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THE OXIDATION AND DIELS-ALDER REACTIONS OF N-METHYL-3-ISOQUINOLONE[1]

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In the course of work on the alkylation of heterocyclic ambident anions[2,3] we have studied 3-hydroxyisoquinoline (1) and its alkylated derivatives. N-Methyl-3-isoquinolone (2) has been previously described as being unstable[4] and as deteriorating rapidly.[5] We report on the oxidation and Diels-Alder chemistry of this compound.

Alkylation of (1) with methyl iodide in a solution of sodium methoxide and methanol gave (2) as a yellow viscous oil. Treatment of (2) with boiling benzene exposed to air gave the N-methyl homophthalimide derivatives (3) and (4). The melting point of (3) and its oxime agree with literature values.[6,7] Spectral data confirmed the structure of (3): IR (Nujol, microns), 5.79 (C=O), 5.85 (C=O), and 5.97 (C=O); nmr (DMSO-d_6), 3.25 ppm. (s, 3H, NCH_3), 7.6-8.4 ppm., (m, 4H, aromatic protons); mass spectrum, molecular ion at m/e = 189.

The diketohydroxyhomophthalimide (4), m.p. 177-179° (decomp.) gave satisfactory elemental analysis. Spectral data were as follows: IR (Nujol, microns), 3.08 (OH,sharp), 5.86 (C=O), 6.00 (C=O); nmr (DMSO-d_6), 3.14 ppm. (s,3,NCH_3), 5.87 ppm. (s, 1, H_4), 7.4-8.1 ppm. (m,4,aromatic protons); mass spectrum molecular ion at m/e = 191. When dry DMSO-d_6 was used as the nmr solvent, the H_4 proton appeared as a doublet at about 5.8 ppm. and the hydroxyl proton as a doublet at about 6.8 ppm. When slightly acidified D_2O was added the two doublets collapsed and a sharp singlet appeared at 5.87 ppm. This sharp singlet must be due to the H_4 proton rather than the H_1 proton since the H_1 proton in isoquinoline systems normally appears downfield at

8.0-9.0 ppm. Compound (4) was also converted to (3) by the action of potassium dichromate in sulfuric acid.[6,7]

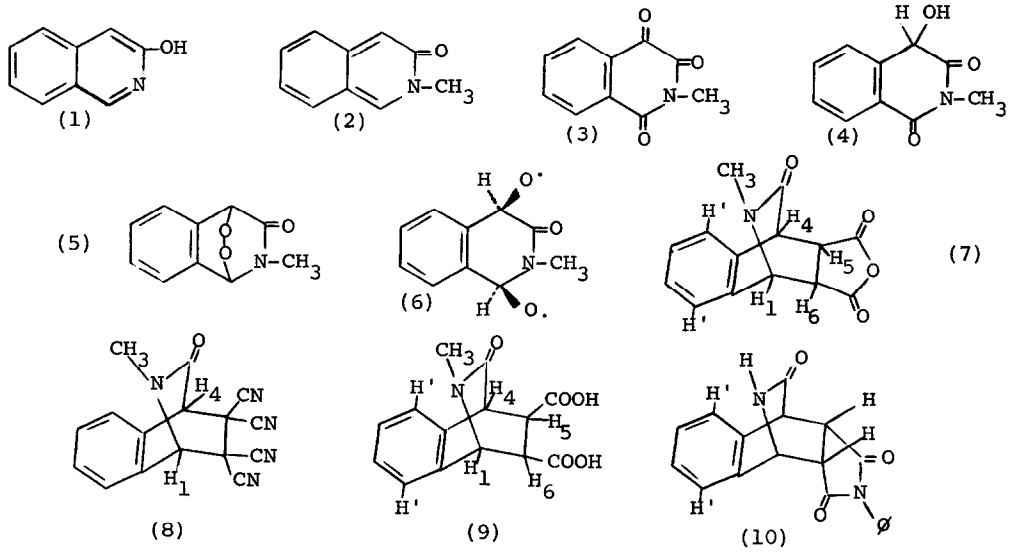
The yields of the oxidation products (3) and (4) were respectively 41% and 37% based on 3-hydroxyisoquinoline. Since methylation under these conditions normally yields 70-80% of methylated product (2), it follows that the two products (3) and (4) are produced in about equal amounts by auto-oxidation of the N-methylisoquinolone (2) and that they are the major products. A mechanism consistent with all of these facts involves the formation of an intermediate endoperoxide (5) *via* either normal free radical auto-oxidation or a single oxygen pathway. The endoperoxide (5) can then give the products (3) and (4) through one or more of a number of pathways. One mechanism which would account for the formation of approximately equal amounts of (3) and (4) involves the formation and homolytic cleavage of the endoperoxide (5) to give (6) which then undergoes a series of disproportionations. An ionic pathway would result from the loss of one of the acidic protons from either the 1- or the 4-position of the isoquinoline ring of (5) followed by opening of the endoperoxide bridge.

