vessel fitted with a reflux condenser and placed in a furnace in a shaking machine. Upon cooling the vessel, the excess pressure was exhausted by means of a valve and the reaction products examined in the same manner as in the First Procedure.

When one mole of isopropyl chloride was treated in this manner with 125 g. of hydrogen fluoride at 43 atm. (650 lb. per sq. in.) pressure and 160° for one day, only a very small amount of residue was obtained. Neither isobutyric acid nor the expected product, the fluoride of this acid, was obtained. In other similar experiments, a method of treating the products was used in which water was not added but still the acid fluoride was not found. In an experiment in which one-half mole of the same chloride was added to 20 g. of water and 90 g. of hydrogen fluoride and treated at 150° and the same pressure for two days, 24.6 g. (56%) of isobutyric acid was obtained. This was identified by its b. p. 150–153°, its neutralization equivalent 90, and its *p*-toluidide, m. p. 104–106°. In another experiment one mole of isopropyl chloride was mixed with 40 g. of methanol and 70 g. of hydrogen fluoride and treated at 150° with carbon monoxide at 53 atm. (800 lb. per sq. in.). After one day, 5.5 g. (7%) of isobutyric acid was found.

Discussion

As the preliminary experiments were done with the formic acid technique in which water is always present, it was thought that the use of carbon monoxide under pressure would result in higher yields of acids. It was surprising to find that under the anhydrous conditions isopropyl chloride did not yield appreciable quantities of isobutyric acid. This cannot be explained as caused by the formation of isopropyl alcohol as an intermediate from a reaction of the halide and the water for two reasons. First: experiments using isopropyl alcohol resulted in only tarry products; and second, the addition of methyl alcohol had a similar effect to the addition of water; and methyl alcohol is not dehydrated under the conditions of the experiments as has been found in this laboratory. An explanation could be offered on the assumption that an intermediate of the fluoride of isobutyric acid is formed in the absence of water or methanol and that the active halogen atom reacts with active hydrogen atoms on adjacent molecules to form chain polymers and tars. In the presence of water, the acid is formed from the acid halide. To test this an experiment was tried using *t*-butyl chloride. The acid halide that would be formed would have no α hydrogen atoms; and, if the above assumption were correct, the acid halide or the acid resulting from its hydrolysis (if water is added) should be formed as a product. This experiment produced only a trace of aliphatic acid. The mechanism of these reactions should probably follow the hypotheses outlined by Sprauer and Simons.[6]

Summary

Carbon monoxide has been found to react with certain alcohols and alkyl halides in the presence of hydrogen fluoride. Isobutyric acid has been obtained from isopropyl chloride and from normal propyl alcohol. Isopropyl chloride in the absence of water or methanol and isopropyl alcohol under similar conditions did not yield the acid.

(6) Sprauer and Simons, THIS JOURNAL, **64**, 648 (1942).

STATE COLLEGE, PENNSYLVANIA
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[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Syntheses in the Quinoline Series. IV. 2,4-Disubstituted Quinoline Derivatives

BY FRED J. BUCHMANN[1] AND CLIFF S. HAMILTON

The use of dialkylaminoalkylaminoquinoline derivatives, especially plasmoquin and atebrin, in the treatment of malaria has become well established. Quinoline derivatives with the aliphatic amino side chains in either the two or the four position have been reported[2] but possessed little or no antimalarial activity. The introduction of an hydroxyl group in the 2-position of certain derivatives of pyridine and quinoline has been shown to greatly alter the chemotherapeutic properties of these compounds.[3] Thus, it seemed advisable to attempt the preparation of 2- and 4-dialkylaminoalkylaminoquinoline derivatives with hydroxyl or alkoxyl groups in the 4- or 2-positions as the case might be.

Friedlaender and Weinberg[4] have reported that 2,4-dichloroquinoline reacts with alcoholic potassium hydroxide to produce a chloroethoxyquinoline melting at 43° and they have shown it

(1) Parke, Davis and Company Fellow.

(2) Magidson and Rubtsov, *J. Gen. Chem.* (U. S. S. R.), **7**, 1896 (1937); *Chem. Abs.*, **32**, 564 (1938).

(3) Binz and Rath, *Biochem. Z.*, **203**, 218 (1928).

