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2-METHYL-4-METHOXY-1,2,3-OXADIAZETIDINE. A CORRECTION.

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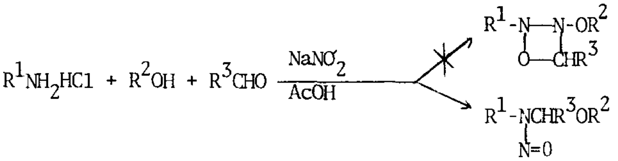
1,2,3-Oxadiazetidines have been considered hypothetical intermediates or transition states.[1-3] Recently, German patents claimed a surprising synthesis of 1,2,3-oxadiazetidines (Ia-c) by diazotization of amino alcohols in the presence of aldehydes[4a,5] or of amines in the presence of aldehydes and alcohols.[4b] However, no data to support the assigned ring structures were reported. In view of our interest in the synthesis of 1,2,3-oxadiazetidines, we undertook a reinvestigation of the reaction of methylamine hydrochloride with aqueous sodium nitrite in the presence of methanol, formaldehyde and acetic acid.

As we had surmised, the product is not the claimed oxadiazetidine (Ia) but a new compound identified as methoxymethyl methylnitrosamine (IIa).



(I)

(II)

a) $R^1=R^2=CH_3$, $R^3=H$

b) $R^1=R^2=CH_3$, $R^3=Ph$

c) R^1-R^2=-(C_3H_6)-, R^3=H, etc.

Following the published procedure,[4b] we prepared and isolated a compound in 10% yield (33% by glpc[6]) having properties [bp 59.0-59.5°/17 Torr (Lit[4b] 55°/14 Torr); $n_D^{25.5} = 1.4299$ (Lit[4b] $n_D^{20} = 1.4340$)] almost identical with those reported for Ia. Based on its elemental analysis (Found: C, 34.39; H, 7.89; N, 27.14; O, 31.04. Calcd. for $C_3H_8N_2O_2$: C, 34.60; H, 7.75; N, 26.91; O, 30.74) and molecular ion peak at 104.058 in the mass spectrum, the molecular formula is $C_3H_8N_2O_2$, the expected one for Ia. Determination of the UV spectrum, however, clearly eliminated Ia as a possible structure and a detailed examination of the product was then undertaken. IR and UV spectra showed the characteristic absorptions of a nitrosamine, one of the possible structures we had envisioned for the product (Table 1).

TABLE 1. Comparison of the IR and UV Spectra of IIa with Those of Dimethylnitrosamine

	Compound IIa	$(CH_3)_2NNO$
IR(cm^{-1}) (neat):	1460(γNO), 1095(γCH_3OCH_2-), 1015(γN-N)	1440(γNO), 1050(γN-N)[7]
UV(λ_{max},ε):	226.5(6300), 358.0(79), 369.5(104), 382.7(87)[a]	232(5900), 351(98), 361(125), 374(105)[8] [b]

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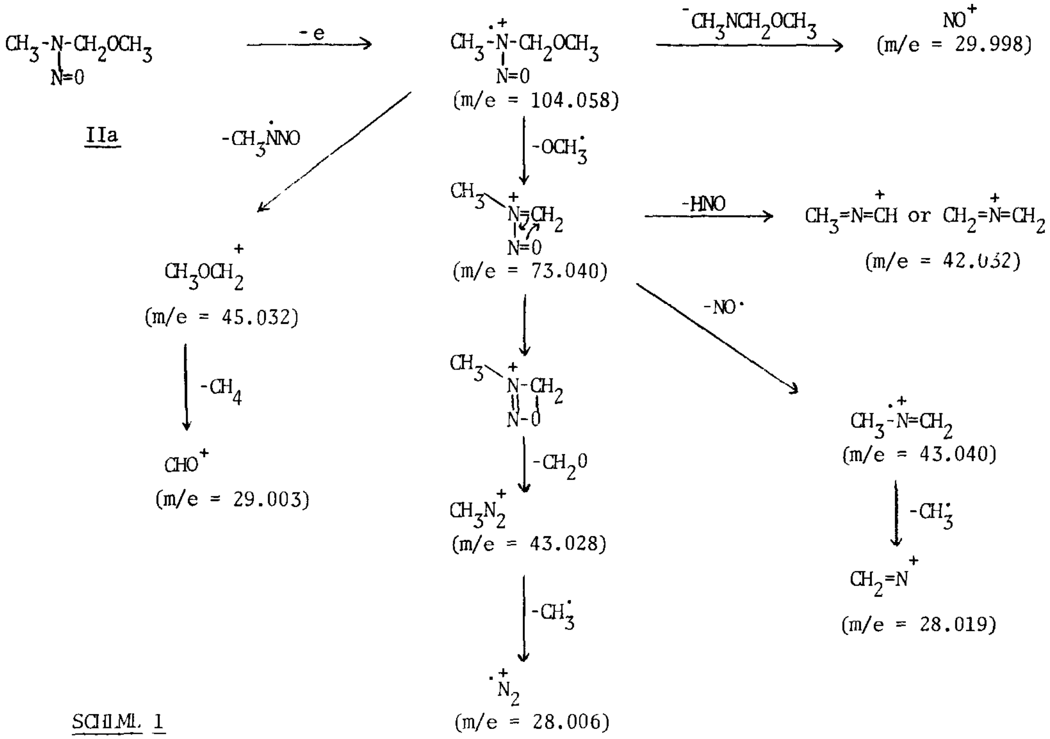
[a] In isooctane [b] In petroleum ether

Furthermore, the high resolution mass spectral fragmentation pattern (Table 2) and polarographic examination supported structure IIa, not Ia. A tentative fragmentation pattern for IIa is shown in Scheme 1. The observation of the parent peak $CH_3OCH_2^+$ and fragment ions, $CH_3\text{-}\overset{+}{N}{=}CH$ or $CH_2{=}\overset{+}{N}{=}CH_2$ and $CH_3\text{-}\overset{\cdot +}{N}{=}CH_2$ are difficult to explain for the ring structure Ia.

