the distillate in 50 ml. of pentane was again washed with sodium thiosulfate solution, water, and concentrated. Slow distillation of the residue in a short-path still at 0.5 mm. with a heating block temperature of 170° yielded 1.71 g. (82%) of a mixture of 1,3- and 2,4-diphenylcyclooctenes as a viscous liquid, $n^{25}D$ 1.5954.

Anal. Calcd. for $C_{20}H_{22}$: C, 91.55; H, 8.45. Found: C, 91.23; H, 8.51.

1,3-Diphenylcyclooctane (V).—A solution in 10 ml. of acetic acid of 0.466 g. of the mixture of 1,3- and 2,4-diphenylcyclooctenes described above was hydrogenated at room temperature and atmospheric pressure in the presence of 0.45 g. of 10% palladium on Norit. Reduction was complete in 45 minutes and resulted in absorption of 102% of one molar equivalent of hydrogen. The catalyst was separated, washed with acetic acid and pentane, and the filtrates were washed with water and sodium carbonate solution to remove acetic acid. Concentration of the pentane solution yielded 0.456 g. of a mixture of *cis*- and *trans*-1,3-diphenylcyclooctanes as an oil which solidified; m.p. 54–66°. The mixture was fractionally crystallized from methanol, and after nine crystallizations the least soluble isomer had m.p. 83.5–85.8° and mixed m.p. with a sample prepared by hydrogenation of 2,4-diphenylcycloöcta-1,4-diene[3] (m.p. 83.6–85.1°) of 83.2–85.8°. Recrystallization of the more soluble isomer obtained from the mother liquors yielded a slightly impure sample, m.p. 56–60° and mixed m.p. with a sample obtained by hydrogenation of 2,4-diphenylcyclooctene[3] (m.p. 60.6–61.0°) of 56.5–60°.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BOSTON COLLEGE]

A Study of the Camps Synthesis of 4-Hydroxy-3-quinolinecarboxylic Acid

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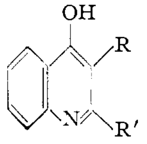
The Camps synthesis of 4-hydroxy-3-quinolinecarboxylic acid from ethyl *o*-formamidophenylpropiolate has been duplicated. The crude reaction product contained, in addition, appreciable amounts of 4-hydroxycarbostyril. The identity of each compound was established by comparison with the corresponding authentic sample. Improved procedures for the preparation of intermediates in the synthesis have been devised. Homer's proposal of intramolecular loss of water from 4-hydroxy-3-quinolinecarboxylic acid on heating to yield a β-lactone has not been substantiated.

During his investigation on the structure of kynurenic acid, Camps[2] claimed to have synthesized 4-hydroxy-3-quinolinecarboxylic acid (I) and an isomer, 4-hydroxy-2-quinolinecarboxylic acid (II). Heating of ethyl *o*-formamidophenylpropiolate (V) under reflux with sodium hydroxide in aqueous ethanol was reported to give I, while similar alkaline treatment of *o*-ethoxalylaminoacetophenone yielded II. Structure I was assigned to kynurenic acid.



I, R = COOH, R′ = H
II, R = H, R′ = COOH

Subsequently, Homer[3] prepared highly purified samples of natural kynurenic acid and showed that this substance was represented correctly by structure II and not by structure I. She successfully duplicated Camps' synthesis of II, but her attempts to prepare I by his method led to the isolation of a material whose structure was not conclusively established. Following the Camps procedure, Homer found that formylation of ethyl *o*-aminophenylpropiolate (IV) with anhydrous formic acid in ether gave little or no yield of V. Attempted conversion of V to I afforded a material whose melting point and quantitative elemental analysis differed from the expected values.

