were separated from the

solution by filtration. The filtrate was made strongly alkaline with 12% sodium hydroxide, the solids filtered off and dried. The material was recrystallized from isopropyl ether. In this manner 2, g. (23.8%) of almost white 6-nitroquinoline which melted at 87-88° was obtained.

Notes

1. Dry ice and chloroform made a convenient cooling bath. Chloroform was added to a depth of approximately one inch in the outer container and dry ice added as needed.
2. "Paragon" practical grade quinoline, dried with sodium hydroxide, was distilled in ground glass equipment protected from moisture with sodium hydroxide in a drying tube. The fraction boiling at 23,-235 /773 mm. was collected.
3. The red precipitate was not identified. Likely possibilities were a dinitroquinoline, a dinitrohydroxyquinoline or a mixture of these compounds.

6-NITROQUINOLINE

The crude 6-nitroquinoline purified in the following procedure was prepared by Dr. T.L. Loo using essentially Mosher, Yanko, and Whitmore's[2)] experimental details for the preparation of 8-methoxy-6-nitroquinoline.

[2)] Org. Syntheses, 27 48 (1947)

PURIFICATION OF 8-NITROQUINOLINE

From small Skraup reaction:

Three hundred-thirty grams of black paste, which had been pressed as dry as possible on a Buchner funnel, was treated with 3700 ml. of 3% hydrochloric acid in a 4-l. beaker, filtered by decantation from an oily material (note 1), decolorized with charcoal and refiltered through two nested fluted filter papers (note 2). The filtrate was allowed to cool and made slightly basic with concentrated ammonium hydroxide. The brown solid was collected on a Buchner funnel and pressed as dry as possible with a rubber dam. The crude product was dissolved in 2-l. of dioxane, decolorized, filtered and cooled. Twelve liters of cold water were placed in a 16-l. battery jar equipped with a mechanical stirrer, and the cool dioxane solution added in a fine stream with vigorous stirring (note 3). Fine light brown crystals appeared immediately, were allowed to settle, and were then separated from the solution using a Buchner funnel; the 8-nitroquinoline was pressed as dry as possible. The filter cake was dissolved in 3-l. of 3% hydrochloric acid, decolorized, filtered twice, and cooled. Two liters of cold water was added and the solution brought to a pH of 7-8 with concentrated ammonium hydroxide. The 8-nitroquinoline was filtered off, dried, and recrystallized from benzene. Two hundred and eighty-seven grams of nearly white 8-

nitroquinoline was obtained. The compound melted at 88-89°.

Notes

1. This treatment aided in the removal of 2-nitroaniline, since the latter is relatively insoluble in 3% hydrochloric acid.
2. Reeve Angel #802, 50 cm. fluted filter paper was used. This paper has a rapid rate of filtration, however two nested papers were found necessary to prevent decolorizing charcoal from passing through into the filtrate.
3. Rapid stirring and slow addition of the dioxane solution was necessary to minimize the formation of lumps.

COMMERCIAL 8-NITROQUINOLINE (MERCK AND CO. INC.)

Method A

Fifty grams of commercial grade 8-nitroquinoline was placed in a single neck 5-l. round-bottom flask, 3.5 l. of isopropyl ether, and several boiling chips were added and the mixture was heated on the steam bath until the ether boiled. The light yellow solution, which contained an estimated 1-2 g. of dark insoluble impurity, was decolorized and then filtered (note 1) through a 11-cm. sintered glass funnel, heated with a Glas-Col heating mantle (note 2), into a 4-l. filter flask. Almost colorless 8-nitroquinoline separated immediately and after cooling the mixture in an ice bath, 35-40 g. of compound

which melted at 88-89°, was collected by filtration. The process was repeated, adding sufficient fresh isopropyl ether to the cooled filtrate to bring the volume to approximately 3.5 l. (note 3). After a final recrystallization procedure, concentration of the solvent to 300-500 ml. (note 4) and cooling, resulted in an additional 8-12 g. of pure 8-nitroquinoline.

Notes

1. Filtration with gentle suction was essential because the solvent volatilized readily and the precipitated 8-nitroquinoline clogged the filter.
2. A heated filter was used to keep the 8-nitroquinoline in solution during filtration. A sintered glass funnel was found to be the only practical filtering medium. In order to remove the decolorizing charcoal, two No. 1 Whatman filter papers were necessary, and it was not possible to keep these papers seated on a Buchner funnel when using hot isopropyl ether.
3. Approximately three 50 g. runs could be made before the funnel had to be cleaned.
4. Isopropyl ether tends to form peroxides and should not be distilled to dryness.

Method B

Five hundred and ten grams of 8-nitroquinoline was dissolved in 750 ml. of dioxane. The solution was treated twice with decolorizing charcoal, filtered hot and allowed to cool. Twelve liters of cold water was added to a 16-l. battery jar containing a mechanical stirrer and the cool dioxane solution added in a fine stream with vigorous stirring. The precipitate of slightly brown crystals was collected by filtration and allowed to air-dry overnight. The material (note 1) was then dissolved in 1500 ml. of 95% alcohol and decolorized twice using "Darco". Following the second filtration, the brown solution was cooled in an ice bath and the precipitated 8-nitroquinoline collected on a Buchner funnel and air dried. Three hundred and one grams of nearly colorless product was obtained which melted at 88-89°. The alcoholic filtrate was then poured into 15 l. of cold water and 18 g. of crude 8-nitroquinoline was recovered (note 2).

Notes

1. This material was not of sufficient quality to permit its conversion to 1-methyl-8-nitro-2-quinoline.
2. This water-precipitated material had a slightly green cast and was not satisfactory for treatment with dimethylsulfate.

Method C

One thousand grams of 8-nitroquinoline was placed in a 4-l. beaker and 3000 ml. of hydrochloric acid added. The suspension was heated on a hot plate to effect solution, decolorized and filtered. The acid solution was allowed to cool, and one half poured in a thin stream into 12-l. of vigorously stirred water contained in a 16-l. battery jar. Ammonium hydroxide was added until the pH was 7-8. The solids were filtered off and air dried overnight. The other half of the acid solution was treated in a similar fashion (note 1). Three liters of 95% alcohol in a 4-l. beaker was saturated with 8-nitroquinoline, decolorized with charcoal and filtered hot (note 2). On cooling in an ice bath, filtering off and drying (note 3), 455 g. of almost colorless 8-nitroquinoline was obtained. The melting point was 87.5-89°. The alcoholic filtrate was again saturated with partially purified 8-nitroquinoline, decolorized and filtered. From the cooled solution, 32.6 g. of nearly colorless product was collected by filtration. This crop of crystals melted at 87-88°. The filtrate was concentrated to approximately 2-l., decolorized, filtered and allowed to stand overnight. Light yellow needles of 8-nitroquinoline (60 g.) precipitated and were collected by filtration. The alcoholic filtrate was poured into 12-l. of water and 42 g. of relatively crude product collected on a Büchner funnel, and combined with other water-precipitated residues for further purification.

Notes

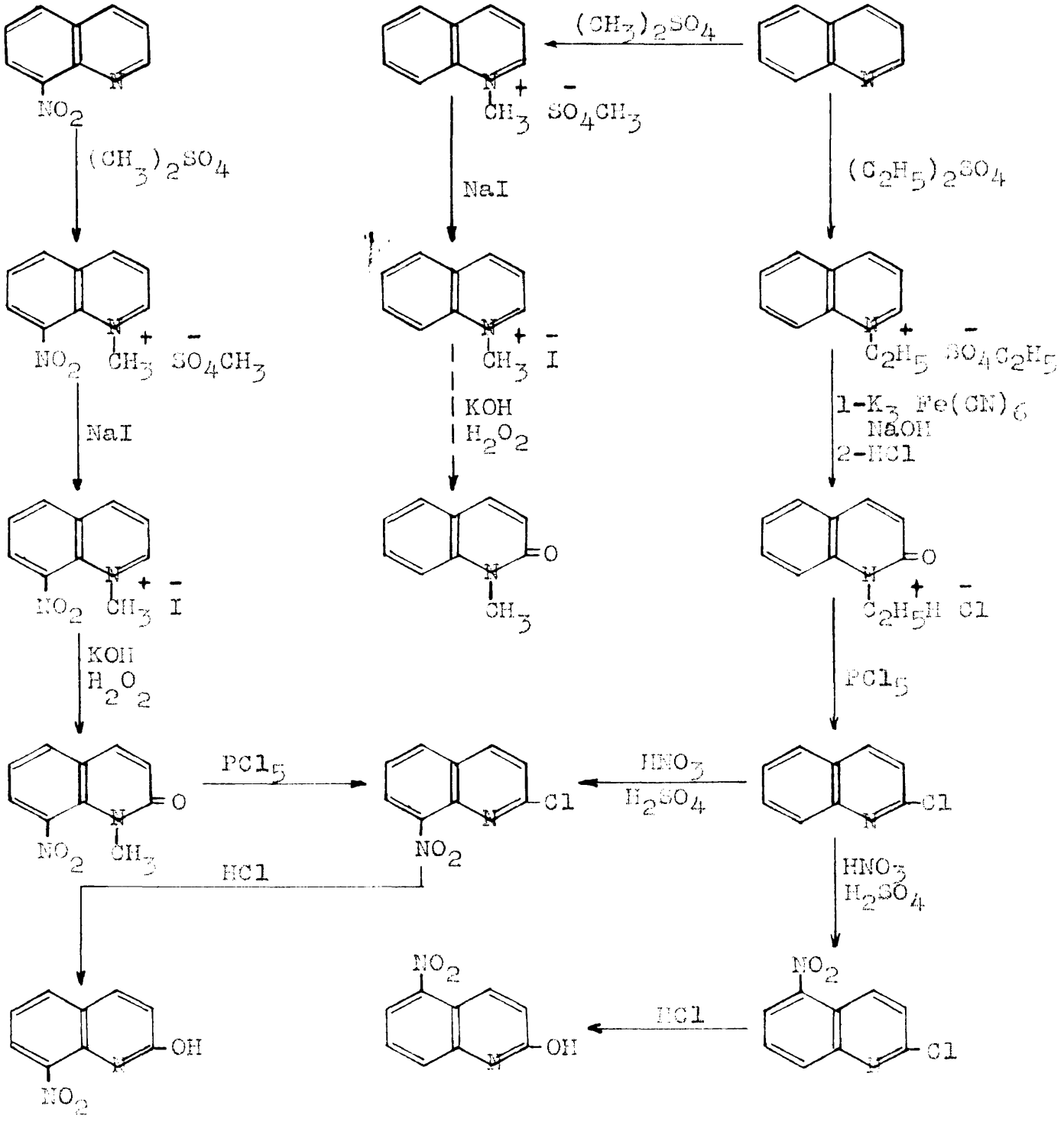
1. Increased dilution aided in the recovery of starting material, and the purification process.

2. Two fluted filter papers were necessary to retain decolorizing charcoal.

3. The recrystallized 5-nitroquinoline was collected on a 10., cm. Büchner funnel, pressed as dry as possible with a dam, and air dried overnight.

CHART II

2-CHLORO-8-NITROQUINOLINE



SECTION II

2-CHLORO-8-NITROQUINOLINE

Discussion

2-Chloro-8-nitroquinoline appeared to offer several chemical reactions which would be of great value for the preparation of intermediates in general quinoline chemistry, and in particular for the synthesis of the 2-hydroxy, 2-chloro and 2-amino-8-nitroquinolines. A very important factor here was determining a synthetic method which could be used on a relatively large scale and which gave a good over-all yield. Therefore, a great deal of time and effort were directed, in the course of this problem, toward the development of a method for the preparation of 2-chloro-8-nitroquinoline, in a manner which was reproducible and would be an acceptable method for "Organic Syntheses".

The two general schemes designated in Chart II, appeared to be the most straightforward approaches to the desired 2-chloro-8-nitroquinoline. It was felt that the final choice of the two methods should be dictated by experimentally determined results. However, several practical considerations were favorable to the method using 8-nitroquinoline as starting material. The compounds without the nitro group had lower melting points than the corresponding nitro derivatives; the nitro compound should be easier to crystallize and manipulate. 8-nitroquinoline was available commercially at

$50.00 per pound compared to 2-chloroquinoline at $75.00 per pound. The nitration of 2-chloroquinoline produced isomers which had to be separated, whereas, the alternate scheme produced only one isomer. Several hundred grams of 6-nitroquinoline were available, also several kilograms of quinoline which could be converted to either 2-chloroquinoline or 6-nitroquinoline.

A review of the literature for the preparation of 2-chloro-6-nitroquinoline starting with quinoline, indicated the possibility of developing a satisfactory synthetic method. The general scheme consisted of forming a quaternary 1-methyl salt, its oxidation to the quinolone and conversion to 2-chloroquinoline, and finally nitration of 2-chloroquinoline and separation of the isomers.

The conversion of quinoline to a quaternary salt using methyl iodide has been accomplished by several workers. Williams[30] treated quinoline with methyl iodide in a tube at 100°. La Coste[31] repeated Williams work at a lower temperature and isolated a salt which melted at 72° when recrystallized from alcohol. Marckwald and Meyer[32] substituted a reflux condenser in place of the closed tube and showed that the product of Williams and of La Coste, which melted at 72°,

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[30]Williams, J. prakt. Chem., 69 359 (1904)

[31]La Coste, Ber., 15 192 (1882)

[32]Marckwald and Meyer, Ibid, 33 1884 (1900)

was a monohydrate which lost water over sulfuric acid. The anhydrous 1-methylquinolinium iodide salt recrystallized from absolute alcohol melted at 133°. Decker[33] used Marckwald and Meyers method on a larger scale but reported no yield or melting point of the product obtained. Freund and Richard[34] used benzene as solvent, decanted the solvent from the salt, washed the salt with ether and reported an almost quantitative yield of 1-methylquinolinium iodide. They also showed that nearly 50% of the product was retained in the mother liquor when alcohol was used as solvent for recrystallization. Kaufmann and Albertini[35] independently worked out a similar procedure to that of Freund and Richard, but did not give the yield or quality of the product which they obtained.

1-Methyl-2-quinolone has been prepared by several chemists. Decker[36] oxidized 1-methylquinolinium iodide with potassium ferricyanide to produce 1-methyl-2-quinolone in unspecified yield and purity. Perkin and Robinson[37] prepared a water solution of the methyl sulfate salt after reacting equal molar quantities of quinoline and dimethyl sulfate, then oxidizing the sulfate salt in this solution to the quino-

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[33] Decker, Ber., 33 2276 (1900)

[34] Freund and Richard, ibid, 42 1107 (1909)

[35] Kaufmann and Albertini, ibid, 42 3779 (1909)

[36] Decker, J. prakt. Chem., [2] 47 31 (1893). Ber., 25 443 (1892)

[37] Perkin and Robinson, J. Chem. Soc., 103 1977 (1913)

lone with potassium ferricyanide. They obtained 55 g. (90%) of nearly pure 1-methyl-2-quinolone. A variety of other methods for preparing 1-methyl-2-quinolone are recorded in the literature, but because of the lack of experimental data, low yields or special equipment required, these methods did not appear suitable for this problem. For example, Friedländer and Müller[38] treated carbostyril with methyl alcohol, methyliodide, and sodium hydroxide and obtained a trace of 1-methyl-2-quinolone. Ostermayer[39] reacted 1-methylquinollinium iodide with zinc chloride and obtained 1-methyl-2-quinolone in an unspecified yield. Roser[40] reacted potassium hydroxide with 2-iodo-1-methylquinollinium iodide and obtained 1-methyl-2-quinolone. Fischer and Neunallinger[41] reported a theoretical yield of 1-methyl-2-quinolone by electrolytic oxidation of the methyl sulfate salt.

2-Chloroquinoline has been prepared from 1-methyl-2-quinolone or from carbostyril. Friedländer and Ostermaier[42] treated carbostyril with phosphorus oxychloride and phosphorus pentachloride at 130-140° and obtained nearly a

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[38] Friedländer and Müller, Ber., 20 2009 (1887)

[39] Ostermayer, Ibid, 18 594 (1885)

[40] Roser, Ann., 202 377 (1880)

[41] Fischer and Neunallinger, Ber., 46 2546 (1913)

[42] Friedländer and Ostermaier, Ibid, 15 333 (1882)

theoretical yield of 2-chloroquinoline. Moser[43] repeated Friedlander and Ostermaier's work but did not confirm the yield. Fischer[44] reacted a mixture of phosphorus pentachloride and phosphorus oxychloride with 1-methyl-2-quinolone to obtain 2-chloroquinoline, in unreported yield. Perkin and Robinson[45] repeated Fischer's work and completed the details for the preparation of 2-chloroquinoline in 85-90% yield. The product melted at 38°. Fischer and Cuthmann[46] used dichlorobenzene as a solvent, dispensed with the phosphorus oxychloride in Fischer's original method and obtained a quantitative yield of 2-chloroquinoline from 1-methyl-2-quinolone. Bing and Rath[47] treated 1-methyl-2-quinolone with a toluene solution of phosgene at 180° and obtained a 70% yield of 2-chloroquinoline, which melted at 37-38°. Ogata, Hishiki and Nanno[48] using essentially the method of Friedländer and Ostermaier obtained 2-chloroquinoline from carbostyril in an 87% yield.

2- and 4-chloroquinoline are nitrated in mixed acid at the 5- or 8-position. Fischer and Cuthmann[49] nitrated 2-

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[43] Moser, op. cit. pp. 376

[44] Fischer, Ber., 31 612 (1898)

[45] Perkin and Robinson, loc. cit.

[46] Fischer and Cuthmann, J. prakt. Chem. 2 93 377 (1916)

[47] Bing and Rath, Ann., 486 76 (1931)

[48] Ogata, Hishiki and Nanno, Bull. Inst. Phys. Chem. Research (Tokyo). C.A. 41 9864 (1947)

[49] Fischer and Cuthmann, op. cit. pp. 382

chloroquinoline and obtained approximately 5% of the 5-nitro isomer and 20% of 8-nitro-2-quinoline. Leinet and Lutz[50] repeated this work with similar results, then developed a method in which they reported a 50% yield of 2-chloro-8-nitroquinoline. They gave a detailed method for this nitration and used steam distillation as a method for separating the 5- and 8-nitro-2-chloroquinolines, the 5-isomer being steam volatile.

Thus it appeared feasible to use Perkin and Robinson's method for the preparation of 2-chloroquinoline in combination with the method of Leinet and Lutz for the nitration of 2-chloroquinoline and separation of the desired 2-chloro-8-nitroquinoline. The yield of the final product should be in the neighborhood of 30%. A problem remained, however, in adapting these methods to a larger scale, since Perkin and Robinson's procedure was based on 50 g. of quinoline, while that of Leinet and Lutz was reported for 30 g. of 2-chloroquinoline.

Various steps in the conversion of 8-nitroquinoline to 2-chloro-8-nitroquinoline have been investigated by early workers in the quinoline field. Lecker[51] prepared the methiodide salt of 8-nitroquinoline by treating a water solution of the methyl sulfate salt with potassium iodide. Lecker and Stravrolopoulos[52] prepared the methyl sulfate salt, oxidized

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[50] Leinet and Lutz, J. Am. Chem. Soc., 68 1329-6 (1946)

[51] Lecker, Ber., 36 251 (1903)

[52] Lecker and Stravrolopoulos, J. prakt. Chem., 68 100 (1903)

the methyl sulfate salt to 1-methyl-8-nitro-2-quinolone with potassium ferricyanide and then converted this quinolone to 2-chloro-8-nitroquinoline with phosphorus pentachloride. Experimental details were lacking and only a statement to the effect that the yield "was good" was recorded. Mislow and Koepfli[52] prepared 2-chloro-8-nitroquinoline through the same sequence of reactions except that they used hydrogen peroxide to oxidize 1-methyl-8-nitroquinolinium iodide to 1-methyl-8-nitro-2-quinolone. Evidently the use of hydrogen peroxide was patterned after an oxidation accomplished by Ing[53] who converted 1,8-dimethyl-8-nitroquinolinium iodide to the corresponding quinolone. Mislow and Koepfli gave no yields or experimental details for the individual steps.

This survey of the literature was encouraging to both reaction sequences except that, in general, the individual steps were carried out on a much smaller scale than was necessary for this problem. An undesirable feature present in both sequences was the use of potassium ferricyanide as an oxidizing agent for the preparation of the 1-methyl-2-quinolones. Another interesting point in connection with the scheme starting with 8-nitroquinoline, concerned apparently a steric hindrance factor of the nitro group in the 8-position. Decker[54] found that 8-nitroquinoline would not

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[52] Mislow and Koepfli, J. Am. Chem. Soc., 68 1554 (1946)

[53] Ing, J. Chem. Soc., 2202 (1931)

[54] Decker, Ber., 38 1144 (1905)

form a methiodide salt directly by treatment with methyl iodide in contradistinction to quinoline. In order to prepare the methiodide salt of 8-nitroquinoline, the methyl sulfate salt was prepared using dimethyl sulfate and then a water solution of this salt was treated with potassium iodide which precipitated 1-methyl-8-nitroquinolinium iodide. Since the method found most satisfactory in this problem involved oxidizing the methiodide salt with hydrogen peroxide, this steric factor of the 8-nitro group, in effect, caused an additional step in comparison to the alternate path. The effectiveness and low volatility of dimethyl sulfate compared to methyl iodide and the ease of converting the methyl sulfate salt to the methiodide with potassium iodide compensated for the additional step.

In connection with the route starting with quinoline, work was done in converting the methyl sulfate salt to the methiodide salt and attempting to use hydrogen peroxide, (5%, 16% and 30%), as an oxidizing agent. These steps were investigated because the use of hydrogen peroxide in the alternate synthetic scheme was found to give a very nearly pure 1-methyl-8-nitro-2-quinolone, whereas potassium ferricyanide produced a very crude quinolone which had to be recrystallized once or twice. Potassium ferricyanide was much less convenient to use than hydrogen peroxide. The results of these investigations were a satisfactory method for making the methiodide salt from the methyl sulfate salt,

but the oxidation step produced only red oils which could not be recrystallized. Therefore the method reported by Perkin and Robinson[55] for the preparation of 2-chloroquinoline in approximately 76% yield was not improved by the experimental work carried out in this research.

Several nitrations of 2-chloroquinoline were carried out, and a separation of the 5- and 8-nitroquinolines attempted by subjecting the mixture to steam distillation. The nitration apparently was satisfactory producing generally 90% of the calculated quantity of a mixture of the 5- and 8-isomers, however the separation was found to be wholly unsuitable for a number of reasons.

Based on ninety grams of 2-chloroquinoline, after eighteen hours of steam distillation, 2-chloro-5-nitroquinoline was not entirely removed. More important, due to the action of the steam, hydrolysis occured to form the respective nitro carbostyrils and hydrochloric acid. This reaction was autocatalytic, the amounts of 5-and 8-nitro carbostyril formed increased as the acid concentration increased.* This created a serious problem since it was desirable to remove as much of the 2-chloro-5-nitroquinoline as possible, yet as the period of steam distillation was continued, the amounts of 5-and 8-nitrocarbostyril also increased.

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[55] Perkin and Robinson, J. Chem. Soc., 103 1977 (1913)

*It is pertinent to draw attention to the preparation of 8-nitrocarbostyril by the acid hydrolysis of 2-chloro-8-nitroquinoline detailed in Section III of this manuscript.

The result of this work on the nitration procedure was the separation of at least four fractions which were mutually contaminated and consequently gave products with large melting ranges.

8-Nitrocarbostyril was obtained as a water soluble fraction by separating the hot solution in the distillation pot from the residue by filtration, and cooling the filtrate in an ice bath. The water insoluble residue was extracted with hot alcohol which left an alcohol insoluble material which melted above 250° and was assumed to be 5-nitrocarbostyril. The crude material obtained from the alcohol extract melted from 100-120° compared to the values of 148° and 152° recorded in the literature for 2-chloro-8-nitroquinoline.

Since it appeared that the steam distillation was undesirable several methods for the separation of the 5-and 8-nitro-2-chloroquinolines were investigated in an attempt to eliminate this process.

It was felt that the salts of the two isomers would have different basicities and that a buffer system could be established which would afford a means of separation. This method of separation proved unworkable because the free bases were quite difficultly soluble and the salts were highly hydrolysed.

2-Chloro-8-nitroquinoline was found to be relatively insoluble in ether and conveniently recrystallized from

acetone. However, 2-chloro-5-nitroquinoline also exhibited similar solubility characteristics. Digestion of the original nitration mixture with either acetone or ether left a residue whose melting range was not appreciably improved by action of these solvents.

Greenbaum[56] reduced the nitration mixture catalytically and attempted to separate an insoluble copper complex of the 8-amino-2-chloroquinoline. His results were not satisfactory.

The experimental work, on the preparation of 2-chloro-8-nitroquinoline utilising 2-chloroquinoline as an intermediate and nitration of the latter compound, indicated the separation of the 5-and 8-nitroquinolines formed in the nitration was a difficult task. As a result of the difficulties encountered in separating these isomers, outlined in the preceeding paragraphs, it was concluded that this preparative scheme was much less satisfactory than the alternate method using 8-nitroquinoline as starting material.

In the method developed for the production of 2-chloro-8-nitroquinoline starting with 8-nitroquinoline, there were several factors which were of prime importance.

It was very necessary to have a good quality of 8-nitroquinoline as starting material. Satisfactory purification procedures have been given in section I of this thesis. It was also found necessary to have the 8-nitroquinoline dry.

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[56] Private communication

Commercial dimethyl sulfate which had been dried and freshly distilled gave the most satisfactory quaternary salt.

1-methyl-8-nitroquinolinium methyl sulfate appeared to be hygroscopic and a satisfactory method of converting the reaction product directly to the methiodide, thus eliminating purification of the methyl sulfate salt, was determined.

In connection with the methiodide salt, two factors were of major importance. Sufficient water to dissolve excess potassium iodide was essential and it was absolutely necessary to recrystallize the 1-methyl-8-nitroquinolinium iodide before the oxidation process.

The working out of a successful oxidation procedure was a matter of determining the proper amounts of solvent, base and hydrogen peroxide and certain other experimental details.

1-Methyl-8-nitro-2-quinolone was dried thoroughly before treatment with phosphorus pentachloride. The chief difficulty with conversion of the quinolone to 2-chloro-8-nitroquinoline using phosphorus penachloride was decomposition of the excess phosphorus pentachloride and phosphorus oxychloride which was formed, without hydrolysing the 2-chloro group. This was accomplished by pouring the hot reaction mass onto the surface of beakers or large glass trays and allowing them to stand overnight. It was possible to add lumps of ice to the solidified reaction mass, in an ice bath, but this procedure was too time consuming and not as satisfactory as the final development.

Several solvents were tried as recrystallizing media for 2-chloro-8-nitroquinoline. Acetone proved to be the most satisfactory, although absolute alcohol could also be used. Important experimental information, in detail, will be found under "notes" in the experimental part of this section.

The final result of considerable experimental work was an eminently satisfactory synthesis of 2-chloro-8-nitroquinoline, in over-all yields of 50-65% based on 8-nitroquinoline. The product melted at 144.4-147.4°. The two steps required in preparing 1-methyl-8-nitroquinolinium iodide proceeded in 80-90% yields. The melting point of the methiodide salt could not be used as an indication of purity, since the salt decomposed between 100 and 140° to a dark oil. It was found that the use of commercial grade 30% hydrogen peroxide as an oxidizing agent for the conversion of 1-methyl-8-nitroquinolinium iodide to 1-methyl-8-nitro-2-quinolone gave 75 to 85% yields based on the methiodide salt. The quinolone was collected on a Büchner funnel, washed thoroughly with water, dried and melted at 131.4-132.4°. It was not necessary to recrystallize this product.

A simplified procedure for the preparation and purification of 2-chloro-8-nitroquinoline from 1-methyl-8-nitroquinolone using phosphorus pentachloride was developed in yields of 80-85%. The product melted at 144.4-147.4° and was of sufficient purity for all other reactions for which it was used.

The experimental directions for the preparation of 2-chloro-6-nitroquinoline have been used with quantities of 6-nitroquinoline from .18 to 4.8 moles. The oxidation procedure, which involved a 20 l. battery jar, was considered as the quantity control factor. It was found convenient to handle approximately 1500 grams of the methiodide salt, and oxidize this salt in three equal portions, over a 16 hour period, rather than utilize larger equipment in the oxidation step.

In view of the satisfactory synthesis based on 6-nitroquinoline and the very real difficulties in the separation of the nitration products of 2-chloroquinoline, it was concluded that the method based on 6-nitroquinoline as starting material, detailed in the experimental part of this section was the most satisfactory procedure for the synthesis of 2-chloro-6-nitroquinoline.

EXPERIMENTAL

1-METHYLQUINOLINIUM IODIDE

Procedure

One hundred and twenty-nine grams of redistilled quinoline was placed in a 1-l. 2-necked flask, and 139 g. (1.1 moles) of redistilled dimethyl sulfate added in a thin stream. The flask was clamped on a steam bath, a mechanical stirrer and reflux condenser fitted into the necks and the mixture heated, with stirring, for four hours. On cooling, greenish-yellow crystals formed a solid mass in the reaction vessel (note 1). The methyl sulfate salt was dissolved in a minimum amount of warm absolute alcohol, transferred to a beaker, and 165 g. (1.1 moles) of solid sodium iodide was added to the vigorously stirred mixture. Stirring was continued for several minutes whereupon a volume of absolute ether, equivalent to that of the alcohol was added. The yellow crystals were collected on a Buchner funnel, pressed as dry as possible, and dried overnight in a vacuum oven at room temperature. This dry salt was digested with benzene (note 2), then separated by filtration and dissolved in absolute alcohol. The alcoholic solution was filtered (note 3), decolorized with charcoal, refiltered and cooled in an ice bath. Absolute ether (300 ml.) was added to the cool solution, yellow crystals precipitated, were removed by filtration and dried in a vacuum desiccator. One hundred and eighty-eight

grams (69.5%) of 1-methylquinolinium iodide, which decomposed above 130° was obtained from this procedure.

Notes

1. An attempt was made to recrystallize this salt from absolute alcohol and absolute ether. The light green crystals apparently are very hygroscopic and would not remain crystalline on exposure to air.
2. Benzene was used to remove any unconverted quinoline.
3. Some unidentified, alcohol insoluble, material was present and was removed at this point.

1-ETHYL-2-QUINOLONE HYDROCHLORIDE

Procedure

One hundred and twenty-nine grams (1 mole) of quinoline (note 1) was placed in a 1-l. 3-necked flask on a steam bath. A stirrer, reflux condenser and dropping funnel was fitted in the flask, the quinoline stirred vigorously, and 139 g. (1.1 moles) of diethyl sulfate (note 2) added dropwise over a two hour period. After addition of the diethyl sulfate, the mixture was heated for two hours, cooled and dissolved in 250 ml. of cold water. The water solution was transferred to a 4-l. Pyrex jar contained in an ice bath, stirred, and allowed to cool to 0°. Two separate solutions,

660 g. (2 moles) of potassium ferricyanide in 2-l. of water (note 3) and 164 g. (4.1 moles) of sodium hydroxide in 300 ml. of water (note 4) were added from dropping funnels at such a rate that all the sodium hydroxide solution had been added when half of the potassium ferricyanide solution was added. The addition of the oxidising agent required approximately 2½ hours, the temperature was maintained at -5° for two hours and +5° for the last half hour. Stirring was continued and the solution was allowed to warm to room temperature over a period of five hours. The strongly basic solution was extracted three times with 500-ml. portions of ether and the combined extracts were dried over potassium hydroxide and concentrated to one-third of their original volume on a steam bath. The ether solution was then saturated with dry hydrogen chloride gas whereupon nearly white 1-ethyl-2-quinolone hydrochloride separated. The product melted at 124.5-129.4° and weighed 102 g. (48%).

