New NO-Donors with Antithrombotic and Vasodilating Activities, Part 16

3-Amino-1,2,4-oxadiazol-5-ones as Prodrugs for Hydroxyguanidines

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Key Words: *1,2,4-oxadiazol-5-ones; hydroxyguanidines; antithrombotic effects; nitric oxide*

Summary

Nineteen 4-substituted 1,2,4-oxadiazol-5-ones (**6a–s**) were prepared as prodrugs for lipophilic hydroxyguanidines which should be metabolized *in vivo* to nitric oxide. This hypothesis was tested indirectly by measuring the antithrombotic properties of these compounds 2 h after oral administration to rats (60 mg/kg). In mesenteric arterioles seven compounds moderately (≥ 10 %) inhibited the formation of thrombi by a laser beam. Maximum effects were observed in **6c** (4-pentyl) and **6f** (4-benzyl). The lack of activity in the corresponding 2-pentyloxadiazolone **10c,** where no formation of nitric oxide seems possible, indirectly suggests that the antithrombotic properties of the title compounds could be mediated by the *in vivo* formation of nitric oxide.

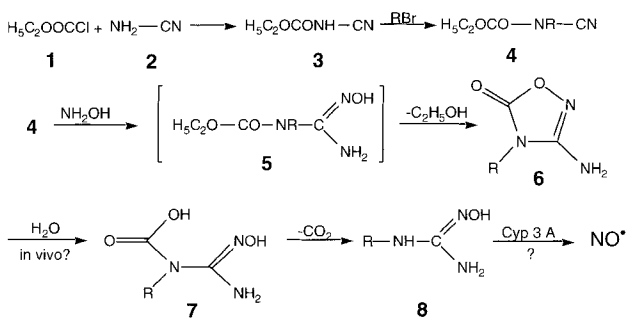
Introduction

During the biosynthesis of nitric oxide L-arginine is oxidized by molecular oxygen to N^{ω}-hydroxyarginine and further to NO. The reaction is catalyzed by nitric oxide synthases and is specific for L-arginine[1]. More recently it has been shown that the hydroxylation of guanidine moieties other than L-arginine can be mediated by cytochromes P_{450}[2]. These catalysts are furthermore able to form NO from N^{ω}-hydroxyarginine[3] and other *N*-hydroxyguanidines[4]. As *N*-hydroxyguanidines are unstable compounds they cannot be regarded as useful NO-donors and hence antithrombotic compounds. This is especially true as for the long term prevention of thrombus formation the **oral** administration of suitable drugs is obligatory. We therefore designed the title compounds as prodrugs for hydroxyguanidines.

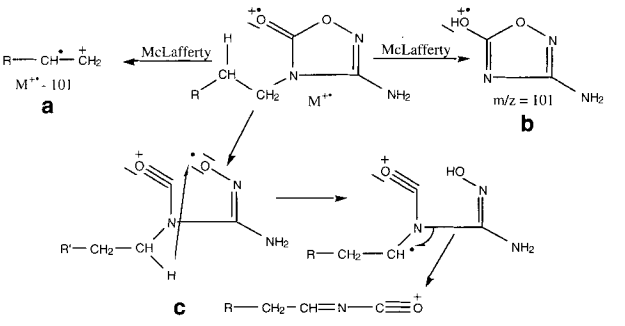
Chemistry

Reports on the synthesis of 3-amino-1,2,4-oxadiazol-5-ones are very scarce[5–8]. Compounds with alkyl or arylalkyl substituents in 4-position and an unsubstituted amino group in 3-position are not known. We therefore developed a convenient synthesis for the desired oxadiazolones **6** (see Scheme 1).

Starting material is cyanamide (**2**) which is acylated with ethyl chloroformate to *N*-cyanourethane **3**[9]. The crude product is reacted with suitable alkyl bromides and a broad variety of *N*-substituted **4** is obtained. The addition of hydroxylamine to the hydroxyguanidine **5** and its cyclization to the oxadiazolone **6** occur in polar organic solvents like DMSO or DMFA at room temp. We investigated the time course of the reaction in [D_6]DMSO by ^{1}H-NMR. When **4e** (R = octyl) was reacted with hydroxylamine (hydrochloride plus triethylamine) one third of **5e** had already formed after 3 min. This is indicated by a quartet at 4.05 ppm (J = 7 Hz, O-CH_2-CH_3) and a triplet at 3.18 (J = 7 Hz, N-CH_2-C_7H_{13}). The amino group of **5e** is observed as a broad singlet at 5.7 ppm. After 30 min the addition is nearly complete. At this time a singlet at 6.66 ppm (NH_2 of **6e**) and a triplet at 3.5 ppm (N-CH_2 of **6e**) indicate that the formation of **6e** has started. The reaction is almost complete after 22 h. Thus type **5** compounds appear to be metastable at room temp. so that we did not isolate them. Type **6** oxadiazolones were obtained in yields up to 86 % (**6e**). They can be characterized well by their electron impact mass spectra. The intensity of the molecular ion is up to 62% (**6k,** R = phenylpropyl). In the 4-alkyl compounds there is an intensive fragment *m/z* = 101 obtained by McLafferty rearrangement of the $M^{+\bullet}$ which even can form the base peak (**6b,** R = butyl). In 4-arylalkyl derivatives the charge remains in



Scheme 1: Synthesis of 4-alkylated 1,2,4-oxadiazol-5-ones and their expected *in vivo* decomposition and transformation to nitric oxide.