Recently, Schofield and Simpson[4] abandoned their efforts to prepare I by the Camps route because of the difficulty encountered in preparing the starting materials. In their hands, esterification of *o*-aminophenylpropiolic acid (III) by the procedure of Baeyer and Bloem[5] yielded primarily a substance believed to be 4-chlorocarbostyril. Moreover, formylation of IV by the Camps method failed. In the light of these facts, a reinvestigation of the Camps synthesis of 4-hydroxy-3-quinolinecarboxylic acid (I) seemed appropriate.[6]

The esterification of III by the procedure of Baeyer and Bloem[5] was modified by us so as to give 60% yields of purified IV consistently. In this modification III was added to a cold, freshly prepared, saturated ethanolic hydrogen chloride solution, the suspension gently warmed until solution occurred, and the reaction mixture kept at 0° overnight. The unmodified procedure[5] gave poor yields (3%) as observed by Schofield and Simpson[4] and by us. The ester IV was also obtained by us by reaction of III with ethereal diazoethane, but the yields were erratic (20–60%).

We were unable to convert IV to ethyl *o*-formamidophenylpropiolate (V) with anhydrous formic acid in dry ether at 0°. Camps[2] reported a 70% yield of purified V under these conditions. Attempted formylation of IV by heating either under reflux or in a sealed tube with ethanolic ethyl formate[7] led only to the recovery of the starting material. The desired formyl derivative V was finally obtained in reproducible high yield (70–87%) by treatment of an anhydrous ethereal solution of IV with mixed formic–acetic anhydride.

Heating V under reflux with sodium hydroxide in aqueous ethanol according to the Camps pro-

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[1] Abstracted in part from the M.S. theses of William J. Reid and Donald J. Torres.

[2] R. Camps, *Ber.*, **34**, 2703 (1901); *Z. physiol. Chem.*, **33**, 390 (1901).

[3] A. Homer, *J. Biol. Chem.*, **17**, 509 (1914); *cf.* also E. Späth, *Monatsh.*, **42**, 91 (1921).

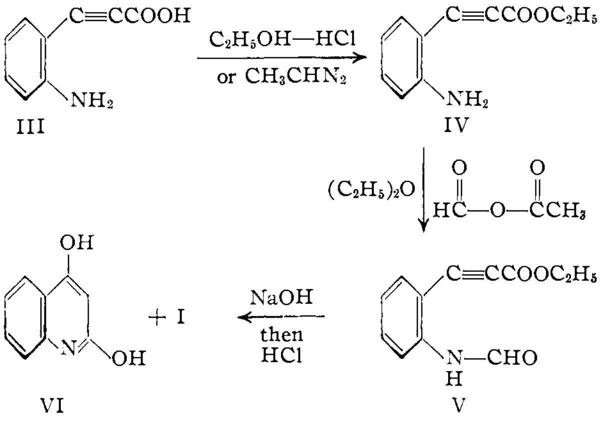
[4] K. Schofield and J. C. E. Simpson, *J. Chem. Soc.*, 1033 (1946).

[5] A. Baeyer and F. Bloem [*Ber.*, **15**, 2147 (1882)] prepared IV by bubbling hydrogen chloride into an ethanolic suspension of III at low temperature; few details were given, however.

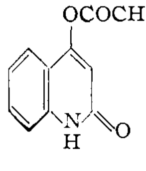
[6] *Cf.* A. W. Johnson, "The Chemistry of the Acetylenic Compounds," Vol. II, Edward Arnold and Co., London, 1950, p. 106, for a more detailed summary of the historical background of this investigation.

[7] J. P. E. Human and J. A. Mills, *J. Chem. Soc.*, 1457 (1948).

cedure afforded a product which was shown to be an approximately 2:1 mixture of 4-hydroxy-3-quinolinecarboxylic acid (I) and 4-hydroxycarbostyril (VI), respectively. The quinolines were separated readily by crystallization from absolute ethanol.[8]



The identity of I was established by comparison with an authentic sample of 4-hydroxy-3-quinolinecarboxylic acid prepared from aniline and ethoxymethylenemalonic ester.[9] Both samples had identical infrared absorption spectra (Nujol mull) and no depression of the melting point of a mixture of the two was observed. The ethyl ester of I as well as the decarboxylation product from I, kynurin (4-hydroxyquinoline), were compared with the corresponding authentic samples[9] and found to be identical. All attempts to prepare an acetyl derivative of I with acetic anhydride either alone, or in the presence of pyridine or concentrated sulfuric or phosphoric acids, were unsuccessful. Heating I with acetyl chloride for several hours at reflux temperature gave unchanged starting material. It is of interest to note that Simpson[10] was similarly unable to prepare an acetyl derivative of the ethyl ester of I (made by the ethoxymethylenemalonic ester synthesis). The identity of 4-hydroxycarbostyril (VI) was established by conversion to the lower melting (mono) acetyl derivative, which gave no depression of the melting point on admixture with an authentic sample.[11] In addition, the infrared absorption spectra (chloroform solution) of both substances were identical and showed two strong bands, one at $5.70\ \mu$ (characteristic of O-acetyl) and the other at $6.03\ \mu$ (possibly characteristic of δ-lactam carbonyl). A reasonable structure for the (mono) acetyl derivative of 4-hydroxycarbostyril (VI), compatible with this infrared evidence, would be VII.



