basic with 33% potassium hydroxide[26] solution and filtered. The filtrate was neutralized by addition of acetic acid and the resulting yellow precipitate was collected by filtration, dried in air overnight and extracted with two 100-ml. portions of absolute ethanol. Removal of the alcohol on the steam bath gave 0.97–1.20 g. (65–83%) of crude 3-isoquinolinol. The crude product was recrystallized from benzene (or, if colored strongly, first from 95% ethanol (with charcoal) then benzene), giving 0.79–0.97 g. (53–65%) of 3-isoquinolinol as light yellow needles, which melted at 195–196°, then resolidified (in a preheated bath). On continued heating the solid gradually darkened, finally melting (dec.) at 257°. When the compound was inserted in the bath at any temperature below 194° and the temperature was raised slowly, it did not melt at 195–196° but slowly darkened and melted at 257°.

Potentiometric titrations. The procedure used for the determination of the pK_a values were patterned after that outlined by Linstead, Elvidge, and Whalley.[27] A Leeds and Northrup pH meter, in conjunction with a glass and calomel electrode, was used. The meter checked to within 0.02 pH units against standard buffers throughout the measurements. The measurements were made at 20 ± 0.05° under purified nitrogen. Each reported value is the mean of fourteen to twenty-one determinations.

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(26) Use of sodium hydroxide complicates the purification because of the insolubility of the sodium salt of 3-isoquinolinol.

(27) R. P. Linstead, J. A. Elvidge, and M. Whalley, *A Course in Modern Techniques of Organic Chemistry,* Academic Press, Inc., New York, N. Y., 1955, p. 153.

[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORIES, UNIVERSITY OF NORTH CAROLINA]

Electrolytic Oxidation of Some Substituted Quinolines to Quinolinic Acids and Acylations with Substituted Quinolinic Anhydrides

JOHN C. COCHRAN[1] AND WILLIAM F. LITTLE

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A series of quinolines bearing substituents on the pyridine ring have been oxidized electrolytically in sulfuric acid. The corresponding quinolinic acids were obtained from 3-fluoro-, 3-chloro-, 3-bromoquinoline and from quinoline itself. 3-Iodoquinoline gave an acidic material that did not contain iodine. Electrolysis of 2- and 4-chloroquinoline caused loss of halogen and yielded polymeric materials. No products were isolated from 2-phenylquinoline and from 3-aminoquinoline. Anhydrides were prepared from 5-fluoro-, 5-chloro-, 5-bromo-, 4-methyl-, and unsubstituted quinolinic acid, and Friedel-Crafts reaction of these anhydrides with benzene yielded in each case a single isomer, the corresponding 3-benzoylpyridine-2-carboxylic acid.

A variety of methods are available for the oxidation of quinoline and substituted quinolines to quinolinic acids, employing oxidizing agents such as potassium permanganate, manganese dioxide and fuming nitric acid.[2–5] One method of particular interest for its simplicity and convenience is the electrolytic procedure described in the thorough study by Kulka[6] of the anodic oxidation of quinoline in concentrated sulfuric acid solutions at different temperatures, employing both platinum and lead dioxide anodes. The application of electrolytic oxidations to heterocyclic derivatives has been but scantily investigated. Yokayama[7] has converted methylpyridines to pyridine carboxylic acids by electrolysis; Fichter and Kern[8] have applied electrolytic procedures to oxidations in the purine series, and Fischer and Chur[9] have oxidized quaternary pyridine salts to pyridines. In the present investigation, the procedure of Kulka[6] has been applied to quinolines substituted in the heterocyclic ring.

The general procedure involved the use of the apparatus described in the Experimental section, where the quinoline was dissolved in 75–80% sulfuric acid and was subjected to electrolysis at temperatures varying from 55° to 90°, employing a platinum gauze or lead dioxide anode. The oxidations of approximately 0.1 mole of the substituted quinolines required approximately eighty hours for completion at 3 to 4 v. and a current of 1 to 1.5 amp. The reaction was conveniently followed by color changes. Initially the electrolysis mixtures turned dark brown to black; at the end of the reaction the reaction mixtures changed from this dark color to a light amber over a period of less than one hour. The substituted quinolinic acids so obtained were conveniently isolated by formation of insoluble copper complexes that were readily de-

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(1) Taken from part of a thesis submitted by John C. Cochran to the University of North Carolina in partial fulfillment of the requirements for the degree of Master of Arts, 1960. Present address, Department of Chemistry, Randolph-Macon Woman's College, Lynchburg, Va.

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(9) O. Fischer and M. Chur, *J. prakt. Chem.,* **93,** 363 (1916).