Scheme 2: Mass spectrometrical fragmentation of 3-alkyl and 3-arylalkyl-1,2,4-oxadiazol-5-ones.

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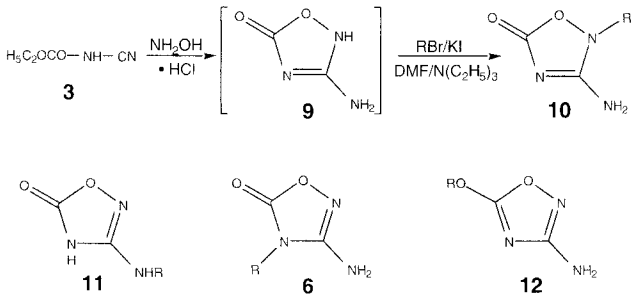
the styryl fragment $M^{+\bullet}$–101 which forms the base peak in **6j** (R = phenylethyl). In 4-benzyl derivatives as expected the most abundant ion is the tropylium ion which is the base peak in all cases (**6f**, **6h**, **6i**, **6n**).

For comparison we were interested as well in 1,2,4-oxadiazol-5-ones in which the 2-position is alkylated. With respect to the formation of nitric oxide according to Scheme 1 these compound are substituted at the "wrong" nitrogen. If the hypothesis shown in Scheme 1 were true, those compounds should not be able to form NO$^\bullet$ and therefore be inactive, i.e. not antithrombotic. The synthesis which we developed is outlined in Scheme 3. The reaction of the cyanourethane **3** with hydroxylamine hydrochloride in methanol at room temp. for 48 h afforded **9**. In spite of impurities we found these reaction conditions more convenient that those reported recently by Suyama et al.[10].

As **9** is very hydrophilic and its purification difficult we alkylated the crude product–after removal of the alcohol–in DMF. We obained **10c** (R = pentyl) or **10f** (R = benzyl), respectively as the only products. Their structure was assured by spectroscopic methods. The ^{1}H-NMR of **10f** shows at 8.3 ppm a singlet for two protons which is exchangeable with D_2O. The benzylic methylene group resonates as a singlet at 4.8 ppm, so that structure **11** can be excluded. The IR spectrum shows a strong absorption at 1741 cm^{-1} which excludes structure **12**. The formation of **6** could be excluded by comparison with authentic **6f**.



Scheme 3: Synthesis of 2-substituted 1,2,4-oxadiazol-5-ones.

Biological Experiments

Antithrombotic Properties

Nitric oxide donors inhibit platelet aggregation and hence are able to show inhibition of thrombosis[11]. Therefore we submitted **6a–s**, **10c** and **10f** to an *in vivo* thrombosis model[12]. Briefly 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. The results are compiled in Table 1. In general in arterioles seven compounds show a moderate (≥ 10 %) inhibition of thrombosis. In venules the effects mostly are smaller than in arterioles. This is generally observed with NO donors. The reason is, that in arterioles the inhibition of the platelet aggregation by NO is more important than in venules for the inhibition of thrombus formation. In addition in venules the formation of a stable thrombus is more difficult to inhibit because the velocity of the blood stream is smaller. In the series of the simple *N*-alkyl derivatives **6a–6e** there is a pronounced dependency of the antithrombotic effect on the kind of the substituent. Its maximum is found in the pentyl derivative **6c**. One might assume that this is connected with the mere lipophilicity of the compounds by improving the absorption from the gastrointestinal tract. The nearly inactive **6e** however indicates that this is not the case. We recently could demonstrate that in polar compounds there is often a substituent of optimum chain length for the interaction with phospholipids[13] and hence with biomembranes[14]. The results for **6c** and **6d** seem to reflect their affinity to cell membranes and possibly their penetration into cells where the expected metabolism (see Scheme 1) could take place. In other studies we found that arylalkyl substituents exhibit such "membranotropic" properties[15]. That is why we synthesized and tested the series **6f**, **h**, **i**, **j**, **k**, **m**, **n**, and **o**. The maximum effects were found for **6f**, **6j**, and **6k**. Substitution of the aromatic ring decreased the antithrombotic effect (see **6h** and **6i**). The same was true for its hydrogenation (see **6g** and **6l**). Compound **6p** was prepared to approach stepwise a hydroxyarginine moiety. As Table 1 shows the ethoxycarbonylbutyl group is quite well tolerated. The introduction of a basic group in a similar distance from the oxadiazolone decreased the antithrombotic effect (**6q**). Consequently we designed the acylamino ester **6r** as a hydroxyarginine prodrug. Surprisingly no antithrombotic properties could be observed. In **6s** the hexyloxadiazolone **6d** is