TABLE 2. High Resolution Mass Spectrum of IIa (70 ev, Direct Insertion Probe, 30°)

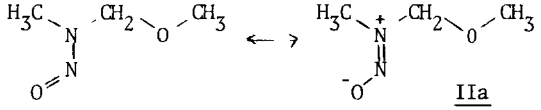
m/e	Rel. Int.	Molecular Formula	Diff. between Calcd. and Obsd. (ppm)
104.058	10	$C_3H_8N_2O_2$ (molecular ion)	5.4
73.040	13	$C_2H_5N_2O$	0.4
45.032	100	C_2H_5O (parent peak)	38.9
43.040	16	C_2H_5N	53.0
43.028	35	CH_3N_2	47.4
42.032	30	C_2H_4N	50.4
29.998	8	NO	10.2
29.003	10	CHO	4.0
28.019	4	CH_2N	1.8
28.006	48	N_2	0



SCHEME 1

As chemical evidence, reduction with formic acid, followed by treatment with concentrated hydrochloric acid, gave dimethylamine hydrochloride (30% yield), a product expected from IIa but not from Ia.

The NMR spectrum (60 MHz) of IIa in carbon tetrachloride showed three singlets at δ 2.97 (3H)(N-CH_3), 3.28 (3H)(O-CH_3) and 5.45 (2H)(-CH_2-). The chemical shift assigned to the N-methyl protons is approximately that of cis-N-methyl protons of other N-methylnitrosamines (δ 2.92-2.96) Further, in benzene-d_6 (20% solution) the methylene protons experienced a higher upfield shift (0.65 ppm) than the other protons (N-CH_3:0.44 ppm, O-CH_3:43 ppm), a result to be expected for stereospecific association of the benzene ring with the trans-methylene protons of the nitrosamine.[10] Thus the NMR data are consistent with the view that nitrosamine IIa exists in solution exclusively in the cis-methyl, trans-methoxymethyl configuration, owing to electron delocalization, as shown:



IIa

Recently, it was reported[11] that the hydrochloride of 1,3,5-trimethylhexahydro-1,3,5-triazine, obtainable by reaction of methylamine hydrochloride with formaldehyde,[12] is a useful methylaminomethylating agent for mercaptans and alcohols.[13] In our attempt,to confirm the structure of IIa by independent synthesis from a known reaction intermediate, 1,3,5-trimethylhexahydro-1,3,5-triazine was prepared by reaction of methylamine hydrochloride, formaldehyde solution, methanol and acetic acid, followed by neutralization with base. Accordingly, the triazine was neutralized with concentrated hydrochloric acid in methanol and then treated with aqueous sodium nitrite under the same conditions as in the patent procedure (acetic acid was also added), giving IIa in 15% yield (glpc). This fact not only supports the structure of IIa, but also suggests that the nitrosamine IIa may be formed through nitrosation of methoxymethylmethylamine hydrochloride.

As confirming evidence that IIa is a N-nitrosamine, we have compared its polarographic characteristics with those of a known nitrosamine, dimethylnitrosamine.

Polarograms were recorded using a Beckman Electroscan 30 and an Elscint Model CHP-1 potentiostat modified for automatic scan and recording. Aqueous solutions in the concentration range 10^{-3} -10^{-5} M nitrosamine in 0.1 M KCl were examined and the pH was adjusted to 1.7 using dilute H_2SO_4. The reference electrode was an SCE and the counter electrode was Pt. All solutions were deaerated with high purity N_2 and kept in a N_2 atmosphere during the scan. The aqueous solutions were stored in the dark.

Solutions of dimethylnitrosamine and IIa yielded almost identical polarograms having $E_{\frac{1}{2}}$ = -0.90 v (vs SCE). The waves were irreversible with values of αn_a = 0.42 for dimethylnitrosamine and 0.74 for IIa. The waves were diffusion controlled as evidenced by linear plots of i_d vs (Hg column height)$^{\frac{1}{2}}$. The diffusion current constants for dimethylnitrosamine and IIa were 2.4 and 2.2 (μ amp/mmole/liter/mg$^{2/3}$/sec$^{-1/6}$, respectively.

The value of E = -0.90 v agrees with an early reported value for dimethylnitrosamine using 0.1 M sulfosalicylic acid as supporting electrolyte.[15] With IIa this supporting electrolyte yielded polarograms having large maxima which could not be entirely eliminated using the usual suppressors. The polarograms were very pH dependent, shifting cathodically with increasing pH.

Structures for IIa containing an azo group were eliminated on the basis of the chemical evidence (formic acid reduction) and $E_{\frac{1}{2}}$.

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