The facile air oxidation of (2) revealed a high chemical reactivity of the 1- and 4-positions of the 3-isoquinolone ring system. This led to treatment of (2) with maleic anhydride and tetracyanoethylene to form Diels-Alder adducts (7) and (8). Jones[5] has recently found that 3-hydroxyisoquinoline and 1-methyl-3-hydroxyisoquinoline react with N-phenylmaleimide to give the Diels-Alder adduct (10).

The adduct (7) was formed from (1) *in situ* in 50% yield, without isolation of the intermediate (2), by refluxing in chloroform for twenty minutes with a 10-fold molar excess of maleic anhydride: m.p. 229-230°; IR (Nujol, microns), 5.59 (C=O), 5.91 (C=O), and 6.00 (C=O); nmr (DMSO-d_6), 2.88 ppm., (s, 3H, NCH_3), 3.7-4.5 ppm., (m, 3H, H_4-H_5-H_6), 5.24 ppm., (m, 1H, H_1), 7.44 ppm., (s, 4H, aromatic protons); mass spectrum molecular ion m/e = 257.

Adduct (7) was hydrolyzed to give the dicarboxylic acid (9), m.p. 203.5-206.0° (decomp.); IR (Nujol, microns), 3.12 (OH), 4.0 (broad and weak, OH), 5.75 (C=O), 5.86 (C=O), and 6.16 (C=O); nmr (DMSO-d_6), 2.80 ppm., (s, 3H, NCH_3), 3.2-4.0 ppm., (m, 3H, H_4-H_5-H_6), 4.85 ppm., (m, 1H, H_1), 7.30 ppm. (s, 4H, aromatic protons); mass spectrum, the dicarboxylic acid (9) dehydrates to the anhydride (7) before electron impact and thus gives a mass spectrum

identical to that of (7) plus a large signal at m/e = 18 for water; elemental analysis (Calculated for $C_{14}H_{13}NO_5$: C, 61.09%; H, 4.76%; N, 5.09%; Found: C, 60.93%; H, 4.79%; N, 5.15%).



Based on the nmr spectral evidence, the adducts (7) and (9) are exo compounds. Jones[5] assigned endo structure to the adduct (10) because the two aromatic protons H' absorbed at 6.5 ppm. due to shielding by the carbonyl groups of the imide system. All seven of the other aromatic protons absorbed further downfield. Cava and Pollack[8] have used these arguments to assign endo and exo structures to N-phenylmaleimide adducts of similar sulfur bridged systems. Furthermore, they found that in the exo isomer, the shielding by the carbonyl groups is absent and that all of the aromatic protons absorb further downfield.

In the case of the adducts (7) and (9), all four of the aromatic protons including those designated H' absorb downfield (7.3-7.4 ppm). It is reasonable to assume that if the geometry of these adducts had been endo the protons H' would have been shielded by the carbonyl groups of the anhydride system and would have absorbed further upfield.

The tetracyanoethylene adduct (8) was prepared in 85% yield (based on compound 1) at room temperature in chloroform; m.p. 202° (decomp.); IR (Nujol, microns) 5.86 (C=O), 7.15, 13.20, 15.15; nmr (CD_3CN), 3.16 ppm. (s, 3H, NCH_3), 4.98 ppm (s, 1H, H_4), 6.00 ppm. (s, 1H, H_1), and 7.75 ppm. (s, 4H, aromatic protons). It gave satisfactory elemental analyses and the nmr spectrum was in complete agreement with the proposed structure. The IR spectrum of adduct (8) exhibits the expected carbonyl absorption but essentially no absorption due to the nitrile groups was observed. The oxygen containing functional groups evidently quenched the nitrile group absorption.[9]

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