

151. Synthesis and Structural Characterization of the Trimeric Furoxan (= Furazan 2-Oxide) System, a New Potent Vasodilating Moiety

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The synthesis, structural characterization, and NO donor properties of a series of terfuroxan (= terfurazan trioxide) derivatives **1a–h** and **2a–j** are reported (*Schemes 1* and *2*). Structural assignments were confirmed principally by mass and ^{13}C - and ^1H -NMR spectroscopy. The extent and the initial rate of NO release in the presence of thiol cofactor was evaluated for each derivative. Vasodilator effects of all the terfuroxan derivatives were evaluated on endothelium-denuded strips of rat aorta precontracted with noradrenaline. Concentration-response curves were also evaluated in the presence of $10\text{ }\mu\text{M}$ oxyhemoglobin (HbO_2), a well known NO scavenger. The whole series displays high vasodilating potency; the most active terfuroxans (**1a**, **b**, **g** and **2i**) are 5–10 times as potent as glyceryl trinitrate taken as reference (see *Table 3*). The potency decrease observed in the presence of HbO_2 agrees with the involvement of NO in the vasorelaxing action. The 4,3':4',4'' connection (series **1**; furoxan numbering) gives rise to the most potent compounds. The conformational factors seem to play important roles in the activity. No clear relationship between physico-chemical properties of the substituents and potencies of derivatives emerges.

1. Introduction. – Nitric oxide (NO) is an important physiological mediator in cardiovascular, immune, central, and peripheral nervous systems. There is today a great interest in chemical species which give rise to nitric oxide under physiological conditions, because they could mimic endogenous NO activities [1]. The classical use of NO donors is in the management of cardiovascular diseases [2]. Organic nitrates and nitrites and sodium nitroprusside are the most important examples of these drugs. They were introduced in therapy many years before it was appreciated that their action involved NO release. Now, many new pharmacotherapeutic possibilities for NO donors are emerging [3] [4]. They include treatment of nervous, sexual, respiratory, and gastrointestinal disorders, enhanced immunological response, and regulation of tumour growth.

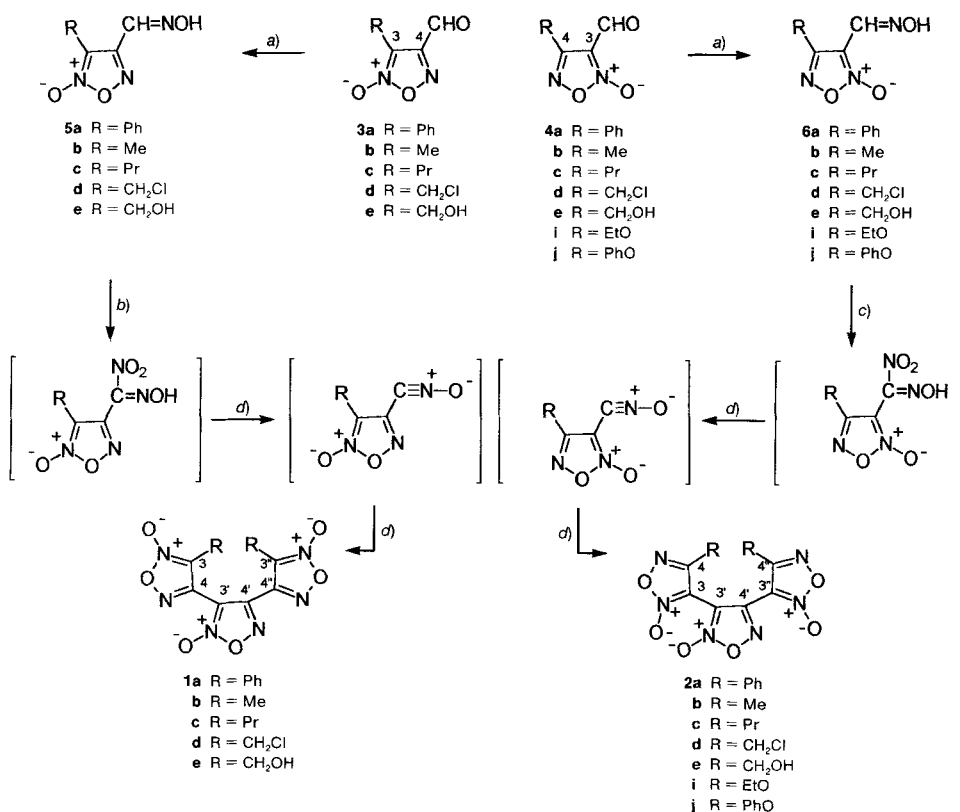
Recently, it was shown that a few furoxan (= furazane 2-oxide)¹⁾ derivatives are able to increase the level of cytosolic cyclic GMP in human platelets [5] and to activate rat liver soluble guanylate cyclase, in the presence of thiol cofactors [6]. This behaviour can be explained by the finding that furoxans can release NO when treated with thiols under physiological conditions [6]. These results prompted the synthesis of many new furoxan derivatives and the study of their pharmacological activities [1].

In a previous paper, we described the synthesis and characterization as a potent vasodilator of derivative **2a** [7]. The present article describes the preparation, structural

¹⁾ Furoxan numbering is used throughout the *General Part* (see *Scheme 1*); systematic names are given in the *Exper. Part*.

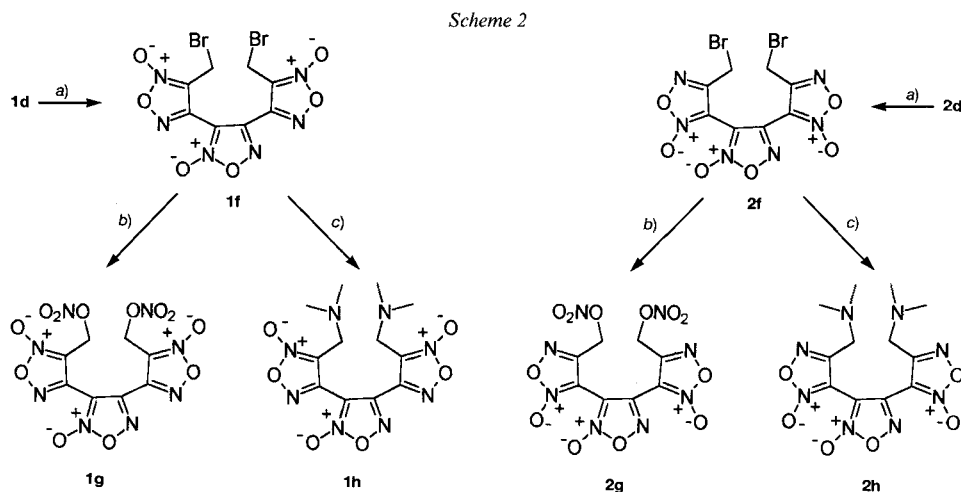
characterization, NO-releasing properties, as well as the vasodilatory activity of a series of furoxan trimers, the terfuroxans **1a–h** and **2a–j**.

2. Results and Discussion. – 2.1. *Synthesis.* The pairs of isomers **1a–e** and **2a–e** and 4,4'-diethoxy-3,3':4',3''-terfuroxan (**2i**) as well as the 4,4'-diphenoxy analogue **2j** were synthesized starting from the appropriate aldehydes **3a–e** and **4a–e,i,j**, respectively (Scheme 1)¹⁾. The latter were transformed into the corresponding oximes **5a–e** and **6a–e,i,j** by hydroxylamine hydrochloride in boiling EtOH containing pyridine. The action of a large excess of N₂O₄, dissolved in CHCl₃ or Et₂O, on the oxime derivatives afforded mainly the corresponding nitrolic acids. This result is noteworthy because the action of an excess of N₂O₄ on aldoximes, as a rule, affords geminal dinitro compounds, while production of nitrolic acids requires a molar ratio 2:1 of the oxime to N₂O₄ [8] [9]. The intermediate nitrolic acids, when heated in an appropriate solvent (see *Exper. Part*) decomposed, losing nitrous acid, with formation of unstable nitrile oxides. These dimerized *in situ* to the expected terfuroxans.

Scheme 1¹⁾

a) NH₂OH · HCl/Py, EtOH, reflux. b) N₂O₄, CHCl₃, 0°. c) N₂O₄, Et₂O, 0°. d) CHCl₃ (AcOEt for **1e** and **2e**), reflux.

The terfuroxans **1f–h** and **2f–h** were synthesized according to *Scheme 2*. The action of LiBr on **1d** and **2d** under phase-transfer conditions produced the two bromomethyl isomers **1f** and **2f**, respectively. Nucleophilic displacement of the Br-atoms, either with AgNO₃ in MeCN or with Me₂NH in THF/H₂O, yielded the expected pairs of isomers **1g, h** and **2g, h**.



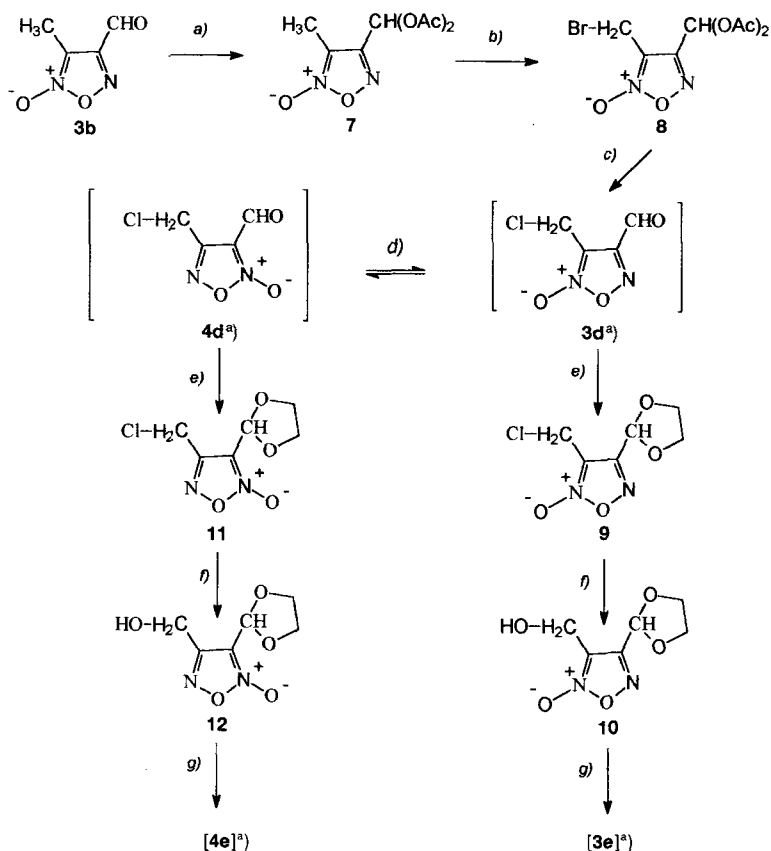
a) LiBr, BuP(Ph)₃Br, CHCl₃. b) AgNO₃, MeCN. c) Me₂NH, THF/H₂O.

