The Alkylation of 6-Bromo-1,4-dihydro-4-oxo-3-cinnolinecarboxylic Acid (1)

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Alkylation of the title compound gave **3a, b + c** and **2a, b + c** in *ca.* equivalent yields. Intermediate **4a** was isolated and its facile decarboxylation to **2a** was studied.

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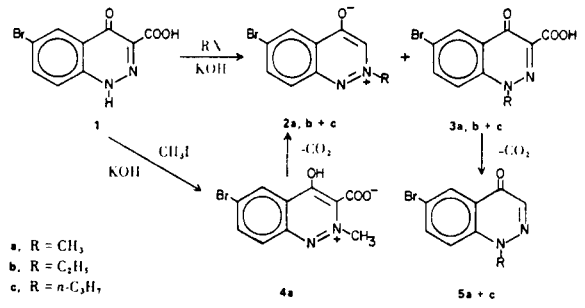
Alkylation of 4-cinnolinones in protic solvents under basic conditions has been studied by Ames and coworkers (2,3). They found that reaction occurs partly at *N*-1 to give 1-alkyl-4(1*H*)cinnolinones (*e.g.*, **5**) but mainly at *N*-2 to give 2-alkyl-4-hydroxycinnolinium hydroxide inner salts (*e.g.*, **2**). 4-Cinnolinones bearing a 3-substituent are reported to constitute an exception to this pattern, largely on the basis of steric factors (2b,3). 3-Methyl-4-cinnolinone gave 43% and 27% of 1- and 2-methylated products, respectively (4). Methylation (2b,5) of 3-methoxy- and of 3-bromo-4-cinnolinone apparently was limited to the 1-position. 3-Carboethoxy-4-cinnolinone (6) and its 6-chloro analog (7) have also been reported to methylate at the 1-position. Ethylation of a 4-cinnolinone bearing a 3-carboxy substituent proceeded similarly giving 1,4-dihydro-4-ethyl-1-oxobenzo[*f*]cinnoline-2-carboxylic acid in modest yield (8). Again, no alkylation of the other *N* atom is reported.

We have studied the alkylation of a 3-carboxy-4-cinnolinone, namely 6-bromo-1,4-dihydro-4-oxo-3-cinnolinecarboxylic acid (**1**) (9), with dimethyl sulfate, ethyl iodide, and propyl bromide in aqueous or aqueous ethanolic potassium hydroxide. Our results contrast with the above work, probably because of a more thorough investigation. We find that *N*-2 is alkylated to about the same extent as *N*-1, and that the hitherto unreported inner salts of 2-alkyl-6-bromo-3-carboxy-4-hydroxycinnolinium hydroxides (*e.g.*, **4a**) decarboxylate very readily. Our alkylations gave, after extensive purification, the decarboxylated 2-alkyl-6-bromo-4-hydroxycinnolinium hydroxide inner salts **2a-c** in 18-37% yield and 1-alkyl-6-bromo-1,4-dihydro-4-oxo-3-cinnolinecarboxylic acids **3a-c** in 19-23% yield. In an nmr study of the crude methylated products (**3a** and **4a**, 85% combined yield), 2-methylation was found to be slightly predominant.



An opportunity to isolate and study an undecarboxylated 2-alkylated product was afforded by the alkylation of **1** with dimethyl sulfate in excess 2*N* potassium hydroxide. This reaction occurs rapidly at room temperature and affords a product mixture wherein the 1-methyl **3a** is largely retained in solution but the 2-methyl **4a** is not. A solution of **4a** in 1*N* potassium hydroxide at steam bath temperature is stable, so decarboxylation must take place under non-basic conditions. Compound **4a** is stable in trifluoroacetic acid, insoluble in hot dilute hydrochloric acid, and is solubilized and also decarboxylated by heating in dimethylformamide on a steam bath. If decarboxylation occurs *via* an ylid intermediate, this could take place under either basic or neutral conditions, but the additional negative charge afforded by deprotonation of **4a** would tend to stabilize it under basic conditions.

Nmr spectroscopy was used in determining the identity and stability of **4a**. The spectrum of the major component (85%) of the crude **4a** in TFAA-d consisted of 3 aromatic protons, a methyl group at τ 4.78 and one exchangeable proton. This contrasts sharply with the spectrum of decarboxylate **2a**, which displays a methyl signal at τ 5.19 and an additional downfield aromatic signal, namely a 3-H singlet, at τ 0.92. Elemental analysis of the crude **4a** was

