New NO Donors with Antithrombotic and Vasodilating Activities, Part 29

N-(1-Cyanocyclohexyl)-*C*-phenylnitrones and Glyoxaldinitrones☆

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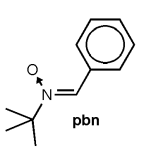
***Key Words**: N-(1-Cyanocyclohexyl)-C-phenylnitrones; glyoxaldinitrones; antithrombotic properties; nitric oxide; cyp 450 surrogate*

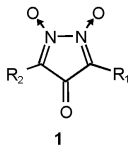
Summary

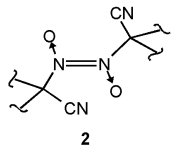
Six *N*-(1-cyanocyclohexyl)-*C*-phenylnitrones **4a–f** (**4b–f** for the first time) and 22 glyoxaldinitrones **7a–v** were prepared and tested for antithrombotic (p.o. administration to rats, 60 mg/kg) effects. Both classes of compounds exhibit considerable antithrombotic activities. Maximum inhibition of thrombus formation in arterioles (21%) was observed in *N*,*N*′-bis-2-phenylethylglyoxaldinitrone (**7o**) and *N*,*N*′-bis-4-nitrobenzylglyoxaldinitrone (**7u**). The compounds form only small amounts of nitric oxide *in vitro* by the addition of a Fe^{3+}-porphyrine complex and an oxygen donor.

Introduction

To date no antithrombotic activities of nitrones have been reported. However, *in vitro* production of nitric oxide from **p**henyl-*N*-*tert*-**b**utyl**n**itrone (**pbn**) and activation of guanylatecyclase by **pbn** were reported in 1993[1]. Konorev et al.[2] in the same year reported vasodilating properties of **pbn**. This prompted us to investigate thoroughly the antithrombotic properties of nitrones. We recently reported that in pyrazol-4-one-1,2-dioxides (**1**)[3] antithrombotic activities are enhanced by electron withdrawing groups near the NO group. Furthermore, it was found that azodioxides with a geminal cyano group (**2**) show antithrombotic activity and are able to form high amounts of NO by spontaneous decomposition[4]. Therefore, first of all derivatives of pbn with electron withdrawing moieties were tested. From previous investigations[5,6] we knew the suitability of doubling the NO moiety. Therefore, we prepared glyoxaldinitrones (**7**) in order to strengthen the above pharmacological effects.







Chemistry

N-(1-cyanocyclohexyl)-*C*-phenylnitrones (**4**) and glyoxaldinitrones (**7**) were prepared according to Figure 1.

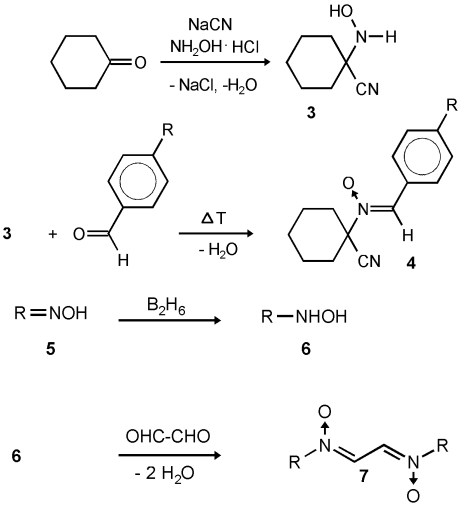


Figure 1. Synthesis of *N*-(1-cyanocyclohexyl)-*C*-phenylnitrones (**4**) from α-hydroxylamino nitriles (**3**) and glyoxaldinitrones (**7**) obtained from hydroxylamines (**6**) by the reduction of oximes (**5**) with diborane.

The first step in the synthesis of **4** is the formation of α-hydroxylaminonitrile (**3**)[7]. The reaction with different aldehydes leads to the desired nitrones **4**.

Glyoxaldinitrones (**7**) were prepared from the corresponding hydroxylamines (**6**) which in general were obtained by the reduction of oximes (**5**) with diborane[8] (which was obtained by the method of Hach[9]).

Compounds **7a**, **b**, **d**, and **7e** were prepared by the method of Zinner et al.[10]. Hydroxylamines were obtained from cyclohexanone[7](**7a**), by the reduction of nitro compounds (**7d**,**e**), or purchased from Aldrich (**7b**).

Biology

Antithrombotic Properties

The influence of the test compounds on the formation of thrombi was assayed in a laser thrombosis model[11]. The title compounds were administered orally to rats (60 mg/kg). After 2 h the formation of thrombi in mesenteric vessels of rats is induced by the beam of an argon laser via a microscope (35 mW, 50 ms). The number of exposures ("shots") necessary to form a thrombus of defined size is counted. From the average shot number the percentage of inhibition of thrombosis is calculated[12]. The results are compiled in Table 1.

[1)] Part of the PhD Thesis of R. Camehn, FU Berlin, **1999**.

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Table 1. Antithrombotic effects of *N*-(1-cyanocyclohexyl)-*C*-phenylnitrones (**4**) and glyoxaldinitrones (**7**) or acetylsalicyclic acid (**asa**), 2 h after p.o. administration of 60 mg/kg of the test compound. Statistics: Man-Whitney U-test: n.s. = not significant.