TABLE I

SUMMARY OF ELECTROLYTIC OXIDATIONS

Compound	Amount, g.	Electrode	Time, hr.	Temp.	Product	% Yield	M.P.
Quinoline	18.0	PbO_2	83	60–70	Quinolinic acid	44	188–192
3-Bromoquinoline	10.0	PbO_2	61	55–65	5-Bromoquinolinic acid	73	158–161
3-Chloroquinoline	21.1	Pt	113	80–90	5-Chloroquinolinic acid	54	129–130
3-Fluoroquinoline	18.3	Pt	77	85–90	5-Fluoroquinolinic acid	26	125–128
3-Iodoquinoline	12.3	Pt	17	80	5-Hydroxyquinolinic acid-hemihydrate (?)	10	211 dec.
4-Chloroquinoline	11.3	PbO_2	100	60	Polymer	—	—
2-Chloroquinoline	10.0	PbO_2	120	65	Polymer	—	—
3-Aminoquinoline	10.0	Pt	67	70	None isolated	—	—
2-Phenylquinoline	13.9	Pt	72	65–70	None isolated	—	—
2-Phenylquinoline	19.6	Pt	156	75–80	None isolated	—	—

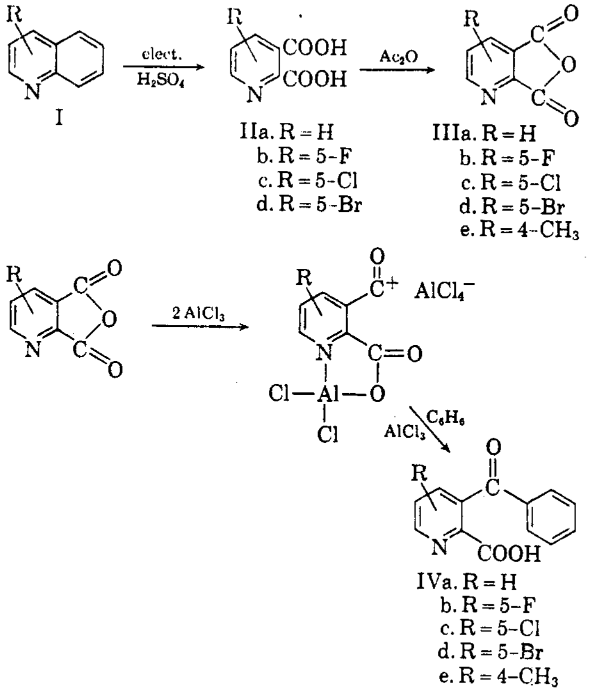

Fig. 1. Electrolytic oxidation of heterocyclic derivatives.

composed with hydrogen sulfide in water. Fig. 1 shows the reaction schemes employed.

Table I lists, with results, the substituted quinolines that were subjected to electrolytic oxidation in this manner. The quinolines that were successfully converted into the corresponding quinolinic acids included quinoline,[6] 3-bromoquinoline, 3-chloroquinoline, and 3-fluoroquinoline to give quinolinic acid, 5-bromoquinolinic acid, 5-chloroquinolinic acid, and 5-fluoroquinolinic acid, respectively. Earlier attempts by Hawkins[10] to prepare 5-fluoroquinolinic acid by permanganate oxidation and with nitric acid from 3-fluoroquinoline were unsuccessful.

Attempted electrolytic oxidation of 3-iodoquinoline to the corresponding iodoquinolinic acid was unsuccessful; oxidation did occur, but iodine was lost and a product was isolated *via* the copper chelate that contained no iodine and gave an analysis that might correspond to the hemihydrate of 5-hydroxyquinolinic acid.

Halogen in the 2- or 4-position of quinoline is lost under the reaction conditions, as might be expected. 2-Chloro- and 4-chloroquinoline resulted in red polymeric products with loss of chloride.

No products were isolated from attempted oxidations of 3-aminoquinoline or 2-phenylquinoline. Ueda[11] has reported that 2-phenylquinoline yields 2-phenylbenzoxazole upon oxidation with potassium permanganate. This product was not sought in the reaction mixture.

Friedel-Crafts reactions with substituted quinolinic anhydrides. The anhydrides of the quinolinic acids prepared by electrolysis and that of 4-methylquinolinic acid were prepared by reflux with acetic anhydride. The properties of these anhydrides are listed in Table II.

