some small nitrogen peroxide concentration. This corresponds rather well with the observations of Foord and Norrish.[17]

5. Induction Periods and Explosion Limits with Varying Oxygen and Inert Gas Pressures.— As has been stated in Part I[2] of this investigation, the third body in reaction c must be either O_2 or inert gas. The rate of reaction d is governed by diffusion and is therefore proportional to $1/(M)$. ϕ thus becomes a quadratic function of both the concentrations of O_2 and inert gas. On varying, for instance, the O_2 pressure and keeping the H_2 and NO_2 pressures constant, two explosion limits are obtained, and the induction periods follow a curve similar to that shown in Fig. 1 in agreement with the observations of Foord and Norrish.[18] Furthermore, Foord and Norrish[5] have established the existence of an upper explosion limit for added N_2 and A. The experiments were not carried to the range where the lower explosion limit is expected to appear.

(17) Ref. 5, Fig. 3, p. 204.
(18) Ref. 5, Fig. 6, p. 207.

Summary

If the explosion condition is formulated on the basis of the thermal theory it is not possible to find any plausible specific reaction mechanism that describes the effect of pressure and mixture composition on the upper critical NO_2 concentration. This includes the mechanism proposed by Foord and Norrish.

In a previous publication, the isothermal branched-chain theory was used to derive a specific reaction mechanism consistent with the trend of the critical concentrations. This mechanism is now extended to describe the observations of Foord and Norrish on the induction periods in the explosive and non-explosive reaction and related observations. This furnishes a complete description of the experimental data and thus allows a decision to be made in favor of the isothermal branched-chain theory of explosion.

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Utilization of Aryloxy Ketones in the Synthesis of Quinolines by the Pfitzinger Reaction[1]

BY PAUL K. CALAWAY[2,3] WITH HENRY R. HENZE

Although the utilization of aldehydes and ketones in the synthesis of quinoline derivatives has been studied frequently, no attempt appears to have been made to use keto ethers in this manner. We have been interested in the possibility of converting such substituted ketones into substituted quinoline acids which might have value as anti-malarials.

The availability of isatin and of four aryloxy ketones suggested employing the method of Pfitzinger[4] in the production of cinchoninic acids with substituents in the 2- or 2,3-positions. Through this procedure from an unsymmetrical ketone, RCH_2COCH_2R', two isomeric products might be obtained, the mechanism of reaction having been formulated as shown.[5]

Thus, while the utilization of methyl ethyl ketone has resulted chiefly in the production of 2,3-dimethylcinchoninic acid,[4c] the simultaneous formation of 2-ethylcinchoninic acid has been established.[6] Since the keto ethers available were aryloxyacetones, no experience was at hand from which to predict with certainty whether the chief product of their reaction, by means of the Pfitzinger procedure, would be the 2-aryloxymethyl or the 2-methyl-3-aryloxycinchoninic acid.

We have studied the condensation of isatin with phenoxyacetone, α- and β-naphthoxyacetone and thymoxyacetone, respectively. The product in each instance has been shown to be the 3-aryloxy-4-quinaldinecarboxylic acid. The

(1) Presented before the Division of Organic Chemistry at the 97th meeting of the American Chemical Society at Baltimore, Md., April 3–7, 1939.
(2) From the Ph.D. dissertation of Paul K. Calaway, June, 1938.
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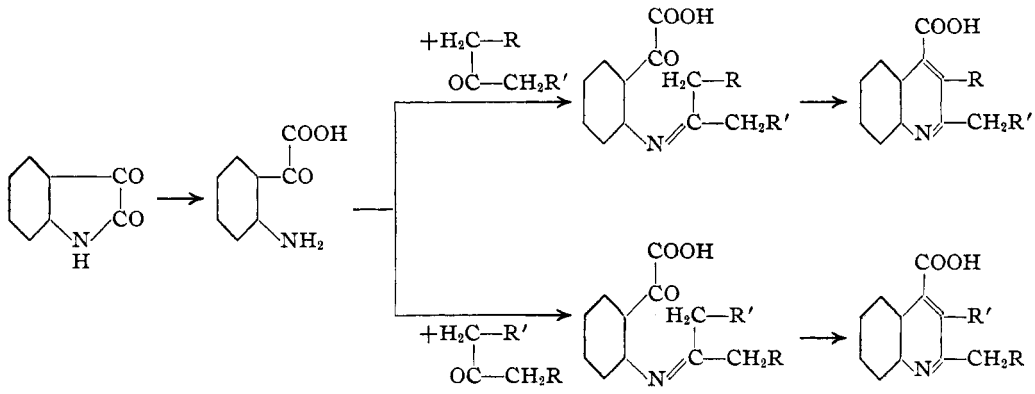
(4) Pfitzinger, (a) *J. prakt. Chem.*, **33**, 100 (1886); (b) *ibid.*, **38**, 582 (1888); (c) *ibid.*, **56**, 283 (1897).
(5) Halberkann, *Ber.*, **54**, 3090 (1921).
(6) Von Braun, Gmelin and Schultheiss, *ibid.*, **56**, 1344 (1923).



