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THE BASE-INDUCED DECOMPOSITION OF N-NITROSO-N-METHYLUREA

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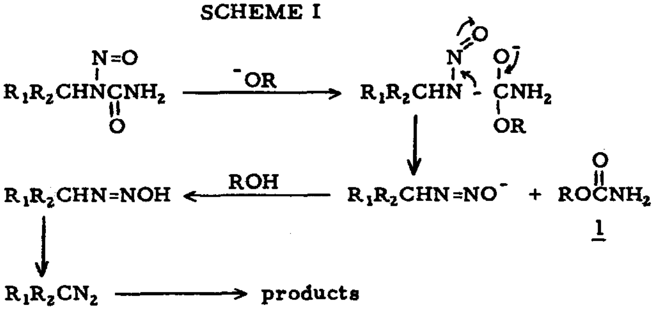
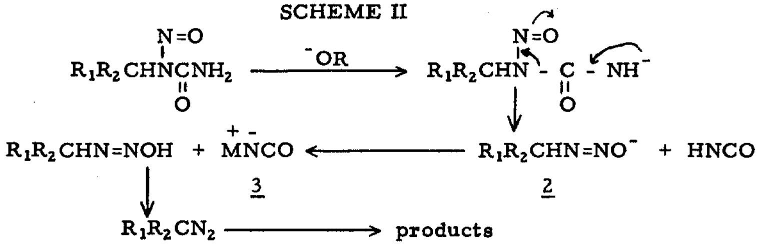
To date three mechanisms have been proposed for the base-induced decomposition of N-nitroso-N-alkylureas. A mechanism involving initial nucleophilic attack on the carbonyl moiety of the urea (Scheme I) had been assumed[1,2] to be correct, by analogy with the decomposition of N-nitrosoamides and urethanes,[3-5] until it was correctly shown by Jones, Muck and Tandy[6] that carbamate 1, which should have been generated as a stable product during the course of the reaction, was not formed.

SCHEME I



An alternate mechanism (Scheme II) involved initial abstraction of a proton from the urea nitrogen. A salient feature of the scheme was the generation of a diazotate (2) and a cyanate (3), both of which were observed reaction products.[6-8] However, Jones and his coworkers[6] rejected this mechanism for the decomposition of N-nitroso-N-(2,2-diphenylcyclopropyl)urea on the basis of the observed stability of lithium-2,2-diphenylcyclopropyldiazotate (2) to lithium ethoxide and to isocyanic acid in tetrahydrofuran. As an alternative they proposed a third mechanism (Scheme III), involving initial nucleophilic attack on the nitroso moiety of the urea and subsequent intramolecular proton transfer. The intermediate 4 could then afford the unstable diazohydroxide 5[9] or the diazoether 6, either of which would decompose to the observed products, presumably *via* a diazocyclopropane inter-

SCHEME II

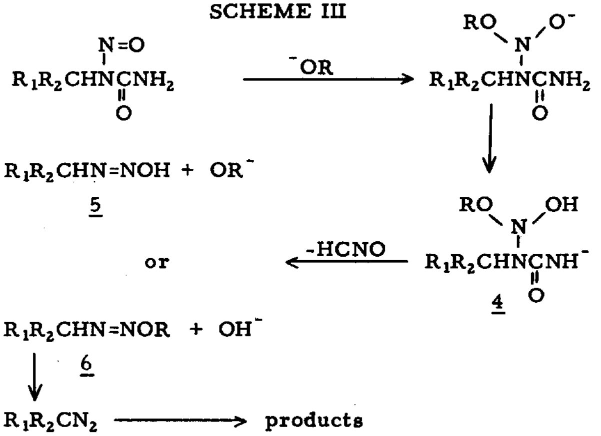


mediate. Evidence consistent with this mechanism[10, 11] had been reported prior to the work of Jones, *et al.*,[6] who provided some additional supporting evidence. The mechanistic conclusions reached by Jones, *et al.*[6] were limited to a discussion of the decomposition of N-nitroso-N-(2,2-diphenylcyclopropyl)urea. Unfortunately, at least one subsequent review has extrapolated these results further, indicating their validity for "several nitrosoureas."[12] We therefore wish to discuss our findings for the simplest member of the N-nitroso-N-alkylurea series, namely N-nitroso-N-methylurea, which apparently decomposes by a different mechanism than N-nitroso-N-(2,2-diphenylcyclopropyl)urea.