VII

Homer[3] reported the isolation of a substance from alkaline treatment of V by the Camps procedure[2] whose elemental analysis was consistent with a monohydrate of 4-hydroxy-3-quinolinecarboxylic acid (I). The molecule of water survived two recrystallizations from ethanol and drying at 120°. The melting point of this material was 235–265° and on gentle heating to 270° yielded a sublimate (no analysis reported) melting sharply at 250°; no evolution of carbon dioxide was observed. On the other hand, strong heating of the substance melting at 235–265° afforded carbon dioxide and a new sublimate, m.p. 202°, believed by Homer to be kynurin (no analysis given due to scarcity of material). Both the original product, m.p. 235–265°, and the sublimate, m.p. 202°, gave a positive Jaffe color reaction[12] for a 4-hydroxyquinoline, whereas the sublimate melting at 250° did not do so, unless first warmed with dilute aqueous sodium hydroxide. On the basis of these observations, Homer proposed that 4-hydroxy-3-quinolinecarboxylic acid (I) could be decomposed thermally in two ways. (I) can either lose carbon dioxide to give kynurin or lose a molecule of water intramolecularly from the hydroxyl and carboxyl functions to yield a β-lactone. This latter suggestion appears to be untenable from steric grounds because the β-lactone would be expected to have considerable double-bond character in the α,β-position. In our hands, ring closure of V in alkaline solution always afforded a mixture of I and VI. We found no evidence for a hydrated form of I under the conditions reported by Homer. Quantitative studies on the effect of heat on I showed nearly the theoretical amounts (94%) of carbon dioxide were always evolved. No evidence of elimination of water was ever obtained during the pyrolyses; the residues appeared to consist solely of kynurin. Vacuum sublimation of I at 170–235° and 0.5 mm. yielded the original compound unchanged.

Experimental[13]

Ethyl o-Aminophenylpropiolate (IV).—To 200 ml. of commercial absolute ethanol, freshly saturated with hydrogen chloride at 0° under anhydrous conditions, was added 10.0 g. (0.062 mole) of *o*-aminophenylpropiolic acid.[14] When the reaction mixture had warmed slightly by standing at room temperature for several minutes a vigorous reaction set in which was quenched by cooling the reaction vessel in a salt-ice-bath. Further gentle warming of the reactants gave a clear brown solution which was refrigerated overnight. The reaction mixture was diluted with an equal volume of cold water and made basic to litmus by adding with good cooling a saturated solution of sodium carbonate. Cooling the mixture 2 hours afforded 7.0 g. (60%) of ethyl *o*-aminophenylpropiolate (IV), after one recrystallization from petroleum ether (b.p. 30–65°), as light lemon-colored needles, m.p. 55.2–56.0° (lit.[5] m.p. 55°). Reproducible yields of 60% were obtained in four preparations.

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[8] Camps (reference 2) reported that 4-hydroxycarbostyril (VI) could be detected in the reaction product by the Friedländer color test [P. Friedländer and A. Weinberg, *Ber.*, **15**, 2683 (1882)], but made no mention of having isolated the purified compound. He advanced an explanation of the origin of VI based on the reasonable assumption that under the alkaline conditions of the reaction some ethyl *o*-aminobenzoylacetate (or the free acid) was formed which would be expected to undergo cyclization.

[9] R. G. Gould and W. A. Jacobs, THIS JOURNAL, **61**, 2890 (1939); B. Riegel, *et al.*, *ibid.*, **68**, 1264 (1946).

