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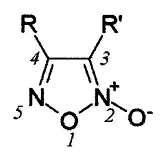
JMS Letters

Dear Sir,

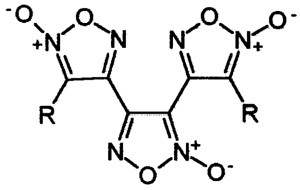
Mass Spectra of Methyl- and Phenyl-substituted Terfuroxan (Terfurazan Trioxide) Derivatives

Derivatives of the furoxan system (1,2,5-oxadiazole 2-oxide, furazan oxide) **I** have attracted the attention of many researchers for their intriguing chemistry and for a debate about their structure.[1]

The discovery that furoxans can behave as NO donors gave rise to additional interest in this class of compounds.[2,3] Mass spectrometry is normally used as a routine analytical tool in their characterization.[4,5] The most important ions that occur are [M − NO]$^+$, [M − 2NO]$^{+\cdot}$ and [NO]$^+$. This behaviour can be rationalized by assuming ring opening to the dinitroso compound followed by cleavage for one or both N—C bonds. This is why the mass spectra of furoxan isomers (**I**, R ≠ R′) are relatively similar. In some cases, the [M − 2NO]$^{+\cdot}$ ion can undergo additional fragmentation, affording the $C_3H_3^+$ fragment of the C_nH_{2n-3} alkyne series. Pathways to explain the formation of all of these ions are shown in Schemes 1 and 2, exemplified in the case of dimethylfuroxan (**I**, R = R′ = CH_3). Some diarylfuroxans[4] show additional important peaks at [M − O]$^+$ and [M/2]$^+$. The latter is due to a retro-1,3-dipolar cycloaddition, as depicted in Scheme 2, in which the main fragmentation processes of diphenylfuroxan (**I**, R = R′ = C_6H_5) are outlined.