Bernthsen[12] reported the reaction of quinolinic anhydride and aluminum chloride with benzene to yield only the 3-benzoylpyridine-2-carboxylic acid. Subsequent investigations showed that quinolinic anhydride as a Friedel-Crafts acylation agent yields only the pyridine-2-carboxylic acid product with substrates including toluene,[14] *m*-xylene,[15] naphthalene,[16] acenaphthene,[16] and biphenyl.[15] The production of 3-acylpyridine-2-carboxylic acid to the exclusion of the other isomer in each case, the 2-acyl-3-carboxylic acid isomer, along with the report by Rubidge and Qua[17] that at least two molar equivalents of aluminum chloride are needed for each mole of an anhydride in a Friedel-Crafts reaction, is consistent with the consumption two moles of aluminum chloride in the salt as the acylating agent, as represented in Fig. 1.

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(16) C. M. Jephcott, *J. Am. Chem. Soc.*, **50**, 1189 (1928).

(17) C. R. Rubidge and N. C. Qua, *J. Am. Chem. Soc.*, **36**, 732 (1914).

TABLE II

QUINOLINIC ANHYDRIDES

Quinolinic Anhydride	M.P.	Yield from Quinolinic Acid, %	Formula	Nitrogen, %	
				Calcd.	Found
Quinolinic anhydride	134–135.5[a]	54	—	—	—
5-Bromo-	137–140[b]	42	—	—	—
5-Chloro-	146–148	58	$C_7H_2ClNO_3$	7.63	7.55
5-Fluoro-	107.5–110	38	$C_7H_2FNO_3$	8.38	8.24
4-Methyl-	164–165.5	30	$C_8H_5NO_3$	8.58	8.37

[a] Lit.,[3] m.p. 133–134°. [b] Lit.[13] m.p. 136–138°.

TABLE III

FRIEDEL-CRAFTS REACTION PRODUCTS FROM QUINOLINIC ANHYDRIDES WITH BENZENE

Quinolinic Anhydride	Reaction Product	M.P.	Yield, %	Formula	Nitrogen, %	
					Calcd.	Found
Quinolinic anhydride	3-Benzoylpyridine-2-carboxylic acid	146–148[a]	53			
5-Bromo-	3-Benzoyl-5-bromopyridine-2-carboxylic acid	146.5–165.5	25	$C_{13}H_8BrNO_3$	4.59	4.22, 4.18, 4.29
5-Chloro-	3-Benzoyl-5-chloropyridine-2-carboxylic acid	140–141	31	$C_{13}H_8ClNO_3$[b]	5.35	5.04, 5.03
5-Fluoro-	3-Benzoyl-5-fluoropyridine-2-carboxylic acid	136–137.5	32	$C_{13}H_8FNO_3$	5.71	5.64
4-Methyl-	3-Benzoyl-4-methylpyridine-2-carboxylic acid	172–173	25	$C_{14}H_{11}NO_3$	5.81	5.67

[a] Lit.,[12] m.p. 147°. [b] Calcd. for $C_{13}H_8ClNO_3$: C, 59.67; H, 3.08. Found: C, 59.35; H, 3.33.

Quinolinic anhydride, 5-bromo-, 5-chloro-, 5-fluoro-, and 4-methyquinolinic anhydride were allowed to react with benzene in the presence of two molar equivalents of aluminum chloride, and in each case but one product was obtained. The isomer obtained was in each case assigned the structure corresponding to the 2-carboxylic acid in view of the mentioned reports of this as the sole isomer in other experiments with quinolinic anhydride, itself, and in view of the isolation of these products as insoluble copper chelates that would be expected to form readily with pyridine-2-carboxylic acids. The properties of the Friedel-Crafts reaction products are listed in Table III.

EXPERIMENTAL

All melting points are uncorrected.

The nitrogen analyses were performed in this laboratory; the carbon and hydrogen analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

3-Chloroquinoline. Method A. 3-Chloroquinoline was prepared by ring expansion of indole with chloroform and potassium hydroxide according to the method of Boyd and Robson[18] in 15% yield.

Method B. Slightly better results were obtained by a Gattermann reaction on 3-aminoquinoline. 3-Aminoquinoline (20 g., 0.14 mole) was dissolved in 400 ml. of concd. hydrochloric acid and 200 ml. of water. At a temperature below 5°, a solution of 15.6 g. (0.14 mole) of sodium nitrite in 35 ml. of water was added dropwise with stirring. After the addition was complete, 34.8 g. of copper bronze, previously activated by the procedure of Kleider and Adams,[19] was added in small enough portions to maintain the low temperature. After all the copper bronze had been added, the reaction mixture was allowed to warm to room temperature and was then heated overnight on a steam bath. The mixture was filtered and made alkaline with sodium hydroxide and was steam distilled. Ether extraction of the steam distillate with a continuous liquid-liquid extractor overnight yielded in extract which, after drying with magnesium sulfate and removal of the ether solvent, distilled as an oil at 95–97° at 7 mm. The yield was 7.7 g., 34%.

