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# FORMATION OF N-ALKYL-N-(1-HYDROPEROXYALKYL)NITROSAMINES FROM N-ALKYL-N-(1-ACETOXYALKYL)NITROSAMINES[1]

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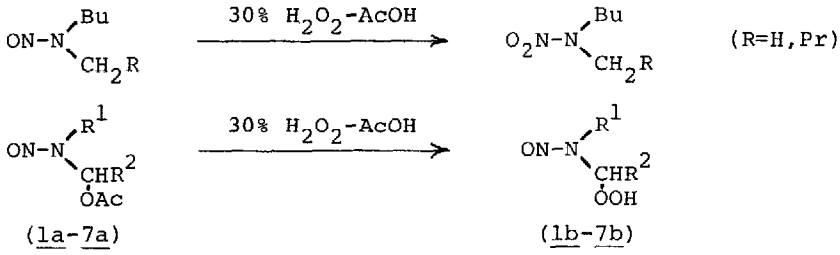
Abstract: N-Alkyl-N-(1-hydroperoxyalkyl)nitrosamines were prepared by treatment of the corresponding 1-acetoxyalkyl nitrosamines with hydrogen peroxide in acetic acid through an acid-catalyzed nucleophilic substitution.

Carcinogenic and mutagenic N,N-dialkylnitrosamines require metabolic activation. One probable pathway by which these compounds are transformed into biologically effective species is through α-hydroxylation.[2] By enzyme-mediated hydroxylation of the α-carbon atom, the nitrosamines are converted into unstable intermediates, N-alkyl-N-(1-hydroxyalkyl)nitrosamines, which spontaneously decompose to provide reactive electrophilic species capable of alkylating biological nucleophiles. Because of their high reactivity, none of these intermediates has so far been isolated and their role in carcinogenesis and mutagenesis has not been directly investigated.

N-Alkyl-N-(1-acetoxyalkyl)nitrosamines have been receiving considerable attention,[3] since on enzymatic hydrolysis, they may yield the 1-hydroxyalkyl compounds.[4] In our studies on the chemical reactivity of 1-acetoxyalkyl nitrosamines, the formation of N-alkyl-N-(1-hydroperoxyalkyl)nitrosamines by treatment of 1-acetoxyalkyl compounds with hydrogen peroxide was observed. The hydroperoxides formed are found to be good precursors for the synthesis of the 1-hydroxyalkyl nitrosamines.[5]

N,N-Dialkylnitrosamines are known to be oxidized at the nitroso function with trifluoroperacetic acid to the corresponding dialkylnitramines.[6] Oxidation of N,N-dibutylnitrosamine with 30% hydrogen peroxide (10 mol equivalent) in acetic acid at 50°C for 24 h gave N,N-dibutylnitramine in 45% yield with recovery of the starting material in 32%. The same treatment of N-butyl-N-methylnitrosamine afforded the corresponding nitramine in 39% yield and the recovery in 32%. Under similar conditions, 1-acetoxyalkyl nitrosamines, prepared as described previously,[7] were converted to the corresponding 1-hydroperoxyalkyl nitrosamines.




(1a-7a) (1b-7b)

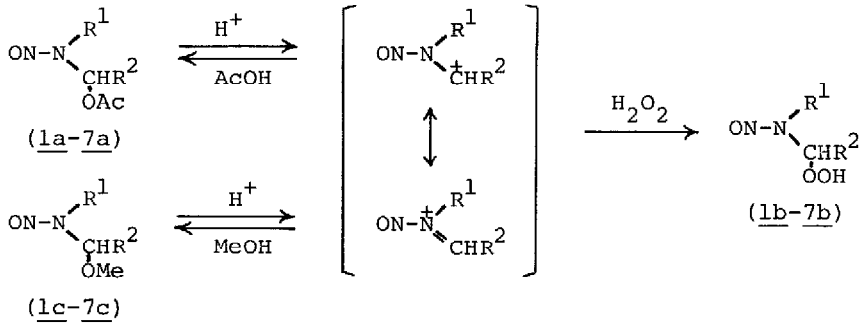
Table. Preparation and spectral properties of N-alkyl-N-(1-hydroperoxyalkyl)nitrosamines

