The Thermal Decomposition of Ethyl 4-Quinolonecarboxylates and Related Compounds

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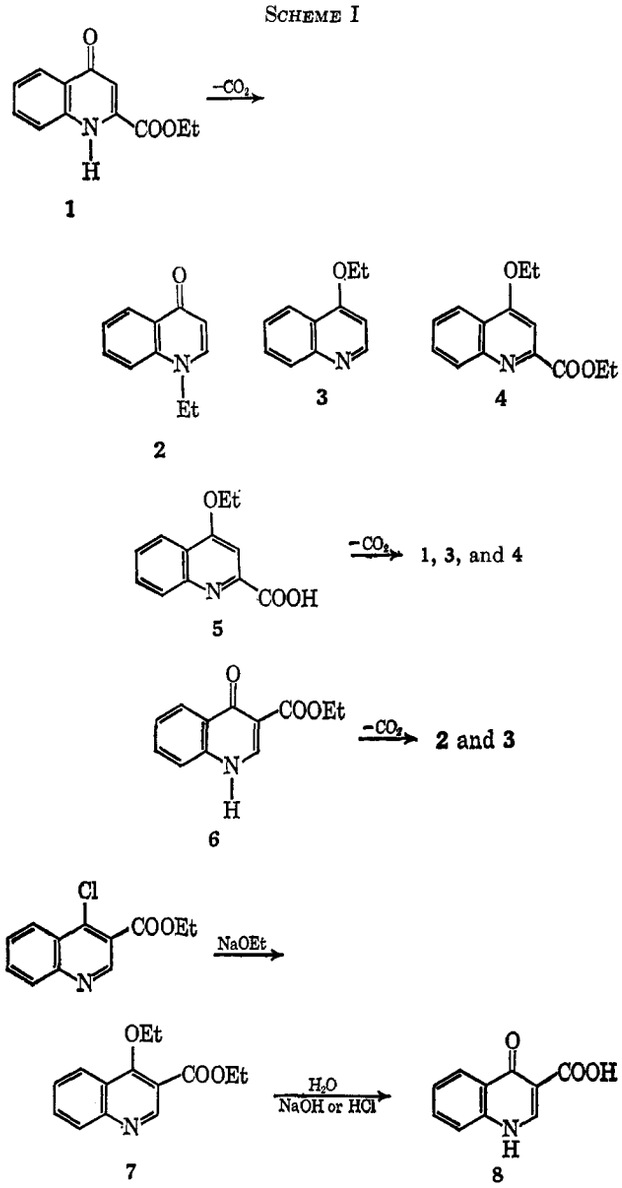
The thermal decomposition of alkyl esters of 4-hydroxypicolinic and of chelidamic acid, which proceeds with formation of carbon dioxide and O- and N-alkylated derivatives of pyridine, was recently reported.[1] This paper deals with an extension of that investigation to the quinoline series. Ethyl kynurenate[2] (**1**) (Scheme I) was found to behave like the related ethyl 4-hydroxypicolinate. Heated to 260° it evolved carbon dioxide and from the residue N-ethyl-4-quinolone (**2**) was isolated as main product. Small amounts of 4-ethoxyquinoline (**3**) and ethyl 4-ethoxyquinaldate (**4**) were also obtained.

When 2-ethoxyquinoline-4-carboxylic acid is heated above its melting point it is converted to ethyl 2-quinoline-4-carboxylate, ethyl 2-ethoxyquinoline-4-carboxylate, and 2-quinolone-4-carboxylic acid.[3] It was found that 4-ethoxyquinaldic acid (**5**) reacts similarly. Although decarboxylation to 4-ethoxyquinoline is the predominant course of reaction, ethyl kynurenate and ethyl 4-ethoxyquinaldate were isolated as additional decomposition products. These observations demonstrate that at elevated temperatures ethyl groups may be transferred in either direction, from carbethoxyl to an oxo group or from ethoxyl to a carboxy group.