cinchoninic acids are surprisingly resistant to reduction by means of concentrated hydriodic acid and red phosphorus. It has been possible to decarboxylate these acids, yielding new 3-aryloxyquinaldines; likewise, decarboxylation occurs upon attempts to cleave the ether linkage and 3-hydroxyquinaldine is formed. In order to study further the behavior of these 3-aryloxyquinoline derivatives, 3-(1-naphthoxy)-4-quinaldinecarboxylic acid was selected as being typical and was shown to be capable of phthalonation; when subjected to nitration, substitution takes place in the naphthalene nucleus.

Experimental

Preparation of Phenoxyacetone.[7]—A mixture of 47 g. of phenol (0.5 mole) and 300 cc. of benzene was introduced into a one-liter, three-necked, round-bottomed flask equipped with an efficient mercury-sealed, mechanical stirrer, a dropping funnel, and a condenser. The stirrer was started and 11 g. of finely divided sodium was added over a period of several hours. The mixture was heated then on a steam-bath until all the sodium had reacted. After cooling, 68.5 g. of bromoacetone (0.5 mole) was dropped in and the mixture heated again to complete the reaction. The sodium bromide was removed by filtration and the benzene by distillation under diminished pressure. The residual liquid was fractionated and 40 g. of phenoxyacetone (53% yield) was obtained as a colorless oil boiling at 115° (12 mm.).

Anal. Calcd. for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.70; H, 6.87.

Preparation of 1-Naphthoxyacetone.[8]—In preparing this ketone, sodium hydroxide was dissolved in water and treated in order with equimolar quantities of α-naphthol and bromoacetone, causing the separation of the crude naphthoxyacetone as an oil. The latter was taken up in ether, shaken repeatedly with sodium hydroxide solution, freed from ether, diluted with acetone, and again washed with warm alkaline solution. Addition of much water caused the separation of the naphthoxyacetone which was dissolved in alcohol and the solution clarified with Norite. After removal of the alcohol under diminished pressure the viscous oil was dried for several days over calcium chloride in a vacuum desiccator, since the product tends to decompose upon distillation.

Anal. Calcd. for $C_{13}H_{12}O_2$: C, 77.97; H, 6.04. Found: C, 77.74; H, 6.18.

Preparation of 2-Naphthoxyacetone.[8]—This compound was prepared similarly to its isomer, but could be purified more simply by crystallization from alcohol; m. p. 78.4° (corr.).

Anal. Calcd. for $C_{13}H_{12}O_2$: C, 77.97; H, 6.04. Found: C, 78.02; H, 6.12.

Preparation of Thymoxyacetone.—Into a mixture of 13.33 g. of sodium hydroxide (0.33 mole), 50 g. of thymol (0.33 mole) and 150 cc. of water was dropped 46 g. of bromoacetone (0.33 mole) over a period of one hour. As the reaction proceeded a brown oil separated from solution. After reaction was complete the solution was made strongly alkaline with sodium hydroxide and subjected to steam distillation. The thymoxyacetone distilling over was separated and dried over calcium chloride before being fractionated. The portion boiling at 115–117° (3 mm.) was obtained as a colorless oil with a sweet, pungent odor. The yield was 65% of the theoretical.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.48; H, 9.00.

