A NOVEL DISPLACEMENT REACTION OF 1-ETHYL-6,7-METHYLENEDIOXY-QUINOLINES WITH NUCLEOPHILES

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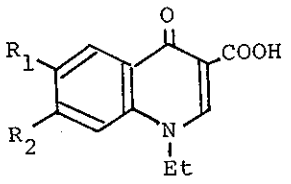
The reaction of 4-amino-(3a) and 4-anilino-3-carboethoxy-1-ethyl-6,7-methylenedioxyquinolinium iodide (3b) with nucleophilic reagents produced 7-substituted 4-amino-3-carboxy-1-ethyl-6-hydroxyquinolinium betaines (5b-d) and 7-substituted 1-ethyl-1,4-dihydro-6-hydroxy-4-phenylimino-3-quinolinecarboxylic acid (6b-d), respectively, which led to 7-substituted 1-ethyl-1,4-dihydro-6-hydroxy-4-oxo-3-quinolinecarboxylic acids (1b-d) by alkaline hydrolysis.

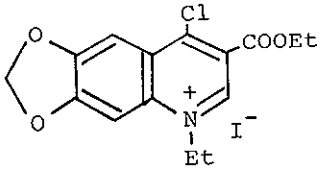
Many investigations on the displacement reactions of quinoline derivatives with nucleophiles have been published. These reactions, however, have been limited to those on the pyridine moiety of quinoline skeleton except the reaction[1] of 7-halogenoquinolines with nucleophiles.

In the course of a study on 1-alkyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids,[2] we found that treatment of 4-amino-3-carboethoxy-1-ethyl-6,7-methylenedioxyquinolinium iodide (3a)[3] with methanolic potassium hydroxide results in 4-amino-3-

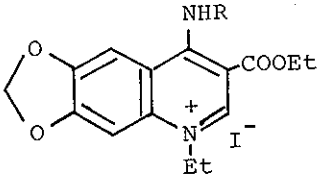
Scheme 1



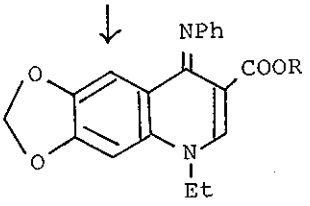
(1a) $R_1=R_2=OCH_2O$
(1b) $R_1=OH$; $R_2=OMe$
(1c) $R_1=OH$; $R_2=OEt$
(1d) $R_1=OH$; $R_2=SEt$
(1e) $R_1=OMe$; $R_2=OH$



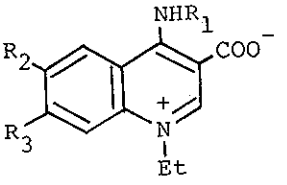
(2)



(3a) R=H
(3b) R=Ph

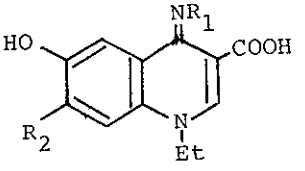


(4a) R=H
(4b) R=Et



(5a) $R_1=H$; $R_2=R_3=OCH_2O$
(5b) $R_1=H$; $R_2=OH$; $R_3=OMe$
(5c) $R_1=H$; $R_2=OH$; $R_3=OEt$
(5d) $R_1=H$; $R_2=OH$; $R_3=SEt$
(5e) $R_1=Ph$; $R_2=OH$; $R_3=OMe$

(1b-d)