Table

Compound	Solvent	Nmr (a) 3H	5H	7H	8H	N-CH_3	N-CH_2	Ir (b)
5c	Deuteriochloroform	2.19	1.60	2.22	2.64	---	5.63	6.18, 6.30 (c)
2c	Deuteriochloroform	2.04	1.56	2.25	2.32	---	5.58	6.25
2b	Deuteriochloroform	2.05	1.56	2.26	2.34	---	5.45	6.22, 6.28
2a	Deuteriochloroform	2.10	1.54	2.23	2.33	5.71	---	6.23, 6.27
2a	TFAA-d	0.92	1.26	1.69	1.69	5.19	---	
3a	TFAA-d	---	1.13	1.54	1.78	5.20	---	5.80, 6.35
3b	TFAA-d	---	1.13	1.55	1.71	---	4.76	5.76, 6.35
3c	TFAA-d	---	1.13	1.56	1.76	---	4.92	5.72, 6.34
4a (d)	TFAA-d	---	1.18	1.61	1.61	4.78	---	

(a) Chemical shifts are expressed in the τ scale using internal TMS as the standard. (b) Spectra were determined on potassium bromide pellets. Absorption bands between 5.0-6.4 μ, all of which were strong, are reported. (c) Weak absorption at 6.35 μ was also seen. (d) This compound contained *ca.* 15% impurities.

concordant. This suggests the isomeric **3a** as one of its impurities, as did the nmr spectrum.

The expectation that **3** should be more resistant than **4** to decarboxylation led to the structures given. Confirmation of the decarboxylated products as inner salts **2** rather than the isomeric 1-alkyl-4-cinnolinones **5** was accomplished in part by comparison with published data for 6-bromo-1-methyl-4(1*H*)cinnolinone (**5a**) and 6-bromo-4-hydroxy-2-methylcinnolinium hydroxide (**2a**). Ellis and Lovesey (10) have reported the chemical shifts of **5a** and **2a** in trifluoroacetic acid; however, we could not positively correlate our values with theirs. The melting points were subsequently published by Ames, *et al.* (2b) (**5a**, 148-149°; **2a**, 224-225°). The melting point (229-230°) of our product agrees with that assigned by these workers to **2a**.

Decarboxylation of **3** giving either **2** or **5** as product, should establish the structure of alkylated carboxylic acids **3**, and also confirm the identity of the inner salt products **2**. Thermal decarboxylation of **3c** at 310° followed by preparative TLC gave 6-bromo-1-propyl-4(1*H*)cinnolinone (**5c**) in 23% yield.

EXPERIMENTAL

The following spectrometers were used: nmr, Varian HA-100; ms, Jeolco JMS-OISC; ir, Perkin-Elmer 21. Final melting points are corrected unless otherwise stated.

Alkylation with Dimethyl Sulfate (**2a**, **3a** and **4a**).

Compound **4a**.

Dimethyl sulfate (0.16 ml., 1.7 mmoles) was added to a stirred solution of **1** (9) (125.1 mg., 0.0456 mmole) in 2*N* potassium hydroxide (3.0 ml., 6.0 mmoles) at 27°. Within 10 minutes so much solid had separated that additional 2*N* potassium hydroxide (2.0 ml.) was added to facilitate uniform stirring. Twenty minutes thereafter, the solid was collected (filtrate saved, see **3a** below), washed with 2*N* potassium hydroxide, and dissolved in water (10 ml.). The solution was acidified with 3*N* hydrochloric acid to *p*H *ca.* 3 while being stirred vigorously. The off-white solid which precipitated was collected, washed with water, and dried to give 57.5 mg. (43%) of crude **4a**. The nmr spectrum (TFAA-d) displayed three CH_3 signals, one of which (τ 4.78) integrated for 85% of the total and another of which (τ 5.19) was consistent with the isomeric **3a**.

Anal. Calcd. for $C_{10}H_7BrN_2O_3$: C, 42.43; H, 2.52; N, 9.90. Found (Sealed tube): C, 42.41; H, 2.85; N, 10.12.

Compound **2a**.

Crude **4a** obtained from a similar methylation of 17.8 g. (0.066 mole) of **1** was successively decarboxylated by recrystallization from DMF, triturated with hot aqueous 10% potassium bicarbonate, and recrystallized from ethanol to give 5.2 g. of 6-bromo-4-hydroxy-2-methylcinnolinium hydroxide inner salt (**2a**), m.p. 229.2-230.4° [lit. (2b), 224-225°] in 33% overall yield.

Anal. Calcd. for $C_9H_7BrN_2O$: C, 45.21; H, 2.95; N, 11.72. Found: C, 45.37; H, 2.94; N, 11.41.

Compound **3a**.

The above 2*N* potassium hydroxide filtrate was acidified (hydrochloric acid), and the crude **3a** thus precipitated was collected, washed with water, and dried to obtain 56.1 mg. (42%) of a cream solid whose nmr (TFAA-d) accorded with a mixture of 10% of **4a** (2-CH_3, τ 4.76) and 70% **3a** (1-CH_3, τ 5.18) contaminated by an unidentified impurity.

Crude **3a** similarly obtained from the above larger methylation experiment was triturated with aqueous potassium bicarbonate and insoluble material was filtered off. The product was again precipitated by acidification of the filtrate. Two recrystallizations from DMF gave 3.6 g. (19%) of 6-bromo-1,4-dihydro-1-methyl 4-oxo-3-cinnolinecarboxylic acid (**3a**), m.p. 290.6-291.6° dec.