[10] J. C. E. Simpson, *J. Chem. Soc.*, 1035 (1946); 1104 (1950).

[11] J. N. Ashley, W. H. Perkin and R. Robinson, *ibid.*, 388 (1930).

[12] M. Jaffe, *Z. physiol. Chem.*, **7**, 399 (1883).

[13] Melting points are corrected and were taken in open capillaries. Infrared measurements were made using a Baird double beam recording spectrophotometer, equipped with a sodium chloride prism. Analyses were performed by Dr. Carol K. Fitz, Needham Heights, Mass.

[14] A. Baeyer, *Ber.*, **13**, 2254 (1880); K. Schofield and J. C. E. Simpson, *J. Chem. Soc.*, 512 (1945).

Ethyl *o*-Formamidophenylpropiolate (V).—Anhydrous formic acid was prepared by distilling the commercial product (98–100%) from phthalic anhydride.[15] Mixed formic–acetic anhydride was made by the procedure described by Clemo and Swan.[16] To a solution of 4.0 g. (0.021 mole) of ethyl *o*-aminophenylpropiolate in 100 ml. of sodium-dried ether was added with moderate cooling 3.2 ml. of mixed formic–acetic anhydride. After standing at room temperature overnight, the solution was concentrated under a stream of nitrogen while warming in a bath at 30–35°. The resultant straw-colored oil, which usually solidified on standing for several hours at room temperature, was dissolved in the minimum volume of boiling 55% ethanol, the solution heated with Norit, filtered and the filtrate refrigerated overnight. Filtration gave 3.2 g. (70%) of V as long, white, felted needles, m.p. 78–79.5°, sufficiently pure for use in the following reaction. The average yield in four preparations was 76%. The analytical sample was recrystallized successively from 50% ethanol (twice) and petroleum ether (b.p. 30–65°) to give m.p. 78.5–79.5°.

Anal. Calcd. for $C_{12}H_{11}O_3N$: C, 66.34; H, 5.11. Found: C, 66.3; H, 5.1.

Camps[2] reported m.p. 83° for V prepared, in a yield corresponding to 70%, from IV and anhydrous formic acid in ether solution at 0°. His procedure was completely unsuccessful in our hands.

Reaction of Ethyl *o*-Formamidophenylpropiolate (V) with Sodium Hydroxide in Aqueous Ethanol. A. 4-Hydroxy-3-quinolinecarboxylic Acid (I).—In a 1-l. three-necked flask equipped with a stirrer, a condenser and a dropping funnel was placed a solution of 4.0 g. (0.018 mole) of ethyl *o*-formamidophenylpropiolate in 71 ml. of commercial absolute ethanol. The stirred, light-green solution was warmed in an oil-bath at 70°, and 494 ml. of water was added dropwise over a 30-minute period. During the addition the temperature of the heating bath was raised gradually so that, as the last of the water was being added, the solution was refluxing. Sodium hydroxide (8.24 g., 0.21 mole) in 82 ml. of water was added to the stirred, boiling solution, which thereupon displayed a strong, greenish-blue fluorescence. After being heated under reflux for 2 hours, the solution, which had turned light green, was cooled in an ice-bath and freed of a small amount of flocculent material by filtration. The filtrate was made acidic to congo red with 20% hydrochloric acid. After refrigeration of this mixture, the product was collected by filtration, washed with a small volume of cold water, and dried at 100° for 1 hour. The cream-colored material (mixture of I and VI) weighed 2.2 g. and yielded 1.1 g. (32%) of 4-hydroxy-3-quinolinecarboxylic acid (I) as white needles after recrystallization from 500 ml. of absolute ethanol (Norit), m.p. 263.0–263.5° dec. The ethanolic mother liquor was saved. A second recrystallization of I from ethanol had no effect on the m.p. The analytical sample was dried at 100° and 0.1 mm. for 5 hours in the presence of phosphorus pentoxide.

Anal. Calcd. for $C_{10}H_7O_3N$: C, 63.45; H, 3.73; N, 7.40; neut. equiv., 189.2. Found: C, 63.6; H, 3.8; N, 7.4; neut. equiv., 190.0.