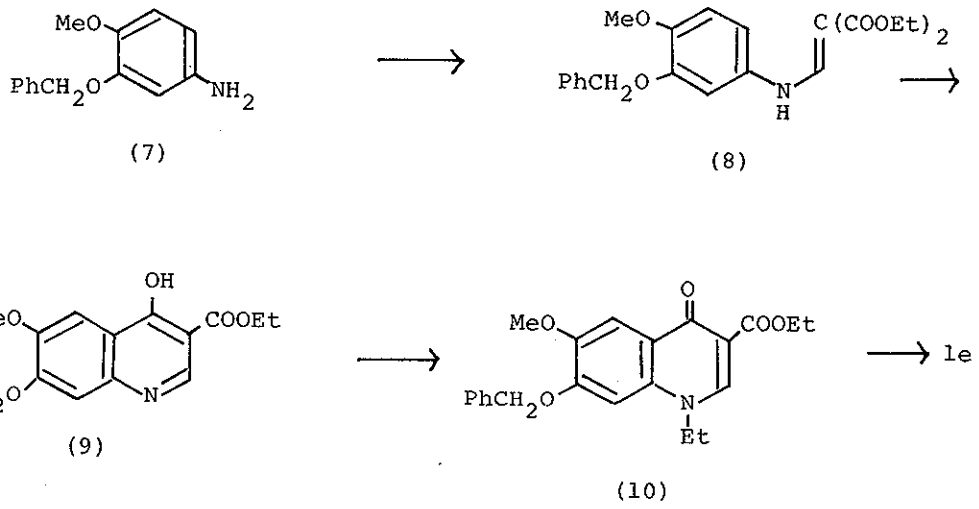


(6a) $R_1=H$; $R_2=OMe$
(6b) $R_1=Ph$; $R_2=OMe$
(6c) $R_1=Ph$; $R_2=OEt$
(6d) $R_1=Ph$; $R_2=SEt$

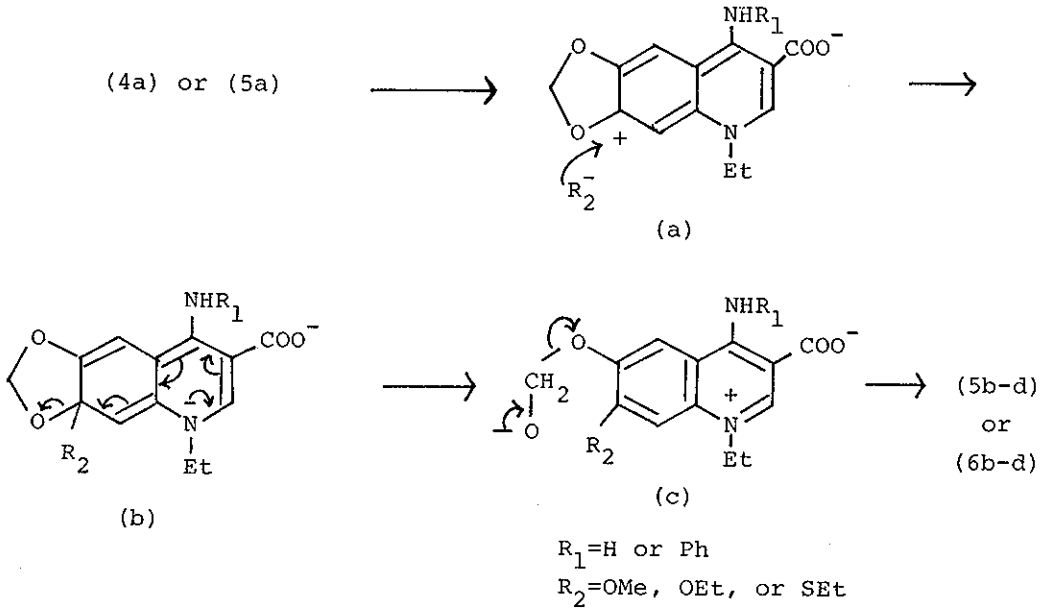
carboethoxy-6-hydroxy-7-methoxyquinolinium betaines (5b). We have become interested in this novel displacement reaction, because 1-ethyl-1,4-dihydro-6-hydroxy-7-methoxy-4-oxo-3-quinolinecarboxylic acid (1b),[4] which might readily be derived from 5b, has been known as one of the metabolites of oxolinic acid (1a).[5] This communication describes the reaction of 1-ethyl-6,7-methylenedioxyquinolines with alcoholic or thioethanolic potassium hydroxide, and the mechanism of the reaction is proposed.

When compound (3a) was refluxed in methanolic potassium hydroxide for 50 hr, there was obtained a mixture of a phenolic compound (5b) and 1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic acid (1a), which was separated into their respective pure forms, 5b, m.p. 319-320° (decomp.), and 1a, m.p. 315-316° (decomp.) in 70 and 4 % yields, respectively, on the basis of a differential solubility in dimethylformamide. The nmr spectrum of 5b indicates the absence of OCH_2O and OEt, the presence of OMe, NEt, and three aromatic protons. In order to determine the structure of 5b, compound (5b) was converted to the corresponding 4-oxo-3-quinolinecarboxylic acid (1b), m.p. 309° (decomp.); nmr (CF_3COOH-TMS): δ 1.83 (t, J=7Hz, CH_3), 4.32 (s, CH_3), 4.58 (q, J=7Hz, CH_2), 7.53, 8.12, and 8.92 (each s, ring protons); m/e 263 (M^+). On the other hand, 1-ethyl-1,4-dihydro-7-hydroxy-6-methoxy-4-oxo-3-quinolinecarboxylic acid (1e)[6] was synthesized in a four step sequence starting with 3-benzyloxy-4-methoxyaniline (7), as shown in Scheme 2. Condensation of 7 with diethyl ethoxymethylenemalonate gave diethyl 3-benzyloxy-4-methoxy-