Table 1: Antithrombotic effects of type **6** 1,2,4-oxadiazol-5-ones or acetylsalicylic acid (ASA). 2 h after p.o. administration of 60 mg/kg to rats. Statistics: Man-Whitney U-test: n.s. = not significant

Compound	R	Inhibition of thrombus formation in arterioles % ± σ (p^2)	venules % ± σ (p^2)
6a	methyl	6 ± 3 (0.01)	6 ± 3 (0.05)
6b	*n*-butyl	10 ± 2 (0.002)	5 ± 3 (0.02)
6c	*n*-pentyl	15 ± 2 (0.002)	15 ± 4 (0.002)
6d	*n*-hexyl	13 ± 2 (0.002)	7 ± 4 (0.02)
6e	*n*-octyl	5 ± 4 (0.05)	n.s.
6f	benzyl	17 ± 3 (0.002)	12 ± 2 (0.002)
6g	cyclohexylmethyl	6 ± 3 (0.01)	6 ± 3 (0.05)
6h	4-chlorobenzyl	8 ± 2 (0.01)	4 ± 2 (0.1)
6i	4-nitrobenzyl	8 ± 2 (0.01)	7 ± 2 (0.002)
6j	2-phenylethyl	16 ± 2 (0.002)	12 ± 3 (0.002)
6k	3-phenylpropyl	17 ± 3 (0.002)	17 ± 5 (0.002)
6l	3-cyclohexylpropyl	n.s.	n.s.
6m	3-phthalimidylpropyl	11 ± 4 (0.01)	11 ± 3 (0.002)
6n	1-naphthylmethyl	9 ± 2 (0.002)	4 ± 2 (0.02)
6o	cinnamyl	6 ± 2 (0.01)	7 ± 3 (0.1)
6p	5-ethoxycarbonyl-butyl	13 ± 2 (0.002)	9 ± 3 (0.002)
6q	3-aminopropyl	8 ± 2 (0.01)	7 ± 3 (0.01)
6r	$(CH_2)_3$-CH-$COOCH_3$ (NHAc)	n.s.	n.s.
6s	1,6-hexane-bis	5 ± 2 (0.05)	n.s.
10c	*n*-pentyl	n.s.	n.s.
10f	benzyl	6 ± 3 (0.02)	4 ± 2 (0.02)
ASA	benzyl	48 ± 10 (0.002)	20 ± 5 (0.002)

substituted with a second oxadiazolone group. The disappointing result was a strong decrease in activity. In summary we had obtained a number of oxadiazolones which indeed exhibited the expected antithrombotic effects. In order to prove that they are mediated by NO we tried to simulate the metabolism of the title compounds *in vitro* by incubation **6f** with S9 mix and/or rat liver microsomes at 37 °C. The reaction mixture was assayed for NO by the chemiluminescence method. Up to 24 h no nitric oxide could be detected. However the lack of activity in **10c** and the very small effects seen in **10f** where the substituent is at the "wrong" oxadiazolone nitrogen give at least a hint that the antithrombotic properties seen in 4-substituted 1,2,4-oxadiazol-5-ones could be mediated by the *in vivo* formation of nitric oxide. However other mechanisms may be present as well.

Experimental Part

Chemistry[1)]

Mp (uncorr.): Lintström.– Elemental analysis: Perkin-Elmer element analyzer 240 C and Elementar Vario EL.– IR: Perkin-Elmer 1420 and ATI Mattson Genesis Serie FTIR.– NMR: Bruker WM 250 and AC 300.– MS (EI): Varian MAT CH 7 A and Kratos MS 25 RF. FAB-MS: CH-5-DF-MAT-Varian.– Rotational chromatography: Chromatotron, Harrison Research. Silica Gel 60 PF_{250} with plaster, thickness 4 mm.

*Alkylation of N-cyanocarbamic acid ethyl ester (**3**)*

30 mmol **3**[9], are dissolved in DMSO and 22.5 mmol of the alkyl bromide and a small amount of KI as catalyst added and kept at 80 °C for 1h. (Low boiling alkyl bromides are reacted 5h at room temp.). The mixture is poured into water and a precipitate forms. (If an oil forms the mixture is extracted with an equal volume of ether for three times.) The solid is sucked off, dissolved in ether, washed with water, dried, filtered, and the ether removed *in vacuo*.