| Compound | $R^1$ / $R^2$ | Time[a] h | Yield[b] % | UV(EtOH) nm(ε) | IR(neat)[c] $cm^{-1}$ O-H / N=O | NMR($CDCl_3$) ratio[d] % (E) / (Z) | δ (TMS) HOO | O-CHX-N (E) / (Z) | N-$CH_2$X (E) / (Z) | X[e] |
|---|---|---|---|---|---|---|---|---|---|---|
| 1b | Me / H | 2 | 18 | 227(7100) / 362( 80) | 3200 / 1460 | 97 / 3 | 10.35 | 5.83 / 5.23 | 3.12 / 3.91 | |
| 2b | Et / H | 2 | 28 | 230(6500) / 366( 73) | 3250 / 1450 | 94 / 6 | 9.90 | 5.75 / 5.14 | 3.63 / 4.26 | 1.09 / 1.43 |
| 3b | Pr / H | 2 | 24 | 230(6300) / 366( 74) | 3250 / 1460 | 93 / 7 | 9.91 | 5.81 / 5.19 | 3.59 / 4.22 | 1.54 / 0.87 |
| 4b | Bu / H | 2 | 29 | 231(6800) / 366( 79) | 3250 / 1460 | 94 / 6 | 10.13 | 5.81 / 5.21 | 3.63 / 4.27 | 1.4 / 0.95 |
| 5b | tert-Bu / H | 0.5 | 19 | 237(5200) / 384( 61) | 3250 / 1430 | 7 / 93 | 9.47 | 5.93 / 5.28 | | 1.41 / 1.60 |
| 6b | Bu / Pr | 1 | 53 | 231(6900) / 358( 71) | 3250 / 1460 | | 10.45 | 6.16 | 3.53 | 1.5 / 1.0 |
| 7b | Me / Pr | 1 | 21 | 228(7500) / 353( 72) | 3200 / 1460 | | 9.73 | 6.18 | 2.97 | 1.6 / 1.0 |

a) Reaction time at 50°C. b) Yeilds were not optimized, and up to 40% of unreacted acetates were recovered in the syntheses of 1b-5b, where prolonged heating did not increase the yield of the product because of the subsequent decomposition, but decreased the recovery of the starting material. c) 5b was a crystal of mp. 57°C(decomp.) and was measured as KBr disk. d) (E)/(Z) isomer ratio was determined by the peak-height ratio in NMR, and those of 6b and 7b were not measurable on the basis of their NMR. e) X shows alkyl or H.

In a typical experiment, N-butyl-N-(1-acetoxybutyl)nitrosamine (6a) (20 mmol) in acetic acid (25 ml) was treated with 30% hydrogen peroxide (200 mmol) at 50°C for 1 h. Water and methylene chloride were added to the reaction mixture and the product was extracted with methylene chloride. The organic layer was washed with water and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to give a yellow oil which was purified by silica gel column chromatography. Elution the column with a mixture of hexane, ether, and

methylene chloride (8 : 3 : 2) afforded N-butyl-N-(1-hydroperoxybutyl)nitrosamine (6b) in 53% yield. The product, 6b, liberates iodine from potassium iodide, and has a correct elemental analysis and reasonable spectral properties as its structure. Other hydroperoxides were prepared similarly and are listed in Table. NMR, IR, and UV spectral data which established the structure are also shown in the table.




The reaction of 6a in formic acid instead of acetic acid was carried out at a low temperature of 25°C, but the yield was low because of the subsequent decomposition of the product. Methanol served as the solvent for the reaction of 4a and 6a, although the rate was slow and the yield of the hydroperoxides was low, and the major products of the reaction were the corresponding 1-methoxyalkyl compounds, 4c and 6c, respectively. This reaction was accelerated by the addition of hydrochloric acid; the rate of the decrease of 6a (44 mM) and the concomitant increase of 6b and 6c was accelerated about 10 times in the presence of 2.5 mM hydrochloric acid. Without hydrogen peroxide, the 1-acetoxyalkyl compounds, 4a and 6a, were converted into the corresponding 1-methoxyalkyl compounds, 4c and 6c, respectively, easily by methanol-hydrochloric acid treatment. The catalytic property of acid was shown by the increase of the rate of the reaction with the increase of acid concentration; 6a (45 mM) was converted to 6c in 2 ml of 70% aqueous methanol at 25°C with 60 h of half-life, whereas the presence of 1, 10, 100, and 200 mM of hydrochloric acid reduced the half-life to 42, 4.9, 0.51, and 0.23 h, respectively, and p-toluenesulfonic acid served also as catalyst to give a half-life of 0.23 h with 200 mM concentration. Conversion of the methoxymethyl nitrosamines into the corresponding acetoxymethyl compounds was already reported.[7] 1-Methoxyalkyl compound, 4c, was also converted into 1-hydroperoxyalkyl compound, 4b, by a similar treatment with 30% hydrogen peroxide in acetic acid, though higher temperature 90°C was required.[8]

These conversions can be explained by the initial acid-catalyzed formation of iminium and carbonium ions which are stabilized by the adjacent N-nitroso function, followed by nucleophilic attack with hydrogen peroxide, acetic acid, or methanol to give the hydroperoxides, the acetates, or the methoxides,

respectively. The involvement of the carbonium and iminium ions as electrophilic center was postulated recently in the solvolysis of 1-acetoxyalkyl nitrosamines.[9] The hydroperoxides were considerably stable in aqueous solution and showed potent mutagenic effects in Escherichia coli WP2 and WP2 hcr⁻, and Salmonella typhimurium TA1535 in the absence of microsomal activation.[5]

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