No.	R	Inhibition of thrombus formation in arterioles		venules	
		% ± s_x	$p \leq$	% ± s_x	$p \leq$
4a	H	13 ± 1	0.002	10 ± 1	0.002
4b	$N(CH_3)_2$	0 ± 1	n.s.	0 ± 1	n.s.
4c	Cl	0 ± 1	n.s.	0 ± 1	n.s.
4d	CN	4 ± 1	0.2	1 ± 1	n.s.
4e	NO_2	12 ± 1	0.002	6 ± 1	0.02
4f	CF_3	**17** ± **1**	0.002	**8** ± **1**	0.002
7a	1-CN-cyclohexyl	9 ± 1	0.002	6 ± 1	0.01
7b	cyclohexyl	14 ± 2	0.002	9 ± 1	0.002
7c	CH_3	9 ± 1	0.002	6 ± 1	0.02
7d	C_2H_5	16 ± 1	0.002	11 ± 1	0.002
7e	C_3H_7	11 ± 1	0.002	8 ± 2	0.002
7f	C_4H_9	7 ± 1	0.01	5 ± 1	0.01
7g	C_5H_{11}	13 ± 1	0.002	8 ± 1	0.002
7h	C_6H_{13}	20 ± 1	0.002	11 ± 1	0.002
7i	C_7H_{15}	10 ± 1	0.002	7 ± 1	0.002
7j	C_8H_{17}	13 ± 2	0.002	6 ± 1	0.01
7k	$C_{10}H_{21}$	1 ± 2	n.s.	0 ± 1	n.s.
7l	CH_2-cyclohexyl	4 ± 1	0.05	1 ± 1	n.s.
7m	Ph	7 ± 1	0.01	3 ± 1	0.2
7n	CH_2-Ph	15 ± 2	0.002	11 ± 1	0.002
7o	C_2H_4-Ph	21 ± 1	0.002	13 ± 1	0.002
7p	C_3H_6-Ph	13 ± 1	0.002	9 ± 1	0.002
7q	CH_2-Ph-4-CH_3	13 ± 1	0.002	9 ± 1	0.002
7r	CH_2-Ph-4-OCH_3	10 ± 1	0.002	7 ± 1	0.01
7s	CH_2-Ph-4-Cl	13 ± 1	0.002	8 ± 1	0.002
7t	CH_2-Ph-4-CF_3	14 ± 1	0.002	9 ± 1	0.002
7u	CH_2-Ph-4-NO_2	21 ± 1	0.002	15 ± 1	0.002
7v	CH_2-Ph-2-NO_2	7 ± 1	0.02	4 ± 1	0.05
asa		48 ± 10	0.002	20 ± 5	0.01

In general, glyoxaldinitrones exhibit a moderate (≥ 10%) inhibition of thrombosis in arterioles. The effects in venules are weaker. This is not surprising because it is more difficult to inhibit the formation of thrombi in venules[13]. In the *N*-(1-cyanocyclohexyl)-*C*-phenylnitrones (**4**) the results present a mixed picture. Substitution of the phenyl ring by the electron donating dimethylamino group (**4b**) gave an inactive nitrone, probably due to a more stable compound[14]. The compounds with electron withdrawing nitro (**4e**) or trifluoromethyl (**4f**) substituents showed antithrombotic effects in the order of the unsubstituted phenyl one (**4a**). Most surprisingly, the 4-chloro (**4c**) and 4-cyano (**4d**) derivatives were inactive, so that the electronic effect is not determining the antithrombotic effect. In the class of glyoxaldinitrones (**7a**–**v**) most of the compounds showed antithrombotic activities in arterioles and to a smaller extent also in venules. The biscyanocyclohexyl derivative **7a** had been synthesized in analogy to the mono nitrone **4a** and because of good experience relating to antithrombotic effects with this cyanocyclohexyl moiety[4]. It showed a small but significant antithrombotic effect. Surprisingly, **7b** which lacks the cyano group was even more active, indicating that cyano substitution is not essential and suggesting that the lipophilicity and membranotropic properties might play a role. We therefore prepared **7c**–**7k**. It was surprising that the ethyl derivative **7d** already showed considerable antithrombotic properties even in venules. The results in **7g**–**7j** were in accordance with former results[13,15,16] in other classes of antithrombotic compounds. The maximum activity in the hexyl derivative (**7h**) is also typical. The same is true in the series of **7m**–**7p** where the strongest effect is found in the 2-phenylethyl derivative **7o**. This substituent corresponds to a chain length of six carbon atoms. Compounds **7q**–**7v** were synthesized to investigate the influence of electron donating or electron accepting substituents in the phenyl ring. Comparison with the unsubstituted aromatic ring (**7n**) shows that this alteration is of minor importance. Only a nitro group in 4-position enhances the antithrombotic effect. This group in 2-position however decreases the activity indicating that steric requirements are more important than electronic ones.

In Vitro Formation of Nitric Oxide

The *in vitro*[1] release of NO from pbn was reported. However, no formation of NO from *N*-(1-cyanocyclohexl)-*C*-phenylnitrones and glyoxaldinitrones hitherto has been stated. The formation of nitric oxide was determined by the method of Duchstein and Riederer[17]. Briefly the spontaneous release of nitric oxide is checked in argon atmosphere (anaerobic, **method A**, 28 min). The release of NO is measured by chemiluminescence[17]. The results are compiled in the 2nd column of Table 2. In contrast, the oxidative formation of nitric oxide from nitrones by liver cells[18] is mimicked *in vitro* by the addition of an Fe^{3+}-porphyrin complex (as cytochrome surrogate) and an oxygen donor, i.e. (bis-trifluoroacetoxy)iodobenzene, to the ethanolic solutions of selected compounds (aerobic, **method B**). The results are summarized in the 3rd column of Table 2. For this purpose were chosen **7d, 7h, 7o,** and **7u** which had shown the highest antithrombotic activity. For comparison the inactive **pbn** (*in*

Table 2. *In vitro* formation of NO from 3 mol of **pbn**, **7d**, **h**, **o,** and **7u** (n = 3) or **SIN 1** in ethanol within 28 min at 37 °C.

