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RING EXPANSION OF ANTHRANIL TO QUINOLINE 1-OXIDES (1)

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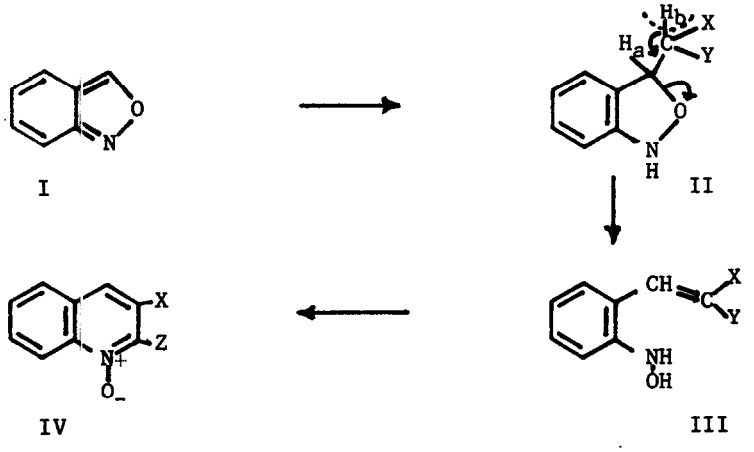
It is well known that anthranil (I) reacts with alkoxides, strong alkali, barium hydroxide, etc. to give esters or salts of anthranilic acid, while certain other bases such as hydroxylamine and hydrazines give rise to derivatives of o-hydroxylaminobenzaldehyde (2). We have found that a variety of active methylene compounds ($NC-CH_2-Y$ and EtO_2C-CH_2-Y) react with I to give quinoline 1-oxides (IV) in almost quantitative yield.

Thus, anthranil and malononitrile in ethanol solution in the presence of a catalytic amount of piperidine react exothermically with the instantaneous separation of 2-amino-3-cyanoquinoline 1-oxide in quantitative yield. Ethyl cyanoacetate and cyanoacetamide react analogously with I. With less reactive methylene components (dimethyl malonate, phenylsulfonyl acetonitrile) it was advantageous to employ their sodium or potassium salts, which led to rapid separation of the corresponding salts of the quinoline 1-oxide. Table I lists the compounds prepared by this ring expansion reaction.

TABLE I

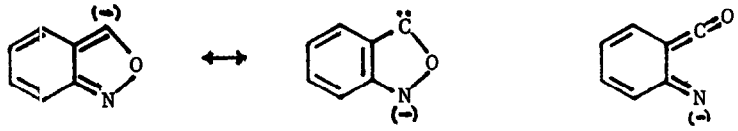
Active methylene reagent	Product	Yield
Malononitrile	2-Amino-3-cyanoquinoline 1-oxide	99
Ethyl cyanoacetate	1-Hydroxy-3-cyano-2(1H)-quinolinone	97
Cyanoacetamide	2-Amino-3-carbamoylquinoline 1-oxide	98
Dimethyl malonate	1-Hydroxy-3-carbomethoxy-2(1H)-quinolinone	80
Phenylsulfonyl acetonitrile	2-Amino-3-phenylsulfonylquinoline 1-oxide	82

We believe that this conversion of anthranil to quinoline 1-oxides is initiated by addition of the anion of the active methylene component to the 3-position of anthranil (3) to give the adduct II.



Abstraction of the acidic methylene proton (H_b) by the basic catalyst with consequent cleavage of the O_2-C_3 bond gives an o-hydroxylaminobenzylidene derivative (III) of the active methylene compound. Subsequent ring closure by intramolecular addition of the -NHOH grouping to either the -CN or -COOR grouping of III gives IV.

It has been claimed (4) and recently reemphasized (2) that the reaction of anthranil with bases involves the preliminary abstraction of the C-3 proton to give an incipient carbene (V) or ketene (VI), which then leads to product by



readdition of the base. We have shown this interpretation to be untenable under the conditions employed here. A solution of I in DMSO solution containing D_2O and triethylamine failed to undergo exchange of the C-3 proton even after 3 days, as judged by nmr spectroscopy. Moreover, the nmr spectrum of 2-amino-3-cyano-quinoline 1-oxide, isolated from the reaction of I with malononitrile in DMSO solution containing triethylamine and D_2O, showed the C-4 proton as a sharp singlet at 9.1 ppm, integrating for one proton, thus indicating that no exchange (as required by the participation of either V or VI) had taken place. It seems likely that all ring cleavage reactions of anthranil initiated by bases proceed by addition at C_3 followed by cleavage either of the N_1-O_2 bond (to give derivatives of anthranilic acid), or of the O_2-C_3 bond (to give derivatives of o-hydroxylaminobenzaldehyde)(5).

REFERENCES

1. This work was supported by a generous grant to Princeton University from the Smith Kline and French Laboratories, Philadelphia, Pa.

2. K.-H. Wunsch and A. J. Boulton in Advances in Heterocyclic Chemistry, Vol. VIII, (A. R. Katritzky and A. J. Boulton, eds.) Academic Press, N. Y., In Press, pp. 303-342.

3. This presumed position of initial attack corresponds to a Michael addition to the α,β-unsaturated anil system present in anthranil.

4. G. Del Re, Tetrahedron, 10, 81 (1960).

5. The mode of cleavage will depend not only upon the relative acidities of H_a and H_b, but also upon the fate of the products formed upon ring opening. Thus, with hydroxide ion as the base, H_b is more acidic than H_a, but O_2-C_3 cleavage gives o-hydroxylaminobenzaldehyde itself, which reforms anthranil under the reaction conditions. O_2-C_3 cleavage in this case should thus be reversible, and the actual product isolated (e.g., sodium anthranilate) is the result of irreversible cleavage of the N_1-O_2 bond.