Notes

1. "Paragon" practical grade quinoline dried over sodium hydroxide and freshly distilled was used as starting material.
2. The supply of dimethyl sulfate was temporarily exhausted and diet yl sulfate used as a substitute. According to Decker[57] diethyl sulfate is inferior to dimethyl sulfate

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[57] Decker, Ber., 38 1149 (1905)

for this type reaction.

3. The solution of potassium ferricyanide was prepared in advance by heating the solid salt with the water and allowing the solution to cool in the Pyrex separatory funnel. A length of copper wire was necessary to keep the funnel unclogged, since the potassium ferricyanide had a tendency to crystallize on cooling.

4. The sodium hydroxide solution was prepared in advance and kept in an ice bath until used.

2-CHLOROQUINOLINE

Procedure

One hundred and two grams (.52 mole) of 1-ethyl-2-quinolone hydrochloride was placed in a 1-l. 3-necked flask, equipped with magnetic stirrer, thermometer and reflux condenser. One hundred and ten grams (.53 mole) of powdered phosphorus pentachloride (note 1) was added and the mixture warmed gently (note 2) until liquid. The brown solution was stirred and heated under reflux (note 3) for about six hours, then allowed to stand overnight. Eight hundred milliliters of ice water was added slowly (note 4) while the mixture was kept cold in an ice bath. A 10% sodium hydroxide solution was added until the suspension was somewhat basic (note 5) and extracted three times with 200 ml. portions of ether.

The combined ether extracts were dried over magnesium sulfate and the ether was removed on a steam bath. The residue was distilled under good water pump vacuum; the fraction collected at 13₄-14₄°/15 mm., as a light yellow oil solidified to nearly white crystals on cooling.

Notes

1. It was necessary to handle the phosphorus pentachloride and run the reaction in an efficient hood.
2. The reaction is exothermic. The mixture was heated cautiously until the solids liquified. A Glas-Col mantle was used to supply heat.
3. The internal temperature was 110°.
4. Ice water was added very slowly to the flask, in the hood, until unreacted phosphorus pentachloride had decomposed.
5. Base was added until alk-acid paper indicated a pH of 8-10.

NITRATION OF 2-CHLOROQUINOLINE

Procedure

In a 4-l. battery jar, nested in an 8-l. battery jar was placed 450 ml. (8.25 moles) of concentrated sulfuric acid and 300 ml. (8.76 moles) of fuming nitric acid (note 1).

A mechanical stirrer (note 2) and thermometer were adjusted in the center jar, 2 to 3 inches of chloroform added to the outside jar and the acid mixture stirred vigorously. Dry ice was added to the chloroform bath until the temperature of the mixed acid dropped to -10°. A previously prepared solution of 90 g. (.55 moles) of commercial 2-chloroquinoline in 60 ml. (1.0 moles) of fuming nitric acid (note 1) was added dropwise over a period of one hour. The temperature was kept at -10° ± 5 during this addition period, by placing dry ice in the chloroform bath, and then at -10° for an additional hour. The solution was stirred continuously for 16 hours and allowed to come to room temperature during this period. The yellow solution was poured onto 4-1. of cracked ice and allowed to stand until most of the precipitate had settled. The solids were separated by filtration, and washed with water until nearly acid free. The nitration mixture was transferred to a beaker, containing 400-500 ml. of water. The suspension was manually stirred and concentrated ammonium hydroxide added until the slurry was basic. The solids were collected on a Buchner funnel and washed several times with water. The precipitate was air-dried on the filter overnight, transferred to a 3-l., 3-necked flask and subjected to steam distillation until 2-chloro-5-nitroquinoline no longer came over (note 3).

The steam volatile 2-chloro-5-nitroquinoline was dried and a sample recrystallized from ether. Nineteen grams (16.5%)

of 2-chloro-3-nitroquinoline which melted at 119-125° was obtained in this manner. After recrystallization from ether, this material melted at 128.4-130.4°.

The contents of the steam pot was filtered hot, insoluble material was allowed to dry, and the filtrate cooled in an ice bath. From the filtrate, 7.3 g. of water soluble material, which melted at 130-136°, was collected on a Buchner funnel, transferred to a 1-l. round-bottomed flask containing 175 ml. of 20% hydrochloric acid (note 4) and heated under reflux for two hours. Five hundred milliliters of water was added and the solution again brought to a boil, filtered, and the filtrate cooled in an ice bath. Bright yellow 6-nitrocarbostyril (6.6 g.) which melted at 144.4-146.4° was obtained as the water soluble fraction.

The water insoluble residue was treated with 1500 ml. of hot alcohol; insoluble material was discarded and the alcoholic solution was decolorized and concentrated to approximately 600 ml. Forty grams of very crude 2-chloro-3-nitroquinoline, which melted at 100-120°, was obtained from this solution. The crude material was recrystallized twice from acetone using decolorizing charcoal in each operation. The yield of 2-chloro-3-nitroquinoline, which melted at 134.4-139.4° was 23 g. (20%).

Notes

1. Commercial grade fuming nitric acid was used which had

a specific gravity of 1.5.

2. A Hershberg stirrer made from tantalum wire was found to be satisfactory.

3. The steam distillation was carried on for 16 hours continuously and on the following day for 9 hours.

4. Approximately 20% hydrochloric acid was made by diluting 87 ml. of concentrated acid to a volume of 175 ml.

1-METHYL-6-NITROQUINOLINIUM Iodide

Procedure

Three hundred grams (1.72 moles) of purified 6-nitroquinoline (note 1) was placed in a 2-l., 2-necked round-bottomed flask which was clamped on a steam bath. A Hershberg stirrer was fitted in the flask and 220 g. (1.74 moles) of freshly distilled dimethyl sulfate (note 2) was added in a thin stream. A reflux condenser was attached to the second opening and the mixture was heated on a steam bath with stirring, for six hours (note 3). The addition product was allowed to stand overnight, then dissolved in 400 ml. of water and transferred to a 3-l. beaker equipped with a stirrer. To this cool stirred solution was added 260 g. (1.73 moles) of sodium iodide in 165 ml. of water, and then 26 g. (.17 moles) of solid sodium iodide. The mixture was

stirred for one-half hour at room temperature and then for three-quarters of an hour in an ice bath. The heavy red precipitate was collected on a Büchner funnel, pressed as dry as possible, then spread in a glass tray and air dried overnight. The orange-red 1-methyl-6-nitroquinolinium iodide (note 4) was recrystallized from absolute alcohol (note 5), separated by filtration, and washed well with absolute ether (note 6). The yield was 4.96 g. (91%) of orange-red product.

Notes

1. The satisfactory quality of 6-nitroquinoline was nearly white and melted no lower than 68-69°. It was also dry.

2. Dimethyl sulfate was conveniently purified by drying for twenty-four hours over barium oxide, filtering and distilling in glass apparatus with ground glass connections. Stopcock grease could not be used. The fraction distilling at 185-189°/760 mm. was collected in a dark brown glass-stoppered bottle.

3. It was necessary to check the stirring frequently because in some cases the salt solidified before the termination of the heating period.

4. This compound is a vigorous sternutator. It should be kept in a closed container and handled in a hood.

5. It was absolutely necessary to recrystallize the meth-

iodide salt before the oxidation process. Approximately 3200 ml. of absolute alcohol were required for this recrystallization.

6. Washing with ether removed some unidentified material from the salt and aided in drying the product.

1-METHYL-6-NITRO-2-QUINOLONE

Procedure[6]

An 8-l. Pyrex battery jar, nested inside a 20-l. battery jar, was equipped with a Hershberg stirrer and thermometer. Four hundred and ninety-six grams (1.56 moles) of 1-methyl-6-nitroquinolinium iodide and 2,480 ml. of alcohol were added and the suspension stirred rapidly while a solution of 250 g. (4.45 moles) of potassium hydroxide in 995 ml. of water (note 1) was added at a rate such that the temperature did not rise above 30°. Ice was then added to the outer battery jar, and 1985 ml. of 30% hydrogen peroxide (note 2) was added dropwise at such a rate that the temperature of the reaction mixture remained between 30 and 35°. This operation required approximately two hours. The suspension was stirred for 20 minutes more, 300-400 g. of ice was added and 1-methyl-6-nitro-2-quinolone was separated from

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[6]An alternate method of preparation of this compound is described in the author's M.S. thesis, University of Maryland 1953.

the solution by filtration at a temperature of 10°. The granular brown precipitate washed with water changed to a lemon-yellow solid (note 3). The product was air-dried overnight, then in an oven at 60° to constant weight. The 1-methyl-3-nitro-2-quinolone melted at 131.4-132.8° and weighed 2.7 g. (76%).

Notes

1. The potassium hydroxide solution was prepared in advance and kept in an ice bath until the temperature was about 15-20°.

2. Commercial 30% hydrogen peroxide was found satisfactory. The specific gravity was checked for each bottle, and from tabular values in Lange's Handbook[58], the percent in the samples examined was found to be in the range 27-30%.

3. If the washed product is dull yellow and appears to be waxy, rather than nicely crystalline, it must be dried without heating and recrystallized. Benzene or methanol are satisfactory recrystallizing solvents.

2-CHLORO-3-NITROQUINOLINE

Procedure

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[58] N.A. Lange, "Handbook of Chemistry", 4th edition Sandusky, Ohio: Handbook Publisher, Inc., 1946 pp. 1336

In a 1-l. single-necked flask equipped with a Glas-col heating mantle (note 1) and magnetic stirrer, was placed 131 g. (.635 moles) of 1-methyl-3-nitro-2-quinolone. One hundred and forty-one grams (.677 moles) of phosphorus pentachloride was powdered (note 2), added to the reaction flask and a reflux condenser attached. The flask was shaken to effect mixing of the powder and then heated cautiously until the solids were liquified (note 3). The solution was stirred and heated under reflux for six hours. The hot black liquid was poured onto the inner surface of a 4-l. beaker (note 4), where it rapidly solidified, and permitted to stand in the hood overnight. The light gray solids were then quenched with 2-3 l. of ice cold water, washed and powdered as much as possible, collected on a Büchner funnel and air-dried overnight. The gray solids were powdered as fine as possible, washed with 6 l. of ice water (note 5), and dried. The 2-chloro-3-nitroquinoline was recrystallized from acetone with use of decolorizing charcoal. One hundred and sixteen grams (67%) of 2-chloro-3-nitroquinoline was obtained which melted at 145.4-147.4° (note 6).

Notes

1. The metal holder for the Glas-col must be omitted when using a magnetic stirrer. It is necessary to run this reaction in a good hood.

2. A good grade of phosphorus pentachloride was necessary.

It was found most desirable to store the phosphorus pentachloride bottle in a metal container containing calcium chloride, and sealed with adhesive tape. The phosphorus pentachloride was pulverized and handled in the hood.

3. The reaction is exothermic and the heat must be controlled until the initial vigorous reaction subsides.

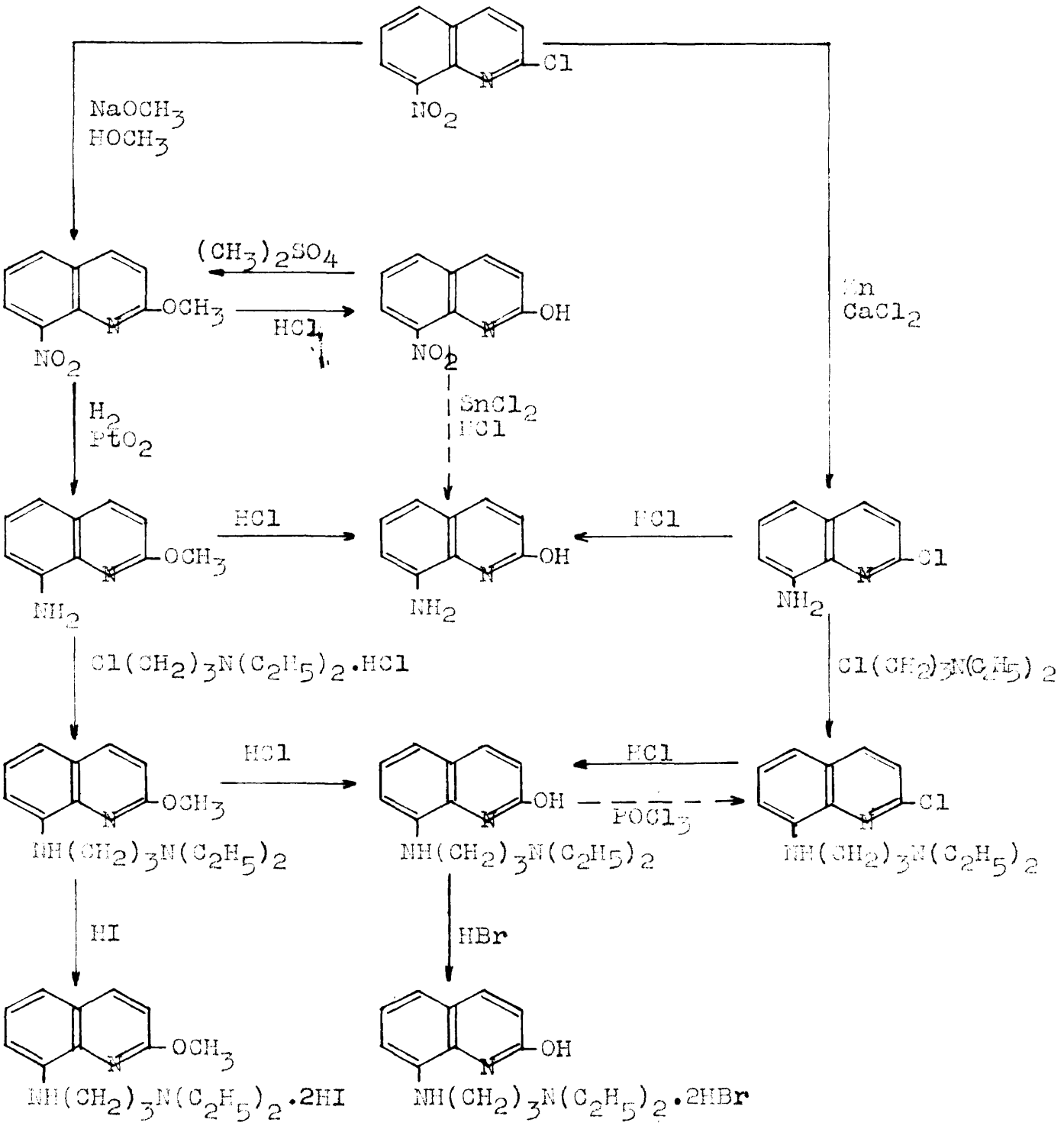
4. Pyrex glass trays are more satisfactory if they are available.

5. It was important to grind the crude precipitate as fine as possible in order to wash out the acidic materials before recrystallisation. A pebble mill would be most suitable.

6. The acetone filtrate was diluted with water to precipitate a brown residue. Similar residues from other runs were recrystallized from acetone to obtain further quantities of 2-chloro-6-nitroquinoline.

CHART III

8-(3-DIETHYLAMINOPROPYLAMINO)-CARBOSTYRIL



SECTION III

8-(3-DIETHYLAMINOPROPYLAMINO)-CARBOSTYRIL

Discussion

Three ideas were considered basic in the preparation of the desired 2-hydroxy, 2-amino and 2-chloro-8-(diethylamino-propylamino)-quinolines. First in order to minimize negative results, three individual routes to the final products were investigated. Second, a slight priority was assigned to what would appear to be the most direct synthesis, e.g., the synthesis of the corresponding 8-amino-2-substituted quinoline and coupling with 1-chloro-3-diethylaminopropane. Third, it was tentatively considered that the 2-chloro and 2-hydroxy compounds should be interconvertable, and that the 2-amino compound should logically follow from the 2-chloro drug. As a consequence of this third consideration, a good source of 2-chloro-8-nitroquinoline was essential.

Superimposed on these ideas was the factor of the amount of final product required, consequently the need for individual steps of high yield was an important consideration. To emphasize the importance of this practical aspect, it is noted that the preparation of 8-(3-diethylaminopropylamino)-carbostyril required eight steps. As a minimum goal, it was felt that individual steps should be developed to a yield of 70%. Thus for one hundred grams of

6-(3-diethylaminopropylamino)-carbostyril eleven hundred and forty grams of 6-nitroquinoline would be required. Not considering other necessary chemicals, the cost for starting material alone would be approximately ($12.00).

The three schemes selected for the initial investigation of a suitable synthesis for 6-(3-diethylaminopropylamino)-carbostyril starting with 2-chloro-6-nitroquinoline are given in chart III. The most direct route, which was considered first, visualized the formation of 6-aminocarbostyril ("nucleus") and coupling with 1-diethylamino-3-chloropropane.

Lecker and Pollitz[59] prepared 6-nitrocarboxtyril from 2-bromo-6-nitroquinoline, by hydrolysis, using concentrated hydrochloric acid. Lecker and Stravrolopoulos[60] hydrolysed 2-chloro-6-nitroquinoline to 6-nitrocarbostyril using concentrated hydrochloric acid. Fischer and Guthmann[61] repeated the hydrolysis of 2-chloro-6-nitroquinoline with concentrated hydrochloric acid and recorded a melting point of 168° as compared to the previously reported value of 163°. Mislow and Koepfli[62] used Fischer and Guthmann's method for the preparation of 6-nitrocarbostyril. None of these investigators gave any experimental details for their work. A

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[59] Lecker and Pollitz, J. prakt. Chem., 2 64 91 (1901)

[60] Lecker and Stravrolopoulos, Ibid, 2 66 101 (1903)

[61] Fischer and Guthmann, Ibid, 93 353 (1916)

[62] Mislow and Koepfli, J. Am. Chem. Soc., 68 1354 (1946)

method, in detail will be found in the experimental part of this section for the preparation of 8-nitrocarbostyril in a yield of 92%. The product melted at 160.7-162.7°.

A search of the literature revealed that all of the aminocarbostyrils had been prepared except the 3 and 8-aminocarbostyrils. Since 5,6,7 and 8-nitrocarbostyrils had long been known, the question arose as to why the 8-amino compound had not been prepared. Considerable work indicated that this compound was not readily available by a reduction of 8-nitrocarbostyril. A resume of the aminocarbostyrils will be found in section IV of this work, with a summary of the reductions attempted and the final synthesis, by two methods, of the hitherto unknown 8-aminocarbostyril.

A second method for the preparation of 8-(3-diethylaminopropylamino)-carbostyril appeared feasible through 8-amino-2-chloroquinoline, thence to 2-chloro-8-(3-diethylaminopropylamino)-quinoline and by hydrolysis to the desired product. The difficulties here seemed to lie in finding a suitable method for reducing the 8-nitro group without removing the active 2-chloro group, and to determine under what conditions the chloro group could be replaced by the hydroxy group with the "side chain" attached. These steps were determined in the final synthesis of 2-chloro-8-(3-diethylaminopropylamino)-quinoline and are recorded in section V. The preparation of 8-(3-diethylaminopropylamino)-carbostyril from the hydrolysis of the 2-chloro drug, on an experimental

basis, is included in the experimental part of this section.

The third method proposed for preparing 8-(3-diethylaminopropylamino)-carbostyril involved the greatest number of steps, but appeared to be the second most promising way of obtaining the desired product, since Mislow and Koepfli[63] had prepared 8-(3-diethylaminopropylamino)-2-methoxyquinoline for testing as an anti-malarial drug (SN 13058). Therefore, if hydrolysis of the 2-methoxy group could be effected efficiently, this sequence of reactions should lead to the 2-hydroxy drug. Because of the difficulty encountered in preparing 8-aminocarbostyril, the preparation of 8-(3-diethylaminopropylamino)-carbostyril was realized through the hydrolysis of 8-(3-diethylaminopropylamino)-2-methoxyquinoline. However some very important improvements were made in the method Mislow and Koepfli used in preparing SN 13058. It is pertinent to describe these improvements and compare the results obtained in this research with that reported by the above workers.

Mislow and Koepfli used 8-nitroquinoline as starting material and prepared 2-chloro-8-nitroquinoline using essentially the same reagents as reported in section II of this thesis. They converted 2-chloro-8-nitroquinoline to 8-nitrocarbostyril using hydrochloric acid. The 8-nitrocarbostyril was then converted to 2-methoxy-8-nitroquinoline

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[63] Mislow and Koepfli, J. Am. Chem. Soc., 68 1553-1555 (1946)

using the method of Decker and Pollitz.[4] This method consisted of treating the sodium salt of 6-nitrocarbostyril with dimethyl sulfate in the presence of sodium hydroxide. Mislow and Koepfli did not give experimental details or yields for any of the six steps but recorded a 16% overall yield, of 2-methoxy-6-nitroquinoline based on 6-nitroquinoline.

The synthesis of 2-methoxy-6-nitroquinoline developed in this problem eliminated the formation of 6-nitrocarbostyril. A method was determined for converting 2-chloro-6-nitroquinoline to 2-methoxy-6-nitroquinoline in essentially quantitative yields.* The over-all yield of 2-methoxy-6-nitroquinoline, detailed in section II and III of this thesis, was accomplished in 45 to 60% yields compared to 16% reported by Mislow and Koepfli.

The reduction of 2-methoxy-6-nitroquinoline to 6-amino-2-methoxyquinoline was carried out catalytically in absolute alcohol using platinum oxide as the catalyst. Mislow and Koepfli reported a yield of 90% on this step compared to 80-85% obtained in this work. This particular step was found to be the least satisfactory of the sequence, because of the limited size of the equipment available for low pressure hydrogenation. Some thirty individual catalytic reductions

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[4]Decker and Pollitz, J. prakt. Chem., 64 92 (1901)

*The author wishes to thank Mr. Y.I. Pratt for determining the experimental details in converting 2-chloro-6-nitroquinoline to 2-methoxy-6-nitroquinoline and preparing some 100 grams of the latter compound for this problem.

were made in preparing 8-amino-2-methoxyquinoline. This factor was conducive to some investigations in alternate methods of reduction. Several attempts were made to reduce the nitro group using sodium hydrosulfite under various conditions and with different solvents. These preliminary experiments were not successful.

It is interesting to note that reports have been made of the rearrangement of the 2-methoxy group to the isomeric 1-methyl-2-quinolone under the influence of heat.[65,66] Distillation was used in purification of 8-amino-2-methoxy-quinoline at oil bath temperatures of 130-150° and .05 mm. pressure. Eighty to eighty-five percent yields of product were obtained which melted at 72.9-74.9°(literature value 74-75°). The 8-amino-1-methyl-2-quinolone melts at 183.7-184.7° (see section V) and thus on the basis of melting points it appears that under the distillation conditions used, rearrangement of 8-amino-2-methoxyquinoline to 8-amino-2-methyl-2-quinoline was too slight to be detected.

Mielow and Koepfli coupled 8-amino-2-methoxyquinoline with 1-chloro-3-diethylaminopropane hydrochloride in ethyl alcohol solution which was heated under reflux for five days, adding "side chain" hydrochloride (1.1 moles/mole nucleus) on each day. They obtained a 78% yield of final product. It was found that 80-86% yields could be obtained in three days using

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[65]Knorr, Ann., 336 107 (1906)

[66]Meyer and Beer, Monatsh., 34 1173 (1913)

only .4 as much "side chain" hydrochloride. Their over-all yield of 6-(3-diethylaminopropylamino)-2-methoxyquinoline was 11% compared to approximately 33% obtained in this work. They prepared 9 grams of drug (SN 13050); the total prepared in this problem was approximately 200 grams.

The most convincing argument for the necessity of working individual yields to a high level in a problem of this type, may be made most striking, if the amounts of starting material required for the preparation of 200 grams of 6-(3-diethylaminopropylamino)-2-methoxyquinoline by the method available in the literature and the method developed in this investigation are compared. For a 11% over-all yield, 1100 grams of 6-nitroquinoline would be required, compared to 360 g. for a 33% over-all yield.

The above comparison reveals that, experimental details have been determined, one step eliminated and the yield improved three fold for the preparation of 6-(3-diethylaminopropylamino)-2-methoxyquinoline.

Mislow and Koepfli prepared the dihydroiodide salt of 6-(3-diethylaminopropylamino)-2-methoxyquinoline and gave the melting point as 140-141°. To further the evidence that the compound prepared in this work was the same as that obtained by Mislow and Koepfli, a 1 g. sample was converted to the dihydroiodide and the melting points compared. The salt prepared in this laboratory melted at 140.4-141.4° in agreement with the value reported in the previous work.

It has been reported that the 2-and 4-alkoxyquinolines are hydrolyzed under acid conditions. For example, Friedländer and Ostermaier[67] hydrolyzed 2-ethoxyquinoline in a tube at 120° with concentrated hydrochloric acid. Carbostyril and ethyl chloride were given as products. It has also been shown, however, that substituents could effect the ease of hydrolysis very markedly. Buchmann and Hamilton[68] found that 4-chloro-2-ethoxyquinoline was cleaved in 20-30 minutes using 6N (~ 20%) hydrochloric acid, whereas the isomeric 2-chloro-4-ethoxyquinoline required refluxing with 20% hydriodic for 10 hours. In the light of this limited data it was hoped that the hydrolysis of 8-(3-diethylaminopropylamino)-2-methoxyquinoline would occur relatively readily, since the 2-alkoxy group appeared most liable to replacement by the hydroxy group. However, the effect of various substituents, their position and the ease of hydrolysis could not be correlated from this limited data and thus it could not be ascertained what effect the 3-diethylaminopropylamino group in the 8-position would have on the reaction.

Another consideration was the base solubility of the product. Carbostyril itself is acid and base soluble and consequently the 2-hydroxy group exhibits some degree of a phenolic property. The problem arose as to whether

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[67] Friedländer and Ostermaier, Ber., 15 335 (1882)

[68] Buchmann and Hamilton, J. Am. Chem. Soc., 64 1357 (1942)

the desired compound would precipitate from a basic solution. Ammonium hydroxide was used in the experimental procedure to make the reaction medium basic, although subsequent data indicated that the drug was somewhat soluble in other basic materials.

The results, determined experimentally, showed that the conversion of 8-(3-diethylaminopropylamino)-2-methoxyquinoline to 8-(3-diethylaminopropylamino)-carbostyril occurred in 70-75% yields by refluxing with 6N (~20%) hydrochloric acid for periods of 5 to 6 hours. It was found that reflux periods of 4 or less hours with insufficient amounts of 6N hydrochloric acid resulted in partial hydrolysis, leaving a residual liquid which would not crystallize. Retreatment of this residual liquid for 2 hours with 6N hydrochloric acid completed hydrolysis. The crude hydrolyzed product was found to contain an impurity which was not readily soluble in ethylacetate. Since 8-(3-diethylaminopropylamino)-2-methoxyquinoline probably contained some unreacted 8-amino-2-methoxyquinoline, a possibility for this insoluble impurity would be 8-aminocarbostyril resulting from the acid hydrolysis. Although the impurity was never identified as such, the data in section IV on the solubility and the method of preparation of 8-aminocarbostyril indicates that this is a reasonable assumption.

8-(3-diethylaminopropylamino)-carbostyril is a light greenish-yellow solid which decomposed at 62.4-63.8° after

three recrystallizations, first from ethylacetate and twice from acetone using fresh decolorizing charcoal with each recrystallization. The compound was soluble in absolute ethyl alcohol, methyl alcohol, dioxane, benzene, diethyl cellosolve, dimethyl cellosolve, et er and Skelly "F". The drug was soluble in 6N hydrochloric acid and precipitated from acid solution with concentrated ammonium hydroxide. Because of the phenolic nature* of the 2-hydroxy group the compound was soluble in 5% sodium and potassium hydroxide.

8-(3-Diethylaminopropylamino)-carbostyril formed a dihydrobromide which melted at 174.6-179.7° after one recrystallization. One attempt to prepare the dihydroiodide indicated that this salt was unstable.

An attempt was made to determine the percent purity of the drug using the method developed by Craig and co-workers.[69,70,71,72] The ultraviolet absorption spectrum of the drug was obtained in spectro grade isooctane using a Beckman Model DU quarts spectrophotometer. Molar extinction coefficients were determined from the formula $\varepsilon = \frac{A}{ct}$; where ε is the

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*However 8-(3-diethylaminopropylamino)-carbostyril does not give a color with 1% ferric chloride.

[69] Craig, L.C. J. Biol. Chem., 155 519 (1944)

[70] Craig, L.C., Columbic, Highton and Titus, Ibid, 161 321 (1945)

[71] Craig, L.C., Columbic, Highton and Titus, Science, May, 1948

[72] Williamson and Craig, J. Biol. Chem., 168 687-697 (1947)

molar extinction coefficient, A the optical density, c the concentration in moles/l. and t the thickness of the absorbing solution in cm. A plot of ε vs. the wave length was made to determine the absorption maxima. Maxima were found at 245, 275, and 365mμ.

Using these absorption maxima in connection with the counter current distribution technique of Craig et al., it was found that the method was not readily applicable to 8-(3-diethylaminopropylamino)-carbostyril for two reasons. The partition ratio of the drug was not independent of concentration (see table 2) and the organic species was not quantitatively extracted from M potassium hydroxide with benzene or cyclohexane. Using a sodium acetate-acetic acid buffer system with cyclohexane or benzene and M potassium hydroxide, consistent results could not be obtained for a partition ratio using the same reagents and conditions. This was to be expected since the compound showed a definite solubility in bases. Two eleven plate distributions were complete failures. Ammonium acetate-acetic acid buffer was tried with benzene and using 5N ammonium hydroxide to release the organic material to the organic solvent. This system was found to be more reproducible but the partition ratio over the range of concentrations used was not constant.

Ninety-four grams of 8-(3-diethylaminopropylamino)-carbostyril (UM 200 S) was submitted for toxicity tests

using the rhesus monkey.* It was found that this compound was particularly non-toxic. Doses as high as 1/2 Gm./Kg. body weight for two week periods never produced serious toxic reactions. As a result of these tests the drug was not considered applicable as a poliomyelitidal or as an anti-malarial.

The results of these toxicity tests were, in a sense, unexpected, since the particular side chain was chosen, for poliomyelitis work, on the basis of its effect. From the malarial program, it was found that quinoline compounds with a side chain having two or three carbons between the nitrogens, affected the central nervous system[**] and were contraindicated as anti-malarials because of their toxicity. In this work the side chain, (diethylaminopropylamino), was not varied and the major problem was the synthesis of the "nucleus".

1-bromo-3-chloropropane was prepared after the method of Cloke, Anderson, Lochmann and Schmidt[73] by treating trimethylene chlorohydrin with phosphorus tribromide. The resulting 1-bromo-3-chloropropane, after distillation, was

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*The author wishes to express his appreciation to Dr. L.H. Schmidt, Christ Hospital, Mount Auburn, Cincinnati, Ohio for the results of the toxicity tests.

**This type of toxic reaction was termed the plasmocid effect.

[73]Cloke, et al., J. Am. Chem. Soc., 53 2774 (1931)

reacted with diethylamine using essentially the method of Marxer,[74] and the desired 1-chloro-3-diethylaminopropane isolated and purified by distillation.

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[74]Marxer, Helv. Chim. Acta., 24, 209E (1941)

EXPERIMENTAL

8-NITROCARBOSTYRIL

Procedure

In a 5-l. flask were placed 173 g. (.83 moles) of 2-chloro-8-nitroquinoline and 3-l. of 18% hydrochloric acid (note 1). Boiling chips were added and the mixture heated under reflux for four hours. One liter of water was added and the solution brought to a boil again, then filtered hot. The filtrate was cooled in an ice bath, the precipitate separated from the solution by filtration, the filtrate set aside for further separation, and the solid washed with several portions of diluted (note 2) ammonium hydroxide. The bright yellow 8-nitrocarbostyril, dried at 95° for 18 hours, weighed 133 g. (84%) melted at 162-163°. The original filtrate was made basic with concentrated ammonium hydroxide and cooled in an ice bath; the yellow precipitate was collected on a Büchner funnel, washed with water and recrystallized from methyl alcohol (note 3) with use of decolorizing charcoal. Twelve grams of 8-nitrocarbostyril, which melted at 160.7-162.7°, was obtained from the methyl alcohol on cooling (note 4). The total yield of 8-nitrocarbostyril was 92% based on 2-chloro-8-nitroquinoline.