The starting aldehydes **3** and **4** used for the synthesis of the terfuroxans **1** and **2** were prepared in part according to the methods we previously described (**3a–c** and **4a–c**) and in part (**3d, e** and **4d, e**) according to the pathway shown in *Scheme 3*. Briefly, the diacetyl acetal **7**, obtained by treatment of 3-methylfuroxan-4-carbaldehyde (**3b**) with Ac₂O, was brominated with *N*-bromosuccinimide (NBS) in boiling CCl₄ to give **8**. No furoxan thermal isomerization [10] occurred during the reflux. The protecting group present in **8** was hydrolysed with HCl in THF and the halogen exchange, which partly occurred during hydrolysis, was completed by the action of LiCl under phase-transfer conditions, to afford the corresponding 3-(chloromethyl)furoxan-4-carbaldehyde (**3d**). Reaction of ethylene glycol with crude **3d**, in the presence of a catalytic amount of toluene-4-sulfonic acid (TsOH), afforded the oily cyclic acetal **9**. Hydrolysis of the latter in dioxane/H₂O in the presence of LiBr and CaCO₃ yielded the corresponding hydroxymethyl derivative **10**, from which the final 3-(hydroxymethyl)furoxan-4-carbaldehyde (**3e**) was obtained by action of H₂SO₄ in acetone. An identical sequence of reactions was carried out starting from **4d** (**→11→12→4e**; see *Scheme 3*). This isomer was prepared by thermal isomerization of **3d** in boiling toluene and chromatographic separation of the resulting mixture **3d/4d**. Finally 4-ethoxyfuroxan-3-carbaldehyde (**4i**) and the 4-phenoxy analogue **4j** were prepared according to *Scheme 4* from **13a, b** via **14a, b** and **15a, b**.

2.2. Spectroscopic Characterization. Structural assignments of the terfuroxans **1** and **2** were confirmed principally by mass spectrometry and ¹³C- and ¹H-NMR spectroscopy. In the mass spectra of all derivatives, ion peaks derived from the typical furoxan fragmenta-

tion by stepwise NO loss [10] are always present. In a few compounds (*Table 1*), this decomposition affords a series of six ions, alternately even-electron and odd-electron species, due to sequential loss of all six NO moieties present in the trimer structures. A

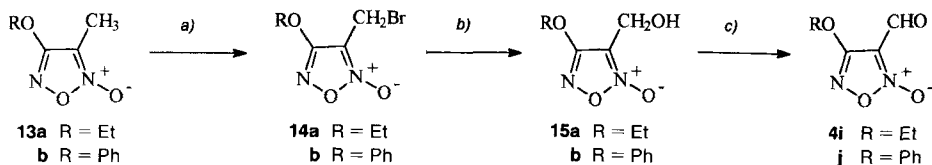
Scheme 3



a) $\text{Ac}_2\text{O}/\text{H}_2\text{SO}_4$. b) NBS, $(\text{PhCOO})_2$, CCl_4 , reflux. c) 1. 4N HCl/THF; 2. LiCl, $\text{PhCH}_2\text{P}(\text{Et})_3\text{Cl}$, CHCl_3 . d) Toluene, reflux. e) Ethylene glycol, TsOH, benzene, reflux. f) CaCO_3 , LiBr, dioxane/ H_2O , reflux. g) 12N H_2SO_4 /acetone, reflux.

a) Derivatives in brackets were used for the following reaction without further purification.

Scheme 4

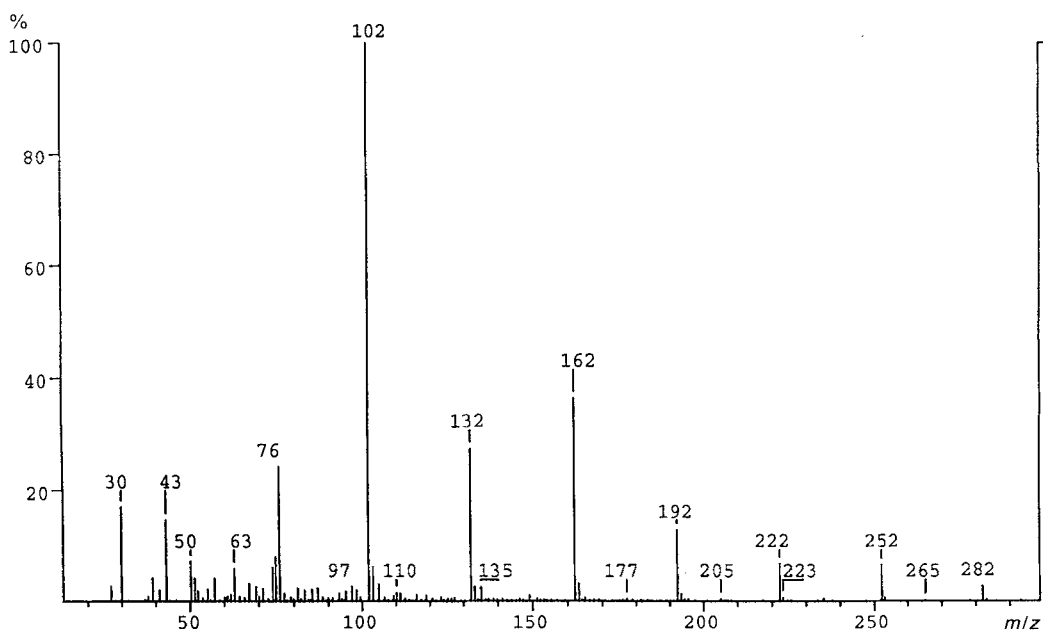


a) NBS, $(\text{PhCOO})_2$, CCl_4 , reflux. b) CaCO_3 , dioxane/ H_2O , reflux. c) MnO_2 , CHCl_3 .

Table 1. *El-Mass Spectrometry Data of Terfuroxans 1 and 2^a*

	M^+	$[M - 30]^+$	$[M - 60]^+$	$[M - 90]^+$	$[M - 120]^+$	$[M - 150]^+$	$[M - 180]^+$	NO^+	Base peak
1a	406 (6)	–	346 (5)	–	286 (12)	–	226 (100)	30 (2)	226 (100)
2a	406 (2)	376 (2)	346 (6)	–	286 (16)	–	226 (100)	30 (4)	226 (100)
1b	282 (6)	252 (9)	222 (13)	192 (16)	162 (43)	132 (33)	102 (100)	30 (17)	102 (100)
2b	282 (20)	252 (2)	222 (13)	192 (9)	162 (61)	132 (35)	102 (100)	30 (15)	102 (100)
1c	338 (2)	308 (5)	278 (5)	248 (3)	218 (52)	188 (11)	158 (100)	30 (8)	158 (100)
2c	338 (11)	–	278 (3)	–	218 (46)	188 (9)	158 (100)	30 (9)	158 (100)
1d^b	350 (2)	320 (4)	290 (11)	260 (7)	230 (14)	200 (14)	170 (11)	30 (47)	135 (100)
2d^b	350 (2)	–	290 (25)	260 (6)	230 (26)	200 (15)	170 (12)	30 (35)	135 (100)
1e	– ^c	284 (28)	254 (56)	224 (41)	194 (51)	164 (50)	134 (100)	30 (87)	134 (100)
2e	314 (19)	284 (5)	254 (29)	224 (18)	194 (100)	164 (41)	134 (72)	30 (53)	194 (100)
1f^b	440 (2)	410 (3)	380 (2)	–	320 (6)	290 (6)	260 (2)	30 (55)	100 (100)
2f^b	440 (10)	–	380 (9)	–	320 (16)	290 (7)	260 (3)	30 (50)	100 (100)
1g	404 (2)	374 (3)	–	–	–	254 (2)	–	30 (100)	30 (100)
2g	404 (16)	–	344 (17)	314 (7)	284 (11)	–	–	30 (100)	30 (100)
1h	– ^d	–	–	–	–	–	–	–	44 (100)
2h	– ^e	–	–	–	–	–	–	–	44 (100)
2i	342 (6)	–	–	–	222 (27)	–	162 (23)	30 (41)	29 (100)
2j	438 (4)	–	–	–	318 (12)	–	258 (87)	30 (24)	77 (100)

^a) Figures in parentheses are relative intensities; not reported if < 2% (–). ^b) For ions containing Cl or Br, only the mass of the most abundant isotope peak is quoted. ^c) CI-MS: 315 (100, $[M + 1]^+$). ^d) CI-MS: 369 (100, $[M + 1]^+$). ^e) CI-MS: 369 (100, $[M + 1]^+$).

Fig. 1. *El-Mass spectrum of terfuroxan 1b*

typical example of such a spectrum, that of **1b**, is given in *Fig. 1*. In the other derivatives, the series of these ions is not complete, but it is possible to detect it by chemical ionization-tandem mass spectrometry.