*N-Cyano-N-methylcarbamic acid ethyl ester (**4a**)*

From 2.10 g (14.8 mmol) iodomethane. Purification by destillation *in vacuo*, bp 65 °C (53 Pa), yield 1.50 g (79 %).– Anal. $C_5H_8N_2O_2$.– IR (film): 2244 cm^{-1} (C≡N), 1750 (C=O).– ^{1}H-NMR ([D]$_6$DMSO): δ = 1.25 (t, *J* = 7 Hz, 3 H, CH_2-CH_3), 3.15 (s, 3H, N-CH_3), 4.26 (q, *J* = 7 Hz, 2H, CH_2).– MS (70 eV): *m/z* (%) = 128 (5) [M^+, $C_5H_8N_2O_2$], 83 (17)[M^+-OC_2H_5], 55 (28) [M^+-OC_2H_5-CO], 29 (100).

*N-Butyl-N-cyanocarbamic acid ethyl ester (**4b**)*

From 5.20 g (28.3 mmol) iodobutane. Colorless oil, bp 95 °C (27 Pa), yield 3.56 g (74 %).– Anal. $C_8H_{14}N_2O_2$.– IR (film): 2243 cm^{-1} (C≡N), 1753 (C=O).– ^{1}H-NMR ($CDCl_3$): δ = 0.97 (t, *J* = 7 Hz, 3 H, N-$(CH_2)_3$-CH_3), 1.36 (t, *J* = 7 Hz 3H, OCH_2-CH_3), 1.43 (q, *J* = 7 Hz, 2H, N-$(CH_2)_2$-CH_2), 1.70 (tt, *J* = 7/7 Hz, 2H, N-CH_2-CH_2), 3.54 (t, *J* = 7 Hz, 2H, N-CH_2), 4.33 (q, *J* = 7 H, 2H, O-CH_2).– MS (70 eV): *m/z* (%) = 170 (2) [M^+, $C_8H_{14}N_2O_2$], 97 (20)[M^+-OC_2H_5-CO], 55 (81) [NC-N^+H = CH_2], 29 (100).

*N-Cyano-N-pentylcarbamic acid ethyl ester (**4c**)*

From 3.33 g (22.05 mmol) bromopentane. Light yellow liquid, yield 3.29 g (81 %).– Anal. $C_9H_{16}N_2O_2$.– IR (film): 2239 cm^{-1} (C ≡N), 1750 (C=O).– ^{1}H-NMR ($CDCl_3$): δ = 0.92 (t, *J* = 7 Hz, 3 H, CH_2-CH_2-CH_3), 1.36 (m, *J* = 7 Hz, CH_3-CH_2-CH_2 and O-CH_2-CH_3), 1.72 (tt, *J* = 7/7 Hz, 2H, N-CH_2-CH_2), 3.52 (t, *J* = 7 Hz, 2H, N-CH_2), 4.32 (q, *J* = 7 H, 2H, O-CH_2).– MS (70 eV): *m/z* (%) = 184 (0.5) [M^+], 111 (60)[M^+-OC_2H_5-CO], 97 (44), 83 (98), 55 (100) [NC-N^+H = CH_2], 29 (79).

[1)] The full set of data is in the PhD thesis of S. Bade, Freie Universität Berlin 1995.

*N-Cyano-N-hexylcarbamic acid ethyl ester (**4d**)*

From 4.66 g (28.23 mmol) bromohexane. Colorless oil, bp 95 °C (2.7 Pa), yield 4.09 g (73 %).– Anal. $C_{10}H_{18}N_2O_2$.– IR (film): 2243 cm^{-1} (C≡N), 1753 (C=O).– ^{1}H-NMR ($CDCl_3$): δ = 0.90 (t, *J* = 6 Hz, 3 H, $(CH_2)_5$-CH_3), 1.36 (m, 9H, N-CH_2-CH_2-$(CH_2)_3$ and O-CH_2-CH_3), 1.71 (m, 2H, N-CH_2-CH_2), 3.53 (t, *J* = 7 Hz, 2H, N-CH_2), 4.33 (q, *J* = 7 Hz, 2H, O-CH_2).– MS (70 eV): *m/z* (%) = 198 (1) [M^+], 125 (35)[M^+-OC_2H_5-CO], 55 (64) [NC-N^+H = CH_2], 29 (100).

*N-Cyano-N-octylcarbamic acid ethyl ester (**4e**)*

From 5.50 g (28.50 mmol) bromooctane. Colorless oil, bp 80 °C (6.7 Pa), yield 4.58 g (71 %).– Anal. $C_{12}H_{22}N_2O_2$.– IR (film): 2240 cm^{-1} (C≡N), 1750 (C=O).– ^{1}H-NMR ($CDCl_3$): δ = 0.88 (t, *J* = 4 Hz, 3 H, $(CH_2)_7$-CH_3), 1.27–1.38 (m, 13H, $(CH_2)_5$-CH_3 and O-CH_2-CH_3), 1.70 (m, 2H, N-CH_2-CH_2), 3.52 (t, *J* = 7 Hz, 2H, N-CH_2), 4.32 (q, *J* = 7 Hz, 2H, O-CH_2).– MS (70 eV): *m/z* (%) = 226 (1) [M^+, $C_{12}H_{22}N_2O_2$], 153 (42)[M^+-OC_2H_5-CO], 139 (17), 125 (50), 111 (75), 97 (74), 83 (72), 69 (39), 55 (96) [NC-N^+H = CH_2], 29 (100).