Notes

1. Thirteen hundred milliliters of concentrated hydro-

chloric acid were added to 1700 ml. of water.

2. Three hundred milliliters of concentrated ammonium hydroxide was diluted to a liter volume and used as wash liquid.

3. Approximately 250 ml. of alcohol was required for this recrystallization.

4. Evaporation of the methyl alcohol solution to 20 ml. gave 3 g. of dark brown material which was discarded.

2-METHOXY-6-NITROQUINOLINE

Method A*

Eight and three-quarter grams (.38 gram atoms) of sodium was dissolved in 1000 ml. (24.7 moles) of absolute methyl alcohol (note 1) contained in a 2-l. single-necked flask. Boiling chips were added to the solution (note 2). Then 45 g. (.22 mole) of 2-chloro-6-nitroquinoline was introduced into the thimble of a Soxhlet extractor and fitted to the flask and the apparatus was supported on a steam bath. The solution was heated under reflux for 7-8 hours, using an efficient condenser. The solution was cooled and poured into 2.5 l. of vigorously stirred ice

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*If commercial sodium methoxide was used in absolute methanol the yield was smaller (72%).

water. A bright white precipitate formed immediately, was collected on a Buchner funnel and washed with water until alkali-free. The 2-methoxy-6-nitroquinoline after drying in a vacuum desiccator overnight weighed 42 g. (95.5%) and melted at 123.5-125.5°.

Notes

1. Absolute methyl alcohol was prepared after the method reported in Vogel.[75]

2. The solution had a tendency to bump toward the end of the reflux period.

Method B

Forty-three grams (.225 mole) of 6-nitrocarbostyril was placed in a 2-l. beaker supported on a steam bath and provided with a mechanical stirrer and thermometer. Sodium hydroxide (9.9 g.) (.25 mole) in 22 ml. of water was added and the suspension was stirred and hot water added until solution was complete. The temperature was raised to 80° and 22 ml. (.236 mole) of dimethyl sulfate added dropwise over a period of one hour. Sodium hydroxide (10 ml. of 30%) was then added followed by 5 ml. of dimethyl sulfate

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[75] A.I. Vogel, "A Textbook of Practical Organic Chemistry including Qualitative Organic Chemistry", Longmans, Green and Co., New York 1948 pp. 168

dropwise. This process was repeated twice more, stirring was continued an additional 30 minutes and the solution was filtered hot. The basic filtrate was set aside for recovery of unreacted 8-nitrocarbostyril by neutralization with hydrochloric acid. The separated 2-methoxy-8-nitroquinoline was washed three times with 500 ml. of water and dried in a vacuum desiccator. The product was recrystallized from ethyl alcohol with use of decolorizing charcoal. Thirty-two grams (69.5%) of 2-methoxy-8-nitroquinoline which melted at 122.5-124.5° was obtained. The methanol mother liquor was poured in water; about 4 g. of partly alkalated material (mp ~ 110) was recovered for retreatment.

8-AMINO-2-METHOXYQUINOLINE

Ten grams (.049 mole) of 2-methoxy-8-nitroquinoline was dissolved in 175 ml. of absolute alcohol, transferred to a "citrate" bottle, 0.1 g. platinum oxide added, and the compound reduced with hydrogen over a forty-five minute period at an initial pressure of 30 p.s.i. The catalyst was separated from the solution by filtration and three more reductions made in a similar manner, using fresh catalyst for each reduction.

A. The combined alcoholic filtrates were evaporated on a steam bath until a brown oil began to form, 5 ml. of absolute alcohol added, the solution decolorized with

charcoal and filtered. On cooling in an ice bath, fine crystals formed readily. The almost white product weighed 22.5 g. (82.5%) and melted at 73.5-74.5°.

B. The combined alcoholic filtrates were transferred to a 1-l. flask and alcohol removed under water pump vacuum. The residue solidified on standing and was distilled in a closed system, that fraction collected which distilled at 109-111°/.05 mm. Twenty-three grams (85%) of nearly white 6-amino-2-methoxyquinoline was collected which melted at 72.5-74.5°.

1-BROMO-3-CHLOROPROPANE

Nine hundred and twenty-five grams (3.4 moles) of phosphorus tribromide was placed in a 5-l. 3-necked flask equipped with stirrer, dropping funnel and thermometer. 1-chloro-3-hydroxypropane (644 g., 6.8 moles) was added dropwise, with stirring, over a twelve-hour period. The mixture was allowed to stir overnight and then heated gradually to 95° and stirred for an additional ten hours. The solution was allowed to cool, poured into 3 l. of water and washed until acid free with 10% sodium carbonate solution. The oily layer was washed with 3 l. of water and dried over calcium chloride for twenty-four hours. The mixture was distilled under prevailing atmospheric pressure (759 mm.), the fraction boiling at 137-143° collected as colorless 1-bromo-3-chloropropane. The product weighed 813 g. (76%).

1-CHLORO-3-DIETHYLAMINOPROPANE

Four hundred and twenty-five grams (3.05 moles) of 1-bromo-3-chloropropane was placed in a 2-l. flask suspended in an ice bath. Five hundred and thirty ml. (5.16 moles) of diethylamine was added dropwise over a period of three hours, keeping the temperature below 80° by intermittent shaking in the ice bath. The suspension was allowed to stand overnight, treated with water, made basic with sodium hydroxide and extracted three times with 500-ml. portions of ether. The combined ether extracts were dried for 24 hours with potassium carbonate, ether and diethylamine were removed on a steam bath and the residue distilled under reduced pressure. The colorless fraction distilling at 39-45°/2.5 mm. was collected as 1-chloro-3-diethylamino-propane and weighed 204 g. (50.5%) based on 1-bromo-3-chloropropane.

1-CHLORO-3-DIETHYLAMINOPROPANE HYDROCHLORIDE

In a 1-l. beaker was placed a solution of 252 g. (1.68 moles) of 1-chloro-3-diethylaminopropane in 700 ml. of Skelly "F" (note 1). Dry hydrogen chloride (note 2) was bubbled into the solution until precipitation of white crystalline 1-diethylamino-3-chloropropane hydrochloride was apparently completed. The white product was collected on a Buchner funnel, washed with Skelly "F" and transferred

to a vacuum desiccator (note 3). The Skelly "F" filtrate and washings were combined and retreated twice with dry hydrogen chloride, in the above manner, obtaining two more fractions of the desired salt (note 4). The products were combined and dried in a vacuum desiccator for 18 hours. 1-Diethylamino-3-chloropropane hydrochloride was stored in a desiccator using potassium hydroxide as desiccant.

Notes

1. All pieces of apparatus were thoroughly dried in an oven at 100°.

2. Hydrogen chloride gas from a commercial cylinder was passed through concentrated sulfuric acid.

3. A vacuum desiccator was previously arranged for immediate use, because the product was extremely hygroscopic. The salt was transferred, in a drying dish, to the desiccator before all the solvent was removed, and the excess solvent cautiously removed under water pump vacuum.

4. Attempted precipitation of the hydrochloride salt for a fourth time resulted in small amounts of oil.

8-(3-DIETHYLAMINOPROPYLAMINO)-2-METHOXYQUINOLINE

Forty-nine grams (.28 mole) of 8-amino-2-methoxyquinoline, 52 g. (.28 mole) of 1-diethylamino-3-chloropropane

hydrochloride, 196 g. (1.29 moles) of sodium acetate, 750 ml. of 95% alcohol and 300 ml. of water were placed in a 2-l. single-necked flask. Boiling chips were added and the solution was heated under reflux for three days, adding an additional 52 g. of "side chain" hydrochloride on the second day. The solution was allowed to cool, poured into 1500 ml. of cold water and made basic with a 30% solution of potassium hydroxide. The solution was saturated with technical potassium carbonate and the alcohol separated from the water phase. The water was extracted once with 300 ml. of ether, the ether combined with the alcohol and this solution concentrated on a steam bath (note 1). The residual solution was dried over magnesium sulfate, alcohol removed under water pump vacuum and "side chain" at 2.5 mm. distilling 40-45° (note 2). A small amount of 2-methoxy-8-nitroquinoline was removed at 125-135°/.075 mm. and the light brown oily residue distilled at 135-155°/.001 mm; the yield was 70 g. (67%).

Notes

1. During concentration of the solution, water and some dissolved solids separated and were removed. A small amount of ether was used to wash the water layer and combined with the water insoluble portion.

2. A carbon-dioxide-chloroform bath was used to condense

the "side chain" during distillation with a vacuum pump.

8-(3-DIETHYLAMINOPROPYLAMINO)-2-METHOXYQUINOLINE DIHYDRIODIDE

One gram of 8-(3-diethylaminopropylamino)-2-methoxyquinoline was dissolved in 4 ml. of ethyl alcohol, the solution stirred and 2 ml. of 47% hydriodic acid (sp. gr. 1.5) in 4 ml. of ethanol added dropwise. The solution was made slightly turbid by adding ether and then cooled in an ice bath. White crystals separated readily, were collected on a Büchner funnel and washed with ether. The product was recrystallized from ethyl alcohol. The salt decomposed at 140.4-141.4°. On standing in a vial over a period of a year the salt darkened and became somewhat gummy.

8-(3-DIETHYLAMINOPROPYLAMINO)-CARBOSTYRIL

Method A

In a 1-l. single-necked flask was placed a solution of 70 g. (.24 mole) of 8-(3-diethylaminopropylamino)-2-methoxyquinoline in 500 ml. of 6N (~ 20%) hydrochloric acid. Boiling chips were added to the solution which was then heated under reflux for 5 hours. The solution was allowed to cool, then poured into 2 l. of cracked ice. The solution was placed in an ice bath and concentrated ammonium hydroxide added slowly with manual stirring until strongly basic.

A greenish-yellow gum formed as neutralization proceeded. The gum was gathered on a glass spatula, transferred to a beaker and dried overnight in a vacuum desiccator. The gum solidified on drying and was recrystallized from ethyl acetate (note 1) containing decolorizing charcoal. The yield was 49.2 g. (74%) of greenish-yellow crystals that decomposed at 80-81°. Recrystallization from ethyl acetate or acetone using decolorizing charcoal improved the decomposition point to 82.,-83.8°.

*Analysis: Calculated for $C_{16}H_{23}O\,N_3$: C, 70.29; H, 8.48; N, 15.36. Found: C, 70.02, 70.08; H, 8.51, 8.81; N, 15.29, 15.46.

Notes

1. Some unidentified material was relatively insoluble in ethyl acetate and was removed from the solution by filtration.

Method B

Four grams (.0086 mole) of 2-chloro-6-(3-diethylamino-propylamino)-quinoline dihydrobromide was dissolved in 50 ml. of 25% hydrochloric acid in a 100 ml. round-bottomed flask. The solution was heated under reflux for seven hours, decolorized with charcoal and filtered hot. The filtrate

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*The author wishes to express his appreciation to Mrs. Mary Aldridge, Mr. Byron Baer, Mr. Joe Tuono and Miss Kathryn Gerdeman for the analytical determinations in this thesis.

was cooled at 3° overnight (note 1) and made strongly basic by adding concentrated ammonium hydroxide slowly. A greenish gum slowly precipitated, was gathered on a glass spatula and dried overnight in a vacuum desiccator. The solids were recrystallized, from ethyl acetate containing decolorizing charcoal and when dry decomposed at 78-79°. The 8-(3-diethylaminopropylamino)-carbostyril was again decolorized and recrystallized from ethyl acetate. The product decomposed at 80.5-81.5°. A mixed decomposition point was determined with an analyzed sample of 8-(3-diethylaminopropylamino)-carbostyril prepared as above in Method A. The mixed decomposition point was found to be 80-82°.

Notes

1. Crystals of a hydrochloride salt were not formed under these conditions. 8-(3-Diethylaminopropylamino)-carbostyril formed a lemon-yellow hydrobromide salt (probably the dihydrobromide) by adding 48% hydrobromic acid in absolute alcohol to an absolute alcoholic solution of the free base. The salt was nicely recrystallized from absolute alcohol and melted at 174.6-179.7°.

ULTRAVIOLET ABSORPTION DATA

A sample of 8-(3-diethylamino propylamino)-carbostyril was weighed out by a member of the microanalytical staff*

*The author wishes to express appreciation to Mr. Byron Baer, Mrs. Mary Aldridge and Miss Kathryn Gardeman for weighing samples of the compounds whose absorption spectra were obtained in this work.

and transferred to a 25-ml. volumetric flask. The dry was dissolved in 25 ml. of isooctane, and the optical density determined at 5 mμ intervals on a sample from this solution. A Beckmann Model DU quartz spectrophotometer was used for the optical density measurements. Quartz cells of 1.00 cm. optical length were used. The data is recorded in table 1 and a plot of the molar extinction coefficients vs. the wave lengths made in figure 2.

PARTITION RATIOS

Partition ratios were determined in the following manner. A sample of 6-(3-diethylaminopropylamino)-carbostyril was added to 10 ml. of cyclohexane and 10 ml. of buffer solution contained in a 30-ml. separatory funnel. The system was equilibrated for two minutes and the phases allowed to separate, then the lower (buffer) phase transferred to a 30-ml. flask. Ten milliliters of cyclohexane was added to the buffer phase and then 5 ml. of 5N ammonium hydroxide to each container. Both containers were vigorously shaken for several minutes and the phases in each container allowed to separate. The optical density of a sample of the cyclohexane solution in each container was determined, using a Beckmann Model DU quartz spectrophotometer at a wave length of 365 mμ. The partition ratios were then calculated as a ratio of optical density solvent/optical density buffer. The data is recorded in table 2.

TABLE 1

ULTRAVIOLET ABSORPTION DATA

6-(3-Diethylaminopropylamino)-carbostyril

$C_{16}H_{23}N_3O$ Mol. Wgt. 273.37

Solvent: Isooctane Concentration: .1764 mg/25 ml.

$\epsilon = \frac{D}{ct}$ t = 1.00 cm. c = 2.581×10^{-5} moles/l.

λ	D	$\epsilon \times 10^{-3}$	λ	D	$\epsilon \times 10^{-3}$
225	.360	13.95	315	.085	3.29
230	.350	13.56	320	.077	2.98
235	.366	14.18	325	.048	1.86
240	.375	14.53	330	.027	1.05
*245	.375	14.53	335	.028	1.09
250	.314	12.16	340	.029	1.12
255	.270	10.46	345	.033	1.28
260	.280	10.85	350	.037	1.43
265	.363	14.06	355	.039	1.51
270	.475	18.40	360	.042	1.63
*275	.520	20.25	*365	.043	1.67
280	.472	18.29	370	.042	1.63
285	.311	12.05	375	.037	1.43
290	.180	6.97	380	.035	1.36
295	.140	5.42	385	.033	1.28
300	.127	4.92	390	.028	1.09
305	.115	4.46	395	.025	1.97
310	.102	3.39	400	.020	.78

*λ max.

FIGURE I

ULTRAVIOLET ABSORPTION SPECTRUM

8-(3-Diethylaminopropylamino)-carbostyril

Solvent: Isooctane

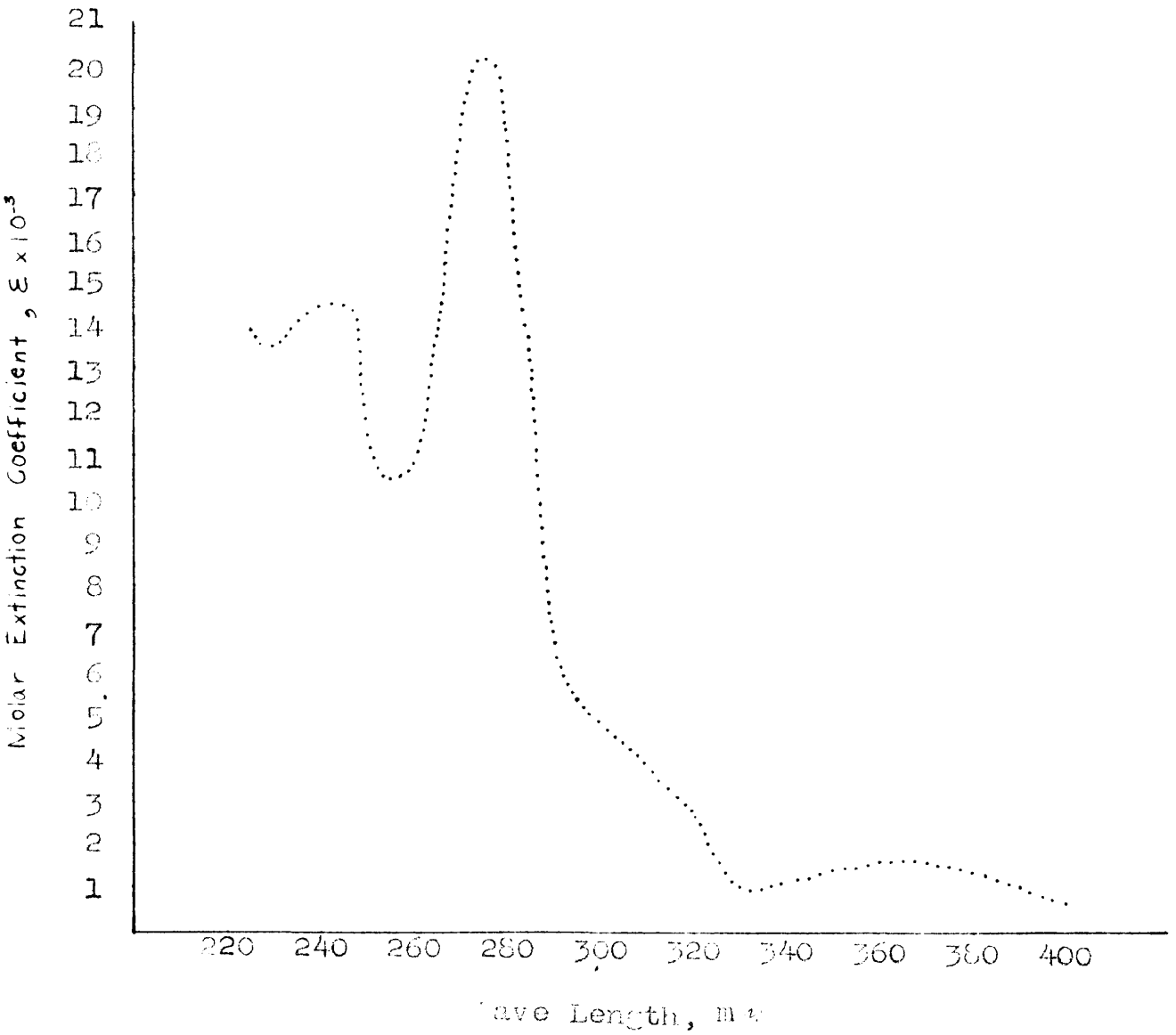


TABLE 2

PARTITION RATIOS

8-(3-Diethylaminopropylamino)-carbostyril

Solvent: Benzene

Buffer: Ammonium acetate-acetic acid, pH 6.95 @ 20°

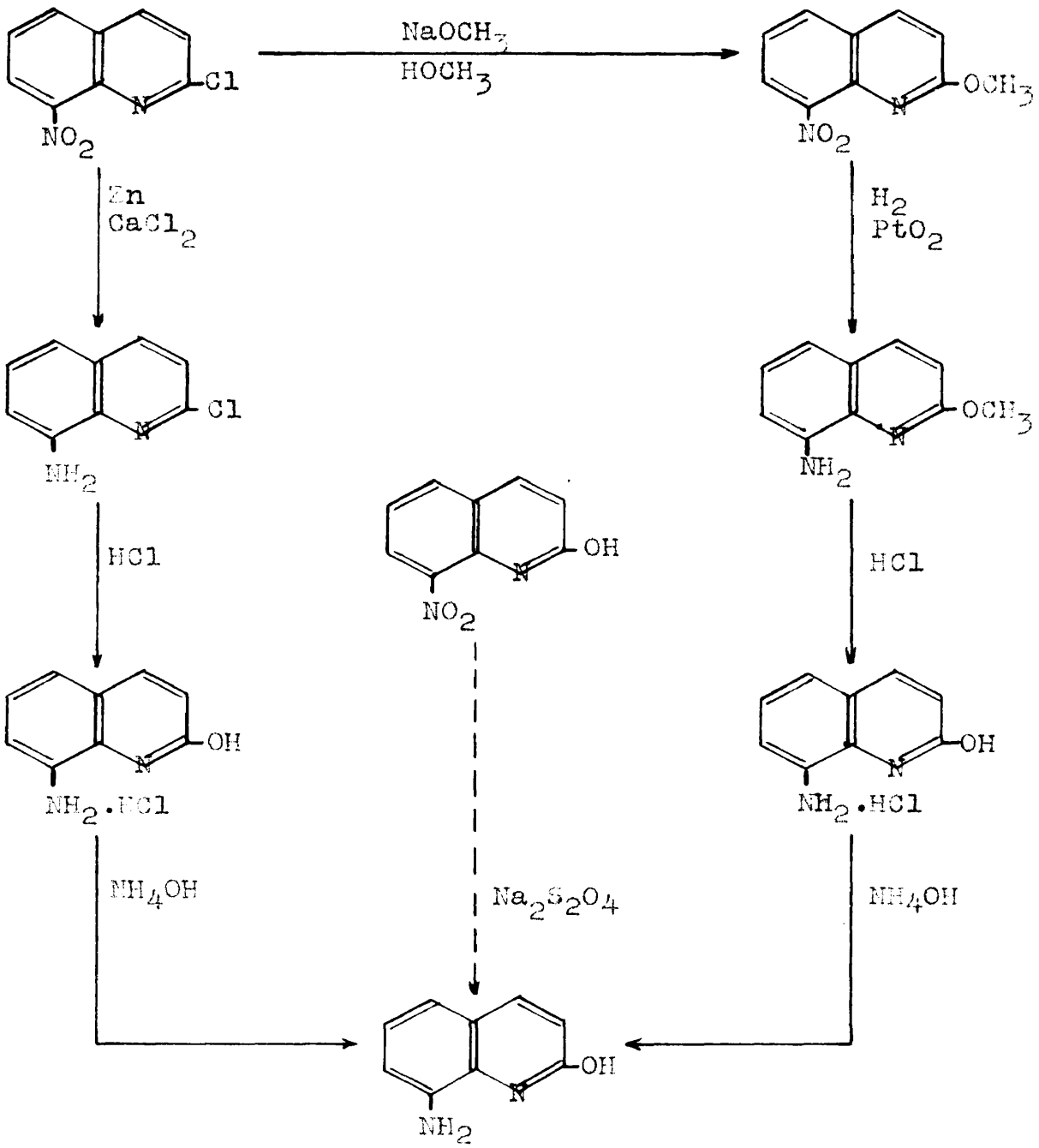
10 ml. each phase

Optical density at 365 mμ.

WGT. SAMPLE	TOTAL CONCENTRATION	OPTICAL DENSITY D.		PARTITION RATIO
Grams	Moles/l x10^5	Buffer	C_6H_6	$\frac{D}{\text{Solvent}/\text{Buffer}}$
.0004	7.33	.164	.144	0.695
.0006	10.95	.227	.172	0.758
.0008	14.63	.340	.283	0.833
.0010	18.30	.375	.335	0.894
.0018	32.90	.630	.725	1.15

CHART IV

8-AMINOCARBOSTYRIL



SECTION IV

8-AMINOCARBOSTYRIL

Discussion

The original purpose for the preparation of 8-aminocarbostyril was as an intermediate for the synthesis of 8-(3-diethylaminopropylamino)-carbostyril. However, a combination of early positive results with the hydrolysis of 8-(3-diethylaminopropylamino)-2-methoxyquinoline and unsatisfactory attempts to reduce 8-nitrocarbostyril relegated the synthesis of 8-aminocarbostyril to a strictly academic status.

For most purposes the practical method of preparing Bz-aminoquinolines is the reduction of the particular nitro compound. Several reagents are available for the reduction of nitro groups and have been summarized by Fieser.[76] Probably the reagents most useful for the reduction of the Bz-nitroquinolines are stannous chloride and hydrochloric acid, iron and dilute acetic acid, and hydrogen activated with nickel or platinum. In some cases stannous chloride and hydrochloric acid cause chlorination along with reduction, and the catalytic process may be accompanied by reduction of the pyridine ring.

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[76] L.F. Fieser, "Experiments in Organic Chemistry", D.C. Heath and Company, New York, 2nd ed. 1941, pp. 415-418.

For the synthesis of 8-aminocarbostyril, two factors merit attention. The compound would be expected to exhibit amphoteric properties, consequently some difficulty might be encountered in separating the material from the reaction medium. More important, 2-hydroxyquinoline is probably best expressed as a mixture of the hydroxy and ketonic forms. The ketonic form can be regarded essentially as an amide and effects certain reactions of carbostyril.[77]

Carbostyril is easily hydrogenated, in comparison to quinoline, to the Py-dihydro and tetrahydroquinolines.[78] Cavallito and Haskell[79] studied the reduction of the quinolinols in dioxane using a palladium sponge catalyst at 25 and 55°. Carbostyril was reduced to 3,4-dihydrocarbostyril and the 5,6,7, and 8-quinolinols were reduced to the 1,2,3,4-tetrahydroquinolinols. All of the quinolinols were reduced more readily than quinoline.

The above evidence shows that the hydroxy group facilitates reduction of the pyridine ring. Since the amino group exhibits some properties similar to the hydroxy group, such as electron-doning, and tautomerism, one might expect strictly from analogy with the quinolinols, that the amino quinolines would also facilitate reduction of the pyridine ring.

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[77] An excellent summary, with references, of the evidence for these contributing forms is presented in R.C. Elderfield (Editor), "Heterocyclic Compounds", Vol. IV, John Wiley and Sons, New York, 1952, pp. 149-152

[78] Spath and Galinovsky, Ver., 69 2057 (1936)

[79] Cavallito and Haskell, J. Am. Chem. Soc., 66 1166 (1944)

Apparently, reduction procedures attempted in this work on 6-nitrocarbostyril resulted in mixtures, which could not be purified by recrystallization and seemed to decompose with treatment. It is believed that reduction of the nitro group occured, and with both a hydroxy and amino group present on the quinoline ring, reduction of the pyridine ring was greatly facilitated.

Several workers[80,81,82,83] have reported the reduction of quinoline to the Py-tetrahydroquinoline using tin and hydrochloric acid.

The literature revealed that the 4,5,6 and 7-aminocarbostyrils had been prepared. Of the three methods recorded for the synthesis of 4-aminocarbostyril none involved the reduction of the nitro group. This compound has been prepared in the following ways: the sodium salt, ester or ether of 4-hydroxycarbostyril was treated with ammonia in an iron vessel at 150-250°;[84] Buchmann and Hamilton[85] refluxed 4-amino-2-ethoxyquinoline with 70% hydriodic acid for five hours; and Schroeder and Rigby[86] cyclized 2-acetamidoben-

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[80]Reichengradsky, Ber., 13 2400 (1880)

[81]Kretschy, Monatsh., 2 83 (1881)

[82]Hoffman and Königs, Ber., 16 727 (1883)

[83]Fischer and Körner, Ibid, 17 765 (1884)

[84]Ger. Pat. 681,900. C.A. 36 P 2273 (1942)

[85]Buchmann and Hamilton, J. Am. Chem. Soc., 64 1357-60 (1942)

[86]Schroeder and Rigby, Ibid, 71 2205-9 (1949)

zonitrile in the presence of sodamide and liquid ammonia. 5-Aminocarbostyril was prepared by Claus and Setzer[87] by boiling 5-nitrocarbostyril with stannous chloride and hydrochloric acid. Friedländer and Lazarus[88] reduced 6-nitrocarbostyril to the aminocarbostyril by boiling with tin and hydrochloric acid. By treating 2,4-dinitrocinnamic acid with tin, stannous chloride and fuming hydrochloric acid, Friedländer and Fritsch[89] prepared 7-aminocarbostyril. Kermack and Webster[90] also prepared 7-aminocarbostyril by decarboxylating 7-aminocarbostyril-4-carboxylic acid.

From the relative drastic conditions employed in preparing the 5,6 and 7-aminocarbostyrils, in comparison to the reduction of quinoline using tin and hydrochloric acid, it would seem reasonable that some Py-hydroquinolines were produced by the above reduction procedures. The original references do not indicate the separation of other reduction products or the yields of the Bz-aminocarbostyrils.

Two attempts were made to reduce 8-nitrocarbostyril to the corresponding amine using stannous chloride, first in hydrochloric acid and then in acetic acid. In both experiments a great deal of trouble was encountered in trying to remove the inorganic material. The usual technique, e.g.,

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[87] Claus and Setzer, J. prakt. Chem., (2) 53 395 (1883)

[88] Friedländer and Lazarus, Ann., 229 246 (1885)

[89] Friedlander and Fritsch, Monatsh., 23 538

[90] Kermack and Webster, J. Chem. Soc., 213 (1922)

removing the tin ions as the complex sodium salts and extracting the amine with ether, was not applicable because the amino carbostyril was soluble in base. Attempts to precipitate the tin ions as the sulfides resulted in considerable amounts of hard solids which were difficult to powder and were not appreciably affected by digestion with alcohol. From alcoholic extracts of these solids, a yellow material was obtained, in both of these reductions, which melted above 200°, and contained a non-fusable material along with organic matter.

Several attempts were made to reduce the nitro group with hydrogen using ethyl alcohol as a solvent and platinum oxide as the catalyst. The reactions were run at room temperature in a low pressure shaker at a starting gauge pressure of 20-25 p.s.i. Reactions were stopped when the theoretical amount of hydrogen had been taken up. A bright orange material was obtained from the charcoal treated alcoholic filtrates on cooling in an ice bath. This material slowly changed from a bright orange color at 170° to a black mass at 270° and gave a carbon and hydrogen analysis as C, 67.37, 67.41; H, 5.72, 5.83. The calculated values for 6-aminocarbostyril are C, 67.48; H, 5.03.

Several methods of purification of the material from the catalytic reductions were investigated. Recrystallization from ethyl alcohol gave a dull brown product. The material was dissolved in dilute hydrochloric acid and filtered to remove any unreduced 6-nitrocarbostyril, then made neutral

to alk-acid paper with sodium hydroxide or ammonium hydroxide. Both procedures resulted in a dark brown precipitate. Ether, dioxane and acetic acid were tried as recrystallizing solvents. The substance produced in these experiments was characterized by insolubility and what was apparently decomposition with treatment.

An attempt was made to reduce 8-nitrocarbostyril with sodium hydrosulfite in boiling water. A slightly yellow organic material was obtained from this reaction which melted above 200° and tended to darken on exposure to air and with recrystallization.

The synthesis of 8-aminocarbostyril was finally realized through the hydrolysis of 8-amino-2-chloroquinoline (cf. section V for preparation of this chloro compound) and 8-amino-2-methoxyquinoline in 20% hydrochloric acid. The hydrolysis of 8-amino-2-methoxyquinoline proceeded smoothly, but the hydrolysis of 8-amino-2-chloroquinoline provided some difficulties which were attributed to an insufficient amount of acid and a short reflux period.

The monohydrochloride of 8-aminocarbostyril was prepared in both methods, and the decomposition point of each sample found to be 256.2-257.2°. The analysis, of the hydrochloride salt prepared from the hydrolysis of the methoxy compound, was determined and found in agreement with the calculated values.

Samples of 8-aminocarbostyril prepared from both starting materials decomposed at 295-296°. A mixture of

these two samples showed no depression of the decomposition point. The two samples were analysed and the results were in agreement with the calculated values.

The hydrochloride salt is a white granular solid which is relatively insoluble in absolute alcohol. A 1.5 g. sample required approximately 400 ml. of absolute alcohol for complete solution. However, on cooling to ~ -60° the compound did not crystallize. The addition of Skelly "F" resulted in the precipitation of a white powder. Recrystallization of this salt from 90% ethyl alcohol resulted in hydrolysis to the free base. Ordinarily the amines melt lower than their salts. The hydrochloride of 8-aminocarbostyril and the free base represents an unusual case where this generality is reversed.