(4) Friedlaender and Weinberg, *Ber.*, **15**, 2679 (1882).

to be 4-chloro-2-ethoxyquinoline by conversion to 4-chlorocarbostyril. This latter compound had been prepared by ring closure methods by Baeyer and Bloom.[5]

When 2,4-dichloroquinoline was treated with absolute alcoholic potassium hydroxide during the course of this investigation, it was found that not one but the two possible isomeric chloroethoxyquinolines were formed in approximately equal proportions. The isomers were separated by steam distillation, the 4-chloro isomer distilling first. The structure of the 4-chloro isomer was proved by its conversion to 4-chlorocarbostyril, as indicated by Friedlaender and Weinberg,[4] and also by its preparation from 4-amino-2-ethoxyquinoline by diazotization of the amine in concentrated hydrochloric acid. The structure of the 2-chloro isomer was shown by its conversion to 2,4-diethoxyquinoline. This latter compound was also prepared from both the 4-chloro isomer and 2,4-dichloroquinoline.

A considerable difference was noted in the ease of rupture of the ether linkages in the two chloroethoxyquinolines. While the 4-chloro isomer required only twenty to thirty minutes of reflux with 6 *N* hydrochloric acid, the 2-chloro isomer required several hours of reflux with concentrated hydriodic acid.

The reactivity of the halogen atoms in the various chloroquinolines varied widely. The halogen atom in 4-chlorocarbostyril was quite inactive and could not be reacted with either sodium ethylate in alcohol[6] or amines of high boiling point. In contrast, the halogen atom in 2-chloro-4-hydroxyquinoline was quite active and reacted easily with amines. Both of the halogen atoms in 2,4-dichloroquinoline were quite reactive and gave good yields of diaminoquinolines. The halogen in 2-chloro-4-ethoxyquinoline was fairly reactive and considerably more reactive than the one in its isomeric compound, 4-chloro-2-ethoxyquinoline.

2,4-Dichloroquinoline, 2-chloro-4-ethoxyquinoline and 4-chloro-2-ethoxyquinoline reacted with γ-diethylaminopropylamine giving gummy products which, although distillable in the latter two cases, could not be crystallized as either the free bases or their polyhydrochlorides. 2-(γ-Diethylaminopropylamino)-4-hydroxyquinoline crystallized as the free base after large losses in the recrystallization.

4-Amino-2-ethoxyquinoline[7] was prepared but all attempts to cause this amine to react with compounds containing active halogen atoms failed.

Acknowledgment for assistance is due to Mr. Cliff M. Hollenbeck and to Mr. R. E. Sharpe for Kjeldahl analyses and carbon and hydrogen analyses, respectively, reported in this paper.

Experimental

2,4-Dihydroxyquinoline.—The dihydroxyquinoline was prepared according to the procedure suggested by Brooker and Smith[8] and their yields (28–31%) were duplicated. A further purification was effected by dissolving the product in hot 5 *N* sodium hydroxide (4 ml. per g.), decolorizing the solution with charcoal, and allowing it to stand overnight in an icebox. The crystalline sodium salt (probably the disodium salt) was filtered, dissolved in water and the solution acidified and filtered. The purification reduced the yield to 20% but furnished a product which gave an excellent yield in the next reaction.

2,4-Dichloroquinoline.—Purified 2,4-dihydroxyquinoline (10 g.) was heated on a water-bath at 90° with 50 ml. of phosphorus oxychloride for three hours with vigorous mechanical stirring and then for an additional two hours under gentle reflux with stirring. The reaction mixture was cooled, poured over a large quantity of cracked ice and the whole allowed to stand for two hours with occasional stirring. The product was filtered and on one recrystallization from 80% alcohol–water gave 11.5 g. (93%) of 2,4-dichloroquinoline, melting at 66–67°.