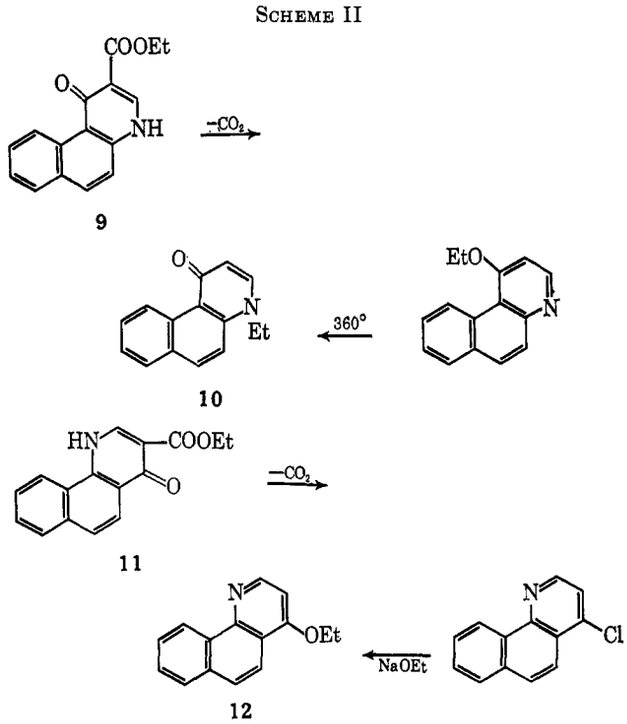
To test if it was necessary that the substituents occupy the 2 and 4 positions of the heterocycle to permit these reactions, the pyrolysis of ethyl 4-quinolone-3-carboxylate[4] (**6**) was carried out. Carbon dioxide was evolved at 290–320° and 4-ethoxyquinoline and N-ethyl-4-quinolone were found as decomposition products, but no ethyl 4-ethoxyquinoline-3-carboxylate (**7**) could be detected. This ester was prepared by independent synthesis so that its properties could be observed, and it was noticed that either dilute hydrochloric acid or dilute sodium hydroxide hydrolyzed not only the ester but also the ether group to form 4-quinolone-3-carboxylic acid (**8**).

The thermal decomposition of ethyl benzo[*f*]-1-quinolone-2-carboxylate[5] (**9**) (Scheme II) produced carbon dioxide and N-ethylbenzo[*f*]-1-quinolone (**10**). No other products were isolated from this decomposition. In contrast to this result ethyl benzo[*h*]-4-

SCHEME I



SCHEME II



(1) D. G. Markees, *J. Org. Chem.*, **29**, 3120 (1964).
(2) B. Riegel, C. J. Albisetti, Jr., G. R. Lappin, and R. H. Baker, *J. Am. Chem. Soc.*, **68**, 2685 (1946).
(3) H. Kondo and T. Nozoe, *J. Pharm. Soc. Japan*, **56**, 6 (1936).
(4) B. Riegel, G. R. Lappin, B. H. Adelson, R. I. Jackson, C. J. Albisetti, Jr., R. M. Dodson, and R. H. Baker, *J. Am. Chem. Soc.*, **68**, 1264 (1946).
(5) R. E. Foster, R. D. Lipscomb, T. J. Thompson, and C. S. Hamilton, *ibid.*, **68**, 1327 (1946).

quinolone-3-carboxylate[5] (**11**) was converted to carbon dioxide and 4-ethoxybenzo[*h*]quinoline (**12**) under similar conditions. A sample of this ether was prepared by independent synthesis and the compound was found to resist thermal conversion to N-ethylbenzo[*h*]-4-quinolone.