Scheme 2



Scheme 3



anilinomethylenemalonate (8) in 88 % yield, which led to ethyl 7-benzyloxy-4-hydroxy-6-methoxy-3-quinolinecarboxylate (9) in 89 % yield by thermal cyclization with Dowtherm A. Ethylation of 9 with ethyl iodide and potassium carbonate in dimethylformamide afforded ethyl 7-benzyloxy-1-ethyl-1,4-dihydro-6-methoxy-4-oxo-3-quinolinecarboxylate (10) in 69 % yield. The compound (10) thus obtained was converted into 1e, by refluxing in concentrated hydrochloric acid, m.p. 265-266°; nmr (CF_3COOH-TMS): δ 1.82 (t, J=7Hz, CH_3), 4.3 (s, CH_3), 4.89 (q, J=7Hz, CH_2), 7.73, 8.05, and 9.18 (each s, ring protons); m/e 263 (M^+).

The samples of 1b and 1e were not identical with each other. Thus the structure of 1b and 5b were unambigously decided. Then the uv spectrum of 5b was taken in order to determine whether the structure exists in the betaine form or in the imino form. The similarity between the uv spectra of 5b [λ_{max}^{MeOH} 227 (log ε 4.53), 273 (4.47), 335 (4.00), and 348 nm (4.62)] and of 4-amino-3-carboxy-1-ethyl-6,7-methylenedioxyquinolinium betaine (5a)[3] [λ_{max}^{MeOH} 265 (log ε 4.46), 274 (4.36), 317 (3.89), 332 (3.94), and 347 nm (3.98)] rather than 1b suggests that compound (5b) may exist in the betaine form rather than in the tautomeric imino form (6a).

Compound (3a), likewise, reacted with ethanolic or thioethanolic potassium hydroxide to give the corresponding 4-amino-3-carboxy-7-ethoxy-1-ethyl- (5c) and 4-amino-3-carboxy-1-ethyl-7-ethylmercapto-6-hydroxyquinolinium betaine (5d) in 95 and 20 % yields, respectively, which led to 7-ethoxy-1-ethyl- (1c) and

1-ethyl-7-ethylmercapto-1,4-dihydro-6-hydroxy-4-oxo-3-quinoline-carboxylic acid (1d) by alkaline hydrolysis, respectively. The position of the ethoxy and ethylmercapto groups in 5c and 5d was assigned by analogy. Reaction of 3a with ethanolic potassium hydroxide at room temperature afforded 5a in 58 % yield, which was converted to a phenolic compound (5c) by treatment with potassium hydroxide in refluxing ethanol.

As an extention of this reaction, the reactions of 4-anilino-3-carboethoxy-1-ethyl-6,7-methylenedioxyquinolinium iodide (3b), obtained from 3-carboethoxy-4-chloro-1-ethyl-6,7-methylenedioxy-quinolinium iodide (2)[8] and aniline, with alcoholic or thioethanolic potassium hydroxide were carried out to afford 7-substituted compounds (6b-d) in 53, 87, and 78 % yields, respectively. The structure assignments for 6b-d are based upon elementary analysis, nmr, ir, and uv spectra, and their conversion to the corresponding 4-oxo-3-quinolinecarboxylic acids (1b-d). The uv spectrum of 6b [λ_{max}^{MeOH} 242 (log ε 3.45), 260 (4.41), and 279 nm (4.42)] which resembles that of 4b [λ_{max}^{MeOH} 243 (log ε 4.42), 265 (4.52), and 285 nm (4.46)] more closely than that of 3b [λ_{max}^{MeOH} 265 (log ε 4.68), 285 (4.62), and 330 nm (4.28)], indicates that the imino form (6b) may predominate over the tautomeric betaine form (5e). The reaction of 3b with one equivalent of ethanolic potassium hydroxide at room temperature afforded the ester (4b) in 90 % yield and the use of three equivalents of ethanolic potassium hydroxide gave the ester (4b) and the acid (4a) in 66 and 17 % yields, respectively. In agreement with the

aforementioned observation with 5a, compound (4a) was converted to 6c by treatment with potassium hydroxide in refluxing ethanol.

From these observations, this novel reaction is explained by a probable mechanistic pathway as given in Scheme 3.

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compound (1e) was synthesized for identification of a metabolite of oxolinic acid. No synthetic procedure for 1e, however, was not given.

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