In the ^{13}C -NMR spectroscopy, the six furoxan C-atoms produce two clusters of three absorptions (*Fig. 2* and *Table 2*). The first cluster appears downfield, in the range 160.2–141.1 ppm, while the second is upfield, in the range from 115.0–97.5 ppm. This is in keeping with the well-known, remarkably large chemical-shift difference between C(3) linked to the N^+-O^- moiety and C(4) in a furoxan system [10]. Structural assignments in

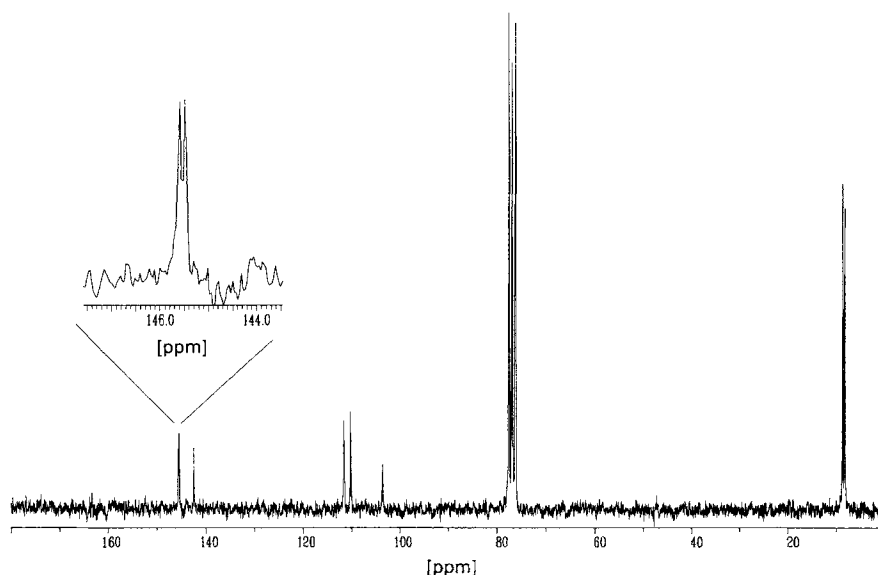
Table 2. ^{13}C -NMR Data of the Terfuroxans **1** and **2**^{a)} (δ [ppm] from rel. to SiMe_4 , solvent CDCl_3)

	C(3')	C(4')	C(3), C(3'')	C(4), C(4'')	R
1a	104.1	141.3	112.7, 112.4	145.0, 144.2	131.4 (2 C), 129.5, 129.1, 128.35, 126.6, 120.8, 120.4 (Ph)
2a	102.2	142.3	102.9, 105.9	154.7, 154.5	132.0 (2 C), 129.5, 129.2, 127.9, 126.6, 124.5, 124.2 (Ph)
1b	103.6	142.5	111.55, 110.2	145.6, 145.5	8.8, 8.35 (Me)
2b	102.5	142.8	108.05, 105.35	153.0, 152.6	11.85, 11.7 (Me)
1c	103.6	142.3	114.5, 113.2	145.8, 145.3	24.85 (2 C, CH_2); 19.1, 18.05 (CH_2); 13.4, 13.4 (Me)
2c	102.8	143.0	107.8, 105.0	156.6, 156.1	28.05, 27.7 (CH_2); 19.9, 19.6 (CH_2); 13.3 (2 C, Me)
1d	103.5	141.1	111.95, 110.7	144.7, 143.9	32.1, 31.7 (CH_2Cl)
2d	102.5	141.7	106.6, 103.8	152.8, 152.2	34.9, 33.9 (CH_2Cl)
1e	104.9	142.8	115.0, 113.7	145.9, 146.0	53.1, 52.2 (CH_2OH)
2e	103.3	143.5	107.6, 103.3	157.2, 158.2	54.4, 56.0 (CH_2OH)
1f ^{b)}	103.5	141.2	112.2, 111.5	144.75, 143.7	15.6 (2 C, CH_2Br)
2f ^{b)}	102.65	141.7	106.7, 104.5	152.9, 152.5	18.8, 17.8 (CH_2Br)
1g	103.95	141.2	108.8, 107.0	144.5, 144.35	61.1, 60.6 (CH_2ONO_2)
2g	102.15	141.7	106.7, 103.8	150.2, 149.4	63.7, 62.75 (CH_2ONO_2)
1h ^{c)}	103.2	140.2	106.5, 105.2	143.2, 142.8	46.0, 45.8 (CH_2); 41.2, 41.3 (Me)
2h ^{c)}	100.9	139.7	105.8, 102.9	146.15, 145.7	48.4 (2 C, CH_2); 41.3 (2 C, Me)
2i	97.5	141.0	100.6, 100.3	160.6, 160.2	67.8, 67.6 (CH_2O); 13.9, 13.8 (Me)
2j	97.9	140.7	100.9, 100.5	160.2, 159.8	151.95, 151.85, 130.0 (2 C), 126.9 (2 C), 119.4 (2 C) (Ph)

^{a)} Furoxan numbering, see *Scheme 1*; systematic names in the *Exper. Part.* ^{b)} Solvent (D_6)DMSO. ^{c)} Dihydrochloride, solvent D_2O .

each pair of isomers agree with the shielding influence exerted by the *N*-oxide group both on the C- and H-atoms of the adjacent CH_2 group [10].

2.3. NO Release and Vasodilating Activity. The extent of NO release in the presence of thiol cofactor was evaluated by incubating the terfuroxans for 1 h at 37° in pH 7.4 buffered H_2O containing a large excess of L-cysteine (1:50). The amount of NO released was evaluated by detecting the nitrites, which are the oxidation products of nitric oxide, by the *Griess* reaction. The results, expressed as % NO_2^- (mol/mol) are summarized in *Table 3*, together with the values obtained for glyceryl trinitrate (GTN). In the absence of L-cysteine, no NO_2^- formation occurred, with the exception of **2j** and of the pairs of propyl and nitrooxymethyl isomers **1c**, **2c** and **1g**, **1g**, respectively. The extent of this formation was small in the former case, large in the latter. Generally speaking, in each pair of isomers, the 3,3''-substituted isomer **1** released a larger amount of NO than the 4,4''-substituted isomer **2**, in the presence of L-cystein. The only exception to this rule is the couple **1g**, **2g** in which a nitric ester moiety, able itself to donate NO by the action of L-cysteine [11], is present.

Fig. 2. ^{13}C -NMR Spectrum (CDCl_3) of terfuroxan **1b**

The initial rates of NO release in the presence of a 5-fold molar excess of L-cysteine were measured using 10^{-4} M physiological solutions of each furoxan. Study of the release over a concentration range was limited by the poor solubility of most of the compounds. In this study, a spectrophotometric technique [12] based on NO-induced oxidation of oxyhemoglobin (HbO_2), according to *Eqn. 1*, was used.



The reaction was followed by detecting the increase of absorbance (ΔA) at λ 401 nm, over the first 3 min. The initial rates of nitric-oxide donation were expressed as $\Delta A \text{ min}^{-1}$. Using as a molar extinction coefficient for the oxidation reaction $\Delta \epsilon = \epsilon_{401}(\text{MetHb}) - \epsilon_{401}(\text{HbO}_2) = 39.9 \text{ mM}^{-1} \text{ cm}^{-1}$ (see *Exper. Part*), these values were transformed into $\mu\text{mol l}^{-1}$ of NO developed within 1 min (*Table 3*). These figures are spread over a wide range, *i.e.*, 4.28 to $< 0.075 \mu\text{mol l}^{-1} \text{ min}^{-1}$. Again, if we compare the initial rates of NO release in each pair of isomers, the 3,3''-substituted terfuroxans **1** is a faster NO donor than the 4,4''-substituted **2**. In contrast, when the whole series is considered, no correlation exists between the % NO released and the rate of release, under the experimental conditions.

Vasodilator effects of all the terfuroxans were evaluated on endothelium-denuded strips of rat aorta precontracted with noradrenaline. All compounds displayed a concentration-dependent relaxation of the strips. Concentration-response curves were also evaluated in the presence of $10 \mu\text{M}$ HbO_2 , a well known NO scavenger. EC_{50} Values are reported in *Table 3*. With most of the compounds, at the maximum concentration tested, only a partial recovery (60–95%) of the noradrenergic tone occurred after 1 h of washing

Table 3. NO Release and Vasodilating Activity of Terfuroxans **1** and **2**

	EC_{50} [μ M] ^{a)}	EC_{50} [μ M] (in the presence of HbO ₂) ^{a)}	μ mol l ⁻¹ min ⁻¹ NO [0.1 mM] ^{a)}	Absence of Cys mol/mol NO ₂ ⁻ [%] ^{a)}	Presence of Cys mol/mol NO ₂ ⁻ [%] ^{a)}
1a	0.0019 ($\pm$ 0.0005)	0.014 ($\pm$ 0.004)	– ^{b)}	– ^{b)}	– ^{b)}
2a	0.042 ($\pm$ 0.004)	0.053 ($\pm$ 0.003)	– ^{b)}	– ^{b)}	– ^{b)}
1b	0.0018 ($\pm$ 0.0002)	0.016 ($\pm$ 0.003)	0.446 ($\pm$ 0.012)	0	60 ($\pm$ 1)
2b	0.021 ($\pm$ 0.007)	0.067 ($\pm$ 0.006)	< 0.075	0	33 ($\pm$ 2)
1c	0.0072 ($\pm$ 0.0009)	0.022 ($\pm$ 0.004)	– ^{b)}	6 ($\pm$ 0.5)	65 ($\pm$ 4)
2c	0.044 ($\pm$ 0.009)	0.19 ($\pm$ 0.05)	– ^{b)}	5 ($\pm$ 0.3)	8 ($\pm$ 1)
1d	0.022 ($\pm$ 0.004)	0.23 ($\pm$ 0.03)	4.28 ($\pm$ 0.14)	0	99 ($\pm$ 3)
2d	0.22 ($\pm$ 0.05)	0.63 ($\pm$ 0.05)	0.265 ($\pm$ 0.173)	0	37 ($\pm$ 2)
1e	0.033 ($\pm$ 0.007)	0.24 ($\pm$ 0.05)	0.328 ($\pm$ 0.045)	0	40 ($\pm$ 1)
2e	0.19 ($\pm$ 0.03)	0.79 ($\pm$ 0.09)	< 0.075	0	30 ($\pm$ 1)
1f	0.027 ($\pm$ 0.005)	0.58 ($\pm$ 0.08)	1.12 ($\pm$ 0.09)	0	98 ($\pm$ 2)
2f	0.22 ($\pm$ 0.06)	0.65 ($\pm$ 0.08)	< 0.075	0	40 ($\pm$ 3)
1g	0.0028 ($\pm$ 0.0006)	0.027 ($\pm$ 0.006)	– ^{b)}	21 ($\pm$ 2)	74 ($\pm$ 1)
2g	0.030 ($\pm$ 0.005)	0.13 ($\pm$ 0.02)	– ^{b)}	34 ($\pm$ 3)	93 ($\pm$ 2)
1h	0.043 ($\pm$ 0.012)	0.14 ($\pm$ 0.02)	0.539 ($\pm$ 0.058)	0	44 ($\pm$ 3)
2h	0.27 ($\pm$ 0.02)	1.0 ($\pm$ 0.10)	0.158 ($\pm$ 0.006)	0	24 ($\pm$ 1)
2i	0.0040 ($\pm$ 0.0008)	0.027 ($\pm$ 0.004)	– ^{b)}	0	37 ($\pm$ 2)
2j	0.011 ($\pm$ 0.002)	0.13 ($\pm$ 0.01)	– ^{b)}	8 ($\pm$ 1)	15 ($\pm$ 1)
GTN ^{d)}	0.0224 ($\pm$ 0.0039)	– ^{c)}	< 0.075	0	45 ($\pm$ 1)

^{a)} Standard error in parentheses. ^{b)} Not soluble. ^{c)} Not tested. ^{d)} Glyceryl trinitrate.

the aortic preparations with fresh *Krebs* solution. With derivatives **1d**, **2d** and **1f**, **2f**, the recovery ranged from 20 to 50 %.