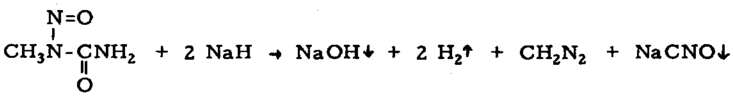
In light of the reports[7, 13] that treatment of diazotates with water gives rise to gas evolution and products derived from diazoalkanes and carbonium ions, presumably *via* initial proton abstraction from water (pKa 16), the observed stability of lithium 2,2-diphenylcyclopropyldiazotate (2) to isocyanic acid (pKa 3.9[14]; Scheme II) seemed curious. We wish to report that the diazotate derived from N-nitroso-N-methylurea did not share this stability, but reacted with isocyanic acid (1:1 molar ratio, 0°C, tetrahydrofuran) to afford gas evolution (N_2) and, in the presence of suitable reactants, products derived from diazomethane, as would be predicted on the basis of acid-base equilibria. Since Jones and his coworkers had also pointed out that the diazotate derived from the methoxide-induced decomposition of N-nitroso-N-benzylcarbamate was protonated by methanol prior to its conversion to a diazoalkane, it was also puzzling that the corresponding diazotate, derived from N-nitroso-N-(2,2-diphenylcyclopropyl)urea, was reported stable to the reaction conditions that would have resulted from treatment of the urea with lithium ethoxide.[6] This treatment consisted of the combination of the diazotate, as the lithium salt, with one equivalent of lithium ethoxide. These conditions, however, are not analogous to those under which the urea was originally decomposed, since the equivalent of lithium ethoxide added to the urea was utilized in the generation of the diazotate itself. Having generated the diazotate, no lithium ethoxide would be present in the reaction mixture, but an equivalent of ethanol would have been formed. In our hands, treatment of the diazotate derived from N-nitroso-N-methylurea with ethanol, under conditions actually analogous to those used for decomposition of the urea (tetrahydrofuran, 0°C), resulted in gas evolution and the immediate destruction of methyl diazotate. The product distribution (80% diazomethane; 20% diazotate) was very similar to that reported by Jones, *et al.* [6] for the decomposition of N-nitroso-(2,2-diphenylcyclopropyl)urea with a single equivalent of lithium ethoxide in ether (76% gas evolution; 75% diphenylallene; 17% diazotate). The mechanism outlined in Scheme II may not, therefore, be eliminated as a mechanistic possibility for the formation of diazomethane, on the basis of published work.

At least two lines of evidence may be offered in support of the proton abstraction

SCHEME III



mechanism (Scheme II) for the decomposition of N-nitroso-N-methylurea, neither of which is consistent with the mechanism outlined in Scheme III. First, the decomposition of N-nitroso-N-methylurea could be effected by sodium hydride in dry 1,2-dimethoxyethane to afford CH_2N_2, [15] according to the equation



$$CH_3\overset{N=O}{\overset{|}{N}}\text{-}\underset{\underset{O}{\|}}{C}NH_2 + 2\,NaH \rightarrow NaOH\downarrow + 2\,H_2\uparrow + CH_2N_2 + NaCNO\downarrow$$

In a molecular environment which contains the relatively labile urea protons (pKa 16 [14]), it seems reasonable to suggest that a strong base, such as sodium hydride (pKa 40), might effect proton abstraction *directly* from the urea, rather than *via* initial addition to the nitroso moiety in nucleophilic fashion, thereby generating the much weaker nitroso anion (pKa ~10-12)[16] as a prelude to intramolecular proton abstraction. Consistent with this interpretation is the observation that the diazomethane derived from the decomposition of N-nitroso-N-methylurea with sodium hydride could be employed in the quantitative conversion of an equivalent amount of *p*-nitrobenzoic acid to its methyl ester. On the other hand, the mechanism outlined in Scheme III predicts the formation of methyl diazene, CH_3-N=N-H, from the reaction of sodium hydride with N-nitroso-N-methylurea. This species has been reported[17] to be "surprisingly stable" in aqueous base, and to decompose over a period of hours in that medium to methane and nitrogen, but not to diazomethane.

An additional line of evidence may be inferred from the decomposition of N-nitroso-N-methylurea with triethylamine, a reasonably strong base (pKa 10.65) which exhibits poor nucleophilic character due to steric constraints. This decomposition proceeds readily at room temperature to afford gas evolution (N_2) and products derived from diazomethane. The results of decomposition obtained for N-nitroso-N-(2,2-diphenylcyclopropyl)urea and N-nitroso-N-methylurea may be compatible on the basis of stereochemical considerations of the intermediate diazotates. Similar differences in reactivity exist between *syn*-alkyl diazotates and their *anti* isomers.[18] This aspect of the decomposition is currently under investigation.

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15. The decomposition could not have been effected by sodium hydroxide, either present in trace amounts in the sodium hydride or generated during the course of the reaction, since N-nitroso-N-methylurea was found to be stable to a suspension of sodium hydroxide in 1,2-dimethoxyethane under the reaction conditions.
16. We estimate this pKa on the basis of the pKa of 7-9 associated with a variety of oximes. See, e.g., ref. 14.
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