The m.p. of an authentic specimen of 4-hydroxy-3-quinolinecarboxylic acid (from aniline and ethoxymethylenemalonic ester)[9] was 263.5–264.0° dec., and mixed m.p. with I obtained from V was 263.5–264.0° dec. The m.p. was found to be a function of the rate of heating. Both I and the authentic sample, in ethanol solution, gave faint orange-red colorations with dilute aqueous ferric chloride (different from blank!). The authentic sample of I and that obtained from V had identical infrared spectra (Nujol mull). The average yield of purified I in two preparations was 27%. Camps[2] reported m.p. 263° for crude I (90% yield) and m.p. 266–267° for a purified sample of I.

A sample of I was decarboxylated by heating at 285° to 4-hydroxyquinoline (kynurin), which was recrystallized from a mixture of acetone and petroleum ether (b.p. 30–65°); m.p. 201–202°, not depressed on admixture with an authentic specimen.[9] An aqueous solution of kynurin (from the pyrolysis of I) was colored blood-red on addition of 10% ferric chloride; same for authentic sample.

The ethyl ester of I was prepared by boiling under reflux for 6 hours a mixture of 55 mg. of I, 10 ml. of commercial absolute alcohol and six drops of concentrated sulfuric acid. The cooled solution was concentrated almost to dryness under a stream of nitrogen and the residue slurried with 10 ml. of cold 10% sodium carbonate. The solid was collected by filtration and recrystallized from ethanol. The yield of white crystalline product was 19 mg. (30%), m.p. 269.0–271.0°, not depressed on admixture with authentic sample.[9] A mixture of I and the ethyl ester (from I) had m.p. 249.0–256.5°.

B. **4-Hydroxycarbostyril** (VI).—Concentration of the ethanolic mother liquor (from which I crystallized above) under reduced pressure to a volume of *ca.* 25 ml. yielded 0.6 g. of VI as a cream-colored solid, m.p. 338–342° dec. The compound was purified by dissolving in 10% sodium hydroxide, boiling the solution with Norit, filtering, and acidifying the filtrate with concentrated hydrochloric acid. One recrystallization of the air-dried precipitate from 50% acetic acid gave VI as colorless needles, m.p. 344–347° dec. after partial darkening at 300°; lit.[17] m.p. 352–354°.

Anal. Calcd. for $C_9H_7O_2N$: C, 67.08; H, 4.38; N, 8.69. Found: C, 66.8; H, 4.6; N, 8.65.

Both VI (from V) and an authentic sample of VI[17] gave greenish-blue colorations with the Friedländer color reaction,[8] as modified by Gabriel.[18]

The (mono) acetyl derivative of VI had m.p. 218–219° and an authentic specimen had m.p. 217–218°[17]; mixed m.p. was 217–218°. The infrared spectra of both samples (chloroform solution) were identical and exhibited two strong bands (5.70 and 6.03 μ).

Pyrolysis of 4-Hydroxy-3-quinolinecarboxylic Acid (I). Quantitative Determination of Carbon Dioxide.—The carbon dioxide was determined gravimetrically. The sample was decomposed in a 100-ml. three-necked flask which was heated in a bath of silicone oil. During the pyrolysis, a slow stream of purified nitrogen was allowed to flow into the flask and the gases then passed successively through a tube of Anhydrone and an absorption flask containing Ascarite, which was suitably protected from the atmosphere. The apparatus was checked by heating at 135° a sample of benzylmalonic acid, which served as a standard; 99% of the theoretical amount of carbon dioxide was collected. Two samples of I, weighing 0.2832 and 0.3117 g., respectively, were thermally decomposed at 285–290° (each sample was heated for 30 minutes). Calcd. for one mole from $C_{10}H_7O_3N$: 0.0659 g. and 0.0726 g., respectively. Found: 0.0628 g. (95.3%) and 0.0672 g. (92.6%).

No evidence of the formation of water was found when I was pyrolyzed; only 4-hydroxyquinoline was isolated from the residues.

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(15) Schering-Kahlbaum, A.-G., British Patent 308,731 (1928).

(16) G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, 603 (1945).

(17) E. H. Huntress and J. Bornstein, THIS JOURNAL, **71**, 745 (1949).

(18) S. Gabriel, *Ber.*, **51**, 1504 (1918).