4-Chloro-2-ethoxyquinoline and 2-Chloro-4-ethoxyquinoline.—Potassium hydroxide (15 g. of 85%) was dissolved in 400 ml. of absolute alcohol and 40 g. of 2,4-dichloroquinoline added. The whole was refluxed for two hours, then much of the alcohol removed by distillation, the solution cooled, diluted with water and allowed to stand in a refrigerator for two hours. The solid product was separated by filtration and subjected to steam distillation. The colorless oil in the distillate crystallized on cooling and the crystalline product melted sharply at 43°. So long as this melting point was maintained the distillate was saved as a unit. On the lowering of the melting point a small second fraction was obtained and with the rise in melting point to 75–80° a third fraction was obtained. The first fraction was almost pure 4-chloro-2-ethoxyquinoline[4] as was proved by subsequent reaction. The third fraction was purified by refluxing for one hour with 6 *N* hydrochloric acid, cooling, filtering, and precipitating a solid with sodium hydroxide. This solid recrystallized from alcohol–water giving white needles belonging to the orthorhombic system, melted at 84° and analyzed for a chloroethoxyquinoline.

Anal. Calcd. for $C_{11}H_{10}ClNO$: N, 6.75. Found: N, 6.73.

This compound was shown to be 2-chloro-4-ethoxyquinoline by subsequent reactions. The products and yields obtained in the reaction were: 4-chloro-2-ethoxy-

(5) Baeyer and Bloom, *Ber.*, **15**, 2147 (1882).
(6) Friedlaender and Muller, *ibid.*, **20**, 2009 (1887).
(7) Wojahn, *Arch. Pharm.*, **274**, 83 (1936).
(8) Brooker and Smith, THIS JOURNAL, **59**, 67 (1937).

TABLE I

AMINOQUINOLINES

Quinoline	Description	Crystallizing solvent[a]	M. p., °C.	Formula		Analyses, % Nitrogen Calcd.	Nitrogen Found	Hydrogen Calcd.	Hydrogen Found
2,4-Di-(N-morpholino)-	Glistening, laminated plates	EtOH	167–169	$C_{17}H_{21}N_3O_2$	N	14.04	13.86		
2,4-Di-(8′-quinolineamino)-	Yellow, tetragonal needles	Bz	208–210	$C_{27}H_{19}N_5$	N	16.94	16.72[b]		
4-Ethoxy-2-N-morpholino-	White, triclinic needles	EtOH	146–147	$C_{15}H_{18}N_2O_2$	N	10.85	11.06		
4-Ethoxy-2-N-piperidino-	Stout, monoclinic white needles	EtOH	115	$C_{16}H_{20}N_2O$	C	74.96	74.74	7.86	8.10
2-Ethoxy-4-N-morpholino-	White crystals	Pet. ether	140–150[c]	$C_{15}H_{18}N_2O_2$	C	69.78	69.88	7.03	7.29
4-Hydroxy-2-N-morpholino-	White orthorhombic needles	EtOH–H_2O	289–290d.	$C_{13}H_{14}N_2O_2$	C	67.81	68.01	6.13	6.30
2-(γ-Diethylaminopropylamino)-4-hydroxy-	White orthorhombic needles	EtOH–H_2O	254–256d.	$C_{16}H_{23}N_3O$	N	15.40	15.50		

[a] Used in recrystallizing the amine. [b] By the Dumas method; all other nitrogen analyses are by the Kjeldahl method. [c] Sublimes at 110°.

quinoline, 13.5 g. (32%); 2-chloro-4-ethoxyquinoline, 13 g. (31%); 4-chlorocarbostyril, 2 g. (5.5%) and unseparated material, 3 g. (7% based on chloroethoxyquinoline); total yield, 75%.

4-Chlorocarbostyril.[4,5]—4-Chloro-2-ethoxyquinoline (1 g.) was refluxed for thirty minutes with 15 ml. of 6 *N* hydrochloric acid and a white crystalline compound separated during the heating. Filtration and recrystallization from much alcohol gave an almost quantitative yield of 4-chlorocarbostyril melting at 254°. This compound has been reported previously[4,5] to have m. p. 246°.

Anal. Calcd. for C_9H_6ClNO: N, 7.80. Found: N, 8.01.

4-Chloro-2-ethoxyquinoline from 4-Amino-2-ethoxyquinoline.—The aminoquinoline (1.88 g.) was dissolved in 25 ml. of concentrated hydrochloric acid, the solution cooled to −5°, and a solution of 0.7 g. of sodium nitrite in 3 ml. of water added dropwise beneath the surface of the solution. The evolution of a gas occurred immediately with the addition of each drop of nitrite solution and no test for diazotization could be obtained. The solution was allowed to stand for thirty minutes, cracked ice was then added and the solution neutralized with 10 *N* sodium hydroxide. Filtration and recrystallization from alcohol–water gave 1.4 g. (67% of theory) of 4-chloro-2-ethoxyquinoline; m. p. 42–44°. No depression of melting point was observed when this product was mixed with the one obtained from 2,4-dichloroquinoline. Further, this product was converted to 4-chlorocarbostyril and mixed melting points remained constant.