8-Aminocarbostyril is a yellowish-green powder readily soluble in 5% sodium hydroxide and 5% hydrochloric acid. The compound is relatively insoluble in ethyl acetate, isooctane, Skelly "F", somewhat soluble in acetone and crystallized nicely from a 90% alcohol solution. With 1% ferric chloride a change in color was noted and a reddish precipitate soon formed. This was a distinctly different reaction from that noted with the 8-(3-diethylaminopropylamino)-carbostyril.

The ultraviolet absorption curve of 8-aminocarbostyril was determined, using a Beckmann Model DU quartz spectrophotometer, for a sample from each method of preparation. The absorption data are recorded in tables 3 and 4 and a

plot of the extinction coefficients vs. the wave lengths made in figure 2. The general character of the two absorption curves agree, indicating that the chemical entity produced by the two methods was essentially the same compound. Both curves exhibited maxima at 235, 270 and 360 mμ. A discrepancy was noted at 345 to 350 mμ in the exact position of the maximum. Since the data was taken at 5 mμ intervals, the actual maximum in all probability does not occur exactly at the 5 mμ intervals. This idea is applicable, of course, to the other maxima. A maximum was found at 295 mμ for the 8-aminocarbostyril prepared from 8-amino-2-methoxyquinoline (table 4). This section of the curve appears as a minor maximum or inflection between 280 and 320 mμ.

The absorption data, in conjunction with the methods of synthesis, decomposition and mixed decomposition points, and the chemical analysis indicate that these procedures are methods for the preparation of 8-aminocarbostyril.

Carbostyril shows two maxima,[91] one at 260 mμ (ε = 7000) and at 327 mμ (ε = 6750). Introduction of the 8-amino group has considerably complicated the absorption by increasing the number of maxima, increasing the extinction coefficient (intensity) at 270 mμ and decreasing the extinction coefficients thereafter. Ewing and Steck[92] obtained the spectrum

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[91] (a)Morton and Rogers, J. Chem. Soc., 127 2695 (1925) (b)Morton and Stubbs, J. Chem. Soc., 1321 (1933)

[92] Ewing and Steck, J. Am. Chem. Soc. 59 $\frac{127}{(1)68}$ 2181 (1946)

of 6-quinolinol and Steck and Nachod[23] compared the spectrum of 8-amino-6-quinolinol with that of 6-quinolinol and concluded that the 8-amino group had very little influence on the spectrum. This is rather unusual since ordinarily an amino group may produce effects, such as bathochromic shift, decrease in fine structure and increase in intensity.

Steck and Nachod[24] determined the spectrum of 8-amino-6-quinolinol in .01 N HCl and found a small bathochromic shift and slight increase in fine structure compared to the free base. Since it was found that 8-aminocarbostyril monohydrochloride was hydrolyzed by recrystallization from ethyl alcohol containing ~ 10% water, it appeared questionable that the compound would exist in appreciable amounts as the salt in .01 N HCl. If 8-amino-6-quinolinol has a comparitive sensitivity to hydrolysis, probably only a very small percent of the amine exists as salt in .01 N HCl and the resultant spectrum would represent a mixture of salt and free base with the latter predominating.

A comparison of the spectra of 8-aminocarbostyril and 8-(3-diethylaminopropylamino)-carbostyril (page 99) shows the curves have the same general shape and comparable intensities. The attachment of the diethylaminopropyl group in the 8-position produced a small bathochromic shift in the curve, a slight decrease in fine structure as exhibited

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[23] Steck and Nachod, J. Am. Chem. Soc., 74 3697 (1952)

[24] Steck and Nachod, loc. cit.

by only one maximum around 365 mμ and only an inflection in the curve between 290 and 300 mμ. Apparently no hindered resonance was introduced by the "side chain." If there was hindered resonance a hypsochromic shift compared to 8-aminocarbostyril would be expected. These curves are graphically compared in figure 2. The data for 8-aminocarbostyril is taken from table 3.

It should be pointed out that isooctane was used as solvent for 8-(3-diethylaminopropylamino)-carbostyril while 95% ethyl alcohol was used for 8-aminocarbostyril. Ethyl alcohol being more polar than isooctane, the spectrum of 8-(3-diethylaminopropylamino)-carbostyril in ethyl alcohol would be expected to show a larger bathochromic shift and a decrease in fine structure compared to the spectrum in isooctane. The spectrum of 8-(3-diethylaminopropylamino)-carbostyril in 95% alcohol should strengthen the idea of no hindered resonance.

Steck and Nachod[95] also made a comparison of the spectra of 8-(3-dimethylamino-1-methylpropylamino)-6-quinolinol, 8-(4-diethylamino-1-methylbutylamino)-6-quinolinol and 8-amino-6-quinolinol in ethyl alcohol, base, and acid medium. They found that the side chains of these compounds indicated some hindered resonance.

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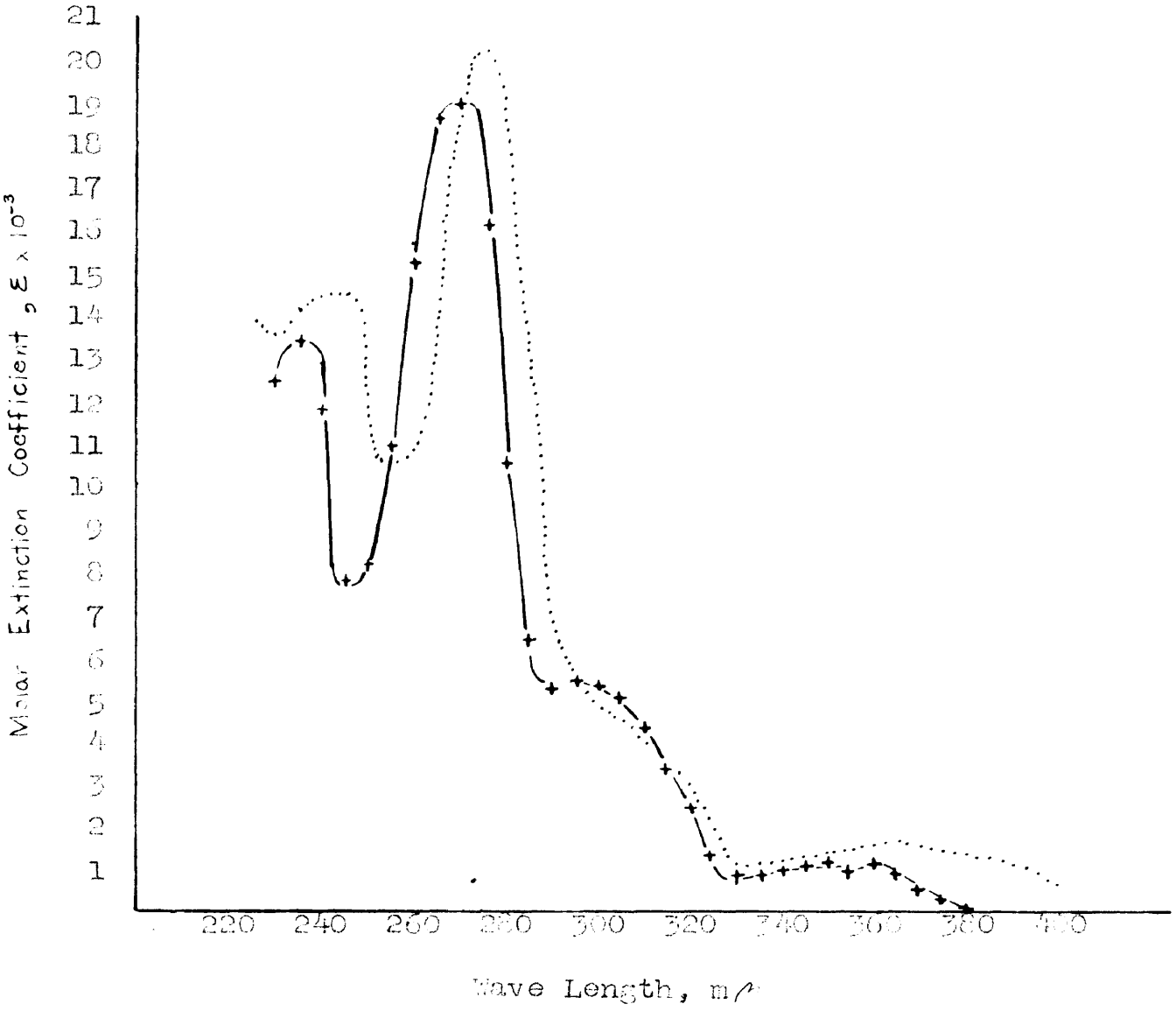
[95] Steck and Nachod, J. Am. Chem. Soc., 74 3699 (1952)

FIGURE 7

ULTRAVIOLET ABSORPTION SPECTRA

• 8-(3-Diethylaminopropylamino)-carbostyril in n-octane

+ 8-Aminocarbostyril in 95% Alcohol



EXPERIMENTAL

8-AMINOCARBOSTYRIL HYDROCHLORIDE

Method A

One and one-half grams (.0086 mole) of 8-amino-2-methoxyquinoline hydrochloride was placed in a 100 ml. round-bottomed flask with 30 ml. of 20% hydrochloric acid. Boiling chips were added and the solution heated under reflux for five hours. The hot solution was decolorized with charcoal and filtered into a glass stoppered erlenmeyer flask. The solution was allowed to stand overnight in a refrigerator at 3°. White granular crystals separated and were removed from the solution by filtration. The filtrate was saved for the preparation of the free base. The precipitate was recrystallized from commercial absolute alcohol, adding alkelly "F" until the solution became turbid. White crystals formed readily, were collected on a Büchner funnel and then dried at 56° for 5 hours. The product decomposed at 256.2-257.2°.

Analysis: Calculated for $C_9H_8N_2O \cdot HCl$: C, 54.97; H, 4.61; N, 14.25. Found: C, 54.73, 54.79; H, 4.83, 5.05; N, 14.40, 14.40.

Method B

Three grams (.0168 mole) of 8-amino-2-chloroquinoline was placed in a 100-ml. round bottomed flask with 40 ml. of 20% hydrochloric acid and heated under reflux for three

hours. Charcoal was added to the hot solution, the solution boiled several minutes and filtered into an erlenmeyer flask. The solution stood in a refrigerator at 3° overnight. Bright yellow crystals precipitated and were collected on a Buchner funnel. This material was recrystallized once from absolute alcohol, decolorizing with charcoal and adding Skelly "F" to the filtrate to precipitate 6-aminocarbostyril hydrochloride. The white product decomposed at 256.2-267.2°.

6-AMINOCARBOSTYRIL

Method A

The filtrate from the hydrolysis of 6-amino-2-methoxyquinoline was cooled in an ice bath, seeded and scratched to obtain an additional quantity of white 6-aminocarbostyril hydrochloride. The salt was treated with several ml. of concentrated ammonium hydroxide and the greenish-yellow solid washed with water and recrystallized from alcohol containing 10% water. The greenish-yellow 6-aminocarbostyril, after drying in a vacuum desiccator overnight decomposed at 295-296°.

Analysis: Calculated for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.39, 67.70; H, 5.09, 5.29; N, 17.30, 17.44.

Method B

One and one-half grams of 6-aminocarbostyril monohydrochloride, prepared from the hydrolysis of 6-amino-2-

chloroquinoline, was recrystallized from 70 ml. of alcohol containing 10% water by volume. The greenish solution was decolorized with charcoal, filtered and cooled in an ice bath. Greenish-yellow crystals separated and were removed from the solution by filtration, then dried at 56° for 3 hours. 8-Aminocarbostyril prepared in this manner decomposed at 295-296°.

Analysis: Calculated for $C_6H_8N_2O$: C, 67.49; H, 5.04; N, 17.49. Found: C, 67.62, 67.72; H, 5.02, 5.09; N, 17.49, 17.57.

ULTRAVIOLET ABSORPTION DATA

Weighed samples of 8-aminocarbostyril from both methods of preparation were dissolved in commercial 95% alcohol and diluted to 25 ml. The absorption spectra from samples of these solutions were immediately obtained using the same equipment designated on page 83. The curves are compared in figure 3. The data is recorded in tables 3 and 4.

TABLE 3

ULTRAVIOLET ABSORPTION DATA

8-Aminocarbostyril[a]

$C_9H_8N_2O$ Mol. Wgt. 160.17

Solvent: 95% Alcohol Concentration: .148 mg./25 ml.

$\varepsilon = \frac{E}{ct}$ t = 1.00 cm. c = 3.696×10^{-5} moles/l.

λ	E	$\varepsilon \times 10^3$	λ	E	$\varepsilon \times 10^3$
230	.460	12.43	310	.155	4.19
*235	.490	13.26	315	.130	3.52
240	.434	11.73	320	.090	2.83
245	.285	7.72	325	.050	1.35
250	.297	88.04	330	.033	.89
255	.405	10.95	335	.032	.87
260	.566	15.30	340	.034	.92
265	.690	18.65	345	.040	1.08
*270	.700	18.95	*350	.043	1.16
275	.597	16.15	355	.033	.89
280	.391	10.57	*360	.042	1.14
285	.237	6.42	365	.034	.92
290	.195	5.28	370	.020	.54
*295	.203	5.50	375	.017	.46
300	.198	5.36	380	.007	.19
305	.188	5.09			

a Prepared by the hydrolysis of 8-amino-2-methoxyquinoline

* λ max

TABLE 4

ULTRAVIOLET ABSORPTION SPECTRA

6-Aminocarbostyril[a]

$C_9H_8N_2O$ Mol. wgt. 160.17

Solvent: 95% Alcohol Concentration: .190 mg./25 ml.

$\varepsilon = \frac{D}{ct}$ t = 1.000 cm. c = 4.745 x 10^{-5} moles/l.

λ	D	$\varepsilon \times 10^{-3}$	λ	D	$\varepsilon \times 10^{-3}$
230	.560	11.80	310	.204	4.30
*235	.660	13.40	315	.158	3.33
240	.525	11.06	320	.080	1.69
245	.331	6.98	325	.065	1.37
250	.354	7.46	320	.047	.99
255	.494	10.42	335	.046	.97
260	.722	15.22	340	.057	1.20
265	.858	18.08	*345	.075	1.58
*270	.870	18.35	350	.061	1.28
275	.735	15.48	355	.046	.97
280	.488	10.29	*360	.065	1.37
285	.270	5.69	365	.034	.72
290	.254	5.36	370	.032	.67
295	.253	5.33	375	.025	.53
300	.249	5.25	380	.009	.19
305	.224	4.72			

a Prepared by the hydrolysis of 6-amino-2-chloroquinoline

* λ max

FIGURE 3

ULTRAVIOLET ABSORPTION SPECTRUM

8-Aminocarbostyril

Solvent: 95% Alcohol
• Table 3
+ Table 4

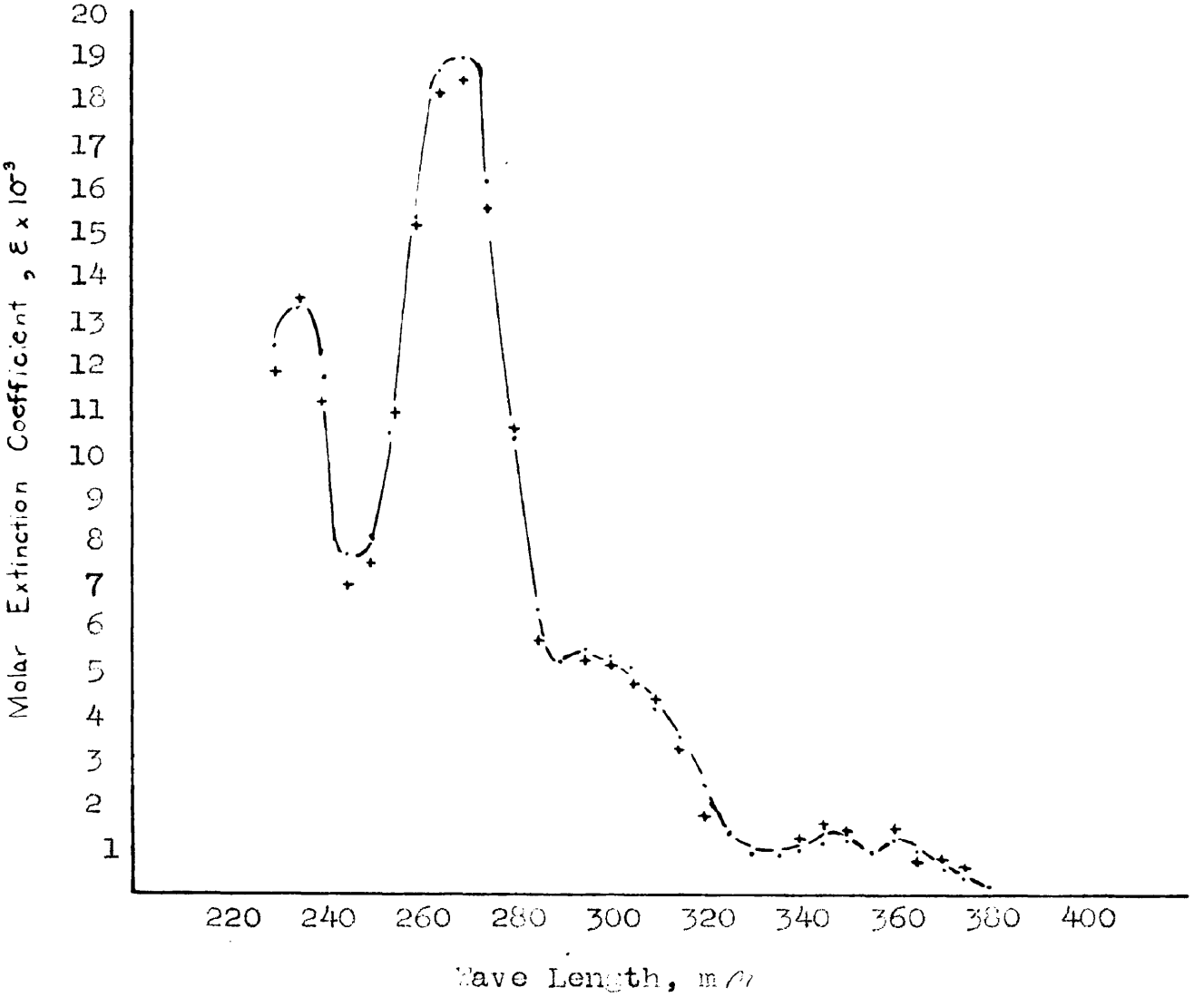
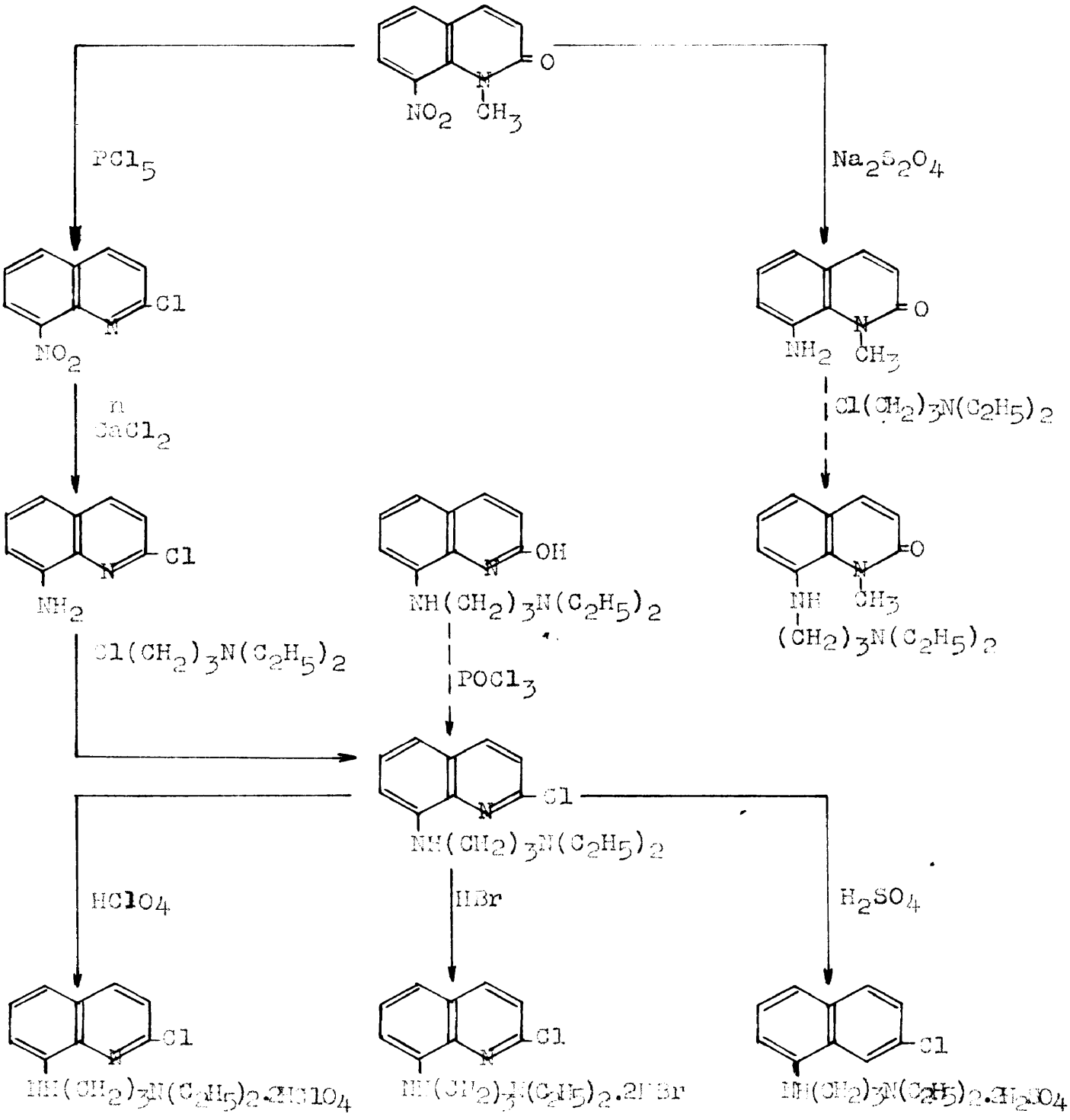


CHART V

2-CHLORO-8-(3-DIETHYLAMINOPROPYLAMINO)-QUINOLINE AND SALTS



SECTION V

2-CHLORO-6-(3-DIETHYLAMINOPROPYLAMINO)-QUINOLINE AND SALTS

Discussion

Halogen atoms located at the 2- and 4-positions of quinoline are reactive to nucleophilic replacement since these positions have low electron densities.[96] Because of this reactivity it was felt that some difficulty would be encountered in preparing 2-chloro-6-(3-diethylaminopropylamino)-quinoline without replacing the chloro group. This reactivity imposed several initial restrictions.

It was doubtful if the free base could be distilled, since the compound could react with itself, for example, at the secondary nitrogen of the side chain. This would, in effect, eliminate attempts to separate unreacted nucleus by distillation. In general, the 2-chloroquinolines are reactive to high boiling amines. As an example, Diepolder[97] found that 2-aminoquinoline reacted with 2-chloroquinoline to form diquinolylamine at 200-210° in the presence of barium oxide.

Another difficulty was postulated in that an attempt to couple 6-amino-2-chloro-quinoline with the side chain in an acid medium would hydrolyze the active halogen. Banks[98]

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[96] Dewar, J. Am. Chem. Soc., 74 3360 (1952)

[97] Diepolder, J. prakt. Chem., 106 41-6 (1923)

[98] Banks, J. Am. Chem. Soc., 66 1127 (1944)

has presented evidence that displacement of chlorine in a reactive position of a number of heterocyclic compounds is acid catalyzed. Experience in this laboratory supports this evidence. 2-Chloro-6-nitroquinoline is readily hydrolyzed to 6-nitrocarbostyril, in excellent yield, with hydrochloric acid.

Another problem, based on the reactivity of the halogen, was whether 2-chloro-6-nitroquinoline could be reduced without removing the chloro group. Catalytic reduction readily removes the chlorine from the 2-(or the 4-) position.[99] Several important methods of chemical reduction involve acid conditions which would be expected to replace the halogen by hydrolysis.

The exact effect of substituents on the reactivity of the halogens in the 2- and 4-positions, is not known. Apparently electron-donating groups in the 2-position decrease the reactivity of the halogen in the 4-position, whereas electron-donating groups in the 4-position have less effect on the 2-halogen, because of the electron-attracting nature of the carbon-nitrogen double bond. 2-Alkoxy-4-chloroquinolines are less active toward sodium methoxide than 4-alkoxy-2-chloroquinolines,[100] and 4-chloro-2-hydroxyquinoline does not react

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[99] Neumann, Sommer, Kaslow and Shriner, Org. Synthesis 26 45-9 (1946)

[100] Rowlett, Jr. and Lutz, J. Am. Chem. Soc., 68 1288 (1946)

with high boiling amines or sodium ethoxide,[101] while 2-chloro-4-hydroxyquinoline is reactive toward high boiling amines. When 2-chloro-5-,6-, and 8-nitroquinolines are treated with ten parts of concentrated ammonium hydroxide at about 150°, the chloro group is replaced by the amino group in 20, 10 and 6-7 hours respectively[102](yields not specified). Comparing 5-, 6-, and 8-nitro-2-chloroquinolines, it appears that the 5-nitro group facilitates the ease of nucleophilic attack at the 2-position, relative to the 6-nitro group. The 8-nitro group apparently has the greatest activating influence in this type of reaction.

One of the most convenient means of preparing 2-chloroquinolines is by the treatment of the 2-hydroxy group with phosphorus oxychloride or phosphorus pentachloride, or mixtures of these two reagents. The most logical synthesis of 2-chloro-3-(3-diethylaminopropylamino)-quinoline appeared to be from the 2-hydroxy drug described in section III. Two attempts were made to carry out this reaction, first using phosphorus pentachloride and then with phosphorus oxychloride. Phosphorus pentachloride resulted in a large amount of unextractable tar. However, a thoroughly dried ether extract obtained from this reaction, deposited a gummy material, when treated with dry

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[101] Buchmann and Hamilton, J. Am. Chem. Soc., 64 1357 (1942)

[102] Fischer and Guthmann, J. prakt. Chem., 93 378 (1916)

hydrogen bromide gas. Several attempts to recrystallize this material were unsuccessful. The reaction with phosphorus oxychloride was apparently not acted for a long enough period, and unconverted hydroxy drug was recovered along with a small amount of red oil. Subsequent experience with the 2-chloro drug showed the salts were difficult to handle and it is believed that under the proper conditions the replacement of the 2-hydroxy group, especially with phosphorus oxychloride, should prove applicable in this reaction.

The preparation of 2-chloro-8-(3-diethylaminopropylamino)-quinoline through 8-amino-1-methyl-2-quinoline was thought to be the least promising of the three methods considered for several reasons. Comparatively, not much has been done with the quinolones. Lutz[103] has shown that the conversion of 1-methyl-2-quinolones to the 2-chloro derivative is more difficult than simple replacement of the 2 or 4 hydroxy group. Phosphorus pentachloride is usually required for the former reaction whereas phosphorus oxychloride or a mixture of phosphorus oxychloride and phosphorus pentachloride, at a lower temperature, replaces the 2-hydroxy group. Since the experience outlined above in the treatment of the 2-hydroxy drug with phosphorus pentachloride resulted in considerable tar, some question is presented in the wisdom of attempting this type of a reaction. A steric factor is possible (cf. the reaction of methyl

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[103]Lutz, et al., J. Am. Chem. Soc., 68 1813 (1946)

iodide with 6-nitroquinoline page 30) between the 1-methyl group and attachment of the side chain.

Despite these objections, and the successful synthesis of 2-chloro-6-(3-diethylaminopropylamino)-quinoline from 6-amino-2-chloroquinoline, a considerable amount of work was completed in the reduction of 1-methyl-6-nitro-2-quinolone to the amine. Decker and Angler[104] prepared 6-amino-1-methyl-2-quinolone from 6-nitro-1-methyl-2-quinolone by reduction with ammonium hydroxide and hydrogen sulfide. They reported an 80% yield of the amine, which melted at 180°. The amine was subject to air oxidation. This work could not be duplicated and the use of hydrogen sulfide was undesirable. Several alternate methods of reduction were used with varying results. The chief characteristics of the reduction procedures were the formation of tars, loss of organic material and consequently low yields.

Hydrogen and platinum oxide, with 95% ethanol as solvent on a low pressure shaker, was used in attempts to prepare 6-amino-1-methyl-2-quinolone from the 6-nitro compound. The material isolated from these reductions was apparently impure, difficult to recrystallize and did not melt at the recorded melting point of the amine. Titanium trichloride gave a product from basic solution which melted at 210-215°. Zinc and calcium chloride were used but apparently caused

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[104] Decker and Angler, Ber., 42 1730 (1909)

decomposition.

Several reductions were run using sodium hydrosulfite under various conditions. This method gave 27-35% yields of 8-amino-1-methyl-2-quinolone which melted at 163.7-164.7°, after recrystallization from benzene. Although the melting point of this product was slightly high compared to that reported by Decker and Angler, the carbon and hydrogen analysis were in agreement with the calculated values. This constitutes the only example, by this author, of a successful reduction of the 8-nitro group in several substituted quinolines using sodium hydrosulfite.

Stannous chloride and hydrochloric acid gave a material which melted at 163.7-164.7°, was nicely crystallized from benzene and stable in atmosphere. A sodium fusion and halogen test was run on this material, to see if chlorination had occured in conjunction with reduction or if a tin salt was the product. Only a trace of halogen was indicated in the test. In view of this test it was assumed that the compound was composed of carbon, hydrogen, nitrogen and oxygen. From carbon (62.44%), hydrogen (5.35%), and nitrogen (14.65%) analysis an empirical formula was calculated as C_5H_5NO. Assuming also that the carbon skeleton was reasonably stable, this empirical formula was multiplied by two to give $C_{10}H_{10}N_2O_2$, compared to the formula of 8-amino-1-methyl-2-quinolone, $C_{10}H_{10}N_2O$. The calculated composition of 8-amino-1-methyl-2-quinolone is C, 68.94; H, 5.76 and

N, 16.00. The composition of 6-amino-1-methyl-2-quinolone monohydrate is C, 62.49; H, 6.29; N, 14.56. Although the product from the reduction was recrystallized from benzene and the hydrogen value found to be low compared to the calculated value for the monohydrate, the most reasonable assumption is that the reduction product contained moisture. No further work was attempted to determine, without ambiguity, the identity of this compound.

The most successful method for the preparation of 6-amino-1-methyl-2-quinolone was developed using iron and dilute acetic acid. Yields (50-60%) of product which melted at 179.7-182.7° were obtained. The sodium hydrosulfite and iron-acetic acid procedures are recorded in the experimental part of this section.

6-Amino-1-methyl-2-quinolone is a bright yellow solid, readily soluble in hot water. Addition of dilute sodium hydroxide precipitated brown crystals. The compound was soluble in chloroform, ethylene dichloride, ether and 3N hydrochloric acid, and insoluble in Skelly "F". The amine was conveniently recrystallized from benzene or an ethylene dichloride-Skelly "F" mixture.

2-Chloro-6-(3-diethylaminopropylamino)-quinoline was prepared by coupling the "side chain" with 6-amino-2-chloro-quinoline. Three problems were encountered in this route; first, catalytic and chemical reduction of 2-chloro-6-nitroquinoline apparently removed the chloro group; second

the coupling procedure resulted in considerable amounts of by-product; third, difficulty was met in preparing a satisfactory crystalline salt.