Compound	**A** nmol NO ± SD	**B** nmol NO ± SD
pbn	1.92 ± 0.05	1.99 ± 0.09
7d	0.0	1.02 ± 0.06
7h	1.12 ± 0.02	0.93 ± 0.06
7o	3.44 ± 0.12	4.32 ± 0.39
7u	1.59 ± 0.15	1.72 ± 0.05
SIN 1	4.80 ± 0.2	0.46 ± 0.03

vivo data not shown[1)] and the well known NO donor SIN 1 were included.

The results from methods **A** and **B** show that only small amounts of NO are formed under both conditions. The NO-formation in **7d**, **7o**, and **7u** is enhanced a little in the presence of an oxygen donor (method **B**). It is obvious that in SIN 1 the detection of NO is decreased when oxidative reaction conditions are used. The reason is that in nitrones the N-O nitrogen has the oxidation number –1 while in SIN 1 it is +2 (after opening of the sydnone ring) like in NO itself. This explains why oxidation generally enhances NO formation in type **7** compounds. Consequently in SIN 1 the detected amount of NO is decreased by further oxidation to nitrite.

However, the *in vivo* results from the thrombosis model do not correlate with the *in vitro* oxidative formation. This indicates that the cleavage of the nitrones *in vivo* could be a necessity for their activity. SIN 1 obviously is stable under either *in vitro* conditions. Nevertheless, these data provide no evidence that the antithrombotic effects are related to nitric oxide formation.

Experimental Part

Chemistry[1)]

Mp (uncorr.), Lindström.– Elemental analysis: Elementar VarioEL.– IR: ATI Mattson Genenis Serie FTIR.– UV/VIS: Kontron Instruments UVIKON 930.– NMR: Bruker AC 300 and DPX 400.– 70 eV-MS: Varian MAT CH7 A and Kratos MS 25 RF.-FAB-MS:Varian MAT CH_5-DF.

The synthesis of **4a**[19], **7c**, **7n**[10], and **7m**[20] has been reported in the literature.

*General Procedure for the Synthesis of **4***

Method of Thesing [21]: 10.0 mmol of the α-hydroxylaminonitrile **3** (prepared by the method of Neelakantan and Hartung[7]) and an equal amount of aldehyde in 30 ml toluene were heated at 70 °C for 1.5 h. After water from the reaction has been distilled off azeotropically, the solvent is removed and oily residue deposited in the refrigerator for crystallization. The products were generally recrystallized from ethanol or petroleum ether (exceptions are noted).

*1-[N-(4-Dimethylamino-phenylmethylene)]aminocyclohexanecarbonitrile N-Oxide (**4b**)*

From 1.5 g (0.01 mol) 4-dimethylaminobenzaldehyde. Colorless crystals (petroleum ether), mp 151 °C, yield 0.8 g (26%).– Anal.– **IR** (KBr): ν = 3077 cm^{-1}; 2245 (CN); 1604 (C=N); 1104 (NO).– **^{1}H-NMR**/400 MHz ([D_6] DMSO): d (ppm) = 1.23–2.26 (m, 8H, cyclohexyl-2H-6H-(only eq.)-3H-4H-5H), 2.42 ("d", J = 12.5 Hz, 2H, cyclohexyl-2H-6H (ax.)), 2.99 (s, 6H, 2 × CH_3), 6.73 ("d", J = 9.0 Hz, 2H, aromat.-3H-5H), 7.77 (s, 1H, N=C*H*), 8.21 ("d", J = 9.0 Hz, 2H, aromat.-2H-6H).– **MS** (70 eV): *m/z* (%) = 271 (35) [M^+], 254 (12) [M^+–OH], 108 (53) [$C_7H_{10}N^+$], 81 (100) [108^+–HCN], 41 (38) [$C_3H_5^+$].

*1-[N-(4-Chlorophenylmethylene)]aminocyclohexanecarbonitrile N-Oxide (**4c**)*

From 1.4 g (0.01 mol) 4-chlorobenzaldehyde. Yellowish crystals (petroleum ether), mp 117 °C, yield 0.4 g (15%).– Anal. $C_{14}H_{15}N_2OCl$ **IR** (KBr):ν = 3163 cm^{-1}; 2248 (CN); 1123 (NO).– **^{1}H-NMR**/400 MHz ([D_6] DMSO): δ (ppm) =1.25–2.20 (m, 8H, cyclohexyl-2H-6H-(only eq.)-3H-4H-5H), 2.49 ("d", J = 12.5 Hz, 2H, cyclohexyl-2H-6H (ax.)), 7.60 ("d", J = 8.2 Hz, 2H, aromat.-3H-5H), 8.18 (s, 1H, N=C*H*), 8.45 ("d", J = 8.7 Hz, 2H, aromat.-2H-6H).– **MS** (70 eV): *m/z* (%) = 262 (36) [M^+], 245 (63) [M^+–OH], 108 (66) [$C_7H_{10}N^+$], 81 (100) [108^+–HCN], 41 (39) [$C_3H_5^+$].

*1-[N-(4-Cyanophenylmethylene)]aminocyclohexanecarbonitrile N-Oxide (**4d**)*

From 1.3 g (0.01 mol) 4-cyanobenzaldehyde. Colorless crystals (petroleum ether), mp 150 °C, yield 0.5 g (20%).– Anal.– **IR** (KBr): ν = 3425 cm^{-1}; 2224 (CN); 1129 (NO).– **^{1}H-NMR**/400 MHz ([D_6] DMSO): δ (ppm) = 1.28–2.27 (m, 8H, cyclohexyl-2H-6H-(only eq.),-3H-4H-5H), 2.52 ("d", J = 12.7 Hz, 2H, cyclohexyl-2H-6H (ax.)), 7.99 ("d", J = 8.3 Hz, 2H, aromat.-3H-5H), 8.31 (s, 1H, N=C*H*), 8.56 ("d", J = 8.4 Hz, 2H, aromat.-2H-6H).– **MS** (70 eV): *m/z* (%) = 253 (33) [M^+], 236 (43) [M^+–OH], 108 (79) [$C_7H_{10}N^+$], 81 (100) [108^+–HCN], 41 (47) [$C_3H_5^+$].