3. Structure-Activity Relationship (SAR) and Conclusions. – The whole series of derivatives displays high vasodilating potency. In particular, compounds **1a**, **b**, **g** and **2i** are 5–10 times as potent as GTN taken as reference. The potency decrease shown by the derivatives when tested in the presence of HbO₂ agrees with the involvement of NO in the vasorelaxing action. The log EC_{50} values in the presence and absence of HbO₂ are linearly correlated (*Fig. 3*).

The properties either as NO donors or as vasodilators of the trimer furoxans suggest that the two 4,3':4',4"- and 3,3':4',3"-terfuroxan systems **1** and **2**, respectively, give rise, when substituted, to two different classes of compounds. A preliminary study we have undertaken on the conformational domain of our products shows that the flexibility of the two systems is different. Indeed, in each pair of isomers, the conformational freedom of the 3,3"-derivative **1** is always higher than the one of the 4,4"-analogue **2** (see for an example *Fig. 4*). A comparison of molecular electrostatic potentials (MEP) and molecular lipophilicity potentials (MLP) in each pair of isomers could help to clarify differences in electronic and lipophilic properties of the two systems. The lack of a reasonable parametrization of the furoxan ring to use in this study dissuaded us from undertaking this kind of work. Studies are in progress to overcome this difficulty.

We also tried to understand the effects of the substituents R in the two series **1** and **2**. The small number of derivatives considered, as a consequence of the difficulties connected with their synthesis, the reactivity of some substituents, as well as the narrow variance of the potency in the two series (*ca.* 10–20-fold, if derivative **2i** is considered as an

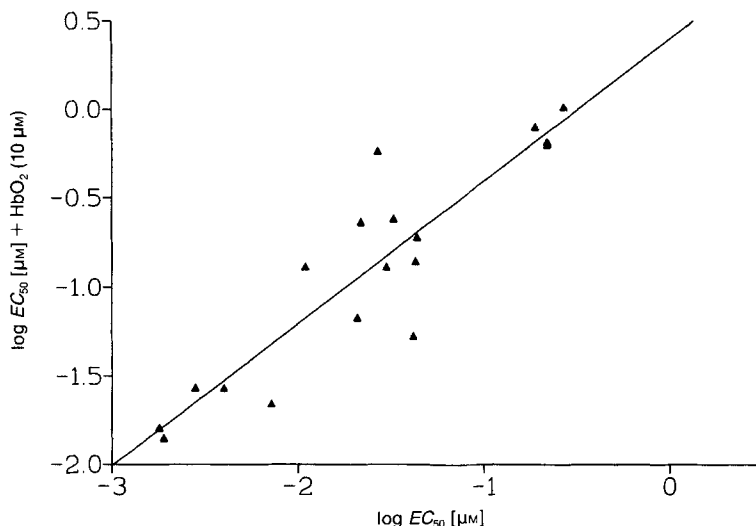


Fig. 3. Plot of $\log EC_{50} [\mu M]$ in the presence of HbO_2 (10 mM) vs. $\log EC_{50} [\mu M]$

outlier in the series **2**) discouraged us from a QSAR approach. Nevertheless, some considerations are possible. In spite of the quite well spanned lipophilic properties depending on the substituents R of **1** and **2**, we did not find a really significant correlation with $\log EC_{50}$. We were also unable to find any correlation between the potency and electronic and steric properties; they could play roles since the thiol-mediated NO release by furoxans involves initial attack of thiolate anion at the ring C-atom adjacent to the exocyclic N^+-O^- moiety (3-position) [6] [20]. This is probably due to a concomitance of factors like the not well spanned electronic and steric properties, the possibility to have different attack sites (3-, 3'-, 3''-positions) by thiolate anion in function of the nature of the substituent, and, in the presence of ionizable functions (derivatives **1h**, **2h**), problems of cell penetration for the reaction with soluble thiol cofactors.

The potency of derivative **2i**, as already pointed out, is surprisingly high. Probably it depends on the strong inductive effect of the EtO group which could influence to a larger extent than the other substituents of the series the reactivity at the 3- and 3''-positions. Also the PhO moiety in **2j** should exert a similar influence, but its different conformational properties could balance this beneficial action. Up to now, we were unable to obtain the corresponding isomers of type **1** to check this hypothesis.

In conclusion, terfuroxan derivatives are a new class of potent *in vitro* vasodilating agents. Their activity is dependent on their capability to behave as NO donors. The 4,3':4',4''-terfuroxan connection (see **1**) gives rise to the most potent compounds. The conformational factors seem to play important roles in the activity. However, structure-activity relationships are complex, and their understanding requires extension of the series and further exploration.

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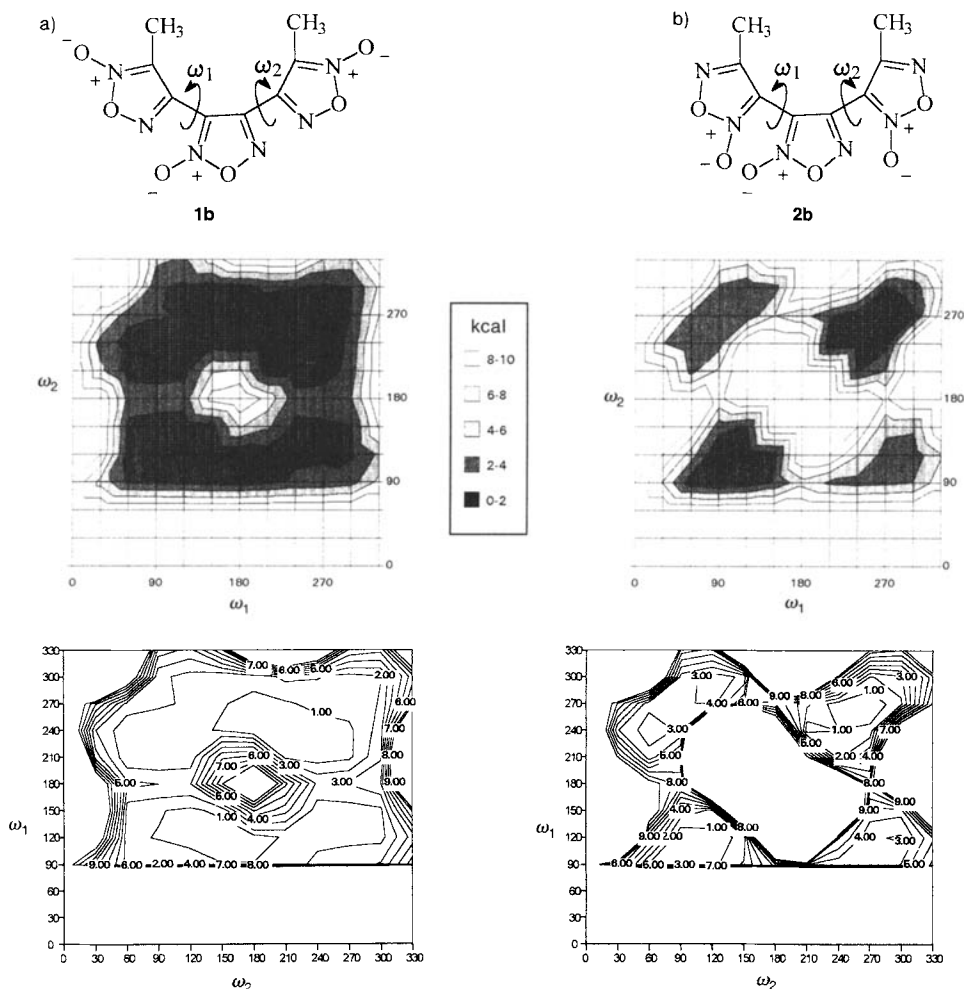


Fig. 4. Conformational energy maps with respect to ω_1 and ω_2 of terfuroxanes a) **1b** and b) **2b**. Theoretical calculations were carried out using the semiempirical approach AM1 [13]; values are in kcal mol⁻¹, and energy values are given relative to the absolute minimum. To obtain reliable structures for the molecules, the models were built up using crystallographic data available for **2a** [7]. The maps were obtained by a systematic and rigid rotation of the two torsional angles ω_1 and ω_2 with steps of 30 degrees.