Preparation of 3-Phenoxy-4-quinaldinecarboxylic Acid.—Thirty-seven grams of isatin (0.25 mole) was dissolved in 175 g. of 33% aqueous potassium hydroxide solution. Then 37.5 g. of phenoxyacetone (0.25 mole) was added and the mixture was heated under reflux on a steam-bath. After about two hours the ketone had dissolved but the heating was continued for twenty hours. The reaction mixture was diluted with water to a volume of 400 cc., boiled with Norite and filtered. The filtrate was cooled to 0° and made barely acid by addition of acetic acid. The light brown solid which separated was filtered, washed with water and dried over calcium chloride. The crude product weighed 61 g. (81% yield) and melted at 243°. The acid was recrystallized from alcohol, dissolved in alkaline solution, again treated with Norite, and reprecipitated by dilute acetic acid. The purified 3-phenoxy-4-quinaldinecarboxylic acid was obtained as a colorless solid which melted at 259.4° (corr.) (dec.).

Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.10; H, 4.69; N,

(7) Stoermer, *Ber.*, **28**, 1253 (1895), had synthesized this compound but by a more tedious and less satisfactory method. He reported b. p. 229–230° (uncorr.).

(8) Stoermer, *Ann.*, **312**, 313 (1900).

5.01; neut. equiv., 279.3. Found: C, 73.01; H, 4.80; N, 5.13; neut. equiv., 277.8.

Preparation of 3-(1-Naphthoxy)-4-quinaldinecarboxylic Acid.—A mixture of 24 g. of 1-naphthoxyacetone (0.12 mole) and 17.5 g. of isatin (0.12 mole) dissolved in 75 g. of 33% potassium hydroxide solution was heated on a steam-bath for twenty hours. A considerable amount of a white solid (the potassium salt of the quinaldinecarboxylic acid) separated and was filtered, washed with cold water and dried over calcium chloride. The filtrate was diluted with water to a volume of 175 cc., boiled with Norite, filtered, cooled to 0°, and acidified with acetic acid; a yellow solid separated, which, after drying, weighed 15 g. An additional 12 g. of purer acid was obtained from the potassium salt. The total weight of acid represented a 68% yield. After purification by recrystallization from alcohol, 3-(1-naphthoxy)-4-quinaldinecarboxylic acid was obtained as a colorless solid melting at 265.5° (corr.) (dec.).

Anal. Calcd. for $C_{21}H_{15}NO_3$: C, 76.58; H, 4.59; N, 4.25; neut. equiv., 329.3. Found: C, 76.80; H, 4.54; N, 4.37; neut. equiv., 327.0.

Preparation of 3-(2-Thymoxy)-4-quinaldinecarboxylic Acid.—To 14.7 g. of isatin (0.10 mole) dissolved in 100 cc. of 33% potassium hydroxide solution was added 20.6 g. of thymoxyacetone and the mixture was heated for thirty-six hours on a steam-bath. After acidification with dilute acetic acid, some unreacted thymoxyacetone and isatin as well as the desired carboxylic acid separated from solution. The ketone was removed by filtration and the isatin by repeated extraction with boiling water. The purified product, weighing 10 g. (33% yield), is a colorless solid of melting point 228° (corr.) (dec.).

Anal. Calcd. for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.17. Found: C, 74.95; H, 6.30; N, 4.47.

Attempted Reduction of the Quinaldinecarboxylic Acid with Hydriodic Acid and Red Phosphorus.—The behavior of 3-phenoxy-4-quinaldinecarboxylic acid was typical also of the two naphthoxy analogs. A mixture of 12 g. of the acid, 12 g. of red phosphorus and 120 cc. of hydriodic acid (sp. gr. 1.7) was heated under reflux on an oil-bath to 145–150° for twenty-four hours. The hot reaction mixture was filtered from phosphorus, the hydriodic acid separated by steam distillation, and the residual solution was evaporated to half-volume. On cooling there separated the unchanged carboxylic acid.

Preparation of 3-Aryloxyquinaldines.—The decarboxylation of the phenoxy acid was typical of that of the two naphthoxy analogs. Twelve grams of 3-phenoxy-4-quinaldinecarboxylic acid was heated in a Claisen distilling flask on an oil-bath at 250–260°. At this temperature the acid melted and carbon dioxide was liberated from the mass. After the effervescence had ceased the liquid was distilled under diminished pressure. A heavy oil distilled at 130–140° (8–10 mm.) and, after treatment with dilute sodium hydroxide solution, solidified; yield, 4 g. (40%), m. p. 72.2° (corr.). The product, 3-phenoxyquinaldine, is soluble in alcohol and ether, and insoluble in water.