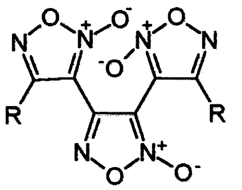


I



R = Ph **1a**

R = CH_3 **1b**

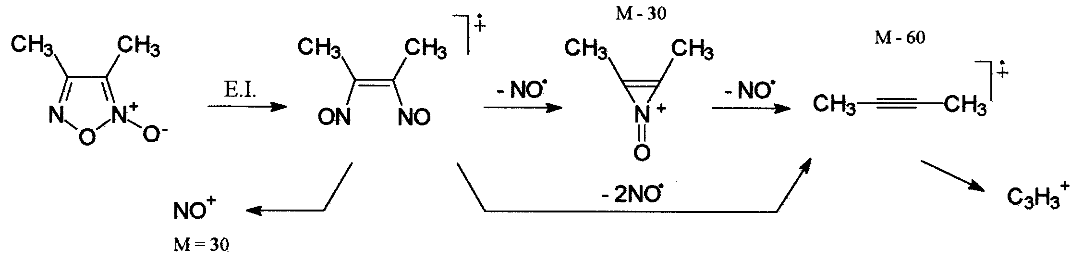


R = Ph **2a**

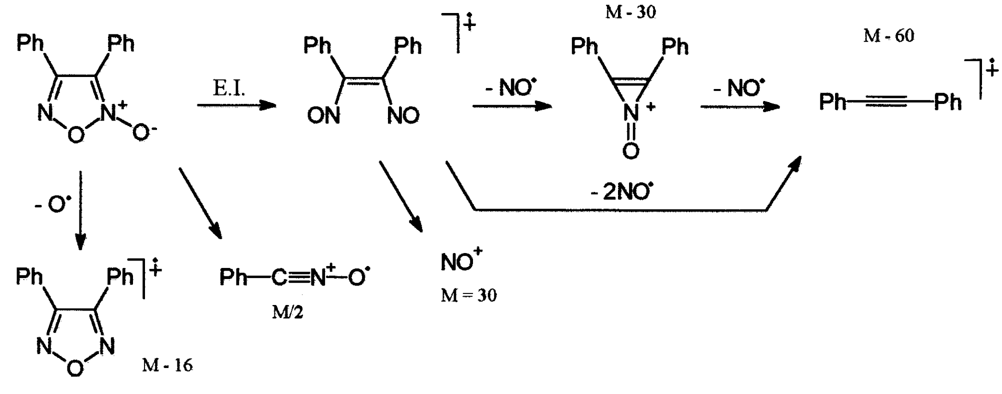
R = CH_3 **2b**

In a recent paper, we described the synthesis and structural characterization of a series of terfuroxan derivatives which display potent vasodilating activity.[6] Here we report the results of a mass spectrometric study undertaken on pairs of isomers 4′,4″-diphenyl-3,3′:4′,3″-terfurazan 2′,5,5″-trioxide (**1a**), 4′,4″-diphenyl-3,3′:4′,3″-terfurazan 2,2′,2″-trioxide (**2a**) and 4′,4″-dimethyl-3,3′:4′,3″-terfurazan 2′,5,5″-trioxide (**1b**), 4′,4″-dimethyl-3,3′:4′,3″-terfurazan 2,2′,2″-trioxide (**2b**). Low-resolution electron ionization (EI), chemical ionization (CI) and tandem mass spectra were recorded with a Finnigan-MAT TSQ-700 instrument. High-resolution EI mass spectra were obtained on a VG TS-250 instrument. Collision-activated decomposition (CAD) mass spectra were acquired using argon as collision gas at 1 mTorr pressure (1 Torr = 133.3 Pa). CI mass were acquired using isobutane as reagent gas at 5500 mTorr pressure. Electric parameters are reported on the basis of default instrumental values. Characteristic spectra of two terfuroxan models are reported in Fig. 1.

All the compounds show M$^{+\cdot}$ ions of abundance <10%, with the exception of derivative **2b** (M$^{+\cdot}$, 16%). Only **1a** leads to a very low abundance [M − O]$^{+\cdot}$ fragment. None of the



Scheme 1



Scheme 2

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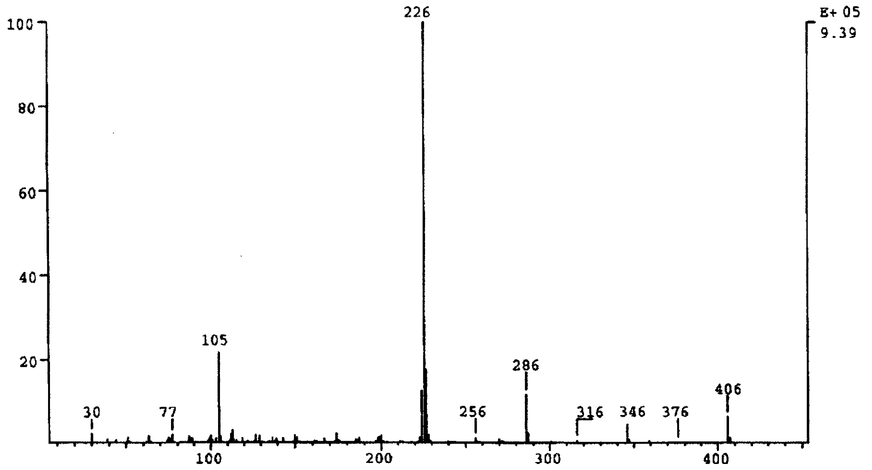
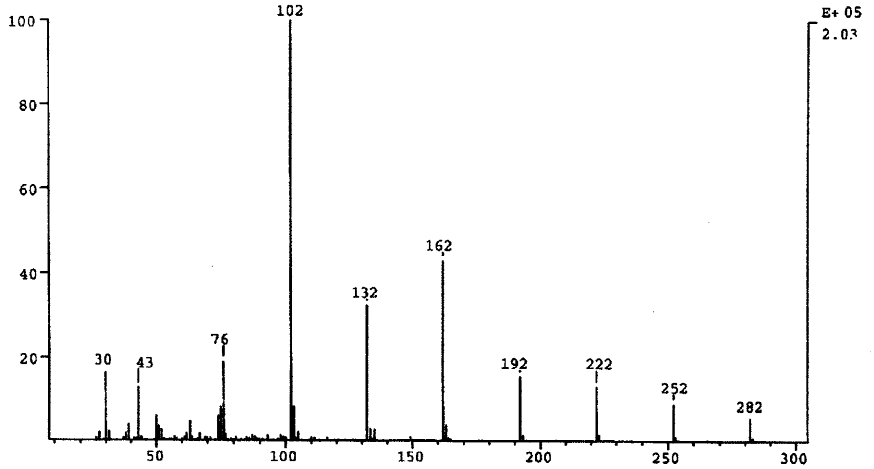


