

THE REACTION OF 4-CHLOROQUINOLINE 1-OXIDE WITH ACTIVATED
ACETYLENES: FURO[3,2-c]QUINOLINES

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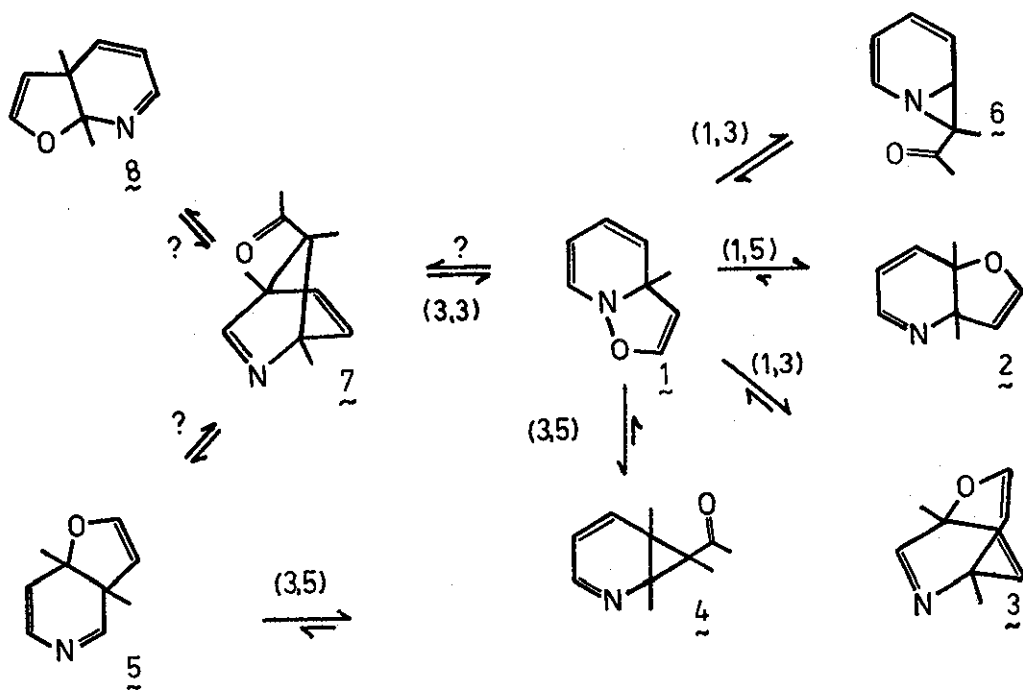
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4-Chloroquinoline 1-oxide and ethyl phenylpropiolate in boiling toluene give a mixture of 2- and 3-keto-alkylated products as well as ethyl 2-phenylfuro[3,2-c]quinoline-3-carboxylate. With ethyl acetylenedicarboxylate only low yields of the 2-keto-alkylated product and of the furoquinoline were formed. This is to be contrasted with the observation that 4-chloropyridine 1-oxide and phenylcyanoacetylene or ethyl phenylpropiolate give high yields of the corresponding furopyridine.

One of us¹ has proposed that when a pyridine 1-oxide reacts with an activated acetylene the 1,2-dihydropyridine (\downarrow) first formed rearranges rapidly and reversibly to an array of dihydropyridines (Scheme 1). The nature of the product formed is determined by the nature of the substituents present in the pyridine ring: irreversible