The various decomposition products were identified by analyses and by comparison with samples prepared by independent synthesis. The ethers 4-ethoxyquinoline, 1-ethoxybenzo[*f*]quinoline, 4-ethoxybenzo[*h*]quinoline, ethyl 4-ethoxyquinoline-3-carboxylate, and ethyl 4-ethoxyquinoline-2-carboxylate were prepared by reaction of the corresponding chloro compounds with sodium ethoxide. The last named ethoxy ester was also obtained by reaction of the sodium salt of ethyl 4-quinolone-2-carboxylate with ethyl iodide. N-Ethyl-4-quinolone[6] and N-ethylbenzo[*f*]-1-quinolone were prepared by heating the ethers **3** and **10**, respectively. The rearrangement of 4-ethoxyquinoline took place at a temperature considerably below the one indicated in the literature[6] and the resulting N-ethyl-4-quinolone, which is inadequately described,[6] could be distilled and crystallized. Reaction with bromine furnished N-ethyl-3-bromo-4-quinolone. The position of the bromine in this compound was ascertained by reaction with phosphorus tribromide which gave 3,4-dibromoquinoline. Similar transformations of N-alkyl-4-pyridones with inorganic acid halides are known.[7,8]

Experimental Section[9]

Decomposition of Ethyl Kynurenate (Ethyl 4-Quinolone-2-carboxylate).—A 6.5-g sample (30 mmoles) of ethyl kynurenate was heated to 260° (bath temperature). Carbon dioxide (28 mmoles) was collected and the residue was distilled. The forerun (0.6 g, 3.5 mmoles), boiling to 140° (1.5 mm), was identified as 4-ethoxyquinoline by conversion to the hydrochloride, mp 162–163° dec. A small intermediate fraction (0.3 g, 1 mmole) solidified on standing and was found to consist mainly of ethyl 4-ethoxyquinaldate, mp 101–103°. The main fraction (3.0 g, 17.7 mmoles), boiling range 190–210° (1.3 mm), solidified and was shown to be N-ethyl-4-quinolone, mp 99–101°, monobromo derivative mp 204–207°.

Decomposition of 4-Ethoxyquinaldic Acid.—A 6.2-g sample (28 mmoles) of this acid (dried at 100°) was decomposed at 195–205° (bath temperature). Carbon dioxide (23 mmoles) was collected and extraction of the residue with petroleum ether (bp 30–60°) and ether yielded 0.2 g (0.6 mmole) of ethyl 4-ethoxyquinaldate, 0.35 g (1.5 mmoles) of ethyl kynurenate, mp 214–216°, and 1.7 g (10 mmoles) of 4-ethoxyquinoline, bp 133–140° (2.5 mm), hydrochloride mp 165–166° dec.

Decomposition of Ethyl 4-Quinolone-3-carboxylate.[4]—This ester (8.7 g, 40 mmoles) was heated to 290–320° (bath temperature). It produced CO_2 (34 mmoles), 0.8 g (4.6 mmoles) of 4-ethoxyquinoline (hydrochloride mp 163–164° dec), and 3.2 g (18 mmoles) of N-ethyl-4-quinolone, bp 210–215° (1.7 mm), mp 98–100°.

Decomposition of Ethyl Benzo[*f*]-1-quinolone-2-carboxylate.[5]—Recrystallized ester **9** (5.3 g, 20 mmoles) was heated to 320° (bath temperature). A total of 18 mmoles of CO_2 was evolved. The dark residue was recrystallized repeatedly (ethanol, charcoal) and sublimed. The final mp 186–187° indicated that the compound was **N-ethylbenzo[*f*]-1-quinolone**.

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.54; H, 5.55; N, 6.57.

Decomposition of Ethyl Benzo[*h*]-4-quinolone-3-carboxylate.[5]—A 5.3-g sample (20 mmoles) of this ester was decomposed at 295–300° (bath temperature) to give 20 mmoles of CO_2. The residue crystallized on cooling. Recrystallization from petroleum ether gave 3.0 g (13 mmoles) of **4-ethoxy-benzo[*h*]quinoline**, mp 115–116.5° after further recrystallization from ethanol and sublimation.

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.71; H, 5.84; N, 6.29.