General procedure for electrolytic oxidation of quinolines to quinolinic acids. The electrolysis apparatus was constructed from a 1-l. beaker equipped with a stirrer and heated with a hot plate. A conical porous ceramic cup measuring 100 mm. in height with a 60-mm. diameter top was placed in the beaker. The inside of the cup contained a mat of copper turnings in 20% sulfuric acid to serve as a cathode. Around the outside of the cup was wrapped the anode, which in some experiments was a piece of 52-mesh platinum gauze, and in others consisted of highly perforated lead foil that had been previously electrolyzed to obtain a lead oxide surface deposit. The source of direct current was a bank of nickel-cadmium batteries producing a voltage of 12 volts. A 12.5-ohm slide-wire resistor connected in series enabled the system to operate at 3–4 volts and 1–1.5 amp.

The quinoline to be oxidized and 0.1 g. of vanadium pentoxide was dissolved in 75–80% sulfuric acid and the solution was poured into the beaker outside the porous cup. The temperature was maintained from 55–80° by the hot plate, and, at the beginning of the current flow, the solution turned dark. When the electrolysis was complete, the mixture turned a light amber color. The anolyte was then removed and was brought to pH 3 with sodium hydroxide. The sodium sulfate that precipitated was removed by filtration, and at 80° a solution of copper sulfate was added to precipitate the light blue chelate of the quinolinic acid. The washed and dried copper chelate was

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(18) W. J. Boyd and W. Robson, *Biochem. J.*, 29, 555 (1935).

(19) E. C. Kleider and R. Adams, *J. Am. Chem. Soc.*, 55, 4225 (1933).

then suspended in hot water on a steam bath and hydrogen sulfide was passed into the suspension for 3 hr. This was sufficient to convert the copper to its sulfide precipitate, leaving the soluble quinolinic acid in the aqueous solution. Cooling the filtered solution yielded crystals of the quinolinic acid. In some cases, the mother liquor was removed with a flash evaporator to yield significant quantities of the product.

The products were recrystallized from water.

The data listing the temperature, time of reaction, type of anode used, and yield of each of the successful oxidations are shown in Table I.

One exception to this general procedure of work-up was 5-fluoroquinolinic acid. When the original anolyte was brought to pH 3 with sodium hydroxide, the 5-fluoroquinolinic acid precipitated with the sodium sulfate that was produced. In this instance the product was obtained by redissolving the sodium sulfate in water and precipitating the copper chelate from that solution. The 5-fluoroquinolinic acid is noticeably less soluble in water than the other quinolinic acids produced.

Attempted preparation of 5-iodoquinolinic acid. 3-Iodoquinoline was subjected to electrolytic oxidation with a platinum anode as described above. A somewhat shorter time was required than for the other haloquinolines for the solution to turn amber. An aliquot of the anolyte was removed, diluted, and tested with silver nitrate to give a yellow precipitate of silver iodide, indicating that iodine was lost from the substrate during the electrolysis. A copper chelate was formed with the anolyte at pH 3, and from the chelate was obtained, by destruction with hydrogen sulfide and evaporation of the filtered solution, a brown solid. Recrystallization from water after treatment with charcoal yielded a white solid that decomposed around 211° and contained no iodine. The identity of this compound was not ascertained. Analysis is in fair agreement with the hemihydrate of 5-hydroxyquinolinic acid.

Anal. Calcd. for $C_7H_5NO_5\cdot 1/2H_2O\cdot$ C, 43.76; H, 3.15; N, 7.29. Found: C, 43.48; H, 3.40; N, 7.77.

On the assumption that this product was the hydroxyquinolinic acid, an attempt was made to form the acetate ester of the hydroxy group with isopropenyl acetate at reflux. Only starting materials were recovered.

Attempted preparation of 4- and 6-chloroquinolinic acid. When both 2- and 4-chloroquinoline were submitted to electrolytic oxidation, the color changes occurred as with the successful preparations and chelates were obtained with copper. However, liberation of the ligands with hydrogen sulfide yielded red-brown polymers that contained no halogen and resisted recrystallization and further purification.

Attempted preparation of 5-aminoquinolinic acid. Electrolysis of 3-aminoquinoline proceeded with the proper color changes, but failed to yield a chelate with copper in the work-up, and further investigation was abandoned.