*1-[N-(4-Nitrophenylmethylene)]amino-cyclohexanecarbonitrile N-Oxide (**4e**)*

From 1.5 g (0.01 mol) 4-nitrobenzaldehyde. Yellowish leaves (petroleum ether), mp 154 °C, yield 0.7 g (26%).– Anal. $C_{14}H_{15}N_3O_3$ – **IR** (KBr): ν = 3104 cm^{-1}; 2220 (CN); 1136 (NO).– **^{1}H-NMR**/400 MHz ([D_6] DMSO): δ (ppm) = 1.32–2.29 (m, 8H, cyclohexyl-2H-6H-(only eq.),-3H-4H-5H), 2.53 ("d", J = 12 Hz, 2H, cyclohexyl-2H-6H (ax.)), 8.38–8.40 (m, 3H, aromat.-3H-5H and N=C*H*), 8.65 ("d", J = 8.9 Hz, 2H, aromat.-2H-6H).– **MS** (70 eV): *m/z* (%) = 273 (11) [M^+], 256 (17) [M^+–OH], 108 (57) [$C_7H_{10}N^+$], 81 (100) [108^+–HCN], 41 (39) [$C_3H_5^+$].

*1-[N-(4-Trifluoromethyl-phenylmethylene)]aminocyclohexanecarbonitrile N-Oxide (**4f**)*

From 1.7 g (0.01 mol) 4-trifluoromethylbenzaldehyde. Colorless crystals (ethanol), mp 119 °C, yield 0.6 g (20%).– Anal. $C_{15}H_{15}N_2OF_3$.– **IR** (KBr): ν = 3158 cm^{-1}; 2244 (CN); 1577 (C=N); 1329 (C-F); 1126 (NO).– **^{1}H-NMR**/400 MHz ([D_6] DMSO): δ (ppm) =1.26–2.33 (m, 8H, cyclohexyl-2H-6H-(only eq.),-3H-4H-5H), 2.46 ("d", J = 12.5 Hz, 2H, cyclohexyl-2H-6H (ax.)), 7.85 ("d", J = 8.3 Hz, 2H, aromat.-3H-5H), 8.25 (s, 1H, N=C*H*), 8.55 ("d", J = 8.3 Hz, 2H, aromat.-2H-6H).– **^{13}C-NMR**/400 MHz ([D_6] DMSO): δ (ppm) = 24.8 (cyclohexyl-C-3 and C-5), 25.3 (cyclohexyl-C-4), 35.8 (cyclohexyl-C-2 and C-6), 76.9 (NC-*C*-NO), 119.4 (CN), 124.2 (CF_3), 127.0 (Ph-C-3 and C-5), 131.0 (Ph-C-2 and C-6), 131.6 (Ph-C-4), 131.9 (ON=C), 135.5 (Ph-C-1).– **MS** (70 eV): *m/z* (%) = 296 (30) [M^+], 279 (39) [M^+–OH], 108 (75) [$C_7H_{10}N^+$], 81 (100) [108^+–HCN], 41 (38) [$C_3H_5^+$].

*General Procedure for the Synthesis of **7***

Glyoxaldinitrones (**7**) were prepared from the corresponding hydroxylamines (**6**) which in general were obtained by the reduction of oximes (**5**) with diborane[8] (production of diborane modified by the method of Hach[9]).

[1)] The full set of data is given in the PhD thesis of R. Camehn, Freie Universität Berlin 1999.

All equipment to be used is oven-dried. The starting aldoxime (20 mmol) is placed in a flask equipped with a magnetic stirrer, calcium chloride tube, nitrogen inlet, and dropping funnel. Sodium borohydride (40 mmol, 1.51 g) is placed in the flask and tetrahydrofuran (75 ml) is added at once. The temperature is kept at 0 °C. The flask is placed in a water-ice bath and a solution of acetic acid (40 mmol) is added carefully (temperature is kept in the 10–20 °C range). After the addition of the solution is completed, the reaction mixture is stirred for 4 h at ambient temperature, removing the solvent *in vacuo*, and lowering the temperature to 0 °C was followed by the addition of 10 ml of 20% hydrochloric acid by means of a syringe, at such a rate that the temperature did not exceed 5 °C. The reaction mixture was refluxed for 1 h. Lowering the temperature to 50 °C was followed by the addition of 15 mmol glyoxal. The glyoxaldinitrones precipitated spontaneously or after few days under refrigeration. The compounds generally recrystallized from ethanol or ethanol/petroleum ether (exceptions are noted).

Compounds **7a**, **b**, **d**, and **7e** were prepared by the method of Zinner et al.[10]. Compounds **7a**, **d**, **e** were prepared from hydroxylamines which were obtained from cyclohexanone[7](**7a**) or by the reduction of nitro compounds (**7 d**,**e**). The hydroxylamine for **7b** was purchased from Aldrich..