Ethyl 4-Chloroquinoline-3-carboxylate.—A mixture of 10.0 g of ethyl 4-quinolone-3-carboxylate[4] and 40 ml of phosphorus oxychloride was refluxed for 6 hr. Excess acid chloride was distilled at reduced pressure and the residue was treated with water and made alkaline with 1 *M* sodium carbonate. Extraction with ethyl acetate followed by removal of the solvent gave 10.5 g (92%) of crude ester. Distillation, bp 163–165° (1 mm), and recrystallization from petroleum ether (bp 90–100°) gave the analytical sample, mp 44–45°.

Anal. Calcd for $C_{12}H_{10}ClNO_2$: C, 61.15; H, 4.27; Cl, 15.04. Found: C, 61.74; H, 4.28; Cl, 15.27.

Ethyl 4-Ethoxyquinaldate. Method A.—Solutions of 30 g of crude ethyl 4-quinolone-2-carboxylate in 300 ml of absolute alcohol and of 4.0 g of sodium in 80 ml of the same solvent were mixed, refluxed for 0.5 hr, and then concentrated to about 200 ml. A solid began to separate and ether was added to the mixture to complete the precipitation. The solid (22 g) was filtered, air dried, and mixed with 50 ml of ethyl iodide and 40 ml of DMF (N,N-dimethylformamide). A clear brown solution was formed after a brief period of heating, the volatile parts were removed, and water was added to the residue. The crude ester (19 g, 59%) was collected and a sample was recrystallized from dilute ethanol, mp 101–103°, undepressed when mixed with material prepared by method B.

Method B.—A solution of 6.0 g of ethyl 4-chloroquinaldate[10] in 10 ml of absolute alcohol and 20 ml of DMF was added to a solution of 0.85 g of sodium in 20 ml of absolute alcohol. The mixture was refluxed for 15 min after the initial reaction had subsided. Excess solvent was removed and the residue was treated with water. Most of the product (2.5 g) crystallized. Another 0.7 g could be extracted with ethyl acetate from the mother liquor, total yield 51%. The crude product was distilled, bp 178–182° (1.6 mm), and the distillate was recrystallized from ethanol, mp 101–103°.

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.41; H, 6.22; N, 5.69.

The following compounds were prepared from the corresponding chloro compounds by essentially the same procedure.

Ethyl 4-ethoxyquinoline-3-carboxylate, yield 79%, showed bp 160–162° (1.4 mm), mp 32–34° [from petroleum ether (bp 30–60°)].

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16. Found: C, 68.44; H, 6.35.

4-Ethoxyquinoline.—The crude product was taken up with ether and distilled, bp 121–123° (1.3 mm), yield 79%; redistilled for analysis, bp 112–114° (1 mm) [lit.[11] bp 186.5° (30 mm)].

Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 75.93; H, 6.72; N, 8.06.

The **picrate** showed mp 207–210° (lit.[12] mp 195°) (from ethanol).

Anal. Calcd for $C_{11}H_{11}NO \cdot C_6H_3N_3O_7$: N, 13.93. Found: N, 14.01.

The **hydrochloride** showed mp 163–164° dec[13] (from ethyl acetate containing a little absolute alcohol).

Anal. Calcd for $C_{11}H_{11}NO \cdot HCl$: Cl, 16.91; N, 6.68. Found: Cl, 17.03; N, 6.74.

1-Ethoxybenzo[*f*]quinoline, yield 88%, showed mp 100–101° (from aqueous alcohol, sample also sublimed).

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.62; H, 5.91; N, 6.32.

(6) H. Meyer, *Monatsh. Chem.*, **27**, 255 (1906).

(7) H. S. Mosher, in "Heterocyclic Compounds," Vol. 1, R. C. Elderfield, Ed., John Wiley and Sons, New York, N. Y., 1950, p 514.

(8) D. G. Markees, *J. Org. Chem.*, **23**, 1490 (1958).

(9) Melting points were determined on a Mel-Temp apparatus and are corrected. Boiling points are not corrected. All solid decomposition products were identified by their infrared spectra and by melting point determinations of mixtures with authentic compounds.

(10) E. Campaigne, R. E. Cline, and L. E. Kaslow, *J. Org. Chem.*, **15**, 600 (1950).