*N-Benzyl-N-cyanocarbamic acid ethyl ester (**4f**)*

From 9.80 g (57.27 mmol) benzyl bromide. Colorless liquid, bp 135 °C (53 Pa), yield 7.13 g (61 %).– Anal. $C_{11}H_{12}N_2O_2$.– IR (film): 2241 cm^{-1} (C≡N), 1750 (C=O).– ^{1}H-NMR ($CDCl_3$): δ = 1.35 (t, *J* = 7 Hz, 3 H, CH_3), 4.34 (q, *J* = 7 Hz, 3H, CH_2-CH_3), 4.65 (s, ph-CH_2), 7.45–7.62 (m, 5H, aromatic H).– MS (70 eV): *m/z* (%) = 204 (20) [M^+], 131 (11)[M^+-OC_2H_5-CO], 91 (100) [tropylium].

*N-Cyano-N-cyclohexylmethylcarbamic acid ethyl ester (**4g**)*

From 4.40 g (24.84 mmol) cylohexylmethylbromide. Solid, mp 33 °C, bp 70 °C (6.7 Pa), yield 2.93g (56 %).– Anal. $C_{11}H_{18}N_2O_2$.– IR (film): 2239 cm^{-1} (C≡N), 1750 (C=O).– ^{1}H-NMR ($CDCl_3$): δ = 0.99 (m, 2H), 1.11–1.29 (m, 3H), 1.36 (t,*J* = 7 Hz, 3H, CH_3), 1.71 (m, 6H), 3.37 (d, *J* = 7 Hz, 2H, N-CH_2), 4.32 (q, *J* = 7 Hz, 2H, O-CH_2).– MS (70 eV): *m/z* (%) = 210 (3) [M^+], 137 (12)[M^+-OC_2H_5-CO], 83 (66), 55 (100) [NC-N^+H=CH_2], 29 (56).

*N-(4-Chlorobenzyl)-N-cyanocarbamic acid ethyl ester (**4h**)*

From 4.80 g (29.81 mmol) 4-chlorobenzyl chloride. Colorless liquid, bp 140 °C (2.7 Pa), yield 6.34 g (93 %).– Anal. $C_{11}H_{11}N_2O_2$.– IR (KBr): 2244 cm^{-1} (C≡N), 1753 (C=O).– ^{1}H-NMR ($CDCl_3$): δ = 1.35 (t, *J* = 7 Hz, 3 H, CH_3), 4.36 (q, *J* = 7 Hz, 2H, CH_2-CH_3), 4.62 (s, 2H, ph-CH_2), 7.31 ("d", *J* = 9 Hz, 2H, aromatic 2-H, 6-H), 7.37 ("d", *J* = 9 Hz, 2H, aromatic 3-H, 5-H).– MS (70 eV): *m/z* (%) = 240 (8), 238 (23) [M^+], 165 (7)[M^+-OC_2H_5-CO], 125 (100) [Cl-tropylium].

*N-Cyano-N-(4-nitrobenzyl)carbamic acid ethyl ester (**4i**)*

From 6.31 g (29.48 mmol) 4-nitrobenzyl bromide. Crystals (isopropanol), mp 69 °C, yield 2.50 g (34 %).– Anal. $C_{11}H_{11}N_3O_4$.– IR (KBr): 2243 cm^{-1} (C≡N), 1749 (C=O).– ^{1}H-NMR ($CDCl_3$): δ = 1.37 (t, *J* = 7 Hz, 3 H, CH_3), 4.37 (q, *J* = 7 Hz, 2H, OCH_2), 4.77 (s, 2H, ph-CH_2), 7.56 ("d", *J* = 8 Hz, 2H, aromatic 2-H, 6-H), 8.27 ("d", *J* = 8 Hz, 2H, aromatic 3-H, 5-H).– MS (70 eV): *m/z* (%) = 249 (38) [M^+], 176 (11)[M^+-OC_2H_5-CO], 136 (93) [NO_2-tropylium], 29 (100).

*N-Cyano-N-(2-phenylethyl)carbamic acid ethyl ester (**4j**)*

From 4.71 g (25.45 mmol) 1-bromo-2-phenylethane. Colorless oil, bp 180 °C (40 Pa), yield 3.89 g (70 %).– Anal. $C_{12}H_{14}N_2O_2$.– IR (film): 2243 cm^{-1} (C≡N), 1753 (C=O).– ^{1}H-NMR ($CDCl_3$): δ = 1.31 (t, *J* = 7 Hz, 3 H, CH_3), 3.01 (t, *J* = 8 Hz, 2H, ph-CH_2), 3.77 (t, *J* = 8 Hz, 2H, N-CH_2), 4.27 (q, *J* = 7 Hz, 2H, OCH_2), 7.22–7.36 (m,5H, aromatic H).– MS (70 eV): *m/z* (%) = 218 (6) [M^+-$C_{12}H_{14}N_2O_2$], 104 (100) [ph-CH=CH_2^+], 91 (30) [tropylium], 29 (18).

