Tetrahedron Letters No. 12, pp. 785-790, 1963. Pergamon Press Ltd.
Printed in Great Britain.

ADDITION REACTION OF NITRILE OXIDES ON AROMATIC NITROSODERIVATIVES. A NOVEL SYNTHESIS OF THE BENZIMIDAZOLE RING

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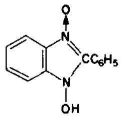
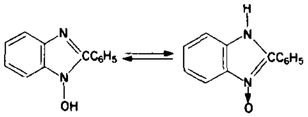
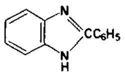
(Received 15 February 1963)

In pursuing our researches on the addition of nitrile oxides on unsaturated systems (1),we have studied the reaction of benzonitrile oxide with aromatic nitrosoderivatives. Nitrosobenzene and benzonitrile oxide react readily in ether solution at room temperature giving an adduct $C_{13}H_{10}O_2N_2$,m.p.216°dec.;the product yields a mono-hydrochloride and dissolves undecomposed in aqueous alkali. The two oxygen atoms are directly bounded to nitrogen,and are easely removed by reducing agents. Cautious reduction with tin chloride and hydrochlorid acid affords a product $C_{13}H_{10}ON_2$ (benzoylderivative m.p.118°),whereas on prolonged treatment with the same reagent,or on catalytic hydrogenation of the sodium salt and of the hydrochloride in the presence respectively of Raney nickel or platinum,2-phenylbenzimidazole (III),m.p.294°,is formed.On the basis of the above results,structures (I) and (IIa,b) can be assigned to the adduct and its product of partial reduction.

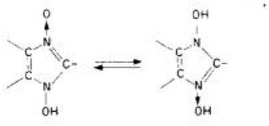

I


IIa IIb

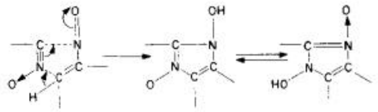

III

Final confirmation of the structure of (II) has been provided by synthesis (reduction of o-nitrobenzanilid with ammonium sulphide).

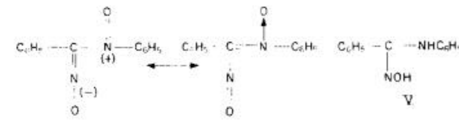
Although formulas like (IIa,b) have been suggested for the so-called oxobenzimidazoles (2),no product containing structure (I) has so far been reported; it offers the possibility of the new type of tautomerism:



On the basis of the interpretation which has been postulated for the so-called 1,3-dipolar cycloaddition (3), the formation of (I) could be represented by the scheme:

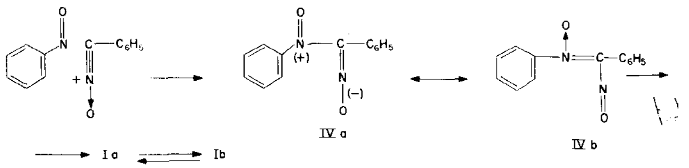


which is similar to that generally accepted for the dimerization of nitrile oxides to furoxans. However, the investigation of the reaction course at low temperature has led us to discard this mechanism. Nitrosobenzene and benzonitrile oxide give at -20° in ether a yellow crystalline adduct (m.p.71°dec.) isomeric of (I). The product exhibits a neutral character; it is fairly stable in the solid state but when dissolved in an indifferent solvent readily rearranges at room temperature with evolution of heat giving (I). This changement, conjointly with the fact that the new product yields N-phenylbenzamidoxime (V), m.p.136°, on catalytic hydrogenation at low temperature, suggests that the primary product of the addition may possess a structure of type(IVa,b

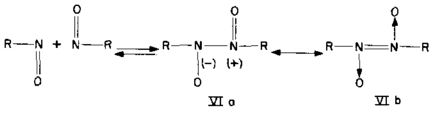


IV a IV b V

The yellow compound (IV) would therefore represent the precursor of (I) in the reaction led at ordinary temperature, as shown by the scheme:



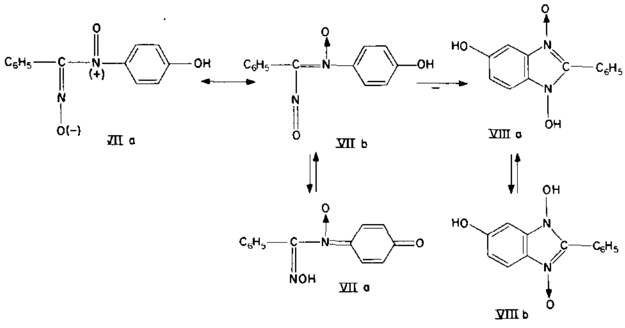
The initial step of the reaction of benzonitrile oxide with nitrosobenzene would be therefore similar to the dimerization of nitrosoderivatives:



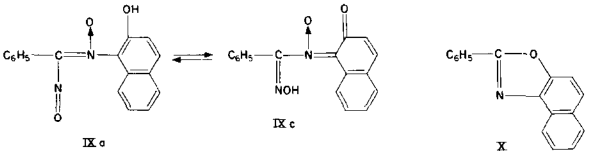
Recent investigations (4) have shown that the contribution of form (VI b) to the resonance of the system is considerably larger than that of form (VI a); it appears reasonable to suppose that similarly in our case the contribution of form (IV b) is prevalent.

The results above reported indicate that the cycloaddition reactions of nitrile oxides could hardly be constrained in a single rigid scheme in which a synchronous shift of electrons results in the formation of two new σ-bonds, particularly in those cases (for instance, addition to quinones) in which the cycloaddition is catalyzed by bases, a fact that would be in favour of an initial nucleophilic attack on the nitrile oxide followed by ring closure.

The general character of the reaction of nitrile oxides with aromatic nitrosoderivatives is demonstrated by the fact that even nitrosocompounds which present the $>\mathrm{C{-}NO} \rightleftarrows >\mathrm{C{=}NOH}$ tautomerism undergo the addition. However, the presence of substituents in the aromatic ring of the nitrosoderivative affects the stability of the intermediate product, and determinate[5] the ultimate course of the reaction. Thus, in the case of p-nitrosodimethylaniline, even when the temperature was kept at -20°, no intermediate of type (IV) could be isolated, and the benzimidazole derivative was the only product obtained.P-nitrosophenol reacts more slowly and yields,even at ordinary temperature,an adduct (m.p.138° dec.) remarkably stable.It possesses structure (VII a,b),as results from its reduction to N-(p-hydroxyphenyl)benzamidoxime (m.p.178°) and its rearrangement to the benzimidazole (VIII a,b) on brief heating at 60°-70° in an inert solvent.

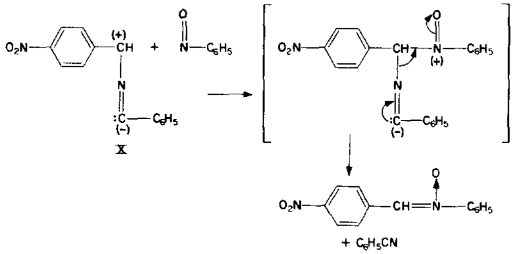


The reduced reactivity of p-nitrosophenol is probably attributable to the tautomeric equilibrium nitrosophenol $\rightleftarrows$ quinone monoxime,and the enhanced stability of adduct (VII) depends on the possibility of tautomerism VII b $\rightleftarrows$ VII c. The behaviour of 1-nitroso-2-naphtol strongly supports this view; either at -20° or at room temperature it affords a stable adduct which possesses structure(IX a,b),as demonstrated by reduction to N-(2-hydroxynaphthyl)benzamidoxime (identifyied through cyclization to the known phenylnaphtoxazole X),and cannot be converted on heating into the benzimidazole derivative.



Its stability is obviously due to the fact that no ortho position is available for cyclization. Whereas adduct (VII) from p-nitrosophenol seems to be present mostly in its phenolic form (VII b)(ready solubility in alkali,absence of bands in the carbonyl region of its I.R. spectrum, easy cyclization to benzimidazole) the product obtained from 1-nitroso-2-naphtol appears to exist chiefly in the quinonic form (IX c)(strong band at 5,9 μ in the I.R. spectrum).

It is probable that the reaction recently investigated (5) of nitrosobenzene with nitrilylidenes (XI), which contain a reactive system resembling in many respects that of nitrile oxides and leads to nitrones, may follow a mechanism similar to that suggested above. Also for this reaction had been postulated a mechanism involving a 1,3-dipolar addition followed by elimination of benzonitrile. In our opinion, this reaction follows most probably the course:


X

Acknowledgements. We are indebted to the Consiglio Nazionale delle Ricerche for the financial support of the plan of research on nitrile oxides chemistry.

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