2,4-Diethoxyquinoline.—This compound was prepared by heating either 2,4-dichloroquinoline or 4-chloro-2-ethoxyquinoline or the chloroethoxyquinoline melting at 84° with an excess of sodium ethylate, thus proving this latter compound to be 2-chloro-4-ethoxyquinoline. The diethoxyquinoline was recrystallized from alcohol–water giving stout needles belonging to the orthorhombic system. The melting points of all three preparations and the mixed melting points of all their possible combinations were quite constant at 54–56°; the purest sample obtained melted sharply at 56°.

Anal. Calcd. for $C_{13}H_{15}O_2N$: N, 6.45. Found: N, 6.46.

2-Chloro-4-hydroxyquinoline.—2-Chloro-4-ethoxyquinoline (6 g.) was refluxed for ten hours with 30 ml. of 70% hydriodic acid, the solution allowed to cool and then made alkaline with sodium hydroxide, charcoaled and filtered. Acidification and recrystallization from alcohol gave 2 g. (40%) of fine, white needles melting at 189–190°.

Anal. Calcd. for C_9H_6ClNO: N, 7.80. Found: N, 7.60.

Aminoquinolines.—With the exception of 4-chlorocarbostyril, which failed to react, the chloroquinolines were condensed with amines. The condensations were carried out by heating the chloro compound with an excess of the amine at the boiling point of the solution or at the required temperature to produce the desired reaction. In the condensation of 2,4-dichloroquinoline and 8-aminoquinoline an excess of the amine was avoided, a procedure which increased the ease with which the product could be purified, and the reaction temperature was 140°. The time of reflux necessary to obtain good yields in the various cases was: 2,4-dichloroquinoline, two hours; 2-chloro-4-ethoxyquinoline, four hours; 2-chloro-4-hydroxyquinoline, six hours; 4-chloro-2-ethoxyquinoline, fifteen hours. The quinoline amines and some of their properties are listed in the accompanying table.

4-Amino-2-ethoxyquinoline.—The amine was prepared by a Hofmann reaction on the corresponding amide according to the procedure of Wojahn.[7] The yield was 50% after several recrystallizations from alcohol–water.

4-Acetamino-2-ethoxyquinoline.—The aminoquinoline was heated under gentle reflux with an excess of acetic anhydride for forty-five minutes, the reaction mixture cooled, diluted with water, neutralized with sodium hydroxide, filtered and the product washed well with water. Two recrystallizations from alcohol–water gave 4-acetamino-2-ethoxyquinoline, white crystals belonging to the monoclinic system and melting at 176–178°.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: N, 12.17. Found: N, 12.17.

4-Aminocarbostyril.—4-Amino-2-ethoxyquinoline (10 g.) was refluxed with 80 ml. of 70% hydriodic acid for five hours, the reaction mixture cooled, diluted with 100 ml. of water and filtered. The product was reprecipitated from dilute sodium hydroxide solution with dilute hydrochloric acid, filtered and recrystallized from much 95% alcohol. The yield was 6 g. (70%). The amine melted at 308–310° and crystallized in the form of small white rods belonging to the tetragonal system.

Anal. Calcd. for $C_9H_8N_2O$: N, 17.49. Found: N, 17.60.

Summary

1. 2,4-Dichloroquinoline was caused to react

with absolute alcoholic potassium hydroxide and the resulting two isomeric chloroethoxyquinolines were separated and their structures proved.

2. 2,4-Dichloroquinoline, 2-chloro-4-ethoxyquinoline, 4-chloro-2-ethoxyquinoline and 2-chloro-4-hydroxyquinoline were condensed with various amines giving several new amino- and diaminoquinolines. 4-Chlorocarbostyril failed to react.

3. 4-Amino-2-ethoxyquinoline failed to react with compounds containing active halogen atoms, however, two derivatives of this amine were prepared.