Capps and Hamilton[105] prepared 8-amino-2-chloroquinoline by reducing 2-chloro-8-nitroquinoline in ethanol at 50° and using unspecified Raney nickel as a catalyst. The product melted at 64° (cor.) and was light green in color. Greenbaum[106] repeated this reduction several times using similar conditions and W-7 Raney nickel, but obtained a low melting compound. Two reductions were run in this laboratory using W-7 Raney nickel. At room temperature and a starting pressure of 26 p.s.i., reduction did not occur; at 35° and 30 p.s.i., the theoretical amount of hydrogen was absorbed in two hours. An orange material was isolated from the latter reaction which melted at 58-60°. The melting point of 8-aminoquinoline is recorded as 65°,[107] 67°,[108] and 70°,[109]. Thus it appeared that catalytic reduction dehalogenated 2-chloro-8-nitroquinoline in addition

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[105] Capps and Hamilton, J. Am. Chem. Soc., 60 210,-6 (1938)

[106] Private Communication

[107] Kaufmann and Zalber, Ber., 50 1627 (1917)

[108] Claus and Kremer, Ber., 18 1245 (1885)

[109] Claus and Setzer, J. prakt. Chem., 2 53 400 (1896)

to reduction of the nitro group.

Several chemical methods of reduction were investigated as a consequence of the results obtained from the above experiments. Stannous chloride and concentrated hydrochloric acid in ethanol gave an orange material which melted at 59-60°. Two reductions were made using iron and dilute acetic acid, which gave an orange colored material, that melted at 66-68°, similar to the product from the catalytic reduction. It was conceivable that the reduction in concentrated hydrochloric acid with stannous chloride resulted in hydrolysis of the halogen, however, the iron-acetic acid reaction conditions were so mild that removal of the halogen was seriously doubted. A reduction was made with zinc dust and calcium chloride in water-alcohol solution. The compound obtained from this reaction melted at 66-68° and when mixed with a sample from the iron-acetic acid reduction showed no depression of the melting point. A sodium fusion and halogen test was made on the product from the zinc-calcium chloride reduction. The test gave excellent positive results for halogen. This compound was mixed with an authentic sample of 8-aminoquinoline (mp 64-65°) and a melting range from 50-65° was found for the mixture. The compound from the zinc-calcium chloride reduction was dried thoroughly and sent for analysis. The values determined for carbon, hydrogen, nitrogen and chlorine agreed with the calculated values for 8-amino-2-chloroquinoline.

The 8-amino-2-chloroquinoline from the zinc-calcium chloride reduction and iron-acetic acid process were separately recrystallized several times in an attempt to duplicate the corrected melting point of 84° recorded by Capps and Hamilton. The highest melting point obtained for 8-amino-2-chloroquinoline produced in this laboratory was 74-75°. It is believed that the low melting product obtained from each of the reductions reported above was actually 8-amino-2-chloroquinoline. Evidence is presented in section VI, which indicates that the activity of the 2-chloro group is considerable decreased when an electron-attracting group in the 8-position is replaced by an electron-doning group.

The initial work on these reductions indicated that the zinc-calcium chloride method gave the highest yields. A summary of the development work on this reaction is listed in table 5

8-Amino-2-chloroquinoline was alkylated by treatment with an excess of 1-chloro-3-diethylaminopropane at 100° for 15 hours. The reaction mass separated into a liquid and solid phase on cooling. From this reaction mass, excess "side chain" was recovered by distillation, unreacted "nucleus" and 2-chloro-8-(3-diethylaminopropylamino)-quinoline were removed by ether extraction and a third unidentified part remained as an ether insoluble portion.

The ether insoluble portion was a dark viscous oil,

soluble in water, alcohol and dilute hydrochloric acid. Attempts to make a crystalline salt from this material failed. Small samples were dissolved in absolute alcohol and an absolute alcohol solution of an acid component added to this solution. Cooling in an ice bath, carbon dioxide-chloroform bath and addition of ether were used in combinations, attempting to prepare a solid derivative of this material. Hydrobromide, hydriodide, phosphate, sulfate, oxalate, perchlorate and citrate were the salts whose preparation was attempted.

The ether soluble portion was thoroughly dried over potassium hydroxide and then magnesium sulfate, and dry hydrogen bromide bubbled into the filtered solution. A pink gum appeared first and soon crystallized to a tan solid which was seperated from the solution by filtration, washed with ether and recrystallized four times from absolute ethanol. The 2-chloro-6-(3-diethylaminopropylamino)-quinoline dihydrobromide prepared in this manner decomposed at 205-210° and is hydrated. Carbon and hydrogen analysis indicated a formula $C_{16}H_{22}ClN_3 \cdot 2HBr \cdot \frac{1}{2}H_2O$.

The ultraviolet absorption curve was determined for this solvated compound, the hydrobromide of 6-amino-2-chloroquinoline, and the hydrobromide of the side chain (see tables 6, 7 and 8 and figure 3). The data indicated a maximum at 355 mμ for these compounds. Using this wave length, the distributions of the hydrobromide salts of 6-amino-2-chloroquinoline and 2-chloro-6-(3-diethylaminopropylamino)-quinoline, were

studied between various buffers and cyclohexane (tables 10 and 11). As mentioned on page 105 it was felt that distillation would not be applicable as a method of separating unreacted nucleus from the drug. However, a difference in basicity of the two components should allow a method of separation. The distribution studies indicated that 7% of 8-amino-2-chloroquinoline went into the organic solvent, while 100% of the drug remained in the acetic acid solution at a pH of 2.15. This method was used in removing unreacted "nucleus" from the mixed salts.

A typical condensation produced 90 g. of hydrobromide salts as a mixture. The mixed salts were dissolved in an acetic acid solution (pH 2.15) and extracted eight times with 250 ml. portions of cyclohexane. The combined cyclohexane extracts were dried over magnesium sulfate and dry hydrogen bromide bubbled into the solution. In this manner 9 g. of 8-amino-2-chloroquinoline hydrobromide was recovered from the crude salts. This indicated that at least 9% of the mixture was unreacted "nucleus". The acetic acid solution was neutralized with sodium hydroxide, the drug extracted with ether and recovered as the dihydrobromide. The salt was recrystallized twice from absolute alcohol, washed with ether and dried at room temperature in a vacuum desiccator. The decomposition point was raised to 212.8-214.8°, analysis indicated $C_{16}H_{22}ClN_3 \cdot 2HBr \cdot \frac{1}{2}H_2O$ and the product weighed 77 g. This was a yield of 66% based on 45 g. of starting 8-amino-

2-chloroquinoline or 76.5% based on the 8-amino-2-chloroquinoline used.

The solvated 2-chloro-8-(3-diethylaminopropylamino)-quinoline dihydrobromide is a very light yellow compound very soluble in water, 2% acetic acid and nicely recrystallized from absolute ethanol. This compound was insoluble in ether, cyclohexane and Skelly "F" and appeared to be subject to change when exposed to the atmosphere. The surface of the light yellow crystals became slightly pink on standing in air, and consequently was stored in a closed container or desiccator. The free base was a brown viscous oil, soluble in ether, dilute acids and insoluble in basic solutions.

The anhydrous salt was prepared by heating the solvated salt under diminished pressure for 18 hours at 56° in the presence of phosphorus pentoxide. 2-Chloro-8-(3-diethylamino-propylamino)-quinoline dihydrobromide melted at 215.7-217.7°.

The free base was converted to the disulfate salt which decomposed at 148.5-151.5° and to the diperchlorate which decomposed at 209.8-211.8°. These salts were prepared by adding, to an absolute alcohol solution of the base, a solution of the respective acids in absolute alcohol. Concentrated sulfuric acid and commercial 70% perchloric acid were used in the preparations. Both salts were nearly white and (along with the dihydrobromide) were affected by the atmosphere. The micro analysis of these salts indicated there was no water associated with either compound.

Both of these salts were very sensitive to ether which caused oils to form rather than crystalline solids.

The diperchlorate was a potential explosive and several qualitative tests were run on this salt before analysis, to determine if the compound would explode. The diperchlorate was stable to 209.6-211.8° at which temperature non-violent decomposition to a dark liquid occured. Small samples of the salt placed on a hot plate sparkled and on pounding with a hammer on sandpaper no tendency to explode was exhibited. The compound was sent for carbon and hydrogen determinations, which were run at 700° and the analyst reported the sample exploded. No damage resulted from this experiment, but duplicate analysis were not made as a precautionary measure.

The ultraviolet absorption curves in distilled water for the hydrobromides of 2-chloro-8-(}-diethylaminopropylamino)-quinoline, 8-amino-2-chloroquinoline and 1-chloro-3-diethylaminopropane are compared in figure 4. The spectrum of the drug showed some changes in the intensities and a loss of bifurcation of the curve around 340 mμ. Qualitatively the attachment of the "side chain" did not materially change the shape of the curve compared to that of the salt of the "nucleus". The fact that attachment of the "side chain" did not materially alter the spectrum of 8-amino-2-chloroquinoline is in agreement with the results of the comparison of the 2-hydroxy drug with 8-aminocarbostyril (section IV). It is interesting to note that the "side chain" salt exhibited a

very similar shaped curve to the quinoline compounds but with much smaller intensities.

The spectrum of 6-amino-2-chloroquinoline in 95% ethyl alcohol was determined and compared to 6-amino-2-chloroquinoline hydrobromide in water. The object was to determine what effect salt formation had on the absorption of 6-amino-2-chloroquinoline. Changing from ethanol to water would be expected to produce a bathochromic shift and perhaps a loss of fine structure. The effect on the spectrum when a salt is formed from an aromatic amine is not clearly known. As observed 6-amino-2-chloroquinoline in ethanol shows a slight bathochromic shift compared to the hydrobromide in water and several more maxima than the salt. The change in intensity at various points of the curve could very easily be the result of a change in sensitivity of the electrical equipment since the absorptions were determined at different times. If the amino compound existed primarily as the salt in water solution a more varied change might be expected* in the spectrum.

2-Chloro-6-(3-diethylaminpropylamino)-quinoline dihydrobromide hemihydrate was subjected to a counter current distribution process after the method of Craig et al., to

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*For example, compare 3-aminopyrene and 3-aminopyrene hydrochloride, figures 45 and 47, Friedel and Orchin, "Ultraviolet Spectra of Aromatic Compounds", John Wiley and Sons, Inc., New York 1951

determine the present homogeneity, (Table 12, figure 6). buffer of pH 7.3) and cyclohexane were used as the two phase system. An eleven-plate distribution indicated the purity of the drug was 99+%.

Sixty-two grams of 2-chloro-4-(3-diethylaminopropylamino)-quinoline dihydrobromide (MW 395 g) was submitted to Dr. L. H. Schmidt, Christ Hospital, Cincinnati, Ohio for toxicity studies. The results of these studies were not available for discussion before publication of this manuscript.

EXPERIMENTAL

6-AMINO-1-METHYL-2-QUINOLONE

Method A

Two grams (.0096 mole) of 1-methyl-6-nitro-2-quinolone was placed in a 100-ml. round-bottomed flask, equipped with a magnetic stirrer and reflux condenser. Water (20 ml.) and 30 ml. of 95% ethyl alcohol were added, then 4 g. (.072 mole) of clean iron fillings (note 1), and 1 ml. of glacial acetic acid added to the stirred suspension and the mixture heated under reflux for twenty minutes. Fullers earth (1 g.) (note 2) and charcoal were added to the mixture which was boiled and the hot components separated by filtration. The clear filtrate was cooled in an ice bath whereupon light yellow crystals formed, which were separated from the solution by filtration and allowed to air dry. One gram (56.8%) of 6-amino-1-methyl-2-quinolone was obtained in this procedure. The compound melted at 179.7-182.7°.

Notes

1. Forty mesh iron filings were washed well with ether, collected on a Buchner funnel and allowed to dry.
2. "Celite" or Fullers earth aided in the filtering process.

Method B

Two grams (.0098 mole) of 1-methyl-6-nitro-quinolone was placed in a 100-ml. beaker clamped on a steam bath. Water (25 ml.) was added and the system heated to 80°. Sodium hydrosulfite (8.3 g.)(.048 moles) was added portion-wise, to the mechanically stirred suspension, over a 30-minute period. The solution was cooled and made slightly basic with ammonium hydroxide, then extracted with three 25-ml. portions of chloroform. The combined chloroform extracts were concentrated to a volume of approximately 20 ml. and Skelly "F" added, until the solution became turbid. On cooling in an ice bath, bright yellow 6-amino-1-methyl-2-quinolone precipitated which was collected on a Büchner funnel. The product weighed .6 g. (35.3%) and melted at 183.7-184.7°.

Analysis: Calculated for $C_{10}H_{10}N_2O$. C, 68.94; H, 5.78. Found: C, 68.64, 68.89; H, 5.66, 5.77.

6-AMINO-2-CHLOROQUINOLINE

Method A

Fifty grams (.24 mole) of 2-chloro-6-nitroquinoline was placed in a 3-l. 3-necked flask which contained 1200 ml. of 70% acetone (note 1). A reflux condenser, and Hershberg stirrer were positioned in the flask and the contents stirred and heated nearly to boiling. Calcium chloride (50 g.)

(.45 mole) in 30 ml. of water and 300 g. (4.6 moles) of zinc dust were added to the vigorously stirred hot solution. The suspension was brought to a boil (note 2) and then heated under reflux for three and a half hours. The hot mixture was filtered with suction through a Büchner funnel, and the filter cake washed once with 30 ml. of acetone. The filtrate was refiltered (note 3) and cooled. The cooled solution was poured into 16 l. of manually stirred ice water. A yellow-brown precipitate formed immediately and was allowed to settle for two or three hours (note 4), then collected on a Büchner funnel and allowed to dry overnight. The crude precipitate weighed 36 g. and was extracted, by decantation, with four 400-ml. portions of boiling Skelly "F" (note 5). The combined Skelly "F" extracts were decolorized with charcoal, filtered and cooled in a carbon dioxide-chloroform bath. Twenty-eight grams of product was obtained as a first crop of crystals. The filtrate was concentrated to 300 ml. (note 6) decolorized, refiltered and cooled in a carbon dioxide-chloroform bath to obtain an additional 5 g. of product. The total weight was 33 g. (77%) of 8-amino-2-chloroquinoline which melted at 63.5-65.5°.

Analysis: Calculated for $C_9H_7ClN_2$. C, 60.51; H, 3.95; N, 15.68; Cl, 19.85. Found: C, 60.46, 60.39; H, 3.86, 3.96; N, 15.64, 15.50; Cl, 19.75, 19.67.

Notes

1. Acetone (640 ml.) was added to 360 ml. of water.
2. An initial exothermic reaction occured which flooded the reflux condenser. Heat, which was supplied by a Glas-col mantle, was cut off until the initial reaction subsided. The reaction must be constantly attended during the initial reaction period.
3. A small quantity of impurity came through the first filter, and a second filtration was necessary to remove this material.
4. The precipitate was not allowed to stand overnight in the water suspension, since this substantially lowered the yield.
5. The Skelly "F" extracts were contaminated with a small amount of insoluble material. This impurity was removed before the combined extracts were decolorized.
6. The Skelly "F" solution was concentrated rapidly on a steam bath, the recovered solvent saved for similar recrystallizations.

Method B

In a 200-ml. round-bottomed flask equipped with stirrer and reflux condenser was placed 3 g. (.0145 mole) of finely ground 2-chloro-3-nitroquinoline, 40 ml. of 70% ethyl alcohol and 1 ml. of glacial acetic acid. The flask was placed in a

TABLE 5

REDUCTION OF 2-CHLORO-6-NITROQUINOLINE

Zinc dust — Reflux period: 3-4 hours

Calcium chloride — Recrystallization from Skelly "F"

RUN	STARTING MATERIAL	SOLVENT PAIR			CRUDE PRODUCT	M P	YIELD
	Gm.	Alcohol	Water	Acetone			
1	5	164	36		2.6	74-75	61
2	5	100	100		3.3	73-74	77
3	25	300	300		17.4	71-72.5	81
4	50	600	600		23.0	66-67	53
5	50	700	700		20.0	72-74	46
6	25	300	300		11.0	67-69	51
7	50	780	420		20.0	71-72	46
8	50	900	300		20.0	73-74	46
9	25	450	150		15.0	64-66	70
10	25		300	300	17.0	---	79
11	50		360	840	33.0	64-66	77

hot water bath at 50° and the contents stirred vigorously while 5 g. of clean iron powder (40 mesh) was added in portions over a 15 minute period. After addition of the iron, the solution was stirred another 15 minutes, Fullers earth added and the hot mixture subjected to filtration. The residue was washed with 20 ml. of hot ethanol which was combined with the original filtrate. The combined filtrates were poured into 800 ml. of stirred ice water and cooled in an ice bath. The yellowish-white precipitate was collected on a Büchner funnel and air-dried. The crude material weighed 1 g. and after recrystallization from Skelly "F", the product weighed .6 g. (23.4%) and melted at 65.5-66.5°.

8-AMINO-2-CHLOROQUINOLINE MONOHYDROBROMIDE

Two grams (.0012 mole) of 8-amino-2-chloroquinoline was dissolved in 30 ml. of absolute ether and dry hydrogen bromide bubbled into the solution until precipitation was complete. The fine cream colored powder was collected on a Büchner funnel, washed with dry ether and dried in the air. The sample was dissolved in absolute alcohol, decolorized with charcoal, filtered and the filtrate cooled in a carbon dioxide-chloroform bath. Faintly yellow crystals were separated from the cold solution by filtration and dried in the atmosphere. The salt turned reddish-brown at 210-215° and decomposed above 300°.

Analysis: Calculated for $C_9H_7ClN_2 \cdot HBr$. C, 41.64; H, 3.12. Found: C, 41.69, 41.73; H, 3.26, 3.16.

6-AMINO-2-CHLOROQUINOLINE MONOHYDROCHLORIDE

One gram (.0056 mole) of 6-amino-2-chloroquinoline was treated with 30 ml. of 20% hydrochloric acid. A white salt formed immediately which was ground as fine as possible, in the acid solution, allowed to stand at 8° for three hours, and then collected on a Büchner funnel. The white 6-amino-2-chloroquinoline monohydrochloride was dried in a vacuum desiccator containing phosphorus pentoxide; it weighed .61 g. The salt began to shrink at 220°, fumed and decomposed to a glue at 230°.

Analysis: Calculated for $C_9H_7ClN_2 \cdot HCl$. C, 50.26; H, 3.74. Found: C, 50.39, 50.26; H, 3.69, 3.68.

2-CHLORO-6-(3-DIETHYLAMINOPROPYLAMINO)-QUINOLINE DIHYDROBROMIDE MONOHYDRATE

Forty-five grams (.252 mole) of 6-amino-2-chloroquinoline and 113 g. (140 ml. or .836 mole) of 1-chloro-3-diethylaminopropane was placed in a 500-ml. flat-bottomed flask with a magnetic stirrer and reflux condenser. Using an oil bath, the external temperature was raised to 95-100° over a one hour period, and maintained at this temperature for fourteen hours. The mixture was stirred during the entire heating

period. After cooling the reaction mixture, a liquid phase was decanted from the gummy solids which were then dissolved in 500 ml. of 5% hydrochloric acid (note 1). The decanted liquid portion was combined with the acidic solution, and the mixture made basic with 10% sodium hydroxide and then saturated with potassium carbonate. The mixture was extracted with four 200-ml. portions of ether, the combined ether extracts were concentrated to a volume of 300 ml. and dried initially over potassium hydroxide, then magnesium sulfate overnight. The remainder of the ether was removed on the steam bath and the residue warmed to 60° at a pressure of 1.5 mm. Hg. (note 2). This residue was dissolved in 1500 ml. of absolute ether and dry hydrogen bromide bubbled into the solution until precipitation was complete (note 3). The light pink solids were collected on a Büchner funnel, washed with absolute ether, dried in a vacuum desiccator; the solids weighed 90 g. The crude precipitate was dissolved in 1000 ml. of acetic acid solution which had a pH of 2.15 (note 4) and extracted with eight 250-ml. portions of cyclohexane (note 5). The acetic acid solution was made slightly basic with 10% sodium hydroxide, saturated with potassium carbonate and extracted four times with 200 ml. portions of ether. The combined ether extracts were dried initially with potassium hydroxide, then magnesium sulfate overnight and the filtered solution saturated with dry hydrogen bromide (note 6). The light tan crystals were separated

by filtration, washed with ether, dried and recrystallized twice from absolute alcohol (note 7). 2-Chloro-6-(3-diethylaminopropylamino)-quinoline dihydrobromide hemihydrate, which decomposed from 212.6-214.6° and weighed 77 g. (76.5%) was prepared in this procedure.

Analysis: Calculated for $C_{16}H_{22}ClN_3 \cdot 2HBr \cdot \frac{1}{2}H_2O$. C, 41.53; H, 5.44; Total halide as Cl, 28.46; N, 9.08. Found: C, 41.79, 41.79; H, 5.37, 5.39; Halide as Cl, 28.53, 27.92; N, 8.97, 8.92.

Notes

1. The solids were somewhat slow to dissolve in the dilute hydrochloric acid and were warmed gently on the steam bath. It was more convenient to decant the liquid phase before dissolving the solids in the acid solution.

2. 1-Chloro-2-diethylaminopropane distills at 39-45/2.5 mm., therefore, most all of the excess "side chain" should be removed under these conditions. Sixty-four grams of "side chain" was recovered at this point which represents 81% of the excess used.

3. A gum formed first, which solidified after much scratching and rubbing. Approximately an hour was required for complete precipitation of the salts.

4. One hundred and fifteen milliliters of glacial acetic acid diluted to 1000 ml. with distilled water gave a solution whose pH was very nearly 2.15.

5. The cyclohexane extracts which contained 8-amino-2-chloroquinoline were combined, dried and the "nucleus" recovered as the salt by saturating the solution with dry hydrogen bromide.
6. About 600-800 ml. of additional absolute ether was required as the saturation proceeded.
7. Approximately 800 ml. of absolute alcohol was required for complete solution. Both solutions were decolorized with charcoal and 400 ml. of absolute ether was added to the alcoholic solution in the second recrystallization.

2-CHLORO-8-(3-DIETHYLAMINOPROPYLAMINO)-QUINOLINE DIHYDROBROMIDE

The hemihydrate salt in an open drying dish was placed in a vacuum oven containing fresh phosphorus pentoxide. The system was continuously evacuated by use of a mechanical pump while heated at 56° for 18 hours. The product melted at 215.7-217.7°.

Analysis: Calculated for $C_{16}H_{22}ClN_3 \cdot 2HBr$. C, 42.37; H, 5.33; Found: C, 42.09, 42.01; H, 5.38, 5.31.

2-CHLORO-8-(3-DIETHYLAMINOPROPYLAMINO)-QUINOLINE DISULFATE

Five milliliters of a dry ethereal solution of the free base was evaporated to an oily residue which was then dissolved in 2 ml. of absolute alcohol. A solution of

2 ml. of concentrated sulfuric acid in 5 ml. of absolute alcohol was added dropwise and the solution cooled in an ice bath. Light pink crystals appeared which were collected by filtration, washed with ether and dried overnight in a vacuum desiccator. The solid was dissolved in absolute alcohol, decolorized, and cooled in a carbon dioxide-chloroform bath. A flocculent yellow solid formed which was collected on a Buchner funnel and washed with absolute ethanol at -51° and then with absolute ether. Nearly white crystals of 2-chloro-6-(3-diethylaminopropylamino)-quinoline disulfate was obtained which after drying in a vacuum desiccator decomposed at 148.5-151.5°.

Analysis: Calculated for $C_{16}H_{22}ClN_3 \cdot 2H_2SO_4$. C, 39.37; H, 5.37; N, 8.61. Found: C, 39.77, 39.72; H, 5.65, 5.61; N, 8.56, 8.68.

2-CHLORO-6-(3-DIETHYLAMINOPROPYLAMINO)-QUINOLINE DIPERCHLORATE

This salt was prepared essentially by the same method as the disulfate, using 70% perchloric acid. The salt was recrystallized once from 2-propanol and a second time from absolute methanol. Almost white 2-chloro-6-(3-diethylaminopropylamino)-quinoline diperchlorate decomposed at 209.6-211.6°. The salt exploded when heated to 700°.

Analysis: Calculated for $C_{16}H_{22}ClN_3 \cdot 2HClO_4$. C, 39.00; H, 4.91. Found: C, 39.28; H, 5.04.

ULTRAVIOLET ABSORPTION DATA

The technique and equipment used in determining the absorption spectra have been described on page 83. Absorption data of the compounds pertaining to this section are recorded in tables 6, 7, 8 and 9 and graphically in figures 4 and 5.

PARTITION RATIOS

The partition ratios for 6-amino-2-chloroquinoline hydrobromide and 2-chloro-6-(3-diethylaminopropylamino)-quinoline hydrobromide hemihydrate were determined using the technique described on page 84. For these compounds the pH of the buffer was varied, samples of the same buffer solution were used for both "nucleus" and drug. Potassium hydroxide (5N) was used to convert the salts to free bases. The results are recorded in tables 10 and 11.

COUNTER-CURRENT DISTRIBUTION

A 25-tube stainless steel distribution machine was used in the counter-current homogeniety analysis of UK 2064. Machine distribution has been described in detail by Craig.* An eleven-plate distribution was made using cyclohexane and an acetate buffer of pH 5.30. The experimental K's were calculated from the formual $K = \frac{r}{n+1-r} \times \frac{\Sigma r}{\Sigma r-1}$, where r = tube number, n= number of plates, Σr and $\Sigma r-1$ = the

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*Craig, L.C., J. Biol. Chem., 155 519 (1944.)

experimental optical density at tube r and r-1 respectively. The theoretical optical densities (Tr) for tube numbers above four were calculated from the formula $Tr = \frac{n+1-r}{1} \times K \times Tr-1$. Those theoretical values for tube numbers below four were calculated from the formula, $Tr = \frac{r+1}{1+1} \times \frac{1}{K} \times Tr+1$. Tube four was the standard point. The experimental and theoretical data are recorded in table 12 and a plot made in figure 6 of the optical densities.vs. tube numbers for the theoretical and experimental data.

TABLE 6

ULTRAVIOLET ABSORPTION DATA

1-Chloro-3-Diethylaminopropane Hydrobromide

$C_7H_{16}ClN.HBr$ Mol. Wgt. 230.590

Solvent: Distilled water Concentration: .1546mg/25 ml.

$\varepsilon = \frac{D}{ct}$ t = 1.00 cm. c = 2.682×10^{-5} moles/l.

λ	D	$\varepsilon \times 10^{-3}$	λ	D	$\varepsilon \times 10^{-3}$
248	.177	6.61	320	.036	1.34
250	.200	7.46	325	.037	1.38
255	.211	7.88	*330	.039	1.45
260	.223	8.32	335	.034	1.27
*265	.225	8.40	340	.032	1.19
270	.210	7.84	345	.033	1.23
275	.187	6.97	350	.034	1.27
280	.167	6.23	*355	.047	1.75
285	.133	4.96	360	.035	1.30
290	.102	3.81	*365	.037	1.38
295	.062	2.31	370	.028	1.04
300	.060	2.24	375	.027	1.00
305	.049	1.83	380	.028	1.04
310	.043	1.60	385	.030	1.12
315	.040	1.49			

* λ_{max}

TABLE 7

ULTRAVIOLET ABSORPTION DATA

8-Amino-2-Chloroquinoline Hydrobromide

$C_9H_7ClN_2.HBr$ Mol. Wgt. 259.546

Solvent: Distilled Water Concentration: .1420 mg/25 ml.

$\varepsilon = \frac{D}{ct}$ t = 1.00 cm c = 2.188×10^{-5} moles/l.

λ	D	$\varepsilon \times 10^{-3}$	λ	D	$\varepsilon \times 10^{-3}$
248	.578	26.38	320	.055	2.51
250	.655	29.90	325	.055	2.51
*255	.735	33.55	*330	.060	2.74
260	.645	29.43	335	.059	2.69
265	.430	19.64	340	.056	2.56
270	.228	10.42	345	.052	2.37
275	.113	5.16	350	.054	2.46
280	.085	3.88	*355	.064	2.92
285	.073	3.33	360	.050	2.28
290	.058	2.65	365	.044	2.01
295	.046	2.10	370	.027	1.23
300	.048	2.19	375	.023	1.05
305	.050	2.28	380	.020	.91
310	.052	2.37	385	.018	.82
315	.055	2.51			

* λ_{max}

TABLE 8

ULTRAVIOLET ABSORPTION DATA

2-Chloro-6-(3-Diethylaminopropylamino)-quinoline
(Dihydrobromide hemihydrate)

$C_{16}H_{22}ClN_3 \cdot 2HBr \cdot \frac{1}{2}H_2O$ Mol. Wgt. 462.676

Solvent: Distilled Water Concentration: .1350 mg/25 ml

$\varepsilon = \frac{D}{ct}$ t = 1.00 cm. c = 1.167×10^{-5} moles/l.

λ	D	$\varepsilon \times 10^{-3}$	λ	D	$\varepsilon \times 10^{-3}$
248	.236	20.02	320	.027	2.31
250	.265	22.70	325	.028	2.40
255	.320	27.45	330	.031	2.66
*260	.361	30.97	335	.033	2.83
265	.350	30.02	340	.034	2.92
270	.292	25.05	345	.034	2.92
275	.171	14.65	350	.035	3.00
280	.095	8.14	*355	.050	4.28
285	.061	5.23	360	.040	3.43
290	.048	4.12	365	.033	2.83
295	.033	2.83	370	.026	2.23
300	.029	2.49	375	.025	2.14
305	.025	2.14	380	.025	2.14
310	.024	2.06	385	.022	1.88
315	.024	2.06			

* λ_{max}

FIGURE 4

ULTRAVIOLET ABSORPTION SPECTRA

2-Chloro-8-(3-diethylaminopropylamino)-quinoline
• Dihydrobromide Hemihydrate

+8-Amino-2-chloroquinoline Monohydrobromide

°1-Chloro-3-diethylaminopropane Monohydrobromide

Solvent: Distilled Water

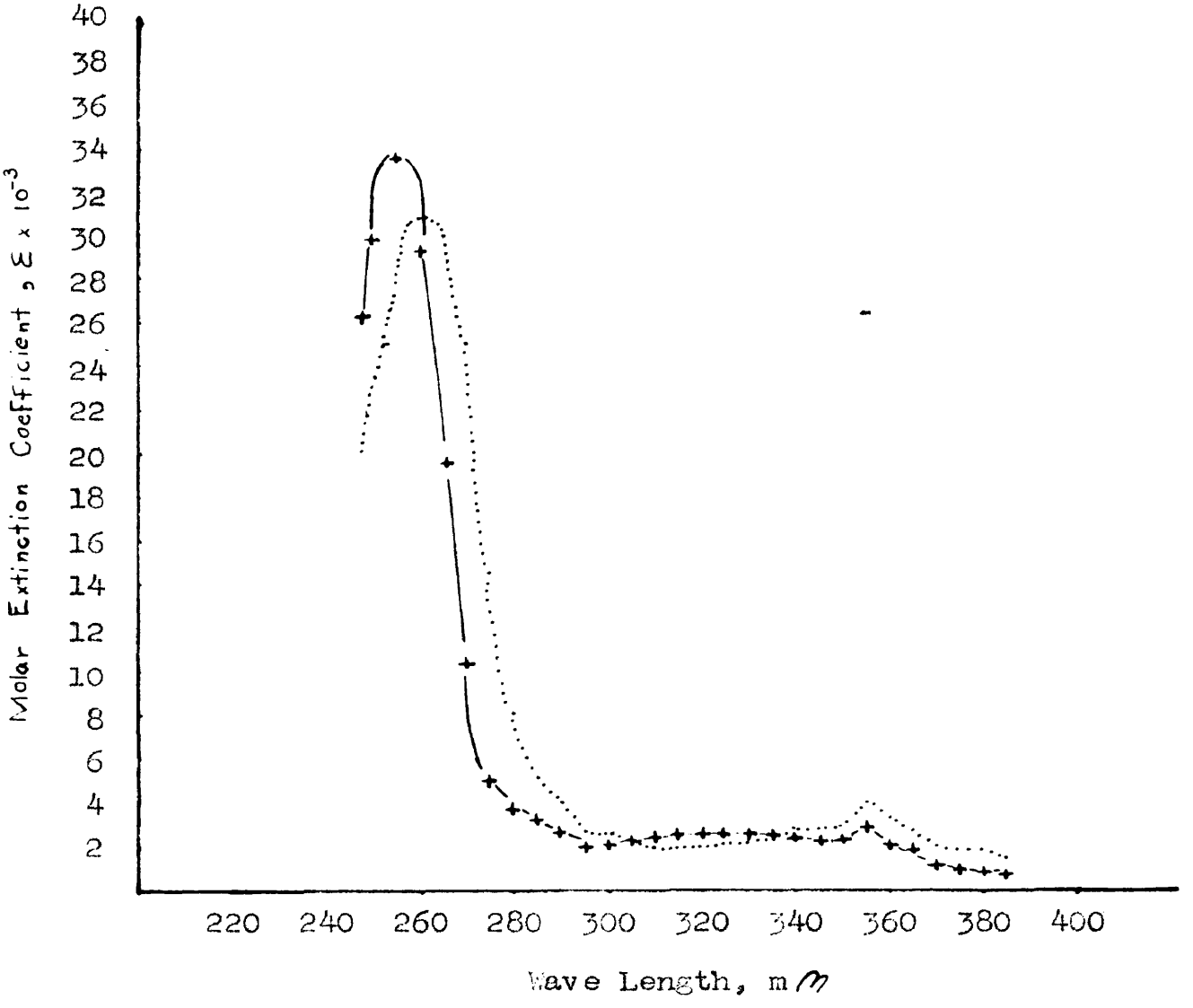


TABLE 9

ULTRAVIOLET ABSORPTION DATA

6-Amino-2-chloroquinoline

$C_9H_7ClN_2$ Mol. Wgt. 178.622

Solvent: 95% Alcohol Concentration: .119 mg/25.7 ml.