N-Cyano-N-(3-phenylpropyl)carbamic acid ethyl ester (**4k**)

From 5.00 g (25.11 mmol) 1-bromo-3-phenylpropane. Light yellow liquid, bp 145 °C (53 Pa), yield 2.10 g (36 %).– Anal. $C_{13}H_{16}N_2O_2$.– IR (film): 2240 cm^{-1} (C≡N), 1750 (C=O).– ^{1}H-NMR ([D$_6$]DMSO): δ = 1.25 (t, *J* = 7 Hz, 3 H, CH_3), 1.91 (m, 2H, CH_2-CH_2-CH_2), 2.64 (t, *J* = 8 Hz,2H, ph-CH_2), 3.25 (t, *J* = 7 Hz, 2H, NCH_2), 4.25 (q, *J* = 7 Hz, 2H, OCH_2), 7.15–7.32 (m, 5H, aromatic H).– MS (70 eV): *m/z* (%) = 232 (16) [M^+], 159 (48) [M^+-OC_2H_5-CO], 117 (100), 91 (98) [tropylium], 29 (67).

N-Cyano-N-(3-cyclohexylpropyl)carbamic acid ethyl ester (**4l**)

From 6.00 g (37.36 mmol) 3-cyclohexylpropyl chloride. Purification by distillation and rotational chromatography ($CHCl_3$/*n*-hexane). Light yellow oil, yield 4.36 g (49 %).– Anal. $C_{13}H_{22}N_2O_2$.– IR (film): 2242 cm^{-1} (C≡N), 1753 (C=O).– ^{1}H-NMR ($CDCl_3$): δ = 0.78–0.94 (m, 2H), 1.11–1.26 (m, 7H), 1.36 (t, *J* = 7 Hz, 3H, CH_3), 1.68–1.79 (m, 6H), 3.50 (t, *J* = 7 Hz, 2H, N-CH_2), 4.34 (q, *J* = 7 Hz, 2H, O-CH_2).– MS (70 eV): *m/z* (%) = 238(13) [M^+, $C_{13}H_{22}N_2O_2$], 165 (63)[M^+-OC_2H_5-CO], 83 (47), 69 (30), 55 (100) [NC-N^+H = CH_2], 29 (76).

N-Cyano-N-[3-(N-phthalimidyl)propyl]carbamic acid ethyl ester (**4m**)

From 6.70 g (24.99 mmol) 1-bromo-3-(*N*-phthalimidyl)propane. Purification by rotational chromatography ($CHCl_3$). Colorless oil, dec. by distillation, yield 4.59 g (61 %).– Anal. $C_{15}H_{15}N_3O_4$.– IR (KBr): 2240 cm^{-1} (C≡N), 1751 (C=O).– ^{1}H-NMR ($CDCl_3$): δ = 1.35 (t, *J* = 7 Hz, 3H, CH_3), 2.14 (m, 2H, CH_2-CH_2-CH_2), 3.62 (t, *J* = 7 Hz, 2H, NC-N-CH_2), 3.79 (t, *J* = 7 Hz, 2H, phth-N-CH_2), 4.32 (q, *J* = 7 Hz, 2H, OCH_2), 7.74 (m, 2H, phth. 5-H, 6-H), 7.85 (m, 2H, phth. 4-H, 7-H).– MS (70 eV): *m/z* (%) = 301 (18) [M^+], 228 (13)[M^+-OC_2H_5-CO], 160 (100) [pth-N^+ = CH_2], 29 (37).

N-Cyano-N-(2-naphthylmethyl)carbamic acid ethyl ester (**4n**)

From 5.68 g (25.69 mmol) 2-naphthylmethyl bromide. Purification by distillation and rotational chromatography ($CHCl_3$/hexane 1:1). Solid mp 37 °C, bp 175 °C (2.7 Pa), yield 0.98 g (15%).– Anal. $C_{15}H_{14}N_2O_2$.– IR (KBr): 2243 cm^{-1} (C≡N), 1753 (C=O).– ^{1}H-NMR ([D6]DMSO): δ = 1.35 (t, *J* = 7 Hz, 3H, CH_3), 4.35 (q, *J* = 7 Hz, 2H, OCH_2), 4.81 (s, 2H, naphth-CH_2), 7.49 (m, 3H, aromatic 3-H, 6-H, 7-H), 7.86 (m, 4H, aromatic 1-H, 4-H, 5-H, 8H).– MS (70 eV): *m/z* (%) = 254 (58) [M^+], 181 (14) [M^+-OC_2H_5-CO], 141 (100) [naphthylium], 29 (10).