1a



1b

Figure 1. 70 eV EI mass spectra of derivatives **1a** and **1b**.

derivatives show $[M/2]^+$ ions, whereas the fragment $[NO]^+$ is always present with low abundance (<20%). The most important aspect shared by these spectra is the presence of a series of six even-mass ions, which are alternatively even- and odd-electron species. This series of ions has the general formula M—*n*NO ($n = 1$–6). In the methyl isomers the first three ions of the series ($n = 1$–3) are of low abundance (< 16%) and the remaining ones of higher abundance. In particular, $[M - 6NO]^{+\cdot}$ represent the base peaks. In the two phenyl isomers the only prominent peak of the series is $[M - 6NO]^{+\cdot}$ (100%); all the others display low or very low abundance. In particular in the derivative **1a**, the abundance of the $[M - NO]^+$ ion is only 0.02%. To understand the origin of these fragments, we have undertaken a study of the parent and fragment ions of each term of the series, in all the terfuroxans considered. Fragment ion analysis shows that each fragment of the series $[M - nNO]^+$ generates all the ions of the series $[M - n'NO]^+$ ($n' = 1, 2, \ldots, 6-n$). Parent ion analysis indicates that each ion of the series $[M - nNO]^+$ is generated by all of the ions of the series $[M - n'NO]^+$ ($n' = 0, 1, 2, \ldots, n - 1$). In conclusion, each $M - nNO]^+$ ion has as parents all the ions of the series with higher mass and as fragments all the ions with lower mass than its own. This means that each ion can subsequently lose the single NO radical that it contains and perhaps two or more of these fragments simultaneously.

In these processes, the charge can be also retained on the NO moiety, as the parent ions of this fragment demonstrate. Appearance potentials of $[M - nNO]^+$ ion series were studied qualitatively in the case of derivatives **1a** and **2a**. No evident differences in the abundances of the ions were observed by lowering the energy of the electron beam in the range 70–14 eV. This means that the extrusion of an NO radical requires a relatively low activation energy. The appearance potential of the nitrosonium ion NO^+ was 11 eV. In the methyl derivatives the $[M - 6NO]^{+\cdot}$ pentacetylene fragments undergo further fragmentation affording ions of the polyalkyne series (Fig. 2).

The second characteristic shared by the mass spectra of the considered terfuroxans is an unusual fragmentation of the furoxan ring, never previously observed. This implies the formation of characteristic ions at $[R + 28]^+$ ($R = CH_3, C_6H_5$). High-resolution mass spectra of these $[R + 28]^+$ fragments indicate that they have elemental composition C_2H_3O and C_7H_5O, respectively. Analysis of fragment and parent ions indicates that they generate the fragment R^+ and are generated mainly by $M^{+\cdot}$ and $[M - NO]^+$ ions. A possible fragmentation scheme able to rationalize the formation of these fragments is reported in Scheme 3. It implies the rearrangement of the lateral 3-methylfuroxan moiety to a 2,6-dioxa-1,3-diaazabicyclo[3.1.0]hex-3-ene system **3**, the first structure proposed by Wieland for the furoxan ring.