Anal. Calcd. for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.96. Found: C, 81.68; H, 5.54; N, 6.10.

Five grams of 3-(1-naphthoxy)-4-quinaldinecarboxylic acid was heated at 265° and yielded 2 g. of 3-(1-naphthoxy)-quinaldine (47% yield), m. p. 102° (corr.).

Anal. Calcd. for $C_{20}H_{15}NO$: C, 84.18; H, 5.30; N, 4.91. Found: C, 84.35; H, 5.42· N, 4.99.

From 2 g. of 3-(2-naphthoxy)-quinaldinecarboxylic acid there was obtained 0.9 g. of 3-(2-naphthoxy)-quinaldine (50% yield); m. p. 95–96.5° (corr.).

Anal. Calcd. for $C_{20}H_{15}NO$: C, 84.18; H, 5.30; N, 4.91. Found: C, 84.25; H, 5.69; N, 5.00.

In an attempted reduction of 3-phenoxyquinaldine with hydriodic acid, the hydroiodide of this quinoline was formed and no reduction occurred. The yellow hydriodide of 3-phenoxyquinaldine melts at 126–130° (corr.). Treatment of this salt with sodium hydroxide solution resulted in the regeneration of 3-phenoxyquinaldine.

Anal. Calcd. for $C_{16}H_{13}NO\cdot HI$: N, 3.86. Found: N, 4.13.

Preparation of 3-Hydroxyquinaldine.—Five grams of 3-(1-naphthoxy)-4-quinaldinecarboxylic acid and 25 cc. of concd. hydrochloric acid were heated together in a sealed tube for fifteen hours at 220°. The reaction mixture was filtered, the filtrate diluted with water, cooled in ice, and barely neutralized with sodium hydroxide. The solid which separated was redissolved in hot sodium hydroxide solution, treated with Norite, and reprecipitated with dilute hydrochloric acid. The colorless precipitate was filtered, dried in the oven for one hour at 110°, and its melting point determined. The compound darkened at 240° and melted at 259.6° (corr.). The solid was identified by a mixed melting point [260° (corr.)] with an authentic sample of 3-hydroxyquinaldine.[9] The yield of purified product was 1 g., corresponding to 40% of the theoretical.

Picration of 3-Aryloxyquinaldines.—The three aryloxyquinaldines, when dissolved in hot alcohol and poured into a saturated aqueous solution of picric acid, yielded yellow, solid picrates.

Picrate of	M. p. °C. (corr.)	Nitrogen, % Calcd.	Found
3-Phenoxyquinaldine	192–193	12.07	12.36
3-(1-Naphthoxy)-quinaldine	208–209	10.89	10.74
3-(2-Naphthoxy)-quinaldine	205.8–206.8	10.89	10.77

Preparation of the Phthalone of 3-(1-Naphthoxy)-4-quinaldinecarboxylic Acid.—Three grams of phthalic anhydride and 6.5 g. of 3-(1-naphthoxy)-4-quinaldinecarboxylic acid were mixed intimately and heated in a distilling flask on an oil-bath at 200–210° for five hours. The mass was dissolved in concd. sulfuric acid and poured over chipped ice. A brown solid separated and was recrystallized from acetic acid to yield the deep-orange colored phthalone, melting at 243–245° (corr.).

Anal. Calcd. for $C_{29}H_{17}NO_5$: C, 75.81; H, 3.73; N, 3.05. Found: C, 75.85; H, 4.06; N, 2.78.

Nitration of 3-(1-Naphthoxy)-4-quinaldinecarboxylic Acid.—A mixture of 300 cc. of water, 300 cc. of concd. nitric acid, and 3 g. of 3-(1-naphthoxy)-4-quinaldinecarboxylic acid was heated, with stirring, on a steam-cone for two hours. The greater part of the acid dissolved and the

(9) Koenigs and Stockhauser, *Ber.*, **35**, 2556 (1902), report m. p. at 260° with softening at 240°.

solution assumed a reddish-brown color. The mixture was removed from the cone, a small volume of concd. nitric acid was added to complete the solution of the solid, and the solution was boiled for five minutes. The reaction mixture was diluted with water and cooled in an ice–salt mixture, causing the separation of a yellow solid which melted with decomposition at 210–213°. The compound was dissolved in sodium hydroxide solution, treated with Norite, cooled, and reprecipitated with dilute acetic acid. The bright yellow solid obtained, after drying in an oven for ten hours at 105°, melted sharply at 221° (corr.) (dec.).