*Ethanediylidenediamine-bis(1-cyclohexanecarbonitrile) N,N′-Dioxide (**7a**)*

From 1.4 g (0.01 mol) 1-hydroxyamino-cyclohexanecarbonitrile[7] (**3**). Light greenish crystals (ethanol), mp 206 °C, yield 0.9 g (21%).– Anal.– **IR** (KBr): ν = 3138 cm^{-1}; 2245 (CN); 1511 (C=N); 1171 (NO); 1134 (NO).– **^{1}H-NMR**/400 MHz ([D_6] DMSO): δ (ppm) = 1.12–2.21 (m, 16H, 2 × cyclohexyl-2H-6H-(only eq.),-3H-4H-5H), 2.35 (“d”, *J* = 13 Hz, 4H, 2 × cyclohexyl-2H-6H (ax.)), 8.12 (s, 2H, N=CH-CH=N).– **MS** (70 eV): *m/z* (%) = 302 (12) [M^+], 285 (9) [M^+–OH], 108 (87) [$C_7H_{10}N^+$], 81 (100) [108^+–HCN], 41 (50) [$C_3H_5^+$], 39 (18).

*Ethanediylidenediamine-dicyclohexane N,N′-Dioxide (**7b**)*

From 1.2 g (0.01 mol) *N*-cyclohexylhydroxylamine-HCl. Colorless crystals (ethanol), mp 230 °C, yield 0.3 g (16%).– Anal.– **IR** (KBr): ν = 3094 cm^{-1}; 1525 (C=N); 1159 (NO); 1144 (NO).– **^{1}H-NMR**/400 MHz ($CDCl_3$): δ (ppm) = 1.14–2.16 (m, 20H, 2 × cyclohexyl-2H-3H-4H-5H-6H), 3.70–3.96 (m, 2H, 2 × cyclohexyl-1H-(ax.)), 7.85 (s, 2H, N=CH-CH=N).– **^{13}C-NMR**/400 MHz ($CDCl_3$): δ (ppm) = 25.3 (2 × cyclohexyl-C-3-C-4-C-5), 31.5 (2 × cyclohexyl-C-2-C-6),77.1 (2 × cyclohexyl-C-1), 127.0 (N=C-C=N).– **MS** (70 eV): *m/z* (%) = 252 (12) [M^+], 235 (12) [M^+–OH], 108 (5) [$C_7H_{10}N^+$], 83 (64) [$C_6H_{11}^+$], 55 (100) [$C_4H_9^+$], 41 (63) [$C_3H_5^+$], 39 (14).

*Ethanediylidenediamine-diethane N,N′-Dioxide, (1,2-bis(ethylimino)ethane N,N′-Dioxide) (**7d**)*

From 6.1 g (0. 1 mol) *N*-ethylhydroxylamine. Colorless leaves (ethanol), mp 150 °C (dec.), yield 0.5 g (7%).– Anal. $C_6H_{12}N_2O_2$.– **IR** (KBr): ν = 3099 cm^{-1}; 1531 (C=N); 1159 (NO); 1122 (NO).– **^{1}H-NMR**/400 MHz ([D_6] DMSO): δ (ppm) = 1.29 (t, *J* = 7.1 Hz, 6H, 2 × CH_3), 3.90 (q, *J* = 7.1 Hz, 4H, 2 × N-C*H*$_2$-CH_3), 7.91 (s, 2H, N=CH-CH=N).– **MS** (70 eV): *m/z* (%) =144 (100) [M^+], 127 (19) [M^+–OH], 30 (31) [NO^+].

*Ethanediylidenediamine-dipropane N,N′-Dioxide (**7e**)*

From 7.5 g (0.1 mol) *N*-propylhydroxylamine. Light greenish crystals (ethanol), mp 153 °C (dec.), yield 0.8 g (9%).– Anal. $C_8H_{16}N_2O_2$.– **IR** (KBr): ν = 3102 cm^{-1}; 1531 (C=N); 1157 (NO); 1122 (NO).– **^{1}H-NMR**/400 MHz ([D_6] DMSO): δ (ppm) = 0.85 (t, *J* = 7.3 Hz, 6H, 2 × CH_3), 1.75 (qt, *J* = 7.1 Hz, 4H, 2 × H_3C-C*H*$_2$-CH_2), 3.86 (t, *J* = 6.8 Hz, 4H, 2 × N-C*H*$_2$-), 7.91 (s, 2H, N=CH-CH=N).– **MS** (70 eV): *m/z* (%) =172 (17) [M^+], 155 (11) [M^+–OH], 43 (100) [$C_3H_7^+$], 41 (48) [$C_3H_5^+$].

*Ethanediylidenediamine-dibutane N,N′-Dioxide (**7f**)*

From 1.74 g (0.02 mol) butanal oxime. Light greenish leaves (ethanol/petroleum ether), mp 135 °C (dec.), yield 1.4 g (72%).– Anal. $C_{10}H_{20}N_2O_2$.– **IR** (KBr): ν = 3102 cm^{-1}; 1532 (C=N); 1157 (NO); 1123 (NO).– **^{1}H-NMR**/400 MHz ([D_6] DMSO): δ (ppm) = 0.88 (t, *J* = 7.3 Hz, 6H, 2 × CH_3), 1.26 (qt, *J* = 7.3/ 7.5 Hz, 4H, 2 × H_3C-C*H*$_2$-CH_2), 1.71 (tt, *J* = 7.0/ 7.2 Hz, 4H, 2 × H_3C-CH_2-C*H*$_2$), 3.89 (t, *J* = 6.8 Hz, 4H, 2 × N-C*H*$_2$-), 7.91 (s, 2H, N=CH-CH=N).– **MS** (70 eV): *m/z* (%) =200 (7) [M^+], 183 (9) [M^+–OH], 45 (100) [$C_2H_7N^+$], 43 (9) [$C_3H_7^+$], 41 (34) [$C_3H_5^+$].