(11) F. Wenzel, *Monatsh. Chem.*, **15**, 453 (1894).

(12) R. Hardman and M. W. Partridge, *J. Chem. Soc.*, 614 (1958). The identity of the compound of mp 195° is not certain.

(13) This melting point depends on the rate of heating. It is lower if the sample is heated very slowly and higher if it is heated rapidly.

4-Ethoxybenzo[*h*]quinoline,[14] yield 98%, showed mp 116–117° (from ethanol) (lit.[5] mp 119–120°).

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.82; H, 5.92; N, 6.35.

N-Ethyl-4-quinolone.—A 4.0-g sample of 4-ethoxyquinoline was heated to 250–270° (bath temperature) until it ceased to boil. Distillation gave 3.0 g (75%) of crude N-ethyl-4-quinolone, bp 210–220° (1.3 mm). The solidified product was redistilled, bp 210–212° (1.3 mm), and recrystallized from toluene, mp 100–101°.

Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.29; H, 6.46; N, 8.14.

The **picrate** of this compound was prepared in the usual manner, mp 212–214° (from ethanol).

Anal. Calcd for $C_{11}H_{11}NO \cdot C_6H_3N_3O_7$: N, 13.93. Found: N, 13.95.

N-Ethyl-4-quinolone hydrochloride was obtained by treatment of the quinolone with alcoholic HCl, mp 204–205°[15] (from acetonitrile).

Anal. Calcd for $C_{11}H_{11}NO \cdot HCl$: Cl, 16.91; N, 6.68. Found: Cl, 16.88; N, 6.74.

N-Ethylbenzo[*f*]-1-quinolone.—A 2.0-g sample of 1-ethoxybenzo[*f*]quinoline was heated to 360° (bath temperature) until the effervescence ceased. Any unchanged ether was removed by keeping the material at 100° and 0.8 mm. The crude product was obtained by sublimation at 250–300° (0.8 mm) and purified by recrystallization from toluene and aqueous alcohol and by final resublimation, mp 185–187°.

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.56; H, 5.96; N, 6.36.

When a 1-g sample of 4-ethoxybenzo[*h*]quinoline was treated similarly, 0.8 g of unchanged ether was recovered. The only contaminant was an unidentified tar and no N-ethylbenzo[*h*]-4-quinolone was detected.

N-Ethyl-3-bromo-4-quinolone.—A solution of 1.6 g of bromine in 12.5 ml of acetic acid was added to a solution of 1.7 g of N-ethyl-4-quinolone in 10 ml of the same solvent. Brief heating on the steam bath produced an orange solution. The crystalline material which separated on cooling was filtered and suspended in water. This mixture was made alkaline with 1 *M* Na_2CO_3, and the new precipitate (1.7 g, 68%) was collected, dried, and recrystallized from ethanol, mp 204–207°.

Anal. Calcd for $C_{11}H_{10}BrNO$: C, 52.40; H, 3.99; Br, 31.70. Found: C, 52.34; H, 4.04; Br, 32.22.

Reaction of N-Ethyl-3-bromo-4-quinolone with PBr_3.—A mixture of 2.0 g of the substituted quinolone and 5 ml of PBr_3 was refluxed for 1 hr. The liquid parts were decanted and decomposed with water. The resulting solution was made alkaline with dilute NaOH and the crude product was extracted with ether. The ethereal solution was washed with water and dried (Na_2SO_4), the solvent was removed, and the remaining 3,4-dibromoquinoline was recrystallized from alcohol, mp 77° (lit.[16] mp 77–79°).

Anal. Calcd for $C_9H_5Br_2N$: C, 37.66; H, 1.75; Br, 55.69. Found: C, 37.57; H, 2.02; Br, 55.59.

Hydrolyses of Ethyl 4-Ethoxyquinoline-3-carboxylate. Method A (NaOH).—A 1-g sample of the ester was refluxed for 4 hr with 10 ml of 5% NaOH. The clear, yellow solution was acidified and 0.3 g of 4-quinolone-3-carboxylic acid was filtered, mp 245° dec[17] (from aqueous alcohol) (lit.[4] mp 269–270°).

Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33; neut equiv, 191. Found: C, 62.64; H, 4.55; N, 7.24; neut equiv, 192.

Method B (HCl).—A 1-g sample of the ester was refluxed with 20 ml of 5% HCl. After a few minutes a solid precipitate began to form and was filtered after 0.75 hr. The crude yield was 0.7 g (90%), mp 245° dec[17] (from aqueous alcohol) (lit.[4] mp 269–270°).

The infrared spectra of both samples were identical with that of authentic 4-quinolone-3-carboxylic acid.[4]

(14) This compound is reported in the literature[6] but no preparative method is given.

(15) Sample dried at 78° (0.8 mm), sealed capillary.

(16) B. Riegel, G. R. Lappin, C. J. Albisetti, Jr., B. H. Adelson, R. M. Dodson, L. G. Ginger, and R. H. Baker, *J. Am. Chem. Soc.*, **68**, 1229 (1946).

(17) Lit.[4] mp 269–270°. The melting point of this acid depends on the rate of heating. The one reported in this paper is observed if the sample is heated slowly.

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Heterocyclic Steroids. IX. 2-Oxa-A-nor Steroids[1,2]

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Upon inspection of acetyl acid[4,5] **1a** it was noted that this secosteroid has the salient features of a disubstituted levulinic[6] acid (2). We have already prepared steroidal pyridazinones[4,7] and pyrrolinones[1] by reactions analogous to those reported[6] with levulinic acid (2). To further evaluate the levulinic acid features of **1a**, the characteristic transformation to angelica lactone analogs was undertaken.

Both forms of angelica lactone, the α and the β, can be obtained under conditions frequently associated with enol lactone formation.[6] Indeed, upon refluxing acid **1a** in acetyl chloride and acetic anhydride, both **3** and **4a** were produced. The 3(5)-ene lactone (the α analog) **3** was readily separated from the 5(10)-ene lactone (the β analog) by thin layer chromatography. The structure of **3** follows from its elemental analysis, infrared spectrum, and nmr spectrum. Infrared bands at 1770 cm^{-1} for the five-membered enol lactone and at 1725 cm^{-1} for the 17-acetate were observed. The nmr spectrum had sharp singlets at 51.5 and 122.5 cps for the 18-methyl and 17-acetate, respectively. The C-3 vinylic methyl appeared as a multiplet centered at 115.5 cps (W_H = 4.5 cps). The splitting of this methyl is the result of homoallylic coupling with the C-6 and C-10 axial protons. Coupling of this type has been reported[8] in α-angelica lactone and other compounds with similar structures.

The 5(10)-lactone **4a** was characterized by its infrared peaks at 1735 for the carbonyls and at 1655 cm^{-1} for the conjugated double bond, as well as its ultraviolet maximum at 219 mμ. In the absence of a proton α to the carbonyl, the usual splitting of the carbonyl bands in the infrared did not occur. Its nmr spectrum

(1) Part VIII: D. M. Piatak and E. Caspi, *J. Org. Chem.*, **31**, 3935 (1966).

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(3) Department of Chemistry, Northern Illinois University, DeKalb, Ill.

(4) E. Caspi, P. K. Grover, and D. M. Piatak, *Chem. Ind.* (London), 1495 (1963).

(5) E. Caspi, P. K. Grover, D. M. Piatak, and Y. Shimizu, *J. Chem. Soc.*, 3052 (1965).

(6) Various reactions of levulinic acid have been reviewed by R. H. Leonard, *Ind. Eng. Chem.*, **48**, 1331 (1956).

(7) D. M. Piatak, R. I. Dorfman, D. Tibbetts, and E. Caspi, *J. Med. Chem.*, **7**, 590 (1964).

(8) D. Gagnaire and E. Payo-Subiza, *Bull. Soc. Chim. France*, 2623 (1963); N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 111.