$\varepsilon = \frac{D}{ct}$ t = 1.00 cm. c = 2.592×10^{-5} moles/l.

λ	D	$\varepsilon \times 10^{-3}$	λ	D	$\varepsilon \times 10^{-3}$
225	.435	16.80	315	.060	2.31
230	.387	14.94	320	.062	2.39
*235	.400	15.43	325	.075	2.89
240	.356	13.72	330	.081	3.12
245	.618	23.90	335	.084	3.24
250	.700	27.00	*340	.089	3.44
255	.860	33.20	345	.085	3.28
*260	.920	25.50	350	.075	2.89
265	.855	33.00	*355	.080	3.09
270	.558	21.55	360	.078	3.01
275	.187	7.22	365	.075	2.89
280	.060	2.31	370	.070	2.70
285	.047	1.81	375	.044	1.70
290	.050	1.93	*380	.057	2.20
*295	.060	2.31	385	.050	1.93
300	.051	1.97	390	.045	1.74
*305	.058	2.24	400	.020	.77
310	.056	2.16			

* λ max

FIGURE 5

ULTRAVIOLET ABSORPTION SPECTRA

+ 8-Amino-2-chloroquinoline Monohydrobromide in Distilled Water

• 8-Amino-2-chloroquinoline in 95% Alcohol

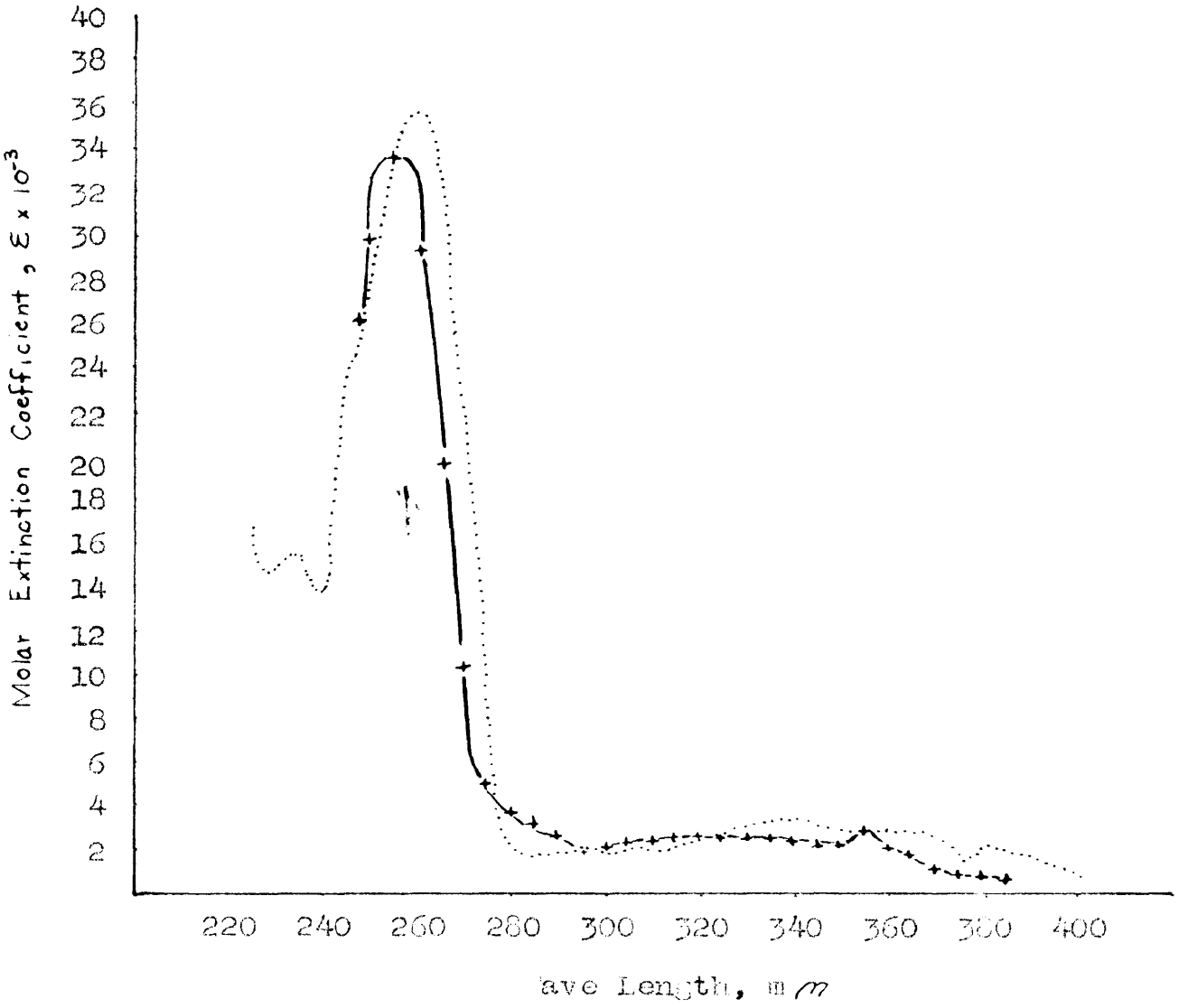


TABLE 10

PARTITION RATIOS

2-Chloro-8-(3-Diethylaminopropylamino)-quinoline Dihydrobromide Hemihydrate

Solvent: Cyclohexane

Buffer system: Sodium Acetate-Acetic Acid

pH's @ 25°

Optical Density @ 355 mμ

pH	OPTICAL DENSITY			PARTITION RATIO	PERCENT IN
	C_6H_6	Buffer	Total	C_6H_6/Buffer	C_6H_6
2.15	0	.159	.159	0	0
3.97	.020	.220	.240	.091	8.33
5.09	.127	.130	.257	.977	49.4
5.75	.317	.026	.343	12.2	92.4
6.19	.501	.025	.526	20.0	95.2
6.57	.205	.012	.217	17.1	95.2
8.01	.535	.012	.544	44.4	97.8

TABLE 11

PARTITION RATIOS

8-Amino-2-Chloroquinoline Hydrobromide

Solvent: Cyclohexane

Buffer System: Sodium Acetate-Acetic Acid

pH's @ 25°

Optical Density @ 355 mμ

pH	OPTICAL DENSITY			PARTITION RATIO	PERCENT IN C_6H_6
	C_6H_6	Buffer	Total	$C_6H_6/_{Buffer}$	
2.15	.307	.079	.386	.389	79.0
3.97	.324	.016	.340	20.2	95.3
5.09	.900	.018	.918	50.0	98.1
5.75	.705	.018	.723	39.2	97.5

Table 12

Solubility at 25° C

2-Chloro-6-[3-dimethylaminopropylamino]-quinoline
dihydrobromide hemihydrate

Solvent: Cyclohexane

Buffer System: Sodium acetate-acetic acid

pH 2.4° 5.30

Optical Density 335 mμ

Tube No.	Optical Density Experimental	Optical Density Theory	Solubility (Mol/L) K
0	.075	.036	
1	.320	.237	
2	.620	.712	
3	1.222	1.185	.602
4	1.540	1.540	.630
5	1.200	1.245	.526
6	.695	.775	.564
7	.311	.334	
8	.141	.100	
9	.063	.029	
10	.029	.005	
11	.005	.000	
Sum	6.577*	6.342	Ave. K .60

Homogeneity $\frac{6.342}{6.577} = 96 \mp 4\%$

* In the calculation of this sum, theoretical values were substituted for those experimental values which were lower than the theoretical figure.

FIGURE 6

HOMOGENEITY OF UM 206 Q

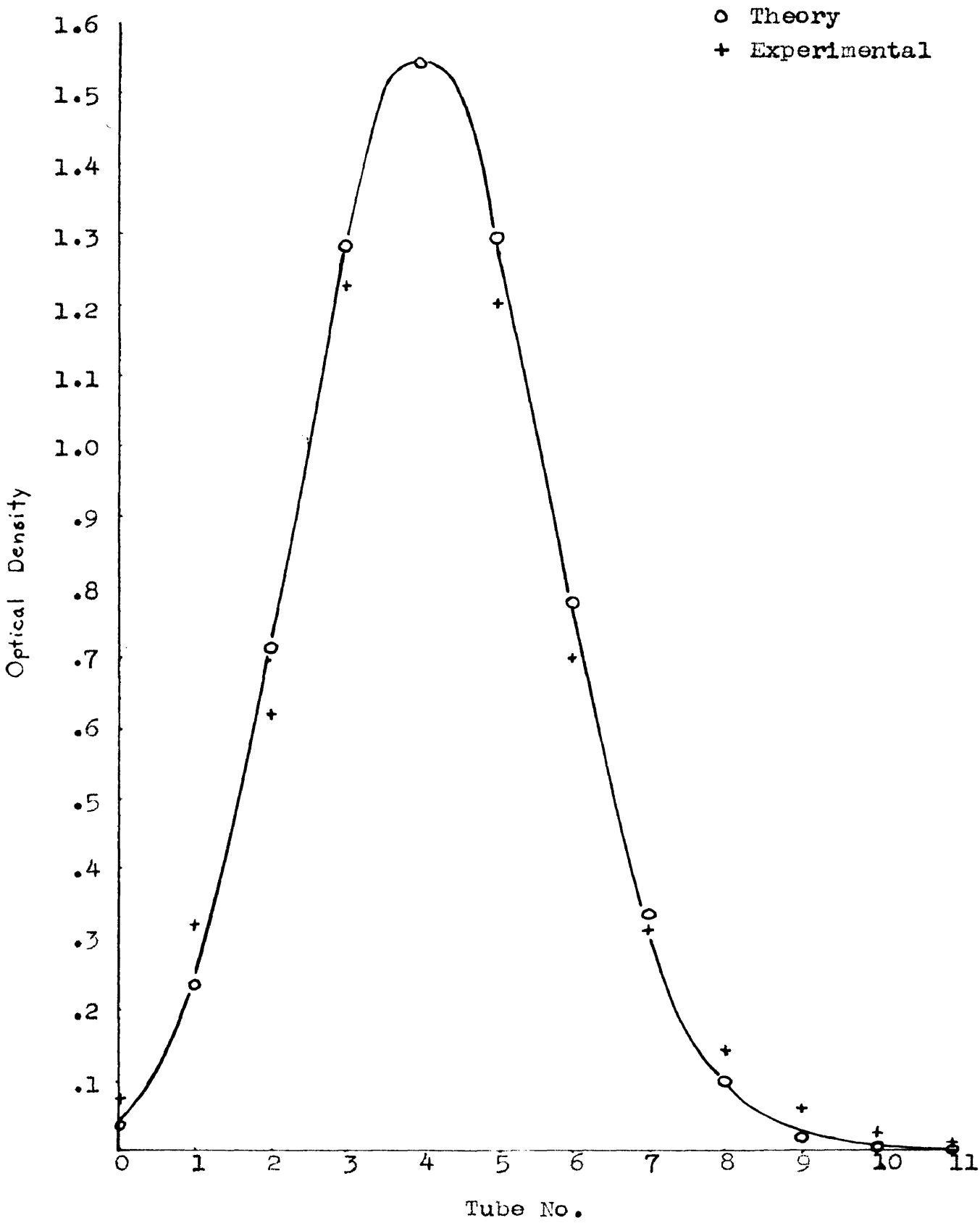
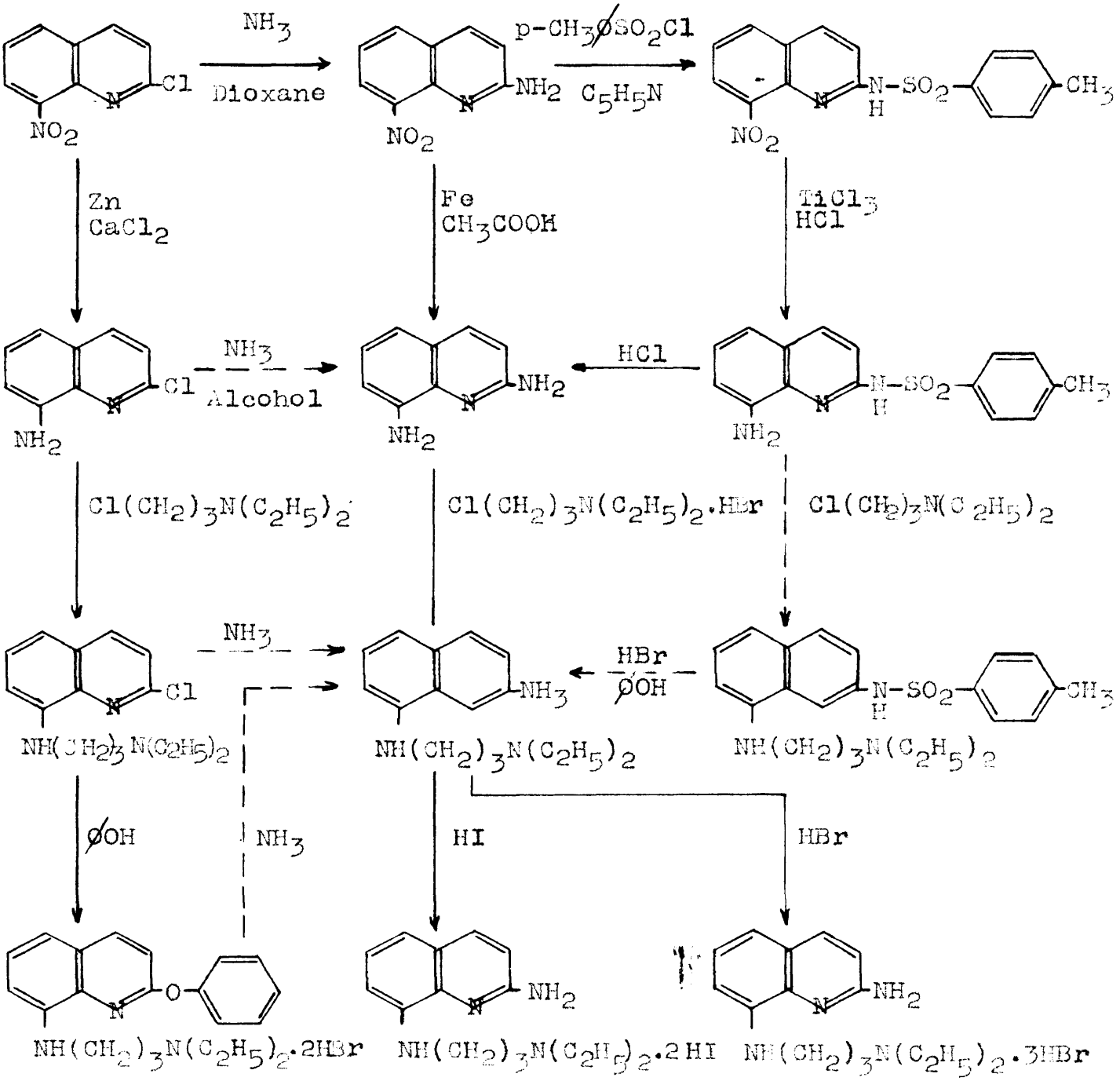


CHART VI

2-AMINO-8-(3-DIETHYLAMINOPROPYLAMINO)-QUINOLINE AND SALTS



SECTION VI

2-AMINO-8-(3-DIETHYLAMINOPROPYLAMINO)-QUINOLINE AND SALTS

Discussion

An important reaction of the 2-bromo- and chloroquinolines (and pyridines) is displacement of halogen with an amino or substituted amino group. This type of a displacement is also useful for many other less active organic halogen compounds and numerous examples are recorded in the literature. To illustrate the various conditions and catalysts which have been useful in this displacement in pyridine and quinoline compounds, it is relevant to review briefly some of the general ammonolytic reactions, which should prove useful in the preparative schemes designated in chart VI.

Ashley et al.,[110] displaced chlorine in 4-chloroquinaldine by heating with alcoholic ammonia in a sealed tube at 190-200° for 8 hours. The yield was 70% of theory. Maier-Bode's[111] method consisted of treating the bromo compound with aqueous ammonia and copper sulfate catalyst under pressure. In this manner he converted 3-and 3,5-dibromopyridine to the corresponding amines in 88 and 56%

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[110] Ashley et al., Proc. Roy. Soc., (London) 113B 295 (1933)

[111] Maier-Bode, Ber., 69 1534 (1936)

yields respectively. Jansen and Wibaut[112] used anhydrous ammonia in the presence of copper powder to prepare 2-aminoquinoline from 2-bromoquinoline. They recorded a yield of 50% in this particular reaction. Utilizing a zinc chloride-ammonia complex with 2-chloropyridine in a sealed tube at 220°, Fischer[113] obtained a nearly quantitative yield of 2-aminopyridine. Jensch[114] treated several substituted 4-chloroquinolines with phenol at 170-180° and bubbled dry ammonia into the hot solution to obtain the corresponding 4-amino compounds.

Backeberg and Maries[115] studied the ammonolysis of 4-chloroquinaldine and 2-chlorolepidine using the reagents recorded above, and summarized the results of their reactions. They indicated that the phenol methods gave an almost quantitative yield of the amino compound from 4-chloroquinaldine, whereas only a small amount of amine was obtained from 2-chlorolepidine; the phenyl ether being the major product. The 2-chlorolepidine was active only with the zinc chloride-ammonia complex. Curd, Raison and Rose,[116] however, prepared 2-amino-4-(3-diethylaminopropylamino)-quinoline from

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[112]Jansen and Wibaut, Rec. trav. chim., 56 709 (1937)

[113]Fischer, Ber., 32 1301 (1899)

[114]Jensch, Ger. pat. 591,480: C.A. 28 2366[3] (1934)

[115]Backeberg and Maries, J. Chem. Soc., 381 (1942)

[116]Curd, Raison and Rose, J. Chem. Soc., 909 (1947)

the analogous 2-chloro compound using the phenol method.

Elderfield et al., [117] reported that 4,7-dichloroquinoline did not react under pressure with either anhydrous or ethereal ammonia at temperatures up to 259°. The displacement of the 2-chloro group in the 5-,6-and 8-nitroquinolines has been cited on page 109.

The particular compounds converted to amino compounds by ammonolysis reviewed above, are probably not as significant as the scope of the reaction. The varied results and conditions used in this reaction make it impractical to attempt predictions on whether ammonolysis would occur on the basis of the influence of various substituents. Rather, the number of variables in ammonolytic reactions, such as temperature, solvents, reagents and catalysts, should favor the determination of some set of conditions which would replace the 2-chloro group in most quinoline compounds.

Therefore, once a satisfactory syntheses of 2-chloro-8-(3-diethylaminopropylamino)-quinoline had been developed, ammonolysis appeared to be the most logical approach for the preparation of the 2-amino compound. This method was given first priority for the preparation of the 2-amino drug. Unfortunately, the proper conditions for this ammonolysis were never discovered in this laboratory.

The results of the ammonolysis of 2-chloro-8-nitro-

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[117] Elderfield et al., J. Am. Chem. Soc., 68 1259 (1946)

quinoline, 2-chloroquinoline, 8-amino-2-chloroquinoline and 2-chloro-8-(3-diethylaminopropylamino)-quinoline forms an interesting pattern.

2-Amino-8-nitroquinoline was prepared, in unspecified yield, by Fischer and Guthmann[118] from 2-chloro-8-nitroquinoline using concentrated ammonium hydroxide, at 150° over a 6-7 hour period. They recorded the melting point of the product at 159°. The method developed in this laboratory for the ammonolysis of 2-chloro-8-nitroquinoline was carried out at 150° in 3.5 to 4 hours with liquid ammonia in dioxane. The yield of 2-amino-8-nitroquinoline was 65-75% of theory. The product melted at 163.8-165.7°.

Diepolder[119] aminated 2-chloroquinoline with a mixture of concentrated ammonium hydroxide, zinc chloride and ammonium chloride at 210° over a period of 8 hours. The yield of the amine was not reported.

8-Amino-2-chloroquinoline was treated with alcoholic ammonia at 170° for 4 hours. From this reaction, approximately 45% of the starting material was recovered, but no 2,8-diaminoquinoline could be isolated.

Five attempts were made to replace the chloro group of 2-chloro-8-(3-diethylaminopropylamino)-quinoline with the amino group under the following conditions:

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[118] Fischer and Guthmann, J. prakt. Chem., 93 385 (1916)

[119] Diepolder, J. prakt. Chem., [2] 106 54 (1923)

1.	NH_3-Dioxane	170°	4 hours
2.	NH_3-Absolute Alcohol	170°	4 hours
3.	NH_3-Dioxane	195°	3 hours*
4.	NH_3-Dioxane	195°	18 hours
5.	NH_3-H_2O-Zinc Chloride	270°	10 hours

From the first three runs, starting material was recovered, as a salt, in undetermined yields. What was apparently an inhomogeneous material, which melted at 130-160°, was obtained from the fourth run in a very small amount, and the fifth run produced extensive decomposition.

Qualitatively, it appears that the electron-attracting Bz-nitro groups activate the 2-position of 2-chloroquinoline toward attack by ammonia, and conversely the electron-releasing amino and substituted amino groups deactivate the 2-position toward the reaction with ammonia. Incorporating the data of Fischer and Guthmann on the 5-and 6-nitro compounds the relative effect of the Bz-substituents on 2-chloroquinoline might be indicated as 8-nitro > 5-nitro > 6-nitro > H > 8-amino and 8-(3-diethylaminopropylamino). The discussion of the experimental work on the ammonolysis of these compounds given previously makes the very qualitative nature of the series obvious.

Several other considerations, from an experimental

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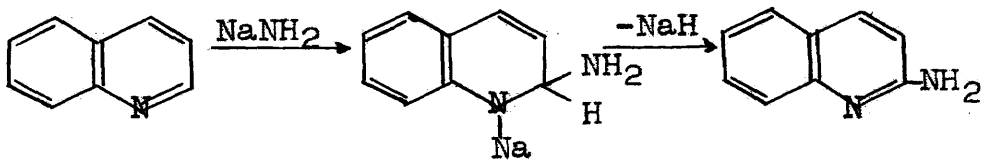
*The thermocouple broke, sometime after three hours during this run.

standpoint, illustrate the difficulty in attempting to rationalize the behavior of many quinoline compounds.

Chichibabin[120] prepared 2-aminoquinoline by amination of quinoline with sodamide in an inert solvent. This reaction has been reviewed by Leffler[121] and a mechanism proposed, which involves addition of sodamide across the carbon-nitrogen double bond, and subsequent splitting out of sodium hydride. Solvents which have been used in this reaction



are xylene, toluene and dimethylaniline.

In this laboratory, three attempts were made to react sodamide with 2-chloro-6-nitroquinoline using toluene as a solvent. The product isolated, in these three reactions, melted between 148 and 152°. 2-Chloro-6-nitroquinoline melted at 149.5-151.5° after one recrystallization from toluene, compared to 2-amino-6-nitroquinoline which melted at 165.2-166.8° after recrystallization from toluene. The aminations were run, while stirred vigorously, under the following conditions; the product was recovered by filtering the hot solution, cooling the filtrate in an ice bath and

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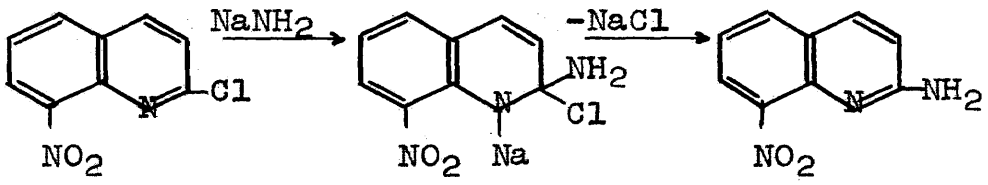
[120]Chichibabin and Zatzepina, J. Russ. Phys. Chem. Soc., 50 553 (1920) C.A. 18 1502 (1904)

[121]"Organic Reaction", John Wiley and Sons, New York, 1942 Vol. I, p. 91.

separating the crystals from the solution by filtration:

	Internal Temp.	Time	M.P. Product	% Recovery
1.	70°	15 min.	150-152	87
2.	113° (reflux)	6 hours	149-151	---
3.	113° (reflux)	20 hours	148-150	---

The conclusion drawn from these experiments was, that the reaction was not a suitable method for preparing 2-amino-8-nitroquinoline. A mechanism, by analogy, for this reaction would be addition of sodamide across the carbon-nitrogen double bond, then splitting out sodium chloride, Sodium



chloride as a byproduct should favor this reaction compared to splitting out sodium hydride in the original Chichibabin reaction. Further, the apparent enhancement, by the 8-nitro group, on the activity of the 2-position toward attact by ammonia as proposed above, should also favor the attact of the negative amino group of sodamide. It is not readily apparent why this reaction did not give a good yield of the desired 2-amino-8-nitroquinoline.

There are other reactions, such as hydrolysis, and methoxylation, which attest to the reactivity of 2-Chloro-8 nitroquinoline. In fact, the reactivity of this compound made it most valuable as an intermediate for the preparation

of substituted 8-aminoquinolines, and accounts, in a large part, for the work on a suitable preparative method, detailed in section II of this manuscript.

However, an impression that the conversion of the 8-nitro group to an amino or substituted amino group completely inactivates the 2-position would not be in accord with the following reactions. 8-Amino-2-chloroquinoline has been hydrolyzed with acid to 8-aminocarbostyril (section IV), and 8-(3-diethylaminopropylamino)-carbostyril has been prepared by the acid hydrolysis of the corresponding 2-chloro drug (section III). An attempt to prepare 2-amino-8-(3-diethylaminopropylamino)-quinoline by bubbling dry ammonia through a phenol solution of the 2-chloro drug at 170-180° for 22 hours resulted in the formation of 8-(3-diethylamino-propylamino)-2-phenoxyquinoline. This compound was isolated as the dihydrobromide. The formation of the phenoxy compound is in agreement with the findings of Backeberg and Marias,[122] ie. 2-chloroquinolines form essentially the phenyl ether in preference to the 2-amino compound under these conditions.

The second method selected for the synthesis of 2-amino-8-(3-diethylaminopropylamino)-quinoline visualized starting with 2-amino-8-nitroquinoline, blocking the 2-amino group, reduction of the 8-nitro group, alkylation of the 8-amino group and hydrolysis of the protective group on the 2-amino position.

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[122] Backeberg and Marias, loc. cit.

The initial problem in this scheme, was determining the most suitable method of blocking the 2-amino group. Since most alkylating procedures involve mineral acid salts, such as the "side chain" hydrochloride, or because acid is formed during the alkylation, it was desirable to have the blocking group reasonably stable to dilute acid hydrolysis. Three common methods for the protection of amino groups are formylation, benzoylation and acetylation. All three of these derivatives are sensitive to acid hydrolysis, the formyl derivatives being the most easily hydrolyzed. It was believed that these three blocking agents would not offer satisfactory protection under the usual conditions of alkylation.

Benzenesulfonyl chloride and p-toluenesulfonyl chloride are used in a similar manner to the above reagents. The primary objection to using the sulfonyl halides, has been the difficulty of hydrolyzing the sulfonamides. This difficulty has been, to a great extent, modified by the determination of more suitable hydrolytic methods. Schreiber and Shriner[123] described one method of hydrolysis using 25% hydrochloric acid which required relatively long reflux periods. Snyder and Heckert[124] determined a method using 48% hydrobromic acid and phenol as the hydrolyzing reagent. Both of these methods were developed primarily on benzene

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[123] Schreiber and Shriner, J.Am. Chem. Soc., 56 1618 (1943)

[124] Snyder and Heckert, J. Am. Chem. Soc., 74 2006 (1952)

derivatives. They have been applied, in two cases, on quinoline compounds prepared in this laboratory.

The synthesis of 2-amino-8-nitroquinoline has been described on page 150. By treating this amine with p-toluenesulfonyl chloride in pyridine, 90% yields of the previously unreported p-tolylsulfonamido derivative were obtained. The compound melted at 199.4-201.4°. 8-Nitro-2-tolylsulfonamidoquinoline was soluble in dilute sodium hydroxide and formed a relatively insoluble hydrochloride with concentrated hydrochloric acid. The white hydrochloride salt was readily hydrolyzed to the yellow free base by adding a small quantity of water to the acid solution. The hydrolyzed material melted at 200-201° after one recrystallization from absolute alcohol. The free base was soluble in chloroform, difficultly soluble in methanol, ethanol, benzene and toluene, and insoluble in Skelly "F" and water.

Reduction of 8-nitro-2-tolylsulfonamidoquinoline produced 8-amino-2-p-tolylsulfonamidoquinoline. It was not possible to isolate the free base, under ordinary laboratory conditions. This caused the preparative scheme for the 2-amino drug using this intermediate to become less promising. Alternate methods of reduction, giving the highest yields, and optimum reaction conditions are difficult to establish under these circumstances.

The use of an intermediate, which had not been purified was considered undesirable in the work. First because the end product was to be evaluated as a poliomyeliticidal and

should be homogeneous. More important, several experiences in this laboratory using crude intermediates directly in a second step have been unsuccessful. For example, extensive work was expended in determining methods for the purification of 8-nitroquinoline because the quality of the commercially available compound gave low yields and unreproducible results when used directly. The oxidation of crude 8-nitroquinolinium methiodide, which resulted in low yields of impure quinolone, is another example of an unsatisfactory result obtained in the use of a crude intermediate.

Several systems were used to reduce 8-nitro-2-p-tolylsulfonamidoquinoline to the corresponding amine. Only the product from titanium trichloride reduction was reasonably well established as 8-amino-2-p-tolylsulfonamidoquinoline. Stannous chloride and hydrochloric acid, and sodium hydrosulfite were used, but the only product isolated from these reductions was unconverted starting material. Iron and dilute acetic acid produced a material which had the same properties as the product from the titanium trichloride reduction.

8-Amino-2-p-tolylsulfonamidoquinoline was soluble in acetic acid, alcohol, ether, ethyl acetate, benzene and toluene, and insoluble in water, dilute ammonium hydroxide and Skelly "F". The addition of Skelly "F" to a toluene or an ethereal solution of the reduction material, produced a flocculent precipitate of nearly white 8-amino-2-p-tolylsulfonamidoquinoline. This method was used to precipitate

the crude amino compound.