N-Cinnamyl-N-cyanocarbamic acid ethyl ester (**4o**)

From 5.68 g (25.69 mmol) 2-naphthylmethyl bromide. Light yellow oil, bp 190 °C (6.7 Pa), yield 3.68 g (53%).– Anal. $C_{13}H_{14}N_2O_2$.– IR (film): 2240 cm^{-1} (C≡N), 1750 (C=O).– ^{1}H-NMR ([D$_6$]DMSO): δ = 1.28 (t, *J* = 7 Hz, 3H, CH_3), 4.30 (m, 4H, OCH_2 and NCH_2), 6.34 (dt, *J* = 16/7 Hz, 1H, ph-CH = *CH*-CH_2), 6.73 (d, *J* = 16Hz, 1H, ph-*CH* = CH), 7.27–7.39 (m, 3H, aromatic 3-H, 4-H, 5-H), 7.49 ("d", *J* = 7 Hz, 2H, aromatic 2-H, 6-H).– MS (70 eV): *m/z* (%) = 230 (48) [M^+], 157 (33) [M^+-OC_2H_5-CO], 117 (100), 91 (15).

N-Cyano-N-(5-ethoxycarbonylbutyl)carbamic acid ethyl ester (**4p**)

From 5.65 g (27.98 mmol) 5-bromopentanoic acid ethyl ester. Light yellow oil, bp 100 °C (6.7 Pa), yield 3.32 g (49%).– Anal. $C_{11}H_{18}N_2O_4$.– IR (KBr): 2241 cm^{-1} (C≡N), 1751 (C=O).– ^{1}H-NMR ($CDCl_3$): δ = 1.26 (t, *J* = 7 Hz, 3H, C-$COOCH_2CH_3$), 1.36 (t, *J* = 7 Hz, 3H, N-$COOCH_2CH_3$), 1.65–1.82 (m, 4H, CH_2-CH_2-CH_2-CH_2), 2.36 (t, *J* = 7Hz, 2H, OCO-CH_2), 3.56 (t, *J* = 7 Hz, 2H, NCH_2),4.14 (q, *J* = 7 Hz, 2H, C-$COOCH_2$), 4.33 (q, *J* = 7 Hz, 2H, $NCOOCH_2$).– MS (70 eV): *m/z* (%) = 242 (4) [M^+], 169 (100) [M^+-OC_2H_5-CO], 155 (41), 141 (35), 29 (91).

N-[(4-Acetylamino-4-methoxycarbonyl)butyl]-N-cyanocarbamic acid ethyl ester (**4r**)

From 1.00 g (3.97 mmol) 5-bromo-2-acetylamino-pentanoic acid methyl ester[16]. Colorless oil, bp 200 °C (2.7 Pa), yield 0.19 g (17 %).– Anal. $C_{12}H_{19}N_3O_5$.– IR (film): 2243 cm^{-1} (C≡N), 1749 (O–C=O), 1659 (N–C=O).– ^{1}H-NMR ($CDCl_3$): δ = 1.36 (t, *J* = 7 Hz, 3H, OCH_2CH_3), 1.67–1.83 (m, 4H, NCH_2-CH_2-CH_2), 2.05 (s, 3H, NHCO-CH_3), 3.56 (t, *J* = 6 Hz, 2H, N-CH_2), 3.78 (s, 3H, $COOCH_3$), 4.33 (q, *J* = 7 Hz, 2H, $COOCH_2CH_3$), 4.68 (m, 1H, AcNH-*CH*-$COOCH_3$), 6.13 (d, *J* = 8 Hz, 1H, NH).– MS ([+]-FAB, DMSO/glycerol): *m/z* (%) = 286 (56) [(M + H^+)], 70 (100), 29 (82).

N,N'-Hexamethylene-bis-N-cyanocarbamic acid ethyl ester (**4s**)

From 3.45 g (14.14 mmol) 1,6-dibromohexane. Colorless oil which becomes solid in the refrigerator, yield 4.10 g (93 %).– Anal. $C_{14}H_{22}N_4O_4$.– IR (film): 2242 cm^{-1} (C≡N), 1753 (C=O). ^{1}H-NMR ($CDCl_3$): δ = 1.34 (t, *J* = 7 Hz, 6H, CH_3), 1.43 (m, 4H, $N(CH_2)_2$-CH_2), 1.74 (m, 4H, NCH_2-CH_2), 3.54 (t, *J* = 7 Hz, 4H, NCH_2), 4.33 (q, *J* = 7 Hz, 4H, OCH_2CH_3).– MS (70 eV): *m/z* (%) = 310 (1) [M^+, $C_{14}H_{22}N_4O_4$], 29 (100).

