

Rapid Nitrosation of Amines in Aqueous Alkaline Solutions by β -Substituted Alkyl Nitrites

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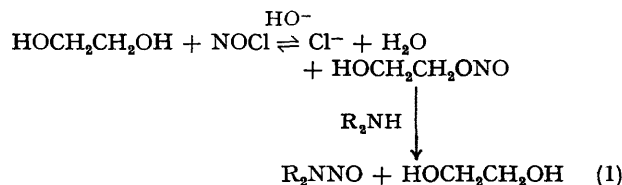
Summary Alkyl nitrites bearing β -electron withdrawing substituents, either synthesized independently (*e.g.* 2-ethoxyethyl nitrite) or formed *in situ* by reaction between nitrosyl gases and an alcohol or carbohydrate group, effect the rapid nitrosation of basic secondary amines in 0.1 M NaOH at 25 °C.

THE nitrosation of amines in aqueous acidic solutions (pH < 4) is well documented,¹ but much less is known about these reactions in non-acidic media. The only reagents for the formation of *N*-nitrosamines in neutral or alkaline aqueous solutions are nitrite in the presence of either acetaldehyde or chloral,² certain aliphatic and aromatic nitro-compounds,³ β -phenethyl nitrite (in aqueous dioxan),⁴ and nitrosyl gases such as N_2O_3 ,⁵ N_2O_4 ,⁵ and NOCl.⁶ Of these, only the nitrosyl gases react at a substantial rate at ambient temperatures. We now report that alkyl nitrites bearing electron-withdrawing β -substituents (either synthesized independently or formed *in situ* by reaction of nitrosyl gases with the corresponding alcohols)

also form *N*-nitrosamines readily under alkaline conditions. These reagents have been reported in the patent literature,⁷ but their capacity to effect *N*-nitrosation in aqueous base has apparently not been realised.

In the absence of alcohols, 1.14×10^{-2} M gaseous NOCl reacts completely in 4 min (time of analysis) with 2×10^{-3} M piperidine in 0.1 M NaOH to give *ca.* 7×10^{-4} M *N*-nitroso-piperidine in addition to NO_2^- by hydrolysis.⁶ Both gaseous N_2O_3 and N_2O_4 react similarly.⁵ Addition of 8% v/v (1.72 M) alcohol (*e.g.* MeOH, EtOH, or Bu^tOH) to the solution prior to reaction reduces the yield of *N*-nitroso-piperidine by *ca.* 90% and the corresponding alkyl nitrite is obtained instead. Further, the amount of *N*-nitroso-piperidine remains constant on leaving the reaction solution for 24 h. This demonstrates that alcohols and alkoxide ions react more readily with nitrosyl gases than HO^- and H_2O , and that simple alkyl nitrites are ineffectual nitrosating agents in the absence of acids. Addition of *ca.* 1.5% v/v (0.5 M) polyhydric alcohol (*e.g.* ethylene glycol) to the aqueous reaction solution has an entirely different effect.

The amount of *N*-nitrosopiperidine formed after 4 min is lowered (*ca.* 4×10^{-4} M), but its concentration steadily increases over a period of 100 min to reach a maximum of 2×10^{-3} M. This suggests that 2-hydroxyethyl nitrite is an effective nitrosating agent for alkylamines in aqueous alkaline solutions [equation (1)].



Confirmation of this deduction was obtained by synthesizing 2-ethoxyethyl nitrite (EtOCH₂CH₂ONO)⁷ and investigating its reactions in aqueous base. In the absence of amine, hydrolysis to nitrite occurred relatively rapidly in accordance with rate = 8.26×10^{-4} l mol⁻¹ s⁻¹ [EtOCH₂CH₂ONO][NaOH] at 25 °C. In the presence of piperidine

TABLE 1. Reaction of 2-ethoxyethylnitrite with secondary amines in 0.1 M NaOH at 25 °C

10^3 [EtOCH ₂ CH ₂ ONO]/M	10^2 [Amine]/M	10^3 k_0 /s ⁻¹
0.726	0.83 Piperidine	2.55 ^a
"	1.67 "	4.15 ^a
"	2.38 "	5.85 ^a
1.90	0.059 "	0.60 ^b
5.10	0.059 "	1.59 ^b
6.11	0.059 "	2.22 ^b
10.1	0.059 "	3.20 ^b
0.726	11.6 Morpholine	0.365 ^a
"	23.2 "	0.710 ^a
"	34.6 "	0.940 ^a
"	45.0 "	1.26 ^a

^a Rate = k_0 [EtOCH₂CH₂ONO]. ^b Rate = k_0 [amine].

or morpholine, however, the corresponding *N*-nitrosamines formed concurrently. Data summarised in Table 1 show their formation followed rate = k_a [EtOCH₂CH₂ONO][amine] with $k_a = 0.278$ and 0.0031 l mol⁻¹ s⁻¹ at 25 °C for piperidine and morpholine, respectively. Thus, towards 2-ethoxyethyl nitrite, piperidine and morpholine are more reactive than HO⁻ by factors of 320 and 3.7, respectively.

TABLE 2. Effect of alcohols and carbohydrates on the reaction of gaseous 1.14×10^{-2} M NOCl with 2×10^{-3} M piperidine in 0.1 M NaOH at 25 °C

Additive	10^4 [N-Nitrosopiperidine]/M ^a	t_{max} /min
0.25 M F ₃ CCH ₂ OH	17	25
0.25 M FCH ₂ CH ₂ OH	16	120
0.05 M (HOCH ₂ CH ₂) ₃ N	10.5	100
0.05 M D-glucose	20	8
0.05 M D-mannose	20	20

^a Maximum yield

The catalysis in aqueous base is not restricted to 1,2 diols. Results summarised in Table 2 show that substantial yields of *N*-nitrosopiperidine are also obtained rapidly in the presence of both β -fluoro- and β -amino-alcohols, and carbohydrate groups. As expected, the rate at which the maximum yield of *N*-nitrosopiperidine is gained relates to the electron-withdrawing capability of the β -substituent.

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