*Ethanediylidenediamine-dipentane N,N′-Dioxide (**7g**)*

From 2.0 g (0.02 mol) pentanal oxime. Light greenish crystals (ethanol/petroleum ether), mp 113 °C (dec.), yield 1.5 g (65%).– Anal. $C_{12}H_{24}N_2O_2$.– **IR** (KBr): ν = 3103 cm^{-1}; 1532 (C=N); 1157 (NO); 1123 (NO).– **^{1}H-NMR**/400 MHz ($CDCl_3$): δ (ppm) = 0.91 (t, *J* = 6.9 Hz, 6H, 2 × CH_3), 1.31–1.38 (m, 8H, 2 × (C*H*$_2$)$_2$-CH_3), 1.92 (tt, *J* = 6.9/ 7.1 Hz, 4H, 2 × N-CH_2-C*H*$_2$), 3.87 (t, *J* = 6.9 Hz, 4H, 2 × N-C*H*$_2$-), 7.81 (s, 2H, N=CH-CH=N).– **MS** (70 eV): *m/z* (%) =228 (8) [M^+], 211 (15) [M^+–OH], 71 (20) [$C_5H_{11}^+$], 55 (13) [$C_4H_7^+$], 43 (100) [$C_3H_7^+$], 41 (49) [$C_3H_5^+$], 30 (12).

*Ethanediylidenediamine-dihexane N,N′-Dioxide (**7h**)*

From 2.3 g (0.02 mol) hexanal oxime. Light greenish crystals (toluene), mp 141 °C (dec.), yield 1.7 g (64%).– Anal. $C_{14}H_{28}N_2O_2$.– **IR** (KBr): ν = 3103 cm^{-1}; 1531 (C=N); 1157 (NO); 1126 (NO).– **^{1}H-NMR**/400 MHz ([D_6] DMSO): δ (ppm) = 0.85 (t, *J* = 6.8 Hz, 6H, 2 × CH_3), 1.12–1.39 (m, 12H, 2 × hexyl-(C*H*$_2$)$_3$-CH_3), 1.72 (tt, *J* = 6.8/ 6.8 Hz, 4H, 2 × N-CH_2-C*H*$_2$), 3.87 (t, *J* = 6.8 Hz, 4H, 2 × N-C*H*$_2$-), 7.91 (s, 2H, N=CH-CH=N).– **MS** (70 eV): *m/z* (%) =256 (11) [M^+], 239 (24) [M^+–OH], 85 (25) [$C_6H_{13}^+$], 55 (27) [$C_4H_7^+$],43 (100) [$C_3H_7^+$], 41 (40) [$C_3H_5^+$].

*Ethanediylidenediamine-diheptane N,N′-Dioxide (**7i**)*

From 2.6 g (0.02 mol) heptanal oxime. Greenish crystals (ethanol/petroleum ether), mp 145 °C (dec.), yield 1.5 g (51%).– Anal. $C_{16}H_{32}N_2O_2$.– **IR** (KBr): ν = 3104 cm^{-1}; 1532 (C=N); 1157 (NO); 1124 (NO).– **^{1}H-NMR**/400 MHz ($CDCl_3$): δ (ppm) = 0.88 (t, *J* = 6.9 Hz, 6H, 2 × CH_3), 1.26–1.32 (m, 16H, 2 × Heptyl-(C*H*$_2$)$_4$-CH_3), 1.92 (tt, *J* = 7.0/ 7.0 Hz, 4H, 2 × N-CH_2-C*H*$_2$), 3.85 (t, *J* = 7.1 Hz, 4H, 2 × N-C*H*$_2$-), 7.79 (s, 2H, N=CH-CH=N).– **MS** (70 eV): *m/z* (%) = 284 (11) [M^+], 267 (42) [M^+–OH], 85 (18) [$C_6H_{13}^+$], 57 (100) [$C_4H_9^+$], 55 (54) [$C_4H_7^+$], 43 (74) [$C_3H_7^+$], 41 (81) [$C_3H_5^+$], 30 (15).

*Ethanediylidenediamine-dioctane N,N′-Dioxide (**7j**)*

From 2.8 g (0.02 mol) octanal oxime. Yellowish-greenish crystals (ethanol/petroleum ether), mp 152 °C (dec.), yield 2.3 g (42%).– Anal. $C_{18}H_{36}N_2O_2$.– **IR** (KBr): ν = 3104 cm^{-1}; 1533 (C=N); 1157 (NO); 1123 (NO).– **^{1}H-NMR**/400 MHz ($CDCl_3$): δ (ppm) = 0.88 (t, *J* = 6.8 Hz, 6H, 2 × CH_3), 1.27–1.32 (m, 20H, 2 × Octyl-(C*H*$_2$)$_5$-CH_3), 1.91 (tt, *J* = 7.1/7.1 Hz, 4H, 2 × N-CH_2-C*H*$_2$), 3.89 (t, *J* = 7.1 Hz, 4H, 2 × N-C*H*$_2$-), 7.86 (s, 2H, N=CH-CH=N).– **MS** (70 eV): *m/z* (%) =312 (19) [M^+], 295 (64) [M^+–OH], 85 (73) [$C_6H_{13}^+$], 83 (19) [$C_6H_{11}^+$], 81 (17), 71 (100) [$C_5H_{11}^+$], 55 (52) [$C_4H_7^+$], 43 (99) [$C_3H_7^+$], 41 (66) [$C_3H_5^+$], 30 (23).