Experimental Part

1. *General.* Derivatives **3a**, **4a** [14], **3b**, **4b** [15], **3c**, **4c** [16], **6a** [7], **13a,b** [17], and **14a** [18] were prepared according to the reported methods. Conformational analysis was performed on a *Silicon-Graphics-Indy* computer using the BIOSYM package of programs [19]. N₂O₄ was distilled from P₂O₅. Petroleum ether (b.p. 40–60°) was used for column chromatography and crystallizations. MgSO₄ was used as drying agent, the solns. were always evaporated *in vacuo*. Column chromatography: silica gel 60 (*Merck*, 230–400 mesh ASTM). M.p.: capillary

apparatus (Büchi 530), uncorrected. IR Spectra: Shimadzu FT-IR 8101 M. ^1H - and ^{13}C -NMR Spectra: at 200 and 50 MHz, resp., Bruker-AC-200 spectrometer; chemical shifts δ in ppm, SiMe_4 as internal standard, coupling constants J in Hz; ^{13}C , fully decoupled spectra. Mass spectra: Finnigan-Mat-TSQ-700 spectrometer, at 70 eV (direct inlet) or by CI (chemical ionization, isobutane). Elemental analyses (C, H, N) were performed by Redox (Cologno M.).

2. Terfuroxans. General Procedures. 2.1. *Method A: 1a–d.* The appropriate oxime (4 mmol) was added portionwise to a stirred and cold (0°) soln. of N_2O_4 (1.84 g, 20 mmol) in CHCl_3 (10 ml). After stirring at 0° for 30 min, the red mixture was refluxed for 1 h, washed with a 3% NaHCO_3 soln. and evaporated. The residue was purified on a short silica-gel column (petroleum ether/ CH_2Cl_2 1:1).

4,4''-Diphenyl-3,3':4',3''-terfurazan 2',5,5''-Trioxide (1a): Yield 72%. Colourless crystals. M.p. $170\text{--}171^\circ$ (CHCl_3 /petroleum ether). ^1H -NMR (CDCl_3): 7.45–7.60 (m, 2 Ph). Anal. calc. for $\text{C}_{18}\text{H}_{10}\text{N}_6\text{O}_6$: C 53.21, H 2.49, N 20.69; found: C 52.89, H 2.51, N 20.44.

4,4''-Dimethyl-3,3':4',3''-terfurazan 2',5,5''-Trioxide (1b): Yield 80%. Colourless crystals. M.p. $139\text{--}140^\circ$ (CHCl_3 /petroleum ether). ^1H -NMR (CDCl_3): 2.21 (s, Me); 2.48 (s, Me). Anal. calc. for $\text{C}_8\text{H}_6\text{N}_6\text{O}_6$: C 34.05, H 2.14, N 29.78; found: C 33.71, H 2.15, N 29.50.

4,4''-Dipropyl-3,3':4',3''-terfurazan 2',5,5''-Trioxide (1c): Yield 65%. Colourless crystals. M.p. $73\text{--}74^\circ$ (CHCl_3 /petroleum ether). ^1H -NMR (CDCl_3): 0.93 (t, $J = 8$, Me); 1.03 (t, $J = 8$, Me); 1.62 (m, CH_2); 1.72 (m, CH_2); 2.55 (t, $J = 8$, CH_2); 2.86 (t, $J = 8$, CH_2). Anal. calc. for $\text{C}_{12}\text{H}_{14}\text{N}_6\text{O}_6$: C 42.61, H 4.17, N 24.84; found: C 42.73, H 4.17, N 24.87.

4,4''-Bis(chloromethyl)-3,3':4',3''-terfurazan 2',5,5''-Trioxide (1d): Yield 80%. Colourless crystals. M.p. $92\text{--}93^\circ$ (CHCl_3 /petroleum ether). ^1H -NMR (CDCl_3): 4.60 (s, CH_2Cl); 4.81 (s, CH_2Cl). Anal. calc. for $\text{C}_8\text{H}_4\text{Cl}_2\text{N}_6\text{O}_6$: C 27.37, H 1.15, N 23.94; found: C 27.35, H 1.13, N 23.97.

2.2. Method B: 2a–e, i, j and 1e. The appropriate oxime (4 mmol) was added portionwise to a stirred and cold (0°) soln. of N_2O_4 (20 mmol) in dry Et_2O (20 ml). After stirring at 0° for 30 min, the red mixture was washed with sat. NaCl soln. and then extracted with aq. 2N NaOH. The combined aq. layers were cautiously acidified with 2N HCl and quickly extracted with CHCl_3 (2a–d, i, j) or AcOEt (1e, 2a). The org. layers were dried and concentrated. The resulting soln. (10 ml) was refluxed for 1 h and then washed with 3% aq. Na_2CO_3 soln., dried, and evaporated. The residue was purified on a short silica-gel column (CH_2Cl_2 /AcOEt 9:1 for 1e and 2e, petroleum ether/ CH_2Cl_2 1:1 for the other compounds).

4,4''-Diphenyl-3,3':4',3''-terfurazan 2,2',2''-Trioxide (2a): Yield 70%. Colourless crystals. M.p. $173\text{--}174^\circ$ (CHCl_3 /petroleum ether) ([7]: $173\text{--}174^\circ$ (dec.; benzene/petroleum ether)). ^1H -NMR (CDCl_3): 7.48–7.64 (m, 2 Ph). Anal. calc. for $\text{C}_{18}\text{H}_{10}\text{N}_6\text{O}_6$: C 53.21, H 2.49, N 20.69; found: C 52.98, H 2.42, N 20.51.

4,4''-Dimethyl-3,3':4',3''-terfurazan 2,2',2''-Trioxide (2b): Yield 65%. Colourless crystals. M.p. $123\text{--}124^\circ$ (CHCl_3 /petroleum ether). ^1H -NMR (CDCl_3): 2.49 (s, Me); 2.63 (s, Me). Anal. calc. for $\text{C}_8\text{H}_6\text{N}_6\text{O}_6$: C 34.05, H 2.14, N 29.78; found: C 33.83, H 2.16, N 29.54.

4,4''-Dipropyl-3,3':4',3''-terfurazan 2,2',2''-Trioxide (2c): Yield 55%. Colourless crystals. M.p. $43\text{--}44^\circ$ (CHCl_3 /petroleum ether). ^1H -NMR (CDCl_3): 1.02 (t, $J = 8$, Me); 1.07 (t, $J = 8$, Me); 1.73 (m, CH_2); 1.85 (m, CH_2); 2.83 (t, $J = 8$, CH_2); 2.96 (t, $J = 8$, CH_2). Anal. calc. for $\text{C}_{12}\text{H}_{14}\text{N}_6\text{O}_6$: C 42.61, H 4.17, N 24.84; found: C 42.48, H 4.15, N 24.74.

4,4''-Bis(chloromethyl)-3,3':4',3''-terfurazan 2,2',2''-Trioxide (2d): Yield 50%. Colourless crystals. M.p. $79\text{--}80^\circ$ (CHCl_3 /petroleum ether). ^1H -NMR (CDCl_3): 4.87 (s, CH_2Cl); 4.81 (s, CH_2Cl). Anal. calc. for $\text{C}_8\text{H}_4\text{Cl}_2\text{N}_6\text{O}_6$: C 27.37, H 1.15, N 23.94; found: C 27.38, H 1.13, N 23.95.

3,3':4',3''-Terfurazan-4,4''-dimethanol 2',5,5''-Trioxide (1e): Yield 70%. Colourless oil. ^1H -NMR ($(\text{D}_6)\text{DMSO}$): 4.50 (s, CH_2OH); 4.63 (s, CH_2OH); 5.85 (br., 2 OH). Anal. calc. for $\text{C}_8\text{H}_6\text{N}_6\text{O}_8$: C 30.58, H 1.92, N 26.75; found: C 30.82, H 2.02, N 26.57.

3,3':4',3''-Terfurazan-4,4''-dimethanol 2,2',2''-Trioxide (2e): Yield 45%. Colourless oil. ^1H -NMR ($(\text{D}_6)\text{DMSO}$): 4.96 (s, CH_2OH); 4.98 (s, CH_2OH); 6.00 (v. br., 2 OH). Anal. calc. for $\text{C}_8\text{H}_6\text{N}_6\text{O}_8$: C 30.58, H 1.92, N 26.75; found: C 30.88, H 2.06, N 26.45.

4,4''-Diethoxy-3,3':4',3''-terfurazan 2,2',2''-Trioxide (2i): Yield 70%. Colourless crystals. M.p. $40\text{--}41^\circ$ (CHCl_3 /petroleum ether). ^1H -NMR (CDCl_3): 1.42 (t, $J = 8$, Me); 1.46 (t, $J = 8$, Me); 4.48 (q, $J = 8$, CH_2O); 4.52 (q, $J = 8$, CH_2O). Anal. calc. for $\text{C}_{10}\text{H}_{10}\text{N}_6\text{O}_8$: C 35.09, H 2.95, N 24.56; found: C 35.39, H 3.12, N 24.24.

4,4''-Diphenoxy-3,3':4',3''-terfurazan 2,2',2''-Trioxide (2j): Yield 60%. Colourless crystals. M.p. $71\text{--}72^\circ$ (CHCl_3 /petroleum ether). ^1H -NMR (CDCl_3): 7.24–7.52 (m, 2 Ph). Anal. calc. for $\text{C}_{18}\text{H}_{10}\text{N}_6\text{O}_8$: C 49.33, H 2.30, N 19.17; found: C 49.12, H 2.30, N 19.00.

2.3. Synthesis of 1f–h and 2f–h. 4,4''-Bis(bromomethyl)-3,3':4',3''-terfurazan 2',5,5''- and 2,2',2''-Trioxide (1f and 2f, resp.). LiBr (3.47 g, 40 mol) and BuP(Ph)₃Br (1.60 g, 4 mmol) were added to a vigorously stirred soln. of 1d

or **2d** (0.44 g, 1 mmol) in CHCl_3 (25 ml). The mixture was kept under stirring at r.t. for 48 h, and then filtered. The solid was washed with CHCl_3 , and the combined org. solns. were evaporated to give a residue which was filtered on a short pad of silica gel with CH_2Cl_2 . Solvent removal gave **1f** or **2f**, resp.

1f: Yield 80%. Colourless crystals. M.p. 115–116° (CHCl_3 /petroleum ether). $^1\text{H-NMR}$ (CDCl_3): 4.38 (s, CH_2Br); 4.62 (s, CH_2Br). Anal. calc. for $\text{C}_8\text{H}_4\text{Br}_2\text{N}_6\text{O}_6$: C 21.84, H 0.92, N 19.10; found: C 21.97, H 0.88, N 19.19.