In an attempt to circumvent the undesirable aspect of not being able to isolate the amine and to establish the identity of 8-amino-2-p-tolylsulfonamidoquinoline, two reactions were carried out, which indicates the amine was the principle product obtained by reduction using titanium trichloride.

A small sample of the crude reduction product was heated under reflux for 48 hours with 25% hydrochloric acid using the method reported by Schreiber and Shriner.[125] Very white 2,8-diaminoquinoline (described in detail below) which melted at 105.6-107.8° after one recrystallization from ether-Skelly "F" was isolated from this reaction.

A dry ethereal solution of the crude 8-amino-2-p-tolylsulfonamidoquinoline was treated with dry hydrogen bromide until precipitation was complete. Light tan crystals formed readily and were separated from the solution by filtration, and dried in a vacuum desiccator. The tan material was recrystallized from absolute alcohol; approximately 50% of the salt was lost in this recrystallization apparently through hydrolysis. The white product decomposed at 156.3-159.3°, and gave a carbon and hydrogen analysis which indicated the salt was solvated. The composition of the solvated substance corresponds closely to that of a monohydrate. Attempts to dry the salt under vacuum at 56° caused considerable discoloration. The salt could not be recrystallized from isopropyl alcohol.

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[125] Schreiber and Shriner, loc. cit.

These two experiments establish reasonably well the titanium trichloride reduction product as 8-amino-2-p-tolylsulfonamidoquinoline.

A small sample of 8-amino-2-p-tolylsulfonamidoquinoline was treated with an excess of 1-chloro-3-diethylaminopropane in a 72% solution of alcohol, and containing potassium acetate. The solution was refluxed for five days, cooled and saturated with potassium carbonate. The alcohol was separated and dried, solvent and "side chain" removed under vacuum and the residue extracted with ether to remove any unconverted "nucleus". Attempts were made to prepare a salt of this ether insoluble residue to characterize the 8-(3-diethylaminopropylamino)-2-p-tolylsulfonamidoquinoline. All attempts to form a salt resulted in oils. The original residue was hydrolyzed using phenol and 48% hydrobromic acid after the method of Snyder and Heckert.[126] The reaction mass was made strongly basic with sodium hydroxide and extracted with several portions of ether. The combined ether extracts were washed well with 10% sodium hydroxide, then water, dried and the ether removed on a steam bath. A light yellow oil remained as residue. On standing in a vacuum desiccator for two weeks, the oil crystallized to a light green solid. This solid was dissolved in ethyl acetate, decolorized, filtered and the filtrate cooled in an ice bath. White crystals were filtered from the cold solution and were

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[126] Snyder and Heckert, loc. cit.

dried under vacuum for several hours. This material melted at 72-75°. Carbon and hydrogen analysis showed that the compound was definitely not 2-amino-8-(3-diethylamino-propylamino)-quinoline. No further work was accomplished to establish the identity of this compound. This attempted synthesis illustrates most clearly a good reason for isolating and identifying, wherever possible, each intermediate produced in a series of chemical reactions.

The third method considered for the preparation of 2-amino-8-(3-diethylaminopropylamino)-quinoline was alkylation of the previously unknown 2,8-diaminoquinoline. This method appeared to be the least promising of the methods proposed, for two important reasons. The first difficulty was the synthesis of the unknown 2,8-diaminoquinoline and the development work necessary for high yields and optimum reaction conditions. In the second place, two position isomers were possible, or a mixture of these and including a 2,8-dialkylated product depending on the conditions used in the alkylation. The possibility of position isomers, of course, demands a proof of structure.

The preparation of 2,8-diaminoquinoline was complicated to some extent, because the compound was found to be water soluble. Consequently when reduction reactions were made basic and extracted with ether, much of the desired compound remained in the water phase. Extraction methods with water soluble compounds are, in general, unsatisfactory, and for this particular compound; which is soluble in hot 15%

potassium hydroxide solution; probably accounts for the original low yields.

The attempt to prepare 2,8-diaminoquinoline by ammonolysis of 8-amino-2-chloroquinoline has been discussed on page 150.

The following reagents were used in attempts to prepare 2,8-diaminoquinoline starting with 2-amino-8-nitroquinoline. Sodium hydrosulfite, hydrogen using a platinum oxide catalyst with ethanol as solvent, and zinc with hydrochloric acid. Sodium hydrosulfite produced a yellow unidentified mixture. In the catalytic reduction the theoretical amount of hydrogen was absorbed in approximately one-half hour, using a starting gauge pressure of 32 p.s.i. Concentration of the solvent on the steam bath resulted in a red oil which resisted crystallization. From the zinc-hydrochloric acid experiment, starting material was the only material isolated from the reaction.

2,8-Diaminoquinoline was prepared from 2-amino-8-nitro quinoline by reduction with stannous chloride and hydrochloric acid, titanium trichloride in hydrochloric acid, zinc and calcium chloride and iron in dilute acetic acid.

The 2,8-diamine was first prepared using stannous chloride in concentrated hydrochloric acid. In this method it was difficult to free the amine from inorganic material. As pointed out above, the water soluble 2,8-diaminoquinoline was not precipitated from solution by addition of base, and consequently the most facile method of removing tin ions

as the complex salts using sodium hydroxide did not prove efficient. The contaminated organic material, which was first isolated was alternately treated with base and acid, and 2,6-diaminoquinoline was finally isolated, from this reduction. The melting point and a method of purification was determined on the small sample of diamine obtained in this experiment. From the standpoint of yield it was completely unacceptable for use in this problem.

Zinc dust and calcium chloride in a 50-50 acetone-water solution was used as a reduction system on 2-amino-6-nitroquinoline. This method was patterned after that developed in section V for the reduction of 2-chloro-6-nitroquinoline. This method gave a 24% yield of 2,6-diaminoquinoline.

Titanium trichloride in a concentrated hydrochloric acid solution was added dropwise, to a hydrochloric acid solution of 2-amino-6-nitroquinoline, until the titanium trichloride was no longer decolorized. The acid solution was neutralized and extracted repeatedly with ether. The ether was concentrated, decolorized, then cooled and the precipitated 2,6-diaminoquinoline removed from the solution by filtration. The highest yield obtained in this method was 35%. The objections to this method followed those with the stannous chloride procedure. It was difficult to free the amine from inorganic matter, and to extract it from the water solution. From an operational standpoint, on making the solution basic, voluminous amounts of titanium salts

were formed which were very difficult to remove from the slurry by filtration, whereas extraction with ether or benzene formed emulsions. This method, based on the decolorization of the titanium trichloride, probably resulted in relatively complete reduction of 2-amino-8-nitroquinoline, the low yield being a matter of not extracting or precipitating the desired compound from the large volume of solution. Sodium chloride and sodium carbonate were added to the basic solution but apparently were not effective in inhibiting emulsion formation or salting out the diamine from the large volume of solution.

Iron and dilute acetic acid was found to be the most suitable reagent for reducing 2-amino-8-nitroquinoline. The procedure consisted of adding the amine to a vigorously stirred mixture of 40 mesh iron powder and 5% acetic acid. solution on a steam bath. The starting material was not soluble in the dilute acetic acid, whereas the diamine was readily soluble. Any unreduced 2-amino-8-nitroquinoline along with excess iron and iron salts were conveniently removed by filtering the reaction mixture at the termination of the reduction. The filtrate was decolorized with charcoal, cooled and saturated with potassium carbonate. Crude 2,8-diaminoquinoline precipitated readily and was collected, along with excess potassium carbonate, on a Buchner funnel. This crude precipitate was partially dried in a vacuum desiccator and then extracted repeatedly with toluene.

The combined toluene extracts were decolorized, filtered and cooled in an ice bath. White 2,8-diaminoquinoline precipitated readily from the cold solution and was separated from the solution by filtration. Yields of 80-87% were obtained by the use of iron and acetic acid as the reducing reagent.

2,8-Diaminoquinoline is a white crystalline material which melts at 110.7-111.7° when crystallized from ether-Skelly "F" solution. Recrystallization of this 2,8-diaminoquinoline from toluene raised the melting point to 113.5-114.5°. The compound may also be recrystallized from water. Toluene is recommended as the most suitable solvent for recrystallization. The diamine is soluble in dilute mineral acid, and soluble in basic solution. Approximately 1 g. is soluble in 60 ml. of a boiling 15% potassium hydroxide solution. The compound is soluble in benzene, dioxane, ethyl acetate, alcohol, acetone and cyclohexane and relatively insoluble in Skelly "F".

The monosulfate salt of 2,8-diaminoquinoline was prepared from concentrated sulfuric acid in absolute alcohol. The bright yellow salt decomposed at 219.8-230.0° and was very insoluble in absolute alcohol. The salt from a .2 g. sample of 2,8-diaminoquinoline required approximately 92 ml. of about 97% alcohol for total solution.

The monophosphate salt was prepared from 85% phosphoric acid in the same manner as the monosulfate. The lemon yellow monophosphate was recrystallized from absolute alcohol-absolute ether; it decomposed at 237.0-239.1°.

The slightly yellow dihydriodide was difficult to handle, did not melt, discolored above 210° and decomposed at 260° to a black mass. The salt was unstable to absolute ether. Hydriodic acid (47%) in absolute alcohol was used to prepare this salt.

The dihydrobromide, was prepared by bubbling dry hydrogen bromide into a toluene solution of the amine. The white salt, although difficultly soluble, was recrystallized from absolute alcohol; it decomposed at 280-290°.

2,8-Diaminoquinoline was diazotized in concentrated hydrochloric acid and coupled with β-napthol. A dark red product was obtained from the reaction which melted at 205-206.5. The carbon and hydrogen analysis indicated that the compound was not analytically pure. Analysis did, however, show that only one molecule of β-napthol had coupled, thereby indicating only one amine group had undergone diazotisation. 2-Aminoquinoline can be diazotized only with difficulty, amyl nitrite and sodium ethoxide are required for this reaction.[127] On the other hand 8-aminoquinoline diazotizes readily and the salt couples normally with the napthols.[128] Based on this evidence, the product of the reaction of diazotized 2,8-diaminoquinoline with β-napthol

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[127] Coates et al., J. Chem. Soc., 401 (1943)

[128] Alber, J. prakt. Chem., 2 71 47 (1905); Mills and Watson, J. Chem. Soc., 97 741 (1910); Meka, Monatsh., 45 287 (1925)

is in all probability 2-amino-8-(2-hydroxy-1-naphthylazo)-quinoline.

2,8-Diaminoquinoline was acetylated with acetic anhydride (∿ 17 mole excess), using essentially the procedure given in Shriner and Fuson.[129] The acetylated product was slow to form in the cold, but precipitated from the buffered solution after warming for twenty minutes on a steam bath. The compound is very difficultly soluble in benzene or cyclohexane and is nicely recrystallized from absolute alcohol. Carbon, hydrogen and nitrogen analysis showed that monoacetylation had occured. On the basis of the evidence for monodiazotization at the 8-position, and the experimental and theoretical considerations presented in the following discussion, it is believed that the product of acetylation was 8-acetamido-2-aminoquinoline.

Although the alkylation of 2,8-diaminoquinoline was considered to be the least satisfactory scheme for the preparation of 2-amino-8-(3-diethylaminopropylamino)-quinoline, it was believed that alkylation would occur preferentially at the 8-amino group. The idea of this selective alkylation, stems from several important differences in the behavior of the 2-and 8-amino groups. In general, differences in behavior of the aminoquinolines may be correlated with the relative basicities of these amino groups.

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[129] Shriner and Fuson, "Identification of Organic Compounds", third ed., John Wiley and Sons, New York, 1950 p. 177, procedure A.

However, experimental evidence indicates that alkylation of basic nitrogen compounds cannot be correlated merely with basicity, but must be limited to the basicity of a primary amino group.

Steck and Ewing[130] have shown from ultraviolet absorption studies of all the monoaminoquinolines that in .01N hydrochloric acid, the first proton is accepted in all cases by the ring nitrogen. This implies that the ring nitrogen donates its unshared pair of electrons to a proton more readily that the nitrogen of the amino group. The ring nitrogen is therefore more basic than the amino nitrogen. Frisch and Bogert[131] treated 5-amino-6,7-dimethoxyquinoline with an excess of 1-chloro-3-diethylaminopropane, and attempted to diazotize and couple the isolated product. They were unable to diazotize this material and therefore concluded that the product was 5-(3-diethylaminopropylamino)-6,7-dimethoxyquinoline and could not be the 1-alkylated product. They repeated this work with 8-amino-6,7-dimethoxyquinoline and found no diazotizable material present. Therefore, in agreement with the results on the 5-amino analogue, the amino group was alkylated and not the cyclic nitrogen, although the latter was indicated as the more basic by Steck and Ewing.

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[130] Steck and Ewing, J. Am. Chem. Soc., 3397 3406 (1949)

[131] Frisch and Bogert, J. Org. Chem., 9 338 (1944)

From the substituted 6-(3-diethylaminopropylamino)-quinolines prepared in this work, and numerous other similar alkylations of this general type recorded in the literature, the author is unaware of an instance where dialkylation of a monoaminoquinoline has occured, even though as many as four moles excess alkylating agent have been used in many cases. Apparently, more drastic conditions are required to cause dialkylation to occur.*

The conclusions to be drawn from these experimental findings may be summarized:

1. Although the cyclic nitrogen of monoaminoquinolines is the more basic nitrogen, a stable alkylation product is not usually formed with the cyclic nitrogen.

2. Dialkylated products are not formed from this type reaction under these conditions.

3. Alkylation occurs preferentially at a primary amino group.

2-Aminoquinoline has been indicated by Albert and Goldacre[132] to be a much stronger base than quinoline. It should react with acids to form salts very readily. In order to undergo diazotization an amino group must be converted

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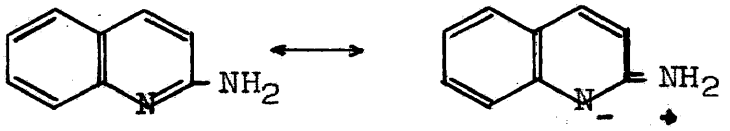
*It is pertinent to note that dialkylation of aromatic amines is generally carried out under pressure and at elevated temperatures. For example, dimethylaniline is commercially prepared by heating certain proportions of aniline, methyl alcohol and sulfuric acid in an autoclave at 235°.

[132]Albert and Goldacre, Nature 153 468 (1944)

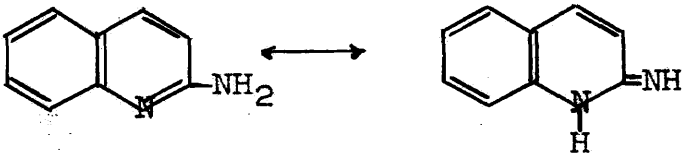
to a salt, but the extreme difficulty of diazotising 2-aminoquinoline has been cited on page 163. The implication here, is that a strong base does not form a salt. This anomoly may be explained on the basis of a contributing structure of 2-aminoquinoline.

Albert and Goldacre proposed the reason for the enhanced basicity of 2-aminoquinoline was resonance involving the quinoid structure as shown.



The important point to note for the polarised structure, is that the basicity (unshared electron pairs) is an enhanced function of the cyclic nitrogen and not the positively charged NH_2 group. It would be highly improbable that a positively charged NH_2 group would add a proton. This contributing structure accounts nicely for the increase in basic strength compared to quinoline and loss in salt forming properties of the 2-amine group.

It is to be noted that 2-aminoquinoline may tautomerise to the imine.



Experimentally it is found that 2-aminoquinoline tautomerizes to an extent sufficiently great to effect its chemical

properties. For example, 2-aminoquinoline yields carbostyril when heated with aqueous ammonia above 200°.[133] The imine structure would not favor alkylation. Morley and Simpson[134] studied the reactions of several substituted 2-and 4-aminoquinolines and pyridines with 4-chloro-6- and 7-nitroquinazolines, and compared the results with alkylation reactions using aniline and Bz-aminoquinolines in place of the 2-and 4-aminoquinolines. Meyer and Bouchet[135] investigated the reaction of 4-chloroquinaldine with several aminoheterocyclic compounds. The experimental work of these authors, led them to agree: alkylation would occur with diazotizable amines but not with tautomerizable amino heterocyclic compounds.

The 3-,5-,6-,7-and8-aminoquinolines diazotize in the normal manner. Frisch and Degert,[136] however, have postulated that the ease with which diazotization occurs may be correlated with the relative basicity of the amino groups. They found when 5,8-diamino-6,7-dimethoxyquinoline was diazotized at 0° with sodium nitrite and 40% sulfuric acid, only one amino group reacted. At 80-90° with the same reagents both amino groups were diazotized. They proposed the 8-amino group was the one more easily diazotized (consequently more basic than the 5-amino group on the basis

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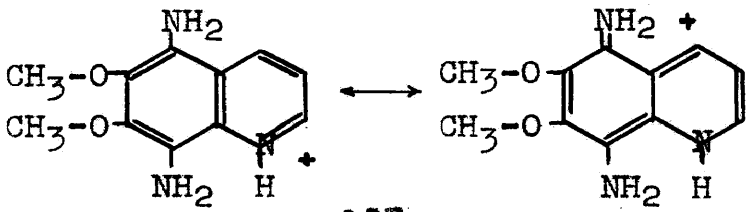
[133] Diepolder, J. prakt. Chem., 106 55 (1923)

[134] Morley and Simpson, J. Chem. Soc., 1014 (1949)

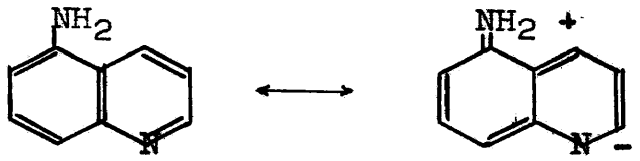
[135] Meyer and Bouchet, Compt. rend., 225 63 (1947)

[136] Frisch and Degert, loc. cit.

of the following structures:



Albert and Goldacre,[137] however, classed 8-aminoquinoline as a weaker base than 5-aminoquinoline. This discrepancy may be interpreted on the basis of electronic formulae. 5-Aminoquinoline has a possible resonance form,



which should exhibit increased basicity. Here again the basicity is a function of the cyclic nitrogen and not the amino group. No similar structure can be written for 8-aminoquinoline, and from the experimental results of Albert and Goldacre appears to be a weaker base than 5-aminoquinoline.

It is important to note that the ionic structure written for 5-aminoquinoline is less important, than the similar contributing form written for 2-aminoquinoline, since 5-aminoquinoline diazotizes in a normal manner. The ionic structure for 5-aminoquinoline cannot be entirely neglected, however, because it allows one explanation for the selective diazotization of the 8-amino group in the presence of the 5-amino group under milder conditions, as proposed by Frisch

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[137] Albert and Goldacre, loc. cit.

and Bogert. The proposal of Frisch and Bogert, that the 8-amino group in 5,8-diamino-6,7-dimethoxyquinoline diazotized more readily than the 5-amino group (and was therefore more basic) was confirmed by Elderfield and Krueger.[138] They prepared and proved the structure of 8-amino-6,7-dimethoxy quinoline and showed that it was not the product obtained by replacing with hydrogen, the diazotized group of 5,8-diamino-6,7-dimethoxyquinoline at 0°.

Frisch and Bogert also found that only a monoalkylated product and a monoacetylated product was obtained from 5,8-diamino-6,7-dimethoxyquinoline. These products were prepared by alkylation with 1-chloro-3-diethylaminopropane and acylation with acetic anhydride. Although an excess of each reagent was used, only a mono-substituted product was formed. They concluded that the 8-amino group was the more reactive center in these reactions, based on the considerations outlined for diazotization.

On the evidence presented above, the mono salts of 2, 8-diaminoquinoline described previously (pp. 164-165) are probably formed by addition of the proton to the cyclic nitrogen. The fact that the mono salts were obtained when recrystallized from alcohol containing considerable amounts of water, indicates the second proton is held rather loosely and is easily hydrolyzed. The second proton of the dihydrobromide and dihydriodide is probably attached to the 8-

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[138] Krueger, Ph.D. Thesis, Columbia University, New York 1950

amino group in preference to the 2-amino group, because of the difficult salt forming properties of the latter.

2,8-Diaminoquinoline was treated with a 4-mole excess of 1-chloro-3-diethylaminopropane in a buffered solution and heated under reflux for five days. The process was repeated a second time using only .07-mole excess of side chain salt and a reflux period of seven days. The dihydriodide and trihydrobromide salts were prepared from the amine obtained in each of these reactions. The melting points and behavior of these salts were the same from both reactions. An excess of side chain would favor chances for reaction at the less likely 2-position and increase the possibility of dialkylation if both positions were reactive. Although a large excess of side chain was used in the first reaction, the salts isolated from both reactions were the same. Apparently, then, alkylation occurs at only one center.

The white trihydrobromide was prepared by bubbling dry hydrogen bromide through an ethereal solution of the amine or by using a solution of 48% hydrobromic acid. The product was recrystallized from absolute alcohol. The trihydrobromide, dried in a vacuum desiccator at room temperature is hydrated, analysis indicating the composition of the hydrated substance corresponds closely to that of a monohydrate. The anhydrous trihydrobromide was prepared by heating the solvated salt in the presence of phosphorus pentoxide at 56° under 1.5-2 mm.

pressure. The hydrated substance decomposed at 209.4-211.4° and the moisture-free salt decomposed at 201.6-203.6°.

The dihydriodide was a bright yellow compound prepared from an alcoholic solution of 47% hydriodic acid. This salt was recrystallized from absolute alcohol. The compound exhibited two unusual changes when a melting point determination was attempted. At 95.7-96.7° the yellow solid shrank then changed to an opaque semisolid, which showed no change up to 162.7-165.7° and then collapsed to an opaque liquid. These changes were observed under a microscope using polarized light.* The salt partially melted to a liquid at 95-105°, and this liquid then formed another crystalline material as heating continued up to 184° at which temperature all crystalline material had decomposed. Individual crystal structure could not be identified.

Based on the results of salt formation, monodiazotization and coupling, monoacetylation and monoalkylation of 2,8-diaminoquinoline, correlated with theoretical considerations and the other experimental work cited, it is reasonable to assume that the preferred products of these reactions are the 8-substituted compounds. In particular, the alkylation of 2,8-diaminoquinoline with 1-chloro-3-diethylaminopropane gives 2-amino-8-(3-diethylaminopropylamino)-quinoline as the preferential product.

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*It is a pleasure to thank Professor C. F. Stuntz of the Chemistry Department for his assistance with the hot stage microscope.

The final proof of such considerations should be verified, wherever possible, by an unambiguous experimental method. Probably the most satisfactory method of proving the structure of this particular compound would be a second synthesis, from which the only product would be 2-amino-8-(3-diethylaminopropylamino)-quinoline. This would be especially desirable in this case in view of the complicated behavior exhibited by the dihydriodide salt on heating.

As a matter of expediency, the synthesis of 8-amino-2-(3-diethylaminopropylamino)-quinoline, proposed as the least likely product from the alkylation of 2,8-diamino-quinoline, was undertaken as a proof of structure. Since there are only two probable position isomers in this reaction, finding the properties of one of them different from the compound obtained by the alkylation of 2,8-diamino-quinoline would constitute good evidence for selective alkylation.

2-Chloro-8-nitroquinoline was treated with a 3-mole excess of 1-amino-3-diethylaminopropane at 170-180° for four to five hours. The reaction mixture was treated with water and potassium carbonate, extracted with ether and the ether and excess "side chain" removed by distillation. Attempts to isolate 2-(3-diethylaminopropylamino)-8-nitro-quinoline as the free base or a salt failed. This nitro compound was reduced using iron and dilute acetic acid. The free base was extracted from an alkaline solution with ether and recovered by distillation under diminished pressure.

8-Amino-2-(3-diethylaminopropylamino)-quinoline was converted to the solvated dihydriodide and trihydrobromide salts for comparison with the salts of 2-amino-8-(3-diethylaminopropylamino)-quinoline.

The syntheses of 8-amino-2-(3-diethylaminopropylamino)-quinoline was repeated starting with 8-amino-2-chloroquinoline and an excess of 1-amino-3-diethylaminopropane. 8-Amino-2-(3-diethylaminopropylamino)-quinoline, isolated as the hydriodide and hydrobromide salts, gave the same decomposition ranges and analysis as the products starting with 2-chloro-8-nitroquinoline.

The yellow dihydriodide of 8-amino-2-(3-diethylaminopropylamino)-quinoline was prepared using 47% hydriodic acid and absolute alcohol. Analysis indicated this salt was solvated. The composition of the solvated substance corresponds closely to a dihydrate. However, analysis of the solvated salt did not change after heating in the presence of phosphorus pentoxide at 110° under a pressure of 1.5-2 mm. This was in contradistinction to the dihydriodide of 2-amino-8-(3-diethylaminopropylamino)-quinoline, which was prepared using the same reagents and technique, and was easily converted to the anhydrous salt at 56° under the same conditions. 8-Amino-2-(3-diethylaminopropylamino)-quinoline dihydriodide dihydrate decomposed at 134.4-136.4°.

8-Amino-2-(3-diethylaminopropylamino)-quinoline trihydrobromide was prepared using 48% hydrobromic acid. The salt was recrystallized from absolute alcohol. This

compound decomposed at 12).4-135.4°, compared to 2-amino-8-(3-diethylaminopropylamino)-quinoline trihydrobromide which decomposed at 201.6-203.6°. A mixture of the two trihydrobromide salts when heated slowly, began to shrink at 83° and decompose at 85°. Decomposition continued as the temperature was raised, and was complete at 210°.*

The apparent differences in the solvated dihydriodide and trihydrobromide of 8-amino-2-(3-diethylaminopropylamino)-quinoline with the dihydriodide and trihydrobromide of the product of the alkylation of 2,8-diaminoquinoline show that the compounds are not the same and therefore as proposed, alkylation of 2,8-diaminoquinoline occurred preferentially at the 8-position to give 2-amino-8-(3-diethylaminopropylamino)-quinoline.

The ultraviolet absorption spectra of 2-amino-8-(3-diethylaminopropylamino)-quinoline trihydrobromide, 8-amino-2-(3-diethylaminopropylamino)-quinoline trihydrobromide and 2,8-diaminoquinoline were obtained using a Beckmann Model DU quartz spectrophotometer. Plots of the molar extinction coefficients vs. the wave lengths were made for these compounds in figure 6.

Three points merit qualitative attention in comparing these extinction curves and in conjunction with the spectra

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*The salts of 8-amino-2-(3-diethylaminopropylamino)-quinoline were very difficult to handle. It was necessary to use freshly purified absolute alcohol as a recrystallizing solvent. Moisture apparently hydrolyzed the salts to low melting or hygroscopic mixtures which were difficult to isolate.

of the other compounds considered in this work. The data for all compounds is summarized in table 13.

Comparing the spectra of the salts of the amines with the free bases, there is no major differences in the λ max values. This implies that when the salts are put in solution, they are hydrolyzed to a large extent, and consequently to obtain the spectrum of the salt, excess acid must be present.

The spectra of these quinoline compounds, represented by both the "nucleus" and drug, have a characteristic relatively high-intensity absorption region at 260-270 mμ and a low-intensity broad band through the region 330-360 mμ. A third absorption maximum occurs in the 235-245 mμ region.

The attachment of the "side chain", use of the salt, or changing the solvent does not materially shift the qualitative position of the absorption maxima. The major difference, among the compounds, rests with the intensity of the absorption. It would appear that the identification of these compounds should rest on the intensity of absorption and to a lesser extent on the wave length of maximum absorption.

A comparison of the spectra of 2-amino-8-(3-diethylaminopropylamino)-quinoline trihydrobromide and 8-amino-2-(3-diethylaminopropylamino)-quinoline trihydrobromide shows that the latter compound resembles the parent 2,8-diaminoquinoline to the greater extent and the important difference between the two position isomers is a considerable difference in the intensity of the absorption.

TABLE 13

Summarised Absorption Maxima

COMPOUND	SOLVENT	λ_{max}	ε max
8-Amino-2-chloroquinoline monohydrobromide	Water	255 330* 355	34000 2800
2-Chloro-8-(3-diethylaminopropylamino)-quinoline dihydrobromide	Water	260 355	31000 4300
8-Aminocarbostyril	95% Alcohol	235 270 345* 360	13000 18000 1500
8-(3-diethylaminopropylamino)-carbostyril	Isooctane	245 275 365	15000 20000 1700
2,8-Diaminoquinoline	95% Alcohol	245 270 345* 355	20000 36000 3300
2-Amino-8-(3-diethylamino-propylamino)-quinoline trihydrobromide	95% Alcohol	240 270 355	40000 75000 6400
8-Amino-2-(3-diethylamino-propylamino)-quinoline trihydrobromide	95% Alcohol	270 330* 345	41000 2300

* The absorption in this region represents a broad low-intensity band. The band tends to show a bifurcation in the cases of the "nuclei" with very close ε max values for individual compounds. ε max tabulated over this broad band represents an average value.

EXPERIMENTAL

8-(3-DIETHYLAMINOPROPYLAMINO)-2-PHENOXYQUINOLINE DIHYDROBROMIDE

Procedure*

A 500-ml. round-bottomed single-necked flask with a gas inlet tube (note 1) was placed in an oil bath in the hood. Ten grams (.3216 moles) of 2-chloro-8-(3-diethylaminopropylamino)-quinoline dihydrobromide hemihydrate and 30 g. (.319 mole) of phenol were added to the flask, and a reflux condenser with an internal thermometer, fitted in the single neck. The mixture was warmed gently until fluid and then gaseous ammonia (note 2) introduced through the inlet tube. The mixture was heated to 170-180° with constant addition of ammonia for 5-6 hours, and then filtered to remove ammonium bromide. More phenol (30 g.) was added (note 3) to the mixture and ammonia bubbled through the mixture at 170-180° for an additional 15-16 hours. The reaction mass was cooled to room temperature and 1 l. of ether added. The dark solution was filtered (note 4) and extracted with two 300-ml. portions of 15% sodium hydroxide, then two 300-ml. portions of 5% sodium hydroxide. The ether

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*This experiment was an attempt to prepare 2-amino-8-(3-diethylaminopropylamino)-quinoline. The product isolated was the salt of the 2-phenoxy compound. There is no apparent reason why the addition of the ammonia could not be dispensed with.

was washed with water until the water phase was only slightly basic, and the ether dried over magnesium sulfate for several hours. The solvent was removed on a steam bath, the residue dissolved in Skelly "F" and dry hydrogen bromide added until precipitation was complete. The light tan crystals were separated from the solution by filtration and dried in a vacuum desiccator. White 8-(3-diethylaminopropylamino)-2-phenoxyquinoline dihydrobromide which melted at 224.8-225.8° was obtained by recrystallizing the light tan product from absolute alcohol.

Analysis: Calculated for $C_{22}H_{27}N_3O.2HBr$. C, 51.67; H, 5.72; N, 8.27. Found: C, 51.56, 51.53; H, 5.47, 5.55; N, 8.12, 7.80.

Notes

1. The gas inlet tube terminated about 1 cm. above the bottom of the flask. Mixing was accomplished by the ammonia gas bubbling into the solution.
2. Ammonia from a commercial cylinder, was passed through a 500-ml. trap before entering the reaction vessel.
3. A large amount of the original phenol had been vaporized during the initial heating period.
4. A considerable amount of suspended ammonium bromide was separated from the solution by the filtration.