*Ethanediylidenediamine-didecane N,N′-Dioxide (**7k**)*

From 3.4 g (0.02 mol) decanal oxime. Colorless crystals (toluene), mp 144 °C (dec.), yield 1.1 g (31%).– Anal. $C_{22}H_{44}N_2O_2$.– **IR** (KBr): ν = 3104 cm^{-1}; 1532 (C=N); 1156 (NO); 1123 (NO).– **^{1}H-NMR**/400 MHz ($CDCl_3$): δ (ppm) = 0.88 (t, *J* = 7.0 Hz, 6H, 2 × CH_3), 1.26–1.32 (m, 28H, 2 × Decyl-(C*H*$_2$)$_6$-CH_3), 1.91 (“q”, *J* = 7.0 Hz, 4H, 2 × N-CH_2-C*H*$_2$), 3.90 (t, *J* = 7.2 Hz, 4H, 2 × N-C*H*$_2$-), 7.86 (s, 2H, N=CH-CH=N).– **MS** (70 eV): *m/z* (%) =368 (9) [M^+], 351 (42) [M^+–OH], 85 (25) [$C_6H_{13}^+$], 83 (16) [$C_6H_{11}^+$],72 (20), 71 (25) [$C_5H_{11}^+$], 55 (57) [$C_4H_7^+$], 43 (100) [$C_3H_7^+$], 41 (67) [$C_3H_5^+$].

*Ethanediylidenediamine-bis(cyclohexylmethane) N,N′-Dioxide (**7l**)*

From 2.5 g (0.02 mol) cyclohexanecarbaldehydeoxime. Greenish leaves (ethanol), mp 201 °C (dec.), yield 1.5 g (55%).– Anal.– **IR** (KBr): ν = 3100 cm^{-1}; 1527 (C=N); 1161 (NO); 1141 (NO).– **^{1}H-NMR**/400 MHz ($CDCl_3$): δ (ppm) = 0.93–1.34 (m, 20H, 2 × cyclohexyl-2H-3H-4H-5H-6H), 2.06–2.15 (m, 2H, 2 × cyclohexyl-1H), 3.72 (d, *J* = 7.2 Hz, 4H, 2 × N-C*H*$_2$-), 7.80 (s, 2H, N=CH-CH=N).– **MS** (70 eV): *m/z* (%) =280(10) [M^+], 263 (30) [M^+–OH], 153 (13), 97 (32) [$C_7H_{13}^+$], 85 (23) [$C_6H_{13}^+$], 55 (100) [$C_4H_7^+$], 41 (34) [$C_3H_5^+$].

*Ethanediylidenediamine-bis(2-phenylethane) N,N′-Dioxide (**7o**)*

From 2.6 g (0.02 mol) (E/Z)-phenylacetaldehyde oxime. Yellowish leaves (ethanol), mp 154 °C (dec.), yield 0.8 g (28%).– Anal. $C_{18}H_{20}N_2O_2$.– **IR** (KBr): ν = 3098 cm^{-1}; 1531 (C=N); 1159 (NO).– **^{1}H-NMR**/400 MHz ([D_6] DMSO): δ (ppm) = 3.04 (t, *J* = 7.1 Hz, 4H, 2 × Ph-C*H*$_2$-CH$_2$), 4.12 (t, *J* = 7.1 Hz, 4H, 2 × N-C*H*$_2$-CH$_2$), 7.20–7.30 (m, 10 H, 2 × Ph), 7.79 (s, 2H, N=CH-CH=N).– **MS** (70 eV): *m/z* (%) =296 (14) [M^+], 105 (88), 104 (100) [$C_8H_8^+$], 91 (29) [$C_7H_7^+$], 77 (19) [$C_6H_5^+$].

*Ethanediylidenediamine-Bis(3-phenylpropane) N,N′-Dioxide (**7p**)*

From 2.98 g (0.02 mol) 3-phenylpropanal oxime. Greenish leaves (ethanol), mp 175 °C (dec.), yield 2.1 g (65%).– Anal. $C_{20}H_{24}N_2O_2$.– **IR** (KBr): ν = 3101 cm^{-1}; 1530 (C=N); 1147 (NO).– **^{1}H-NMR**/400 MHz ($CDCl_3$): δ (ppm) = 2.27 (tt, *J* = 7.1/ 7.1 Hz, 4H, 2 × Ph-CH$_2$-C*H*$_2$), 2.70 (t, *J* = 7.4 Hz, 4H, 2 × Ph-C*H*$_2$-CH$_2$), 3.90 (t, *J* = 7.0 Hz, 4H, 2 × N-C*H*$_2$-CH$_2$), 7.17–7.32 (m, 10H, 2 × Ph), 7.82 (s, 2H, N=CH-CH=N).– **MS** (70 eV): *m/z* (%) =324 (5) [M^+], 307 (7) [M^+–OH], 91 (100) [$C_7H_7^+$], 69 (41), 41 (16).

*Ethanediylidenediamine-bis(4-methylphenylmethane) N,N′-Dioxide (**7q**)*

From 2.7 g (0.02 mol) 4-methylbenzaldoxime. Colorless crystals (ethanol), mp 195 °C (dec.), yield 2.1 g (72%).– Anal. $C_{18}H_{20}N_2O_2$.– **IR** (KBr): ν = 3102 cm^{-1}; 1529 (C=N); 1151 (NO).– **^{1}H-NMR**/400 MHz (CF_3COOD): δ (ppm) = 2.39 (s, 6H, 2 × CH_3), 5.24 (s, 4H, 2 × N-C*H*$_2$-), 7.28–7.32 (m, 8H, 2 × Ph-2H-3H-5H-6H), 8.29 (s, 2H, N=CH-CH=N).– **MS** (70 eV): *m/z* (%) =296 (5) [M^+], 105 (100) [C_7H_7–CH_3^+], 77 (8) [$C_6H_5^+$].