2f: Yield 76%. Colourless crystals. M.p. 89–90° (CHCl_3 /petroleum ether). $^1\text{H-NMR}$ (CDCl_3): 4.52 (s, CH_2Br); 4.69 (s, CH_2Br). Anal. calc. for $\text{C}_8\text{H}_4\text{Br}_2\text{N}_6\text{O}_6$: C 21.84, H 0.92, N 19.10; found: C 22.00, H 0.91, N 19.12.

4,4'-Bis[(nitrooxy)methyl]-3,3':4',3''-terfurazan-2',5,5''- and 2,2',2''-Trioxide (1g and 2g). A soln. of AgNO_3 (0.51 g, 3 mmol) in MeCN (10 ml) was added to a stirred soln. of the appropriate bromomethyl derivative **1f** or **2f** (0.44 g, 1 mmol) in MeCN (10 ml). The mixture was kept at r.t. for 8 h under stirring and then filtered. The solid was washed with a small amount of MeCN, and the combined org. solns. were evaporated. The residue was filtered on a short silica-gel column with CH_2Cl_2 , to give the title products.

1g: Yield 95%. Colourless oil. $^1\text{H-NMR}$ (CDCl_3): 5.49 (s, CH_2ONO_2); 5.69 (s, CH_2ONO_2). Anal. calc. for $\text{C}_8\text{H}_4\text{N}_8\text{O}_{12}$: C 23.77, H 1.00, N 27.72; found: C 23.99, H 1.18, N 27.41.

2g: Yield 94%. Colourless crystals. M.p. 99–100° (CHCl_3 /petroleum ether). $^1\text{H-NMR}$ (CDCl_3): 5.68 (s, CH_2ONO_2); 5.79 (s, CH_2ONO_2). Anal. calc. for $\text{C}_8\text{H}_4\text{N}_8\text{O}_{12}$: C 23.77, H 1.00, N 27.72; found: C 23.42, H 0.86, N 27.82.

N,N,N',N'-Tetramethyl-3,3':4',3''-terfurazan-4,4''-dimethanamine Dihydrochloride 2',5,5''- and 2,2',2''-Trioxide (1h·2 HCl and 2h·2 HCl, resp.). A 40% aq. Me_2NH soln. (6 mmol) was added to a stirred soln. of the appropriate bromomethyl derivative **1f** or **2f** (0.44 g, 1 mmol) in THF (10 ml). After 10 min of stirring at r.t., the mixture was evaporated. The residue was dissolved in 1N HCl (10 ml) and extracted with AcOEt. The aq. layer was basified with 1N NaHCO_3 soln. and extracted with Et_2O . The combined org. phases were evaporated and the title bases so obtained transformed into the corresponding hydrochlorides.

1h·2 HCl: Yield 80%. White solid from H_2O /acetone. Starting from 150°, decomposition occurred over a large temp. range. $^1\text{H-NMR}$ (D_2O): 2.96 (s, MeN); 3.00 (s, MeN); 4.56 (s, CH_2N); 4.70 (s, CH_2N). Anal. calc. for $\text{C}_{12}\text{H}_{16}\text{N}_8\text{O}_6\cdot 2\text{HCl}$: C 32.67, H 4.11, N 25.40; found: C 32.49, H 4.08, N 25.39.

2h·2 HCl: Yield 70%. White solid from H_2O /acetone. Starting from 175°, decomposition occurred over a large temp. range. $^1\text{H-NMR}$ (D_2O): 3.03 (s, MeN); 3.06 (s, MeN); 4.70 (s, CH_2N); 4.86 (s, CH_2N). Anal. calc. for $\text{C}_{12}\text{H}_{16}\text{N}_8\text{O}_6\cdot 2\text{HCl}$: C 32.67, H 4.11, N 25.40; found: C 32.72, H 4.12, N 25.44.

3. Oxime Derivatives 5 and 6. General Procedure. A soln. of the appropriate aldehyde (5 mmol), hydroxylamine hydrochloride (0.41 g, 6 mmol), and pyridine (0.40 g, 6 mmol) in EtOH (25 ml) was refluxed for 1 h. The solvent was evaporated and the residue treated with aq. 1N HCl (25 ml) and then extracted several times with AcOEt. The combined org. layers were washed with sat. NaCl soln., dried, and evaporated to afford the expected oxime.

4-Phenylfurazan-3-carbaldehyde Oxime 5-Oxide (5a): Yield 95%. Colourless crystals. M.p. 143–144° (AcOEt/petroleum ether). $^1\text{H-NMR}$ ((D_6) DMSO): 7.65–7.82 (m, Ph); 8.37 (s, $\text{CH}=\text{N}$); 12.50 (s, $\text{N}=\text{OH}$). $^{13}\text{C-NMR}$ ((D_6) DMSO): 122.7, 128.7, 129.4, 130.6 (Ph); 113.7 (C(4)); 138.0 (C=NOH); 151.4 (C(3)). EI-MS: 205 (M^+). Anal. calc. for $\text{C}_9\text{H}_7\text{N}_3\text{O}_3$: C 52.68, H 3.44, N 20.48; found: C 53.08, H 3.42, N 20.38.

4-Methylfurazan-3-carbaldehyde Oxime 5-Oxide (5b): Yield 92%. Colourless crystals. M.p. 114–115° (AcOEt/petroleum ether). $^1\text{H-NMR}$ ((D_6) DMSO): 2.30 (s, Me); 8.39 (s, $\text{CH}=\text{N}$); 12.62 (s, $\text{N}=\text{OH}$). $^{13}\text{C-NMR}$ ((D_6) DMSO): 8.3 (Me); 111.7 (C(4)); 139.1 (C=NOH); 152.9 (C(3)). EI-MS: 143 (M^+). Anal. calc. for $\text{C}_4\text{H}_5\text{N}_3\text{O}_3$: C 33.57, H 3.52, N 29.36; found: C 33.76, H 3.58, N 29.18.

4-Methylfurazan-3-carbaldehyde Oxime 2-Oxide (6b): Yield 90%. Colourless crystals. M.p. 146–147° (AcOEt/petroleum ether). $^1\text{H-NMR}$ ((D_6) DMSO): 2.55 (s, Me); 8.00 (s, $\text{CH}=\text{N}$); 12.59 (s, $\text{N}=\text{OH}$). $^{13}\text{C-NMR}$ ((D_6) DMSO): 12.4 (Me); 112.6 (C(3)); 135.8 (C=NOH); 154.0 (C(4)). EI-MS: 143 (M^+). Anal. calc. for $\text{C}_4\text{H}_5\text{N}_3\text{O}_3$: C 33.57, H 3.52, N 29.36; found: C 33.53, H 3.51, N 29.41.

4-Propylfurazan-3-carbaldehyde Oxime 5-Oxide (5c): Yield 90%. Colourless crystals. M.p. 43–44° (CHCl_3 /petroleum ether). $^1\text{H-NMR}$ ((D_6) DMSO): 0.90 (t, $J = 7.4$, Me); 1.60 (m, CH_2); 2.71 (t, $J = 7.4$, CH_2); 8.28 (s, $\text{CH}=\text{N}$); 12.52 (s, $\text{N}=\text{OH}$). $^{13}\text{C-NMR}$ ((D_6) DMSO): 13.4 (Me); 18.6 (CH_2); 24.7 (CH_2); 112.2 (C(3)); 139.0 (C=NOH); 152.6 (C(3)). EI-MS: 171 (M^+). Anal. calc. for $\text{C}_6\text{H}_9\text{N}_3\text{O}_3$: C 42.11, H 5.30, N 24.55; found: C 42.18, H 5.32, N 24.57.

4-Propylfurazan-3-carbaldehyde Oxime 2-Oxide (6c): Yield 85%. Colourless crystals. M.p. 85–86° (CHCl_3 /petroleum ether). $^1\text{H-NMR}$ ((D_6) DMSO): 0.98 (t, $J = 7.4$, Me); 1.68 (m, CH_2); 2.82 (t, $J = 7.2$, CH_2); 7.97 (s, $\text{CH}=\text{N}$); 12.52 (s, $\text{N}=\text{OH}$). $^{13}\text{C-NMR}$ ((D_6) DMSO): 13.5 (Me); 19.1 (CH_2); 28.0 (CH_2); 112.2 (C(3)); 135.8 (C=NOH); 157.1 (C(4)). EI-MS: 171 (M^+). Anal. calc. for $\text{C}_6\text{H}_9\text{N}_3\text{O}_3$: C 42.11, H 5.30, N 24.55; found: C 41.98, H 5.28, N 24.54.

4-(Chloromethyl)furan-3-carbaldehyde Oxime 5-Oxide (**5d**): Yield 52% (from **8**). Colourless crystals. M.p. 99–100° (CHCl₃/petroleum ether). ¹H-NMR ((D₆)DMSO): 4.81 (s, CH₂Cl); 8.36 (s, CH=N); 12.76 (s, N=OH). ¹³C-NMR ((D₆)DMSO): 33.7 (CH₂Cl); 112.4 (C(4)); 138.5 (C=NOH); 151.5 (C(3)). EI-MS: 177/179 (*M*⁺). Anal. calc. for C₄H₄ClN₃O₃: C 27.06, H 2.27, N 23.67; found: C 26.94, H 2.27, N 23.57.

4-(Chloromethyl)furan-3-carbaldehyde Oxime 2-Oxide (**6d**): Yield 22% (from **8**). Colourless crystals. M.p. 114–115° (CHCl₃/petroleum ether). ¹H-NMR ((D₆)DMSO): 4.96 (s, CH₂Cl); 7.97 (s, CH=N); 12.69 (s, N=OH). ¹³C-NMR ((D₆)DMSO): 35.3 (CH₂Cl); 111.2 (C(3)); 134.9 (C=NOH); 153.8 (C(4)). EI-MS: 177/179 (*M*⁺). Anal. calc. for C₄H₄ClN₃O₃: C 27.06, H 2.27, N 23.67; found: C 26.70, H 2.29, N 23.39.