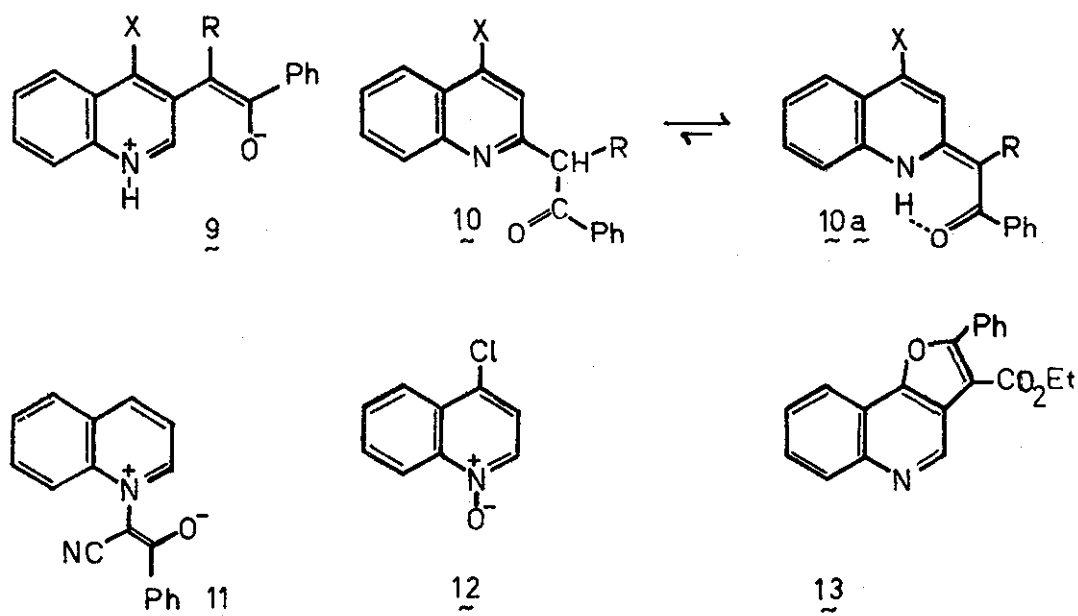
elimination of a suitable substituent appropriately located in one of the intermediates will shunt the equilibrium in the direction of one particular product.



Evidence has been presented for the intervention of $\mathcal{R}^{2,3}$, $\mathcal{R}^{2,4}$, $\mathcal{R}^{3,4}$ and \mathcal{R}^5 (see, however, ref. 4a for an alternate possibility). Evidence for the formation of \mathcal{R} has been sought but not found in the reaction of benzyne with appropriately substituted pyridine 1-oxides⁶.

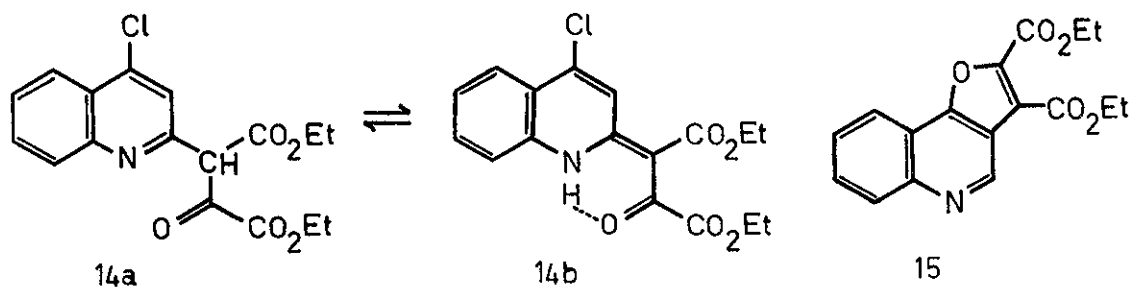
It seems highly probable that, in addition to the nature and position of the leaving or blocking substituents, other structural factors will have an important influence on the nature and ratios of products formed in these reactions. For example, 2,3-fusion of a benzene ring to the pyridine should destabilize intermediates \mathcal{R}