2-AMINO-8-NITROQUINOLINE

Procedure

A suspension of 20 g. (.096 mole) of 2-chloro-8-nitroquinoline in 100 ml. of dioxane was placed in an apparatus for high pressure hydrogenation (note 1). The bomb was cooled in a carbon dioxide-chloroform bath (note 2) and 30 ml. (2.33 moles) of liquid ammonia added. The bomb was closed (note 3) while in the cooling bath, transferred to a shaker and heated with continuous agitation at 150° (note 4) for four hours. The apparatus was allowed to cool to room temperature, the pressure was released, and the contents transferred to a 500-ml. beaker (note 5). The solution from the bomb was filtered and the filtrate allowed to cool to room temperature. The filtrate was added to 2 l. of cold water with manual stirring and the suspension allowed to settle (note 6). The crude precipitate was separated from the solution by filtration, air-dried overnight and recrystallized from toluene (note 7). The yield of yellow 2-amino-8-nitroquinoline melting at 163.2-165.2° amounts to 13.6 g. (75%)

Analysis: Calculated for $C_9H_7N_3O_2$ C, 57.14; H, 3.73; Found: C, 57.12, 57.01; H, 3.93, 3.90.

Notes

1. A standard Aminco hydrogenation bomb of 300 ml. volume

was used for the ammonolysis.

2. The bomb was immersed approximately two thirds in the cooling bath and allowed to cool for twenty minutes before the liquid ammonia was added.

3. The inlet tube was removed from the bomb cap and a solid plug used in place of a pressure gauge.

4. The temperature should be carefully checked. Temperatures above 170° result in substantially lower yields.

5. The bomb contained a considerable amount of solid material and was washed with four 50-ml. portions of dioxane.

6. Allowing the suspension to settle and coagulate, facilitates the subsequent filtration.

7. Approximately 500 ml. of toluene were required for the recrystallization of 12-14 g. of crude 2-amino-8-nitroquinoline.

8-NITRO-2-p-TOLYLSULFONAMIDOQUINOLINE

Ten grams (.053 mole) of 2-amino-8-nitroquinoline, 11 g. (.058 mole) of p-toluenesulfonyl chloride (note 1), and 50 ml. of dry pyridine (note 2) were placed in a 100-ml. round-bottomed flask equipped with a magnetic stirrer and reflux condenser. The solution was stirred and heated under reflux for two hours, then cooled and poured into 400-500 ml. of water. The bright yellow solid was separated from the solution by filtration and washed well with water.

The precipitate was transferred to a beaker, digested with 100 ml. of cold (note 3) alcohol, the solid was collected on a Büchner funnel and dried overnight in a vacuum desiccator. The product melted at 200.4-201.4° and weighed 17 g. (93%).

Analysis: Calculated for $C_{16}H_{13}N_3O_4S$. C, 55.96; H, 3.84. Found: C, 56.21; H, 4.31.

Notes

1. The p-toluenesulfonyl chloride was purified by recrystallizing from Skelly "F". The melting point of the purified material was 69°.
2. Mallinkrodt analytical grade pyridine was refluxed over potassium hydroxide and distilled with the exclusion of moisture. The fraction boiling at 113-115°/758 mm. was collected.
3. The alcohol suspension was cooled in a carbon dioxide chloroform bath and then filtered.

8-AMINO-2-p-TOLYLSULFONAMIDOQUINOLINE

In a 2-l. beaker resting on a hot plate was placed 12 g. (.035 mole) of 8-nitro-2-p-tolylsulfonamidoquinoline with 100 ml. of concentrated hydrochloric acid. The suspension was stirred manually and a hot solution consisting of 11 g. (.23 mole) of titanium dissolved in 350 ml. of

concentrated hydrochloric acid added in 30-ml. portions. After addition of the titanium trichloride solution the reaction mass was boiled for five minutes, then cooled to room temperature in an ice bath. This solution was made basic with concentrated ammonium hydroxide, saturated with sodium chloride and extracted with six 300-ml. portions of ether. The ether extracts were combined and concentrated on a steam bath to a volume of 300 ml., decolorized with charcoal, filtered and the filtrate dried over magnesium sulfate for 18 hours. The drying agent was removed, the ether concentrated to 50 ml. and then 100 ml. of toluene added. The solution was boiled until the odor of ether was no longer discernable, then decolorized with charcoal and refiltered. On addition of Skelly "F" to the cool toluene solution, a flocculent suspension of nearly white 8-amino-2-p-tolylsulfonamidoquinoline formed. The product is unstable and cannot be isolated under ordinary laboratory conditions.

8-AMINO-2-p-TOLYLSULFONAMIDOQUINOLINE MONOHYDROBROMIDE MONOHYDRATE

Dry hydrogen bromide gas was bubbled into a dry ethereal solution of 8-amino-2-p-tolylsulfonamidoquinoline, prepared as above, until precipitation was complete. Very light tan crystals formed readily and were separated by filtration. The crude product was dried overnight in a vacuum desiccator, and recrystallized once from absolute alcohol (note 1). The nearly white 8-amino-2-p-tolylsulfonamidoquinoline mono-

hydrobromide monohydrate was dried under vacuum at room temperature (note 2) in the presence of phosphorus pentoxide. The product melted at 158.2-159.2 (decomposition).

Analysis: Calculated for $C_{16}H_{15}N_3O_2S.HBr.H_2O$ C, 46.62; H, 4.40. Found: C, 46.99; H, 4.59.

Notes

1. Approximately 50% of the salt was hydrolyzed to the free-base during recrystallization. Propanol-2 was less suitable as a recrystallizing solvent.
2. Heating the sample at 56° during the drying procedure resulted in discoloration of the white sample.

2,8-DIAMINOQUINOLINE

In a 250-ml. beaker clamped on a steam bath was placed 20 g. (.35 mole) of clean iron filings (note 1) and 75 ml. of 5% acetic acid solution. The mixture was mechanically stirred and warmed to 50-60°. Ten grams (.053) of 2-amino-8-nitroquinoline was added in portions over a 35 to 40 minute period, and allowed to stir at 50-60° for an additional 20 minutes. The mixture was filtered hot, and the precipitate washed three times with 15-ml. portions of 5% acetic acid (note 2). The filtrate was decolorized with charcoal, filtered and cooled. The cooled solution was saturated with potassium carbonate, the solids collected on a Büchner funnel and pressed as dry as possible. The solids were partially

dried in a vacuum desiccator and extracted by decantation with four 100-ml. portions of hot toluene (note 3). The combined toluene extracts were decolorized with charcoal, filtered and cooled in a carbon-dioxide-chloroform bath. The product consisted of white crystals which weighed 5 g. and melted at 112.7-113.7°. By concentrating the filtrate to 75-100 ml., a second crop of crystals weighing 2 g. was obtained which melted at 110.7-112.7°. The total yield was 7 g. (83.4%).

Analysis: Calculated for $C_9H_9N_3$. C, 67.90; H, 5.69; N, 26.39. Found: C, 67.70, 67.48; H, 5.85, 5.91; N, 26.15, 26.25.

Notes

1. Forty mesh iron filings were washed twice with ether and allowed to dry.
2. The volume of the reaction mixture should be kept at a minimum because the product is water soluble.
3. The solids may be extracted with ether, decolorized and Skelly "F" added to the ether. The yield is somewhat lower (~10%).

2,8-DIAMINOQUINOLINE MONOSULFATE

To a stirred solution of .2 g. (.00125 mole) of 2,8-diaminoquinoline in 10 ml. of absolute alcohol was added dropwise, a solution of 3 ml. (.03 mole) of concentrated sulfuric acid in 3 ml. of absolute alcohol. White crystals

formed readily, were collected on a Büchner funnel and dried in a vacuum desiccator overnight. The product was recrystallized from 90 ml. of absolute alcohol containing 2 ml. of water. The bright yellow 2,8-diaminoquinoline monosulfate decomposed at 219.8-230.0°.

Analysis: Calculated for $C_9H_9N_3.H_2SO_4$ C, 42.01; H, 4.31. Found: C, 41.76; H, 4.05.

2,8-DIAMINOQUINOLINE MONOPHOSPHATE

The monophosphate was prepared in the same manner as the monosulfate. Two ml. of 85% phosphoric acid (.028 mole) in 5 ml. of absolute alcohol were used and the resulting salt, after drying was recrystallized from an approximately 97% alcohol solution. Lemon yellow 2,8-diaminoquinoline monophosphate melted with decomposition at 237.0-239.1°.

Analysis: Calculated for $C_9H_9N_3.H_3PO_4$ C, 42.03; H, 4.71; N, 16.34. Found: C, 42.01, 42.16; H, 4.92, 4.82; N, 16.07.

2,8-DIAMINOQUINOLINE DIHYDRIODIDE

Five-tenths of a gram of 2,8-diaminoquinoline (.0031 mole) was stirred with 5 ml. of 47% hydriodic acid and the solids collected on a Büchner funnel. The slightly yellow compound could not be recrystallized from absolute alcohol or washed with ether without decomposing the salt. The 2,8-diaminoquinoline dihydriodide exhibited no melting point but slowly decomposed to a solid black mass on heating to 260°.

Analysis: Calculated for $C_9H_9N_3 \cdot 2HI$ C, 26.04; H, 2.67. Found: C, 26.15; H, 2.85.

2,8-DIAMINOQUINOLINE DIHYDROBROMIDE

Two-tenths of a gram of 2,8-diaminoquinoline (.00125 mole) was dissolved in 50 ml. of toluene and dry hydrogen bromide bubbled into the solution until precipitation was complete. The crystals were removed from the solution by filtration and dried in a vacuum desiccator. The 2,8-diaminoquinoline dihydrobromide is a white crystalline compound which melted with decomposition at 280-290° after one recrystallization from absolute alcohol.

Analysis: Calculated for $C_9H_9N_3 \cdot 2HBr$ C, 33.67; H, 3.45. Found: C, 33.22; H, 3.73.

8-ACETAMIDO-2-AMINOQUINOLINE

In a 100-ml. Erlenmeyer flask was placed .4 g. (.0025 mole) of 2,8-diaminoquinoline. The diamine was dissolved in 10 ml. of 5% hydrochloric acid and 4 ml. (.042 mole) of acetic anhydride added, followed by a previously prepared solution of 4 g. of sodium acetate trihydrate in 30 ml. of water. The solution was shaken vigorously for several minutes and then warmed on a steam bath to 50° and stirred for ten minutes. The solution was cooled and 20 ml. of benzene added. White crystals separated readily, were collected on a Büchner funnel and washed first with benzene,

then hot cyclohexane. The product was recrystallized from absolute alcohol and dried in the presence of phosphorus pentoxide. White 8-acetamido-2-aminoquinoline melted at 204.6-205.6°

Analysis: Calculated for $C_{11}H_{11}N_3O$. C, 65.66; H, 5.51; N, 21.37. Found: C, 65.76, 65.83; H, 5.64, 5.79; N, 21.26, 21.07.

2-AMINO-8-(3-DIETHYLAMINOPROPYLAMINO)-QUINOLINE DIHYDRIODIDE

In a 500-ml. single-necked round-bottomed flask were placed 17 g. (.107 mole) of 2,8-diaminoquinoline, 30 g. (.306 mole) of potassium acetate, 80 ml. of water, 200 ml. of 95% alcohol and 25.7 g. (.112 mole) of 1-chloro-3-diethylaminopropane monohydrobromide. A magentic stirrer was added and the flask surmounted by a reflux condenser. The mixture was stirred and warmed to complete solution, then heated under reflux for 168 hours. The solution was cooled, made basic with sodium hydroxide and saturated with potassium carbonate. The alcohol was removed and the water phase extracted once with 100 ml. of ether. The alcohol and ether were combined and dried for two hours with potassium hydroxide and then overnight with magnesium sulfate. After removal of the drying agent, the ether and alcohol were removed on a steam bath and a small amount of unreacted side chain collected by heating the residue to 80° at a pressure of 1.5 mm. The residue was dissolved in 10 ml. of absolute

alcohol and 45 ml. of 47% hydriodic acid in 20 ml. of absolute alcohol added. The solids were collected on a Büchner funnel, washed with ether and dried in a vacuum desiccator. 2-Amino-8-(3-diethylaminopropylamino)-quinoline dihydriodide was recrystallized from absolute alcohol containing several ml. of 47% hydriodic acid. The product consisted of lemon yellow crystals which weighed 26 g. (46.3%) and appeared to melt at 95.7-96.7°, partially resolidifying and then decomposed at 162.7-165.7°.

Analysis: Calculated for $C_{16}H_{24}N_4 \cdot 2HI$. C, 36.38; H, 4.96; N, 10.60. Found: C, 36.14, 35.94; H, 4.86, 5.00; N, 10.56, 10.26.

2-AMINO-8-(3-DIETHYLAMINOPROPYLAMINO)-QUINOLINE TRIHYDROBROMIDE

2-Amino-8-(3-diethylaminopropylamino)-quinoline dihydroiodide (4 g.) was treated with 30% sodium hydroxide. The mixture was saturated with potassium carbonate and extracted with three 25-ml. portions of ether which were combined and dried over magnesium sulfate. The ether was removed on a steam bath and the light brown viscous oil treated with 2 ml. of hydrobromic acid (48%). Crystals formed readily, were collected on a Büchner funnel and dried in a vacuum desiccator. The white salt was dissolved in absolute alcohol, ether was added until the solution became turbid and then the mixture was cooled in a carbon dioxide-chloroform bath. The salt was collected on a Büchner funnel, washed with

ether, and dried under diminished pressure at 56° for 18 hours in the presence of phosphorus pentoxide. The white product decomposed at 201.6-203.6°.

Analysis: Calculated for $C_{16}H_{24}N_4 \cdot 3HBr$. C, 37.30; H, 5.28; N, 10.88. Found: C, 37.29, 37.51; H, 5.50, 5.40; N, 10.87, 10.80.

This salt when recrystallized from absolute alcohol and dried in a vacuum desiccator at room temperature in the presence of potassium hydroxide is solvated. The solvated compound decomposed at 209.4-211.4°. Analytical values correspond closely to the monohydrate.

Analysis: Calculated for $C_{16}H_{24}N_4 \cdot 3HBr \cdot H_2O$. C, 36.04; H, 5.48; N, 10.51. Found: C, 35.98, 35.92; H, 5.43, 5.49; N, 10.68, 10.77

8-AMINO-2-(3-DIETHYLAMINOPROPYLAMINO)-QUINOLINE

Method A

In a 100-ml. round-bottomed flask containing a magnetic stirrer were placed 10.4 g. (.05 mole) of 2-chloro-8-nitroquinoline and 28 g. (.20 mole) of 2-amino-3-diethylaminopropane. The solution was heated in an oil bath and vapor allowed to escape until the vapor temperature had increased to 170-180°(note 1). A condenser was then mounted on the flask and the solution heated under reflux for six hours. On cooling, the mixture solidified. The solids were treated with water and potassium carbonate and extracted with five 100-ml.

portions of ether. The ether extracts were combined and dried over magnesium sulfate. The ether was removed on a steam bath, and the residue heated up to 220° (note 3) under water pump vacuum to remove excess side chain. The dark red 2-(3-diethylaminopropylamino)-8-nitroquinoline (note 2) was dissolved in 10 ml. of 50% acetic acid and added portionwise over a period of 45 minutes to a stirred suspension of 15 g. of clean iron filings in 75 ml. of 5% acetic acid contained in a beaker clamped on a steam bath. The temperature of the reducing reagent was kept at 60-70° during addition of the nitro compound. Stirring and heating were continued for 30 minutes after addition of all the nitro compound. The slurry was subjected to filtration and the filter cake washed with five 20-ml. portions of 5% acetic acid. Washings and filtrate were combined, and made basic with potassium hydroxide, saturated with potassium carbonate and extracted with four 50-ml. portions of ether. The ether was removed on a steam bath and the residue distilled. Crude 8-amino-2-(3-diethylaminopropylamino)-quinoline was collected at 160-170°/.01 mm. (note 3) as a light yellow viscous oil. The yield of the crude product was 6 g. (46%) based on 2-chloro-8-nitroquinoline.

Notes

1. The "side chain" apparently contained some low boiling (130-140°) impurity which was allowed to distill from the solution.

2. Attempts to distill the nitro compound at low pressure (.001 mm.) were unsuccessful. Attempts to isolate the nitro compound by recrystallization were also unsuccessful.
3. Temperatures used in distillations are pot temperatures.

Method B*

In a 100-ml. round-bottomed flask containing a magnetic stirrer were placed 14 g. (.079 mole) of 8-amino-2-chloroquinoline and 32.4 g. (.25 mole) of 1-amino-3-diethylaminopropane. The flask was placed in an oil bath and the oil heated to 100-110°. The solution was stirred and kept in the oil bath for 48 hours. At the end of this period the external temperature was raised to 130-140° and maintained for 18 hours. During the latter heating period the reaction mixture solidified. The solids were treated with strong potassium hydroxide, solid potassium carbonate and extracted with ether until all color was removed from the water phase. The ether was dried and removed on a steam bath, whereupon excess "side chain" was removed up to 100°, at 1.5-2 mm. The product was then distilled from a Hickman still under reduced pressure, using an oil bath. The crude product, 18.2 g. (84%), distilled (pot temperature) at 185-190°/.01mm.

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*On the basis of yield and purity of the crude product, this method is recommended for the preparation of 8-amino-2-(3-diethylaminopropylamino)-quinoline in preference to Method A. It is believed that a better yield in Method A would be obtained with longer heating of the two components. A probable impurity in this product is 8-amino-2-chloroquinoline.

The crude free base prepared in the above methods was best purified by conversion to a salt and recrystallization of the salt.

6-AMINO-2-(3-DIMETHYLAMINOPROPYLAMINO)-QUINOLINE DIHYDRIODIDE DIHYDRATE

Five milliliters (.059 mole) of hydriodic acid (47%) was added to 2 g. (.0073 mole) of crude 6-amino-2-(3-diethylaminopropylamino)-quinoline, contained in an ice bath. Bright yellow crystals formed readily and were collected on a Buchner funnel. The salt was dried in a vacuum desiccator and recrystallized from absolute alcohol (note 1). The yield based on the amine was 2.57 g. (60.2%) of bright yellow product which decomposed at 134.4-138.4°. Analysis indicated the salt was solvated. The composition of the solvated salt corresponds closely to the dihydrate. Heating for 18 hours at 110° under diminished pressure in the presence of phosphorus pentoxide did not alter the composition of the solvated salt.

Analysis: Calculated for $C_{16}H_{24}N_4.2HI.2H_2O$. C, 34.06; H, 5.36; N, 9.93. Found: C, 33.98, 33.97; H, 5.48, 5.56; N, 10.03, 9.74.

Notes

1. Absolute alcohol was prepared by boiling commercial absolute alcohol with calcium oxide and distilling the

alcohol from the slurry. Dry alcohol is absolutely necessary for the recrystallization.

8-AMINO-2-(3-DIETHYLAMINOPROPYLAMINO)-QUINOLINE TRIHYDROBROMIDE

Two grams (.0073 mole) of crude 8-amino-2-(3-diethylaminopropylamino)-quinoline in a 50-ml. beaker was treated with 5 ml. (.091 mole) of hydrobromic acid (48%). The solution was stirred and cooled in an ice bath. The light tan crystals which formed were collected on a Büchner funnel, then dried overnight in a vacuum desiccator containing potassium hydroxide. The product was dissolved in freshly purified absolute alcohol, and cooled in a carbon dioxide-chloroform bath. The slightly yellow product was collected on a Büchner funnel, washed with absolute ether and dried under diminished pressure at 56° for 18 hours in the presence of phosphorus pentoxide. 8-Amino-2-(3-diethylaminopropylamino)-quinoline trihydrobromide (1.80 g. 47.6%) which decomposed at 129.4-135.4° was obtained in this procedure.

Analysis: Calculated for $C_{16}H_{24}N_4 \cdot 3HBr$. C, 37.30; H, 5.28; N, 10.88. Found: C, 37.41, 37.19; H, 5.46, 5.40; N, 10.98, 10.68.

ULTRAVIOLET ABSORPTION DATA

The absorption spectra of 2,8-diaminoquinoline, and the trihydrobromides of 2-amino-8-(3-diethylaminopropyl-

amino)-quinoline and 6-amino-2-(3-diethylaminopropylamino)-quinoline were obtained from solutions prepared from the procedure outlined on page 63. The molar extinction coefficients were calculated from the absorption data, which is recorded in tables 14, 15, and 16, using the formula given on page 69 and the molar extinction coefficients plotted vs. the wave lengths in figure 7.

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[illegible]

2,6-Diaminoquinoline

$C_9H_9N_3$ Mol. Wt. 159.186

Solvent: 95% Alcohol Concentration: 0.110 mg./25 ml.

$\varepsilon = \frac{A}{cl}$ l = 1.00 cm. $c = 2.765 \times 10^{-5}$ moles/l.

λ	A	$\varepsilon \times 10^{-3}$	λ	A	$\varepsilon \times 10^{-3}$
220	.563	19.55	310	.103	3.47
225	.491	16.35	315	.083	2.83
230	.538	17.13	320	.066	2.39
235	.545	18.40	325	.066	2.22
240	.570	19.23	330	.070	2.36
245	.560	19.55	335	.073	2.46
250	.530	17.88	340	.075	2.56
255	.705	23.80	345	.097	3.27
260	.860	29.00	350	.093	3.14
265	1.00	33.85	355	.094	3.17
270	1.07	36.05	360	.090	3.04
275	.736	24.90	365	.077	2.59
280	.466	15.78	370	.065	2.19
285	.315	10.62	375	.046	1.55
290	.220	7.43	380	.037	1.25
295	.215	7.25	385	.025	.84
300	.158	5.33	390	.020	.67
305	.125	4.22			

λ max

TABLE 15

ULTRAVIOLET ABSORPTION DATA

2-Amino-8-(3-diethylaminopropylamino)-quinoline trihydrobromide

$C_{16}H_{24}N_4 \cdot 3HBr$ Mol. wgt. 515.156

Solvent: 95% Alcohol Concentration: 0.077 mg./25 ml.

$\varepsilon = \frac{D}{ct}$ t = 1.00 cm c = 0.597×10^{-5} moles/l.

λ	D	$\varepsilon \times 10^{-3}$	λ	D	$\varepsilon \times 10^{-3}$
220	.230	38.55	310	.052	8.72
225	.178	29.80	315	.041	6.87
230	.193	32.30	320	.030	5.03
235	.220	36.88	325	.029	4.86
*240	.238	39.88	330	.025	4.18
245	.235	39.40	335	.023	3.86
250	.234	39.20	340	.028	4.69
255	.255	42.75	345	.034	5.70
260	.303	50.75	350	.037	6.20
265	.375	62.80	*355	.038	6.37
*270	.448	75.20	360	.037	6.20
275	.444	74.30	365	.036	6.04
280	.355	59.50	370	.035	5.86
285	.240	40.20	375	.028	4.69
290	.150	25.10	380	.025	4.18
295	.118	19.76	385	.019	3.18
300	.092	15.40			
305	.070	11.72			

* λ_{max}

TABLE 16

ULTRAVIOLET ABSORPTION DATA

8-Amino-2-(3-diethylaminopropylamino)-quinoline trihydrobromide

$C_{16}H_{24}N_4 \cdot 3HBr$ Mol. wgt. 515.156

Solvent: 95% Alcohol Concentration: 0.122 mg./25 ml.

$\varepsilon = \frac{D}{ct}$ t = 1.00 cm. c = 0.947×10^{-5} moles/l.

λ	D	$\varepsilon \times 10^{-3}$	λ	D	$\varepsilon \times 10^{-3}$
220	.140	14.88	310	.035	3.69
225	.107	11.30	315	.026	2.74
230	.120	12.68	320	.015	1.58
235	.143	15.10	325	.013	1.37
240	.174	18.38	*330	.019	2.02
245	.204	21.50	335	.016	1.69
250	.227	23.99	340	.013	1.37
255	.233	24.62	*345	.024	2.53
260	.258	27.21	350	.023	2.42
265	.305	32.20	355	.021	2.21
*270	.392	41.40	360	.026	2.74
275	.320	33.80	365	.016	1.69
280	.252	26.52	370	.011	1.26
285	.222	23.43	375	.010	1.06
290	.137	14.47	380	.010	1.06
295	.112	11.82	385	.050	.53
300	.078	8.24	390	.050	.53
305	.054	5.71			

* λ max

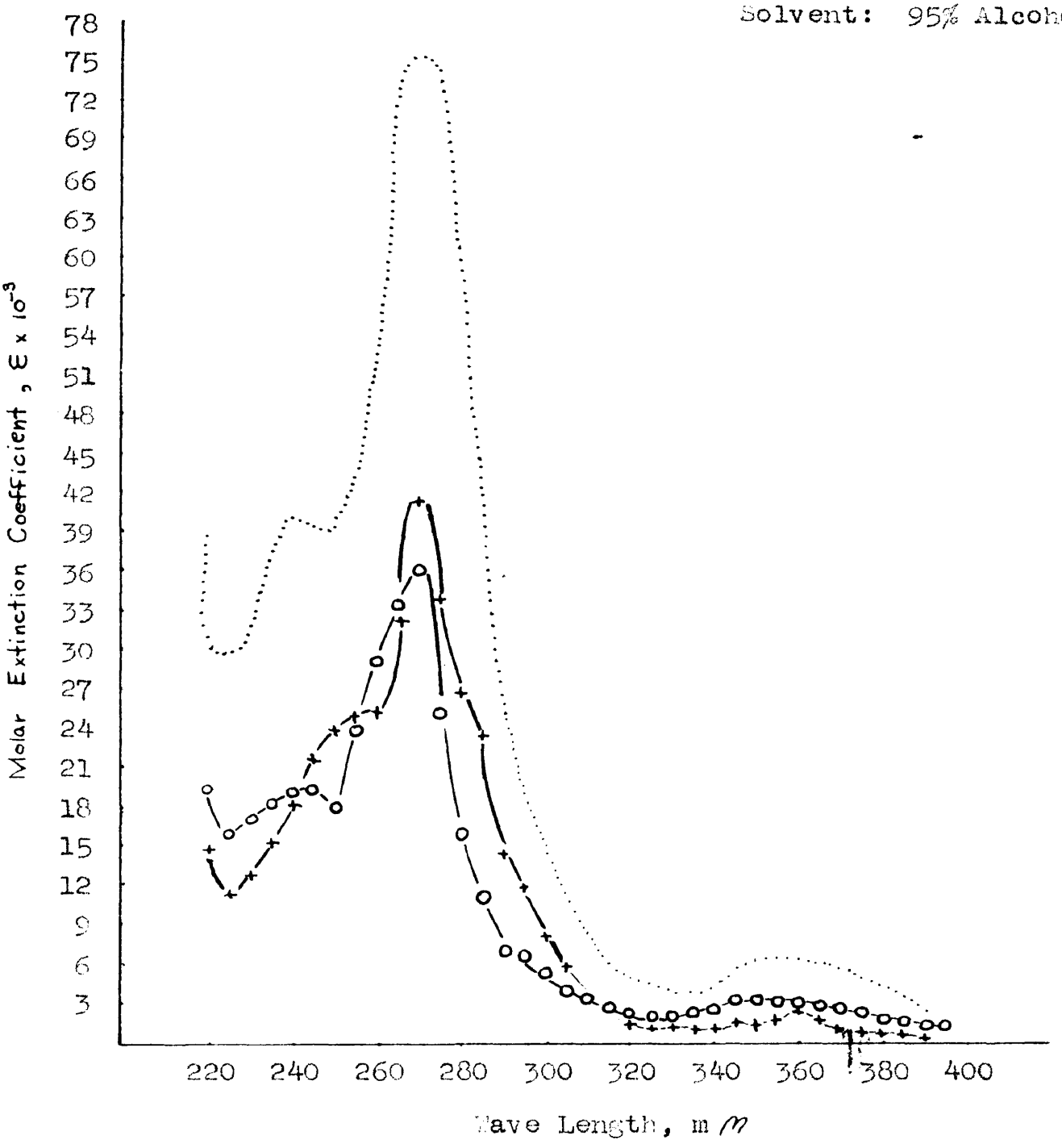
FIGURE 7

ULTRAVIOLET ABSORPTION SPECTRA

. 2,8-Diaminoquinoline

+ 8-Amino-2-(3-diethylaminopropylamino)-quinoline Trihydrobromide

o 2-Amino-8-(3-diethylaminopropylamino)-quinoline Trihydrobromide



ABSTRACT

Douglas N. Christensen, Ph.D. 1953 (B.S. Chem. Eng., Missouri School of Mines and Metallurgy; M.S. University of Maryland)
Title of Thesis: Synthetic Poliomyelitioidals
Thesis directed by Professor Nathan L. Drake
Major: Organic Chemistry
Minors: Physical and Inorganic Chemistry
Pages in thesis, 201. Words in abstract, 236

The synthesis of six quinoline compounds containing a substituent in the 2-position and the diethylaminopropylamino group in the 8-position is described. All of these compounds are new except 8-(3-diethylaminopropylamino)-2-methoxyquinoline. Two of these compounds have been submitted for toxicity tests. In connection with these drugs the preparation of twenty-one additional new compounds is described. Attention has been specifically directed toward the determination of optimum reaction conditions resulting in good yields and methods suitable for large scale reactions.

Three of the drugs were prepared by alkylating the 2-substituted-8-aminoquinoline with 1-chloro-3-diethylamino-propane. 8-(3-Diethylaminopropylamino)-2-methoxyquinoline, 2-chloro-8-(3-diethylaminopropylamino)-quinoline and 2-amino-8-(3-diethylaminopropylamino)-quinoline were prepared in this manner. In the preparation of the latter drug, position isomers were possible and a proof of structure is included to show the preferential position of alkylation.

8-(3-Diethylaminopropylamino)-carbostyril was pre-

pared by the acid hydrolysis of either 8-(3-diethylamino-propylamino)-2-methoxyquinoline or 2-chloro-8-(3-diethyl-aminopropylamino)-quinoline.

Two drugs were prepared, utilizing a substituted 2-chloroquinoline. 8-(3-Diethylaminopropylamino)-2-phenoxy-quinoline was prepared by reacting 2-chloro-8-(3-diethyl-aminopropylamino)-quinoline with phenol. 8-Amino-2-(3-di-ethylaminopropylamino)-quinoline was prepared by reacting 2-chloro-8-nitroquinoline with 1-amino-3-diethylaminopropane and reducing the nitro group, or by treating 8-amino-2-chloroquinoline with 1-amino-3-diethylaminopropane.

The following additional new compounds were prepared. 8-Aminocarbostyril, 8-aminocarbostyril monohydrochloride, 8-amino-2-chloroquinoline monohydrobromide, 8-amino-2-chloro-quinoline monohydrochloride, 2-chloro-8-(3-diethylamino-propylamino)-quinoline dihydrobromide, 2-chloro-8-(3-diethyl-aminopropylamino)-quinoline disulfate, 2-chloro-8-(3-diethyl-aminopropylamino)-quinoline diperchlorate, 8-(3-diethylamino-propylamino)-2-phenoxyquinoline dihydrobromide, 8-nitro-2-p-tolylsulfonamidoquinoline, 8-amino-2-p-tolylsulfonamido-quinoline, 8-amino-2-p-tolylsulfonamidoquinoline monohydro-bromide monohydrate, 2,8-diaminoquinoline, 2,8-diaminoquino-line monosulfate, 2,8-diaminoquinoline monophosphate, 2,8-diaminoquinoline dihydriodide, 2,8-diaminoquinoline dihydro-bromide, 8-acetamido-2-aminoquinoline, 2-amino-8-(3-diethyl-aminopropylamino)-quinoline dihydriodide, 2-amino-8-(3-di-

ethylaminopropylamino)-quinoline trihydrobromide, 8-amino-2-(3-diethylaminopropylamino)-quinoline dihydriodide dihydrate and 8-amino-2-(3-diethylaminopropylamino)-quinoline trihydrobromide.

Improvements have also been made in the preparation of the following eight compounds. 1-methyl-8-nitroquinolinium iodide, 1-methyl-8-nitro-2-quinolone, 2-chloro-8-nitroquinoline, 8-nitrocarbostyril, 2-methoxy-8-nitroquinoline, 8-(3-diethylaminopropylamino)-2-methoxyquinoline, 8-amino-2-chloroquinoline and 2-amino-8-nitroquinoline.

VITA

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