4-(Hydroxymethyl)furan-3-carbaldehyde Oxime 5-Oxide (**5e**): Yield 65% (from **10**). Colourless crystals. M.p. 109–110° (AcOEt/petroleum ether). ¹H-NMR ((D₆)DMSO): 4.57 (*d*, *J* = 5.8, CH₂); 5.58 (*t*, *J* = 5.8, OH); 8.28 (s, CH=N); 12.56 (s, N=OH). ¹³C-NMR ((D₆)DMSO): 52.2 (CH₂OH); 113.6 (C(4)); 136.5 (C=NOH); 152.3 (C(3)). EI-MS: 159 (*M*⁺). Anal. calc. for C₄H₅N₃O₄: C 30.20, H 3.17, N 26.41; found: C 30.35, H 3.15, N 26.40.

4-(Hydroxymethyl)furan-3-carbaldehyde Oxime 2-Oxide (**6e**): Yield 70% (from **12**). Colourless crystals. M.p. 111–112° (AcOEt/petroleum ether). ¹H-NMR ((D₆)DMSO): 4.69 (*d*, *J* = 5.8, CH₂); 5.79 (*t*, *J* = 5.8, OH); 7.95 (s, CH=N); 12.54 (s, N=OH). ¹³C-NMR ((D₆)DMSO): 55.4 (CH₂OH); 111.3 (C(3)); 135.4 (C=NOH); 157.6 (C(4)). EI-MS: 159 (*M*⁺). Anal. calc. for C₄H₅N₃O₄: C 30.20, H 3.17, N 26.41; found: C 30.03, H 3.16, N 26.27.

4-Ethoxyfuran-3-carbaldehyde Oxime 2-Oxide (**6i**): Yield 94%. Colourless crystals. M.p. 167–168° (AcOEt/petroleum ether). ¹H-NMR ((D₆)DMSO): 1.41 (*t*, *J* = 7, Me); 4.45 (*q*, *J* = 7, CH₂O); 7.81 (s, CH=N); 12.57 (s, N=OH). ¹³C-NMR ((D₆)DMSO): 14.2 (Me); 66.9 (CH₂O); 106.0 (C(3)); 134.2 (C=NOH); 161.4 (C(4)). EI-MS: 173 (*M*⁺). Anal. calc. for C₅H₇N₃O₄: C 34.68, H 4.08, N 24.27; found: C 34.39, H 4.10, N 24.08.

4-Phenoxyfuran-3-carbaldehyde Oxime 2-Oxide (**6j**): Yield 92%. Colourless crystals. M.p. 192–193° (dec.; AcOEt/petroleum ether). ¹H-NMR ((D₆)DMSO): 7.34–7.54 (*m*, Ph); 7.93 (s, CH=N); 12.64 (s, N=OH). ¹³C-NMR ((D₆)DMSO): 106.6 (C(3)); 119.8, 126.4, 130.2, 152.8 (Ph); 134.1 (C=NOH); 161.0 (C(4)). EI-MS: 221 (*M*⁺). Anal. calc. for C₉H₇N₃O₄: C 48.88, H 3.19, N 19.00; found: C 48.68, H 3.21, N 18.89.

4. Aldehydes **3** and **4**. 4-Methylfuran-3-ylmethylidene Diacetate 5-Oxide (**7**). Conc. H₂SO₄ (0.3 ml) was added to an ice-water cooled and stirred soln. of **3b** (25.6 g, 0.2 mol) in Ac₂O (30 ml). The mixture was kept under stirring at r.t. for 2 h and then poured into cold H₂O (300 ml). The pure solid separated, was collected by filtration, washed with H₂O, and dried (80%). Colourless crystals. M.p. 44–45° (MeOH/H₂O). ¹H-NMR (CDCl₃): 2.13 (s, 2 Ac); 2.22 (s, Me–C(4)); 7.74 (s, CH). ¹³C-NMR (CDCl₃): 7.6 (Me–C(4)); 20.1 (MeCO); 82.5 (CH); 111.0 (C(4)); 153.1 (C(3)); 167.45 (MeCO). EI-MS: 230 (*M*⁺). Anal. calc. for C₈H₁₀N₂O₆: C 41.75, H 4.38, N 12.17; found: C 41.89, H 4.38, N 12.18.

4-(Bromomethyl)furan-3-ylmethylidene Diacetate 5-Oxide (**8**). *N*-Bromosuccinimide (7.12 g, 40 mmol) and a catal. amount of benzoyl peroxide were added to a stirred soln. of **7** (6.90 g, 30 mmol) in dry CCl₄ (90 ml). The mixture was refluxed under stirring for 40 h and then filtered. The residue obtained after evaporation was purified by FC (petroleum ether/AcOEt 4:1): yellow pale oil (75%). ¹H-NMR (CDCl₃): 2.19 (s, 2 Ac); 4.39 (s, CH₂Br); 7.84 (s, CH). ¹³C-NMR (CDCl₃): 15.7 (CH₂); 20.3 (MeCO); 82.4 (CH); 112.15 (C(4)); 151.8 (C(3)); 167.4 (COO). CI-MS: 309/311 ([*M* + 1]⁺). Anal. calc. for C₈H₉BrN₂O₆: C 31.09, H 2.94, N 9.06; found: C 31.31, H 3.04, N 8.88.

4-(Chloromethyl)furan-3-carbaldehyde 5-Oxide (**3d**). To a stirred soln. of **8** (6.18 g, 20 mmol) in THF (20 ml), 4*N* HCl (20 ml) was added. The mixture was kept under stirring at r.t. for a night. Evaporation gave a residue which was extracted with CHCl₃. The combined org. layers were washed with 3% aq. Na₂CO₃ soln., dried, and concentrated to ca. 40 ml. PhCH₂P(Et)₂Cl (4.52 g, 20 mmol) and LiCl (8.48 g, 0.2 mol) were added, and the resulting mixture was vigorously stirred for 48 h and then filtered. The solid was washed with CH₂Cl₂, and the combined org. solns. were evaporated to give a residue which was filtered on a short silica-gel column (petroleum ether/AcOEt 2:1). Solvent removal afforded **3d** as yellow pale oil, which was used for the next reaction without further purification and characterization.

3-(Chloromethyl)-4-(1,3-dioxolan-2-yl)furan 2-Oxide (**9**). Crude **3d** (see above) was dissolved in benzene (40 ml) and the resulting soln. treated with ethylene glycol (1.4 ml, 25 mmol) and a cat. amount of TsOH and refluxed for 6 h (Dean-Stark apparatus). The mixture was cooled to r.t. and filtered after addition of anh. K₂CO₃. Solvent removal left a residue which was purified by filtration on a short pad of silica gel (petroleum ether/CH₂Cl₂ 1:1): pure **9** (45% from **8**). M.p. 57–58° (CHCl₃/petroleum ether). ¹H-NMR (CDCl₃): 4.08–4.24 (*m*, OCH₂CH₂O); 4.54 (s, CH₂Cl); 6.00 (s, OCHO). ¹³C-NMR (CDCl₃): 31.6 (CH₂Cl); 65.7 (OCH₂CH₂O); 96.8 (OCHO); 112.1 (C(3)); 154.3 (C(4)). EI-MS: 206/208 (*M*⁺). Anal. calc. for C₆H₇ClN₂O₄: C 34.88, H 3.42, N 13.56; found: C 34.82, H 3.44, N 13.50.

4-(1,3-Dioxolan-2-yl)furan-3-methanol 2-Oxide (**10**). To a stirred soln. of **9** (1.03 g, 5 mmol) in dioxane (15 ml), LiBr (0.86 g, 10 mmol), CaCO₃ (2.5 g, 25 mmol), and H₂O (15 ml) were added. The mixture was refluxed under stirring for 10 h and then evaporated. The residue was dissolved in AcOEt and treated with 2*N* HCl until the

carbonate was dissolved. The aq. phase was extracted with AcOEt, the combined org. phase dried and evaporated, and the residue purified by column chromatography (petroleum ether/AcOEt 7.5:2.5): **10** (82%). Pure yellow pale oil. $^1\text{H-NMR}$ ((D_6) DMSO): 3.97–4.14 (*m*, $\text{OCH}_2\text{CH}_2\text{O}$); 4.44 (*s*, CH_2OH); 5.71 (*br.*, *OH*); 6.15 (*s*, OCHO). $^{13}\text{C-NMR}$ ((D_6) DMSO): 51.8 (CH_2OH); 65.3 ($\text{OCH}_2\text{CH}_2\text{O}$); 96.2 (OCHO); 114.6 ($\text{C}(3)$); 156.5 ($\text{C}(4)$). EI-MS: 188 (M^+). Anal. calc. for $\text{C}_6\text{H}_8\text{N}_2\text{O}_5$: C 34.30, H 4.29, N 14.89; found: C 38.58, H 4.41, N 14.59.

4-(Hydroxymethyl)furanan-3-carbaldehyde 5-Oxide (**3e**). To a stirred soln. of **10** (0.75 g, 4 mmol) in acetone (5 ml), 12*N* H_2SO_4 (10 ml) was added and the mixture refluxed for 1 h. Acetone was evaporated and the resulting soln. extracted with AcOEt. The combined org. layers were washed with 5% aq. Na_2CO_3 soln., dried, and evaporated to give **3e** which was used for the oximation reaction without additional purification and characterization.

4-(Chloromethyl)furanan-3-carbaldehyde 2-Oxide (**4d**). A soln. of crude **3d** in toluene (100 ml) was refluxed for 48 h. Evaporation gave **3d/4d** which were separated by column chromatography (petroleum ether containing 20–30% of AcOEt). The less polar **4d** was used for the oximation reaction without additional purification and characterization.

3-(Chloromethyl)-4-(1,3-dioxolan-2-yl)furanan 5-Oxide (**11**) was prepared and purified as described for **9**: **11** (18% from **8**). Colourless crystals. M.p. 68–69° (CHCl_3 /petroleum ether). $^1\text{H-NMR}$ (CDCl_3): 4.07–4.24 (*m*, $\text{OCH}_2\text{CH}_2\text{O}$); 4.67 (*s*, CH_2Cl); 5.96 (*s*, OCHO). $^{13}\text{C-NMR}$ (CDCl_3): 34.3 (CH_2Cl); 65.9 ($\text{OCH}_2\text{CH}_2\text{O}$); 96.3 (OCHO); 112.0 ($\text{C}(4)$); 152.9 ($\text{C}(3)$). CI-MS: 207/209 ($[M + 1]^+$). Anal. calc. for $\text{C}_6\text{H}_7\text{ClN}_2\text{O}_4$: C 34.88, H 3.42, N 13.56; found: C 34.76, H 3.38, N 13.46.