and $\underline{4}$ and render formation of $\underline{3}$ or $\underline{7}$ highly unlikely. 3,4-Fusion, as in isoquinoline 2-oxides,^{4b} on the other hand, would almost certainly make formation of $\underline{2}$, $\underline{3}$, $\underline{4}$, $\underline{7}$ and hence $\underline{4}$, much less likely. It was, therefore, of interest to study the behavior of 4-chloroquinoline 1-oxide ($\underline{12}$) to determine whether it would behave like 4-chloropyridine 1-oxide³ or like quinoline 1-oxide^{4b} which, with phenylcyanoacetylene, give 1-cyano-2-hydroxy-2-phenyl-1-(3-quinolyl)-ethylene ($\underline{9}$; R = CN; X = H) (25.7 %), benzoyl(2-quinolyl)acetonitrile ($\underline{10}$; R = CN; X = H) (11.3 %) and α -cyanoquinolinium phenacylide ($\underline{11}$) (8 %). Pyridine 1-oxide, on the other hand, gives a much higher yield (72.2 %) of β -substitution products in boiling benzene, with only a 2.5 % yield of α -substitution product and 0.4 % of ylide.^{4b}



When 12 was heated with ethyl phenylpropiolate in benzene at 70°C , the compound 9 ($X = \text{Cl}$; $R = \text{CO}_2\text{Et}$) (4.5 %) ⁷ [mp $109 - 110^{\circ}\text{C}$; nmr (CDCl_3) δ 13.80 (NH), 9.01 (s, 1, H_2), 8.60-7.02 (m, 9, ArH), 6.41 (s, α -CH; this suggests the presence of some keto form), 4.37 (overlapping quartets, 2, CH_2), 1.26 (overlapping triplets, 3, CH_3 ; the appearance of the ester protons also suggested the presence of some keto tautomer)] and 10 ($X = \text{Cl}$, $R = \text{CO}_2\text{Et}$) (8 %) [mp $148-149^{\circ}\text{C}$; nmr (CDCl_3) δ 16.81 (br s, 1, NH, exchanges with D_2O), 8.40-7.32 (m, 10, ArH), 3.92 (q, 2, CH_2), 0.76 (t, 3, CH_3); this compound is undoubtedly in the enaminoketone form $10a$ ⁸] were formed. When the reaction was carried out in boiling toluene, 9 (1.7 %) and 10 (7 %) were again obtained together with ethyl 2-phenylfuro[3,2-c]-quinoline-3-carboxylate (13) (6.2 %) [mp $132-133^{\circ}\text{C}$; nmr (CDCl_3) δ 9.30 (s, 1, H_4), 8.30-7.91 (m, 4), 7.70-7.22 (m, 5), 4.37 (q, 2, CH_2), 1.42 (t, 3, CH_3)]. No ylide corresponding to 11 was detected.

Reaction of 12 with diethyl acetylenedicarboxylate in boiling toluene gave none of the ylide or the product of β -substitution. Only low yields of the 2-alkylated product (3.1 %) ($14a \rightleftharpoons 14b$; 1:1 ratio in CDCl_3 solution estimated by nmr) [mp $91-92^{\circ}\text{C}$; nmr (CDCl_3) δ 13.96 (br, s, NH), 8.55-6.88 (m, 5), 5.12 (s, 0.5, α -CH), 4.55-4.00 (m, 4, CH_2), 1.54-0.88 (m, 6, CH_3)] and of the furo[3,2-c]quinoline 15 (3.7 %) [mp $72.5-73.5^{\circ}\text{C}$; nmr (CDCl_3) δ 9.39 (s, 1, H_4), 8.46-8.15 (m, 2), 7.91-7.54 (m, 2), 4.56 (q, 4, CH_2), 1.49 (t, 6, CH_3)] were obtained.



The results suggest that, as expected, the 3,5-sigmatropic shift leading to **4** is more difficult in this series than in the pyridine one, presumably because it would entail loss of aromaticity of the benzene ring, and that when ethyl phenylpropiolate is the reagent regiospecific ring opening of the cyclopropane ring in **4** to give 3-alkylated product and the second 3,5-shift leading to **5** (and thence to the furoquinoline) are more delicately balanced.

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