*Ethanediylidenediamine-bis(4-methoxyphenylmethane) N,N′-Dioxide (**7r**)*

From 3.0 g (0.02 mol) 4-methoxybenzaldoxime. Yellowish-greenish crystals (ethanol), mp 209 °C (dec.), yield 2.2 g (68%).– Anal. $C_{18}H_{20}N_2O_4$.– **IR** (KBr): ν = 3101 cm^{-1}; 1528 (C=N); 1147 (NO).– **^{1}H-NMR**/400 MHz (CF_3COOD): δ (ppm) = 4.01 (s, 6H, 2 × CH_3), 5.26 (s, 4H, 2 × N-C*H*$_2$-), 7.12 (“d”, *J* = 8.5 Hz, 4H, Ph-3H-5H), 7.45 (“d”, *J* = 8.5 Hz, 4H, Ph-2H-6H), 8.37 (s, 2H, N=CH-CH=N).– **MS** (70 eV): *m/z* (%) =328 (2) [M^+], 121 (100) [C_7H_7–OCH_3^+], 78 (8).

*Ethanediylidenediamine-bis(4-chlorophenylmethane) N,N′-Dioxide (**7s**)*

From 3.1 g (0.02 mol) 4-chlorobenzaldoxime. Yellowish-greenish crystals (ethanol), mp 155 °C (dec.), yield 1.4 g (41%).– Anal. $C_{16}H_{14}N_2O_2Cl_2$.– **IR** (KBr): ν = 3100 cm^{-1}; 1528 (C=N); 1151 (NO); 1097 (NO).– **^{1}H-NMR**/400 MHz (CF_3COOD): δ (ppm) = 5.27 (s, 4H, 2 × N-C*H*$_2$-), 7.39–7.46 (m, 8H, 2 × Ph-2H-3H-5H-6H), 8.46 (s, 2H, N=CH-CH=N).– **MS** (70 eV): *m/z* (%) =336 (4) [M^+], 140 (26), 139 (39), 125 (100) [$C_7H_7Cl^+$], 89 (25), 75 (16), 63 (12).

*Ethanediylidenediamine-bis(4-trifluoromethylphenylmethane) N,N′-Dioxide (**7t**)*

From 1.7 g (0.02 mol) 4-trifluoromethylbenzaldoxime. Greenish crystals (chloroform), mp 187 °C (dec.), yield 0.9 g (45%).– Anal. $C_{18}H_{14}F_6N_2O_2$.– **IR** (KBr): ν = 3102 cm^{-1}; 1530 (C=N); 1335 (C-F); 1150 (NO).– **^{1}H-NMR**/400 MHz (CF_3COOD): δ (ppm) = 5.36 (s, 4H, 2 × N-C*H*$_2$-), 7.62 (“d”, *J* = 6.7 Hz, 4H, Ph-2H-6H), 7.75 (“d”, *J* = 6.7 Hz, 4H, Ph-3H-5H), 8.59 (s, 2H, N=CH-CH=N).– **MS** (70 eV): *m/z* (%) = 404 (8) [M^+], 213 (19), 159 (100) [C_7H_7–CF_3^+], 109 (19).

*Ethanediylidenediamine-bis(4-nitrophenylmethane) N,N′-Dioxide (**7u**)*

From 1.6 g (0.02 mol) 4-nitrobenzaldoxime. Brownish powder, mp 148 °C (dec.), yield 1.0 g (56%).– Anal. $C_{16}H_{14}N_4O_6$.– **IR** (KBr): ν = 3097 cm^{-1}; 1522 (C=N); 1156 (NO).– **^{1}H-NMR**/400 MHz ([D_6] DMSO): δ (ppm) = 5.27 (s, 4H, 2 × N-C*H*$_2$-), 7.70 (“d”, *J* = 9.0 Hz, 4H, Ph-2H-6H), 8.23–8.25 (m, 6H, 2 × Ph-3H-5H and 1 × N=CH-CH=N).– **MS** (70 eV): *m/z* (%) =358 (5) [M^+], 150 (52), 144 (24), 136 (34) [C_7H_7–NO_2^+], 91 (16), 89 (46), 78 (53), 77 (38), 51 (42), 50 (32), 43 (20), 41 (17), 39 (26), 32 (14), 30 (100) [NO^+].

*Ethanediylidenediamine-bis(2-nitrophenylmethane)-N,N′-dioxide (**7v**)*

From 3.3 g (0.02 mol) 2-nitrobenzaldoxime. Yellowish crystals (chloroform), mp 157 °C (dec.), yield 2.3 g (65%).– Anal. $C_{16}H_{14}N_4O_6$.– **IR** (KBr): ν = 3092 cm^{-1}; 1520 (C=N); 1446; 1434; 1146 (NO).– **^{1}H-NMR**/400 MHz ([D_6] DMSO): δ (ppm) = 5.48 (s, 4H, 2 × N-C*H*$_2$-), 7.63–7.67 (m, 4H, 2 × Ph-4H-6H), 7.78 (“t”, *J* = 7.4 Hz, 2H , 2 × Ph-5H), 8.05 (“d”, *J* = 7.8 Hz, 2H, Ph-3H), 8.10 (s, 2H, N=CH-CH=N).– **MS** (70 eV): *m/z* (%) =358 (2) [M^+], 146 (17), 136 (38) [C_7H_7-NO_2^+], 135 (35), 91 (36), 89 (29), 79 (34), 78 (100) [$C_6H_6^+$], 77 (52), 76 (43), 75 (14), 74 (12), 38 (47), 30 (27) [NO^+].

Biology

Thrombosis experiments[11] and NO determination[17] were performed as usual.

References

☆ Dedicated to Prof. Dr. F. Eiden on the occasion of his 75th birthday.

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