Attempted preparation of 6-phenylquinolinic acid. Electrolysis of 2-phenylquinoline produced the proper color changes, but failure of the electrolysis product to yield a copper chelate led to the abandonment of this experiment.

Preparation of 4-methylquinolinic acid. 4-Methylquinoline was oxidized with potassium permanganate according to the method of Hoogewerff and Van Dorp.[2] A product was obtained in 21% yield, m.p. 184–185°; lit., m.p. 187°

Preparation of quinolinic anhydrides. The quinolinic anhydrides were prepared according to the method of Kogan and Shchukina[20] from the quinolinic acids and acetic anhydride containing a drop of phosphoric acid at 60–70° for 6 hr. They were recrystallized from chloroform–carbon tetrachloride mixtures. All the quinolinic anhydrides prepared showed two carbonyl absorption peaks in the infrared spectra one at 1850 cm.$^{-1}$ and the other at 1775 cm.$^{-1}$ These are comparable to those found in the spectrum of phthalic anhydride at 1845 cm.$^{-1}$ and 1775 cm.$^{-1}$ [21] In addition the C—O—C absorption was found to be in all cases close to 1300 cm.$^{-1}$

Friedel-Crafts reactions of the quinolinic anhydrides. Each of the quinolinic anhydrides were allowed to react with benzene and aluminum chloride to form benzoylpyridine carboxylic acids. In all cases the only isomer formed was that which derived from opening of the anhydride linkage in a manner to yield a pyridine-2-carboxylic acid.

3-Benzoylpyridine-2-carboxylic acid was obtained from 9 g. of quinolinic anhydride in 100 ml. of redistilled benzene and 17.7 g. of anhydrous aluminum chloride. The procedure was similar to that described below for the reaction of 5-bromoquinolinic anhydride with benzene. The product was obtained in 53% yield (7.2 g.), m.p. 146–148.5°; lit.,[12] m.p. 147°.

3-Benzoyl-5-bromopyridine-2-carboxylic acid. To 100 ml. of redistilled benzene were added 2.1 g. of 5-bromoquinolinic acid and 2.9 g. of aluminum chloride. The mixture was held at reflux for 24 hr. The reaction mixture was hydrolyzed with dilute hydrochloric acid and the benzene was removed with steam. The remaining solution was heated on a steam bath and a hot concentrated solution of copper sulfate was added to precipitate the copper chelate of the Friedel-Crafts product. The fluffy light blue precipitate was collected and washed with water. A suspension of the chelate in water was decomposed with hydrogen sulfide, filtered to remove copper sulfide, and the remaining solution of the product was evaporated to dryness with a rotary evaporator, yielding 0.7 g. (25%) of 3-benzoyl-5-bromopyridine-2-carboxylic acid. Recrystallization from ethanol gave a product melting at 164.5–165.5°.

The mother liquor from the original copper precipitation of the product was examined for the other possible isomer, 2-benzoyl-5-bromopyridine-3-carboxylic acid. This was accomplished by precipitation of the excess copper and some aluminum hydroxide with sodium hydroxide at pH 9, while additional aluminum hydroxide was removed upon bringing the pH back down to 5 with dilute hydrochloric acid. The filtrate at this point was evaporated to dryness, and the residue of salts was extracted in a Soxhlet extractor with chloroform. Evaporation of the chloroform from the extract yielded a few milligrams of a solid that proved to be 3-benzoyl-5-bromopyridine-2-carboxylic acid (that had escaped chelation with the copper) from examination of the infrared spectrum and melting point.

3-Benzoyl-5-chloropyridine-2-carboxylic acid was prepared in 31% yield from 5-chloroquinolinic acid and benzene by a procedure almost identical with that above for 3-benzoyl-5-bromopyridine-2-carboxylic acid. Only the 3-benzoyl isomer was obtained, m.p. 140–141°.

3-Benzoyl-5-fluoropyridine-2-carboxylic acid was prepared from 5-fluoroquinolinic acid by a procedure almost identical with that above for the corresponding bromo compound. Only the one isomer was obtained in 32% yield, m.p. 136–137°.

3-Benzoyl-4-methylpyridine-2-carboxylic acid was prepared in the same manner as those carboxylic acids above in 25% yield, m.p. 172–173°. Only the one isomer was obtained.

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CHAPEL HILL, N. C.

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[20] I. M. Kogan and L. A. Shcukina, *J. Applied. Chem. (U.S.S.R.)*, **19**, 925 (1946); *Chem. Abstr.*, **42**, 572 (1948).

[21] L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, New York, 1958, p. 128.