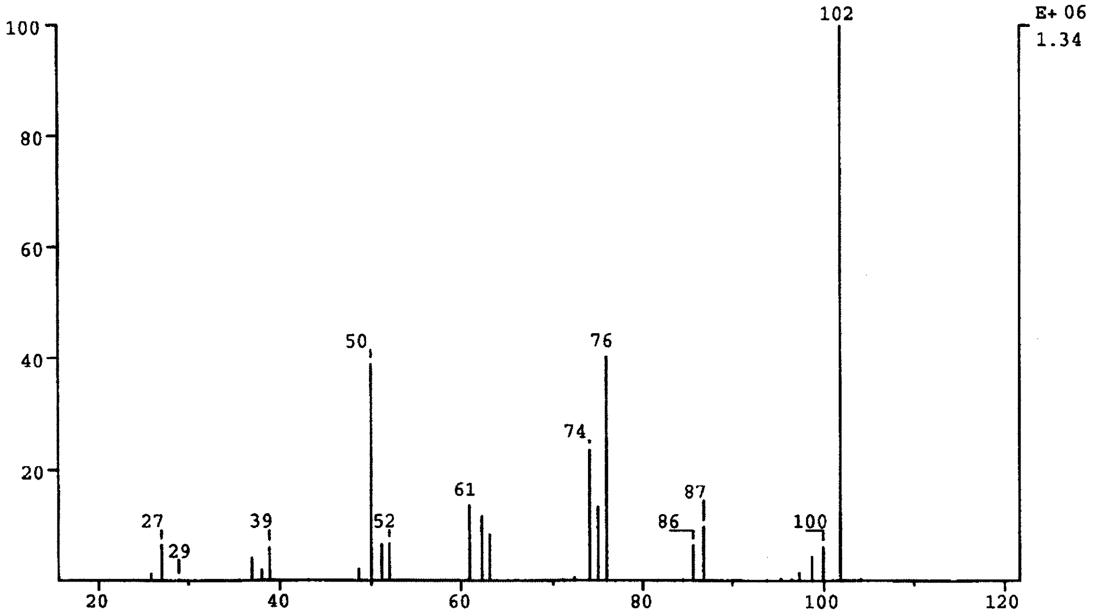


Figure 2. Fragments of 102 Da ion of derivative **1b** obtained by EI tandem mass spectrometry at 100 eV.

EI tandem mass spectrometric experiments on the parent ion $M^{+\cdot}$ of the methyl derivatives **1b** and **2b** by using two different collision energies (20 and 100 eV) show that a high energy the 100% abundance peak was due to the $[M - 6NO]^+$ ion, whereas at low energy it was due to the 43 Da fragment. When the mass spectra of the methyl isomers were recorded under CI conditions, only the $[M + 1]^+$ ion was present. Its fragmentation at two different collision kinetic energies (20 and 35 eV) produced only 43 and 30 Da ions.

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Yours,

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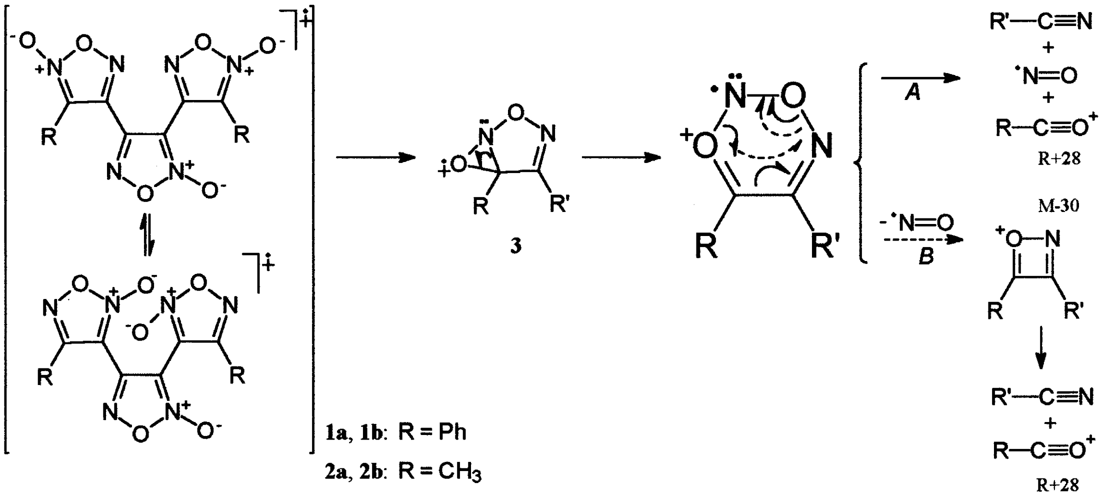

Scheme 3