Anal. Calcd. for $C_{21}H_{14}N_2O_5$: C, 67.38; H, 3.75; N, 7.49. Found: C, 67.39; H, 4.04; N, 7.39.

Two grams of this nitrated product and 15 cc. of concd. hydrochloric acid were heated together in a sealed tube for six hours at 210°. The reaction mixture was filtered and the filtrate poured into 250 cc. of ice water, causing the separation of a light brown solid. The latter was purified by solution in sodium hydroxide solution, treatment with Norite, and reprecipitation with dilute hydrochloric acid. The melting point of the product, which could be shown to be a nitrophenol, was found to be 163° (corr.). A mixed melting point with an authentic sample of 1-hydroxy-4-nitronaphthalene[10] was unchanged.

Anal. Calcd. for $C_{21}H_{14}N_2O_5$: C, 67.37; H, 3.77; N, 7.49. Found: C, 67.39; H, 4.04; N, 7.39.

The hydrochloric acid filtrate, from which the nitronaphthol had separated, was next examined in order to isolate the other cleavage product. Much of the acid present was neutralized with sodium hydroxide and the solution was concentrated to a small volume by evaporation. A colorless solid, evidently a hydrochloride, separated and was filtered and redissolved in a small volume of water. The addition of sodium hydroxide solution caused the formation of a copious precipitate. The latter was washed, dried, and identified by its melting point behavior and by an unchanged mixed melting point with authentic 3-hydroxyquinaldine.

Since 1-hydroxy-4-nitronaphthalene and 3-hydroxyquinaldine were thus obtained as cleavage products by the action of concd. hydrochloric acid on the product of nitration, the latter may be formulated as 3-(4-nitro-1-naphthoxy)-4-quinaldinecarboxylic acid.

(10) Andreoni and Biedermann, *Ber.*, **6**, 343 (1873), report m. p. 164°.

Summary

1. Pfitzinger's method has been extended to include the utilization of aryloxy ketones in the initial synthesis of four examples of a new type of substituted cinchoninic acid. The structure of one of these acids has been elucidated through a study of its degradation products, and the structures of the remaining acids have been formulated on the basis of analogy.

2. These quinaldine carboxylic acids, and the aryloxyquinaldines formed by their decarboxylation, resist reduction by means of concd. hydriodic acid and red phosphorus.

3. The phthalone of 3-(1-naphthoxy)-4-quinaldinecarboxylic acid has been prepared.

4. Nitration of the 1-naphthoxyquinoline derivative occurs in the naphthalene nucleus in the position para to the oxygen linkage.

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Fluorenones and Diphenic Acids. VIII.[1,2] The Ring Cleavage of Fluorenone-4-carboxylic Acids

BY ERNEST H. HUNTRESS AND MARGARET K. SEIKEL[3]

The earliest instance of the rearrangement of substituted fluorenones under the influence of concentrated sulfuric acid was that of 1,6-dichlorofluorenone-5-carboxylic acid (I) into the isomeric 1,6-dichlorofluorenone-4-carboxylic acid (III).[4,5] If the mechanism of this rearrangement were to involve the successive addition and subtraction of water, the intermediate product would be an isophthalic acid derivative (II). A sample of this hitherto unreported acid was therefore desired for an examination of its properties, particularly with respect to its behavior in concentrated sulfuric acid. Since the opening of the ketonic ring of the dichlorofluorenones themselves by means of fusion with potassium hydroxide in diphenyl ether had been accomplished successfully[6] it seemed possible that the same procedure might be applied

(1) For Article VII of this series see Huntress and Seikel, THIS JOURNAL, **61**, 1066 (1939).

(2) Presented before the Division of Organic Chemistry, Baltimore Meeting of the American Chemical Society, April, 1939.

(3) This paper is constructed from part of a dissertation submitted by Miss Seikel to the Faculty of the Massachusetts Institute of Technology in partial fulfilment of the requirements of the degree of Doctor of Philosophy, June, 1938.

(4) Huntress, Cliff and Atkinson, THIS JOURNAL, **55**, 4262–4271 (1933).

(5) Huntress and Atkinson, *ibid.*, **58**, 1514–1518 (1936).

(6) Huntress and Seikel, THIS JOURNAL, **61**, 1066 (1939).