4-(1,3-Dioxolan-2-yl)furanan-3-methanol 5-Oxide (**12**) was prepared and purified as described for **10**: **12** (75%). Pale yellow oil. $^1\text{H-NMR}$ ((D_6) DMSO): 3.95–4.17 (*m*, $\text{OCH}_2\text{CH}_2\text{O}$); 4.57 (*d*, $J = 6$, CH_2OH); 5.79 (*t*, $J = 6$, *OH*); 6.03 (*s*, OCHO). $^{13}\text{C-NMR}$ ((D_6) DMSO): 54.8 (CH_2OH); 65.8 ($\text{OCH}_2\text{CH}_2\text{O}$); 95.5 (OCHO); 113.0 ($\text{C}(4)$); 157.8 ($\text{C}(3)$). CI-MS: 189 ($[M + 1]^+$). Anal. calc. for $\text{C}_6\text{H}_8\text{N}_2\text{O}_5$: C 38.30, H 4.29, N 14.89; found: C 38.64, H 4.43, N 14.89.

4-(Hydroxymethyl)furanan-3-carbaldehyde 2-Oxide (**4e**) was prepared as described for **3e**. The crude oil obtained was directly used for the oximation reaction without further purification and characterization.

3-(Bromomethyl)-4-phenoxyfuranan 2-Oxide (**14b**) was prepared as described for **8**. The residue was purified by column chromatography (petroleum ether/ CH_2Cl_2 1:1): **14b** (76%). Colourless crystals. M.p. 65–66° (MeOH). $^1\text{H-NMR}$ (CDCl_3): 4.34 (*s*, CH_2); 7.37–7.47 (*m*, Ph). $^{13}\text{C-NMR}$ (CDCl_3): 14.5 (CH_2); 107.3 ($\text{C}(3)$); 119.6, 126.5, 129.9, 152.3 (Ph); 161.4 ($\text{C}(4)$). EI-MS: 270/272 (M^+). Anal. calc. for $\text{C}_9\text{H}_7\text{BrN}_2\text{O}_3$: C 39.88, H 2.60, N 10.33; found: C 39.84, H 2.59, N 10.35.

4-Ethoxyfuranan-3-methanol 2-Oxide (**15a**). To a soln. of **14a** (3.35 g, 15 mmol) in dioxane (45 ml), CaCO_3 (7.51 g, 75 mmol) and H_2O (10 ml) were added. The mixture was refluxed for 8 h under stirring and then evaporated. The residue was treated with CH_2Cl_2 (30 ml) and then with 2*N* HCl until dissolution of the white precipitate. The separated aq. phase was extracted with CH_2Cl_2 , the combined org. phase dried and evaporated, and the residue purified on a short silica-gel column (petroleum ether/AcOEt 4:1). Yellow pale oil (90%). $^1\text{H-NMR}$ (CDCl_3): 1.46 (*t*, $J = 7$, Me); 3.24 (*br.*, *OH*); 4.43 (*q*, $J = 7$, CH_2O); 4.54 (*s*, CH_2OH). $^{13}\text{C-NMR}$ (CDCl_3): 14.05 (Me); 51.6 (CH_2OH); 66.5 (CH_2O); 108.8 ($\text{C}(3)$); 162.4 ($\text{C}(4)$). EI-MS: 160 (M^+). Anal. calc. for $\text{C}_5\text{H}_8\text{N}_2\text{O}_4$: C 37.50, H 5.04, N 17.49; found: C 37.78, H 5.20, N 17.23.

4-Phenoxyfuranan-3-methanol 2-Oxide (**15b**) was prepared as described for **15a**. Evaporation of the dried combined org. layers gave a white solid (90%). M.p. 74–75° (CHCl_3 /petroleum ether). $^1\text{H-NMR}$ (CDCl_3): 3.05 (*t*, $J = 6$, *OH*); 4.66 (*d*, $J = 6$, CH_2); 7.30–7.48 (*m*, Ph). $^{13}\text{C-NMR}$ (CDCl_3): 51.9 (CH_2); 108.9 ($\text{C}(3)$); 119.5, 126.3, 129.8, 152.3 (Ph); 161.8 ($\text{C}(4)$). EI-MS: 208 (M^+). Anal. calc. for $\text{C}_9\text{H}_8\text{N}_2\text{O}_4$: C 51.92, H 3.87, N 13.46; found: C 52.01, H 3.90, N 13.51.

4-Ethoxyfuranan-3-carbaldehyde 2-Oxide (**4i**). To a stirred soln. of **15a** (1.60 g, 10 mmol) in CHCl_3 (50 ml), activated MnO_2 (10 g) was added. The mixture was vigorously stirred at r.t. for 6 h and then filtered on a Celite pad. The residue obtained after evaporation was purified on a short silica-gel column (petroleum ether/AcOEt 8.5:1.5): **4i** (80%). Pure yellow pale oil. $^1\text{H-NMR}$ (CDCl_3): 1.49 (*t*, $J = 7$, Me); 4.51 (*q*, $J = 7$, CH_2O); 9.82 (*s*, CHO). $^{13}\text{C-NMR}$ (CDCl_3): 14.0 (Me); 67.3 (CH_2O); 107.7 ($\text{C}(3)$); 160.6 ($\text{C}(4)$); 176.3 (CHO). EI-MS: 158 (M^+).

4-Phenoxyfuranan-3-carbaldehyde (**4j**) was prepared and purified (80%) as described for **4i**. Colourless crystals. M.p. 76–77° (CHCl_3 /petroleum ether). $^1\text{H-NMR}$ (CDCl_3): 7.29–7.51 (*m*, Ph); 9.92 (*s*, CHO). $^{13}\text{C-NMR}$ (CDCl_3): 107.6 ($\text{C}(3)$); 119.75, 126.7, 129.9, 152.1 (Ph); 160.1 ($\text{C}(4)$); 176.0 (CHO). MS: 206 (M^+). Anal. calc. for $\text{C}_9\text{H}_6\text{N}_2\text{O}_4$: C 52.44, H 2.93, N 13.59; found: C 52.56, H 2.96, N 13.60.

Quantitative Nitrite Detection. A soln. of the appropriate terfuranan trioxide (20 μl) in DMSO or distilled H_2O was added to 2 ml of 50 mM phosphate buffer (pH 7.4), containing 5 mM L-cysteine. The final concentration of drug was 10^{-4} M. After 1 h at 37°, 1 ml of this mixture was treated with 250 μl of Griess reagent (sulfanilamide (4 g),

N-naphthylethylenediamine dihydrochloride (0.2 g), 85% phosphoric acid (10 ml) in distilled H₂O (final volume: 100 ml)). After 10 min at r.t., absorbance was measured at 540 nm; 10–80 nmol/ml NaNO₂ standard solns. were used for the calibration curve. The yield in nitrite was expressed as NO₂[−] % (mol/mol) ± standard error.

NO Release Kinetic Study. The rate of NO release was determined using a spectrophotometric technique based on the oxidation of oxyhemoglobin (HbO₂) to methemoglobin (MetHb) [12]. The formation of MetHb was followed by recording the absorbance increase (ΔA) at λ 401 nm, using a *Perkin-Elmer- λ 5* spectrophotometer and a thermostated (37°) cuvette. The reaction was started by adding the drugs dissolved in DMSO or distilled H₂O to a 4 μ M HbO₂ soln. in 50 mM phosphate buffer (pH 7.4), containing a 5-fold molar excess of L-cysteine with respect to the terfurazan trioxide solute (final drug concentration 10^{−4} M). HbO₂ was prepared according to the method previously described [20]. The increase of the absorbance (ΔA) was recorded over the first three min. The initial rates were calculated from the slope of the straight line portion of each curve. Every NO releasing rate is the average of at least three determinations. The molar extinction coefficient $\Delta \epsilon = \epsilon_{401}(\text{MetHb}) - \epsilon_{401}(\text{HbO}_2)$ was determined by quantitative oxidation of five different concentrations (2–6 μ M) of HbO₂ in pH 7.4 phosphate buffer with 7.5 · 10^{−5} M aq. K₃[Fe(CN)₆]. The slope ($\Delta \epsilon$) of the straight line ($r = 0.999$) obtained on plotting the increase of the absorbance ΔA at 401 nm against the HbO₂ concentrations was 39.9 ± 1.4 mm^{−1} cm^{−1}.

Vasoactivity Determinations. Thoracic aortas were isolated from male *Wistar* rats, weighing 180–200 g. The vessels were helically cut, the endothelium removed, and two strips were obtained from each aorta. The tissues were mounted under 1 g tension in organ baths containing 30 ml of *Krebs-Henseleit* soln. (NaCl 137, KCl 2.68, MgCl₂ 0.50, CaCl₂ 2.52, NaH₂PO₄ 0.54, NaHCO₃ 8.93, glucose 8.3, and ascorbic acid 0.1 mM) at 37° and gassed with 95% O₂ – 5% CO₂ (pH 7.4). The aortic strips were allowed to equilibrate for 1 h, and then they were contracted with 1 μ M noradrenaline, which causes a submaximal response. During this first contraction, the absence of intact endothelium was verified by adding 1 μ M acetylcholine, which was found not to induce relaxation. The preparations were then extensively washed with *Krebs-Henseleit* soln., and a second contraction was evoked by 1 μ M noradrenaline. When the response to the agonist plateaued, cumulative concentrations of the vasodilating agent were added. When maximal vasodilation was obtained, aortic strips were washed repeatedly, and a third contraction was induced by 1 μ M noradrenaline so as to verify the reversibility of vasodilation. Effects of oxyhemoglobin on relaxation were evaluated in a separate series of experiments, by exposing aortic strips, precontracted with 1 μ M noradrenaline to 10 μ M oxyhemoglobin for at least 10 min before addition of vasodilating agent.

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