Anal. Calcd. for $C_{10}H_7BrN_2O_3$: C, 42.43; H, 2.52; N, 9.90. Found: C, 42.77; H, 2.33; N, 10.01.

Alkylation with Ethyl Iodide (**2b** and **3b**).

A solution of **1** (13.5 g., 0.05 mole) and ethyl iodide (10 ml., 0.12 mole) in 70 ml. (0.13 mole) of aqueous 10% potassium hydroxide and 140 ml. of ethanol was refluxed for 5.5 hours. Midway through the reflux period, an additional 70 ml. of aqueous 10% potassium hydroxide was added, and at the close of the

reflux period solvents were allowed to boil off, reducing the volume by about one-half. The solution was treated with charcoal, filtered, and poured into 35 ml. of 6*N* hydrochloric acid. The resulting precipitate was collected and dried giving 14.9 g., m.p. 142-145°. Two recrystallizations from ethyl acetate followed by two from ethanol gave 2.9 g. (19%) of 6-bromo-1-ethyl-1,4-dihydro-4-oxo-3-cinnolinecarboxylic acid (**3b**), m.p. 212.2-213.8°.

Anal. Calcd. for $C_{11}H_9BrN_2O_3$: C, 44.46; H, 3.07; Br, 26.90. Found: C, 44.57; H, 3.09; Br, 27.25.

The initial ethyl acetate mother liquor (800 ml.) from the above recrystallization was concentrated to about one-fourth volume and the yellow needles which separated were collected, recrystallized from ethyl acetate and then from ethanenitrile giving 2.3 g. (18%) of 6-bromo-2-ethyl-4-hydroxycinnolinium hydroxide inner salt (**2b**), m.p. 168.4-169.2°.

Anal. Calcd. for $C_{10}H_9BrN_2O$: C, 47.45; H, 3.59; N, 11.07. Found: C, 47.30; H, 3.38; N, 11.40.

Alkylation with Propyl Bromide (**2c** and **3c**).

Compound **1** (16.1 g., 0.06 mole), *n*-propyl bromide (32 g., 0.26 mole), ethanol (150 ml.) and aqueous 10% potassium hydroxide (100 ml., 0.18 mole) were refluxed for 6 hours. Solvents were allowed to boil off, reducing the volume of the solution by about two-thirds. Upon acidification (hydrochloric acid), a gum separated. It was purified by three recrystallizations from ethanol giving 4.4 g. (23%) of 6-bromo-1,4-dihydro-4-oxo-1-propyl-3-cinnolinecarboxylic acid (**3c**), m.p. 210.6-212.2°.

Anal. Calcd. for $C_{12}H_{11}BrN_2O_3$: C, 46.32; H, 3.57; N, 9.01. Found: C, 46.41; H, 3.52; N, 8.94.

The combined ethanolic mother liquors from the first two of the above recrystallizations were concentrated to a small volume and chilled. The precipitate which separated was collected and dissolved in boiling ethanol. Material which crystallized above room temperature was removed by filtration (m.p. $>180°$). The filtrate was then chilled and the solid which separated was collected (m.p. $<150°$) and extracted with warm aqueous 10% potassium hydroxide solution. The undissolved material was collected, washed with water, dried and then recrystallized from ethanenitrile (charcoal) to give 5.3 g. (33%) of 6-bromo-4-hydroxy-2-propylcinnolinium hydroxide inner salt (**2c**), m.p. 151.6-153.0°, M^+ 266.

Anal. Calcd. for $C_{11}H_{11}BrN_2O$: C, 49.46; H, 4.15; N, 10.48. Found: C, 49.64; H, 3.99; N, 10.63.

6-Bromo-1-propyl-4-(1*H*)cinnolinone (**5c**).

6-Bromo-1,4-dihydro-4-oxo-1-propyl-3-cinnolinecarboxylic acid (**3c**) (310 mg.) was heated neat in a 330° oil bath for 50 seconds. The resultant black tar was triturated with about 5 ml. of benzene and filtered. Chromatography of the filtrate on two silica gel plates (Brinkmann PF 254, 20 x 40 cm) using 5 passes with chloroform gave a principal band which was eluted with chloroform. The eluent was concentrated and the residual solid was washed sparingly with hexane. This gave 61 mg. (23%) of **5c**, m.p. 136-138° (uncorrected); M^+ 266.

Anal. Calcd. for $C_{11}H_{11}BrN_2O$: C, 49.46; H, 4.15; N, 10.48. Found: C, 49.46; H, 4.14; N, 10.57.

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(1) This tautomeric compound may alternatively be named 6-bromo-4-hydroxy-3-cinnolinecarboxylic acid. *Chemical Abstracts* uses both nomenclatures.

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