LINCOLN, NEBRASKA RECEIVED JANUARY 20, 1942

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

Higher Hydrocarbons.[1] I. Seven Alkyl Substituted Docosanes

BY FRANK C. WHITMORE, L. H. SUTHERLAND[2] AND J. N. COSBY

While a large amount of excellent work has been done on the systematic study of the lower molecular weight hydrocarbons, there is very little accurate information on hydrocarbons containing over twenty carbon atoms. Outstanding exceptions are the investigations of Mikeska[3] and Landa.[4] Recently another investigation of this type has been reported by Neyman-Pilat and Pilat.[5] Their work includes the properties of seven C_{22} hydrocarbons, previously prepared by Turkiewicz.[6]

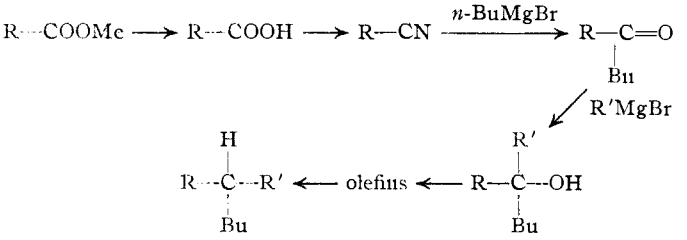
Approximately two hundred aromatic hydrocarbons in this range have been made by various workers for carcinogenic tests. Unfortunately the study of the other properties has been very limited. For this reason their preparation is of only secondary interest to this work and will not be considered in this paper.

The compounds studied and the methods used in the present work have been carefully selected to avoid complications due to rearrangement or other side reactions. Special emphasis has been placed on the purification of the intermediates. Every effort has been made to obtain a high standard of purity in the finished hydrocarbons.

The purity of the products has been determined by means of time–temperature melting curves. Supplementary evidence has been obtained from distillation–refractive index curves and distillation–viscosity curves. A compound is accepted only if those data indicate a purity of over 95% for a quantity of at least 100 g. Additional checks are given by molecular refraction values and failure to show change in composition on solvent extraction and treatment with silica gel.[7]

In this paper seven simple isoparaffins from C_{26} to C_{32} have been prepared and studied. Four of these have a straight C_{22} chain with *n*-butyl groups on the fifth, seventh, ninth, and eleventh carbon atoms, respectively. The other three have the same C_{22} chain, but with *n*-hexyl-, *n*-octyl-, and *n*-decyl groups on the seventh, ninth, and eleventh carbon atoms, respectively. By this selection it was possible to vary widely the symmetry of the molecule.

Two general methods of synthesis have been used in the present work. 7-*n*-Butyl-, 9-*n*-butyl-,



and 11-*n*-butyl-docosanes were made in the steps shown. 5-*n*-Butyl-, 7-*n*-hexyl-, 9-*n*-octyl-, and 11-*n*-decyldocosanes were made as follows

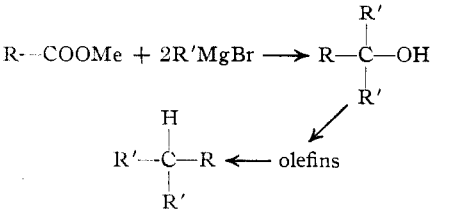


Table I is a summary of the important properties of these hydrocarbons. As the reason for

(1) American Petroleum Institute Project No. 42: Advisory Committee, L. A. Mikeska, C. R. Wagner and L. C. Beard, Jr., Chairman.

(2) Present address, Reilly Laboratories, Indianapolis, Ind.

(3) Mikeska, *Ind. Eng. Chem.*, **28**, 970 (1936); Mikeska and co-workers, *J. Org. Chem.*, **2**, 499 (1938); **6**, 787 (1941).

(4) Landa and co-workers, *Coll. Czechoslovak. Chem. Commun.*, **4**, 538 (1932); **5**, 204 (1933); **6**, 423 (1934).

(5) Neyman-Pilat and Pilat, *Ind. Eng. Chem.*, **33**, 1382 (1941).

(6) Turkiewicz, *Ber.*, **73**, 861 (1940).

(7) Mair and White, *J. Research Natl. Bur. Standards*, **15**, 51 (1935); Willingham, *ibid.*, **22**, 321 (1939)