Formation of 1,2,4-oxadiazol-5-ones (**6**) *from* **4** *and hydroxylamine*

2.77 g (40 mmol) hydroxylamine hydrochloride are suspended in 70 ml dimethylformamide and 4.05 g (40 mmol) triethylamine are added. The mixture is stirred for 15 min and filtered. Then 20 mmol of the alkylated *N*-cyanocarbamic acid ethyl ester are added. The solution is stirred overnight at room temp. Now water is added until a voluminous precipitate forms. It is sucked off, washed with water, dried, and recrystallized.

3-Amino-4-methyl-1,2,4-oxadiazol-5-one (**6a**)

Before adding water most of the DMF has to be removed *in vacuo*. Crystals (DMF/H_2O), mp 168 °C (dec.), yield 1.47 g (34 %).– Anal. $C_3H_5N_3O_2$.– IR (KBr): 3365 cm^{-1} (NH_2), 1756 (C=O), 1644 (C=N).–^{1}H-NMR ([D$_6$]DMSO): δ = 3.02 (s, 3H, CH_3), 6.58 (s, 2H, D_2O exchange, NH_2).– MS (70 eV): *m/z* (%) = 115 (100) [M^+], 58 (61).

3-Amino-4-butyl-1,2,4-oxadiazol-5-one (**6b**)

Crystals (DMF/H_2O), mp 120 °C, yield 0.69 g (21 %).– Anal. $C_6H_{11}N_3O_2$.– IR (KBr): 3396 cm^{-1} (NH_2), 1743 (C=O), 1643 (C=N).– ^{1}H-NMR ([D$_6$]DMSO): δ = 0.89 (t, *J* = 7 Hz, 3H, CH_3), 1.26 (m, 2H, CH_2CH_3), 1.53 (tt, *J* = 7/7 Hz, 2H, NCH_2-CH_2-CH_2), 3.48 (t, *J* = 7 Hz, 2H, NCH_2), 6.61 (s, 2H, D_2O exchange, NH_2).– MS (70 eV): *m/z* (%) = 157 (29) [M^+] 101 (100) [**b**], 98 (46) [**c**], 56 (10) [**a**].

3-Amino-4-pentyl-1,2,4-oxadiazol-5-one (**6c**)

Crystals (CH_3OH/H_2O), mp 124 °C, yield 0.45 g (24 %).– Anal. $C_7H_{13}N_3O_2$.– IR (KBr): 3390 cm^{-1} (NH_2), 1739 (C=O), 1639 (C=N).– ^{1}H-NMR ([D$_6$]DMSO): δ = 0.86 (t, *J* = 7 Hz, CH_3), 1.17–1.33 (m, 4H, H_3C-CH_2-CH_2), 1.55 (tt, *J* = 7/7 Hz, 2H, NCH_2-CH_2), 3.48 (t, *J* = 7 Hz, 2H, NCH_2), 6.60 (s, 2H, D_2O exchange, NH_2).– MS (70 eV): *m/z* (%) = 171 (29) [M^+,$C_7H_{13}N_3O_2$], 101 (84) [$C_2H_3N_3O_2$, **b**], 112 (65) [$C_6H_{10}NO$, **c**], 70 (13) [**a**] 43 (100) [C_3H_7].

3-Amino-4-hexyl-1,2,4-oxadiazol-5-one (**6d**)

Crystals (CH_3OH/H_2O), mp 132 °C, yield 1.56 g (48 %).– Anal. $C_8H_{15}N_3O_2$.– IR (KBr): 3399 cm^{-1} (NH_2), 1744 (C=O), 1641 (C=N).– ^{1}H-NMR ([D$_6$]DMSO): δ = 0.86 (t, *J* = 7 Hz, 3H, CH_3), 1.26 (s, 6H, $N(CH_2)_2$-$(CH_2)_3$), 1.54 (m, 2H, NCH_2-CH_2), 3.47 (t, *J* = 7 Hz, 2H, NCH_2), 6.59 (s, 2H, D_2O exchange, NH_2).– MS (70 eV): *m/z* (%) = 185 (27) [M^+], 126 (11) [**c**], 101 (64) [**b**], 84 (5) [**a**] 43 (100).

3-Amino-4-octyl-1,2,4-oxadiazol-5-one (**6e**)

Crystals (CH_3OH/H_2O), mp 133 °C, yield 4.46 g (86 %).– Anal. $C_{10}H_{19}N_3O_2$.– IR (KBr): 3395 cm^{-1} (NH_2), 1738 (C=O), 1640 (C=N).– ^{1}H-NMR ([D$_6$]DMSO): δ = 0.86 (t, *J* = 6 Hz, 3H, CH_3), 1.25 ("s", 10H, CH_3-$(CH_2)_5$), 1.55 (m, 2H, NCH_2-CH_2), 3.47 (t, *J* = 7 Hz, 2H, NCH_2), 6.59 (s, 2H, D_2O exchange, NH_2).– MS (70 eV): *m/z* (%) = 213 (25) [M^+], 154 (48) [**c**], 101 (58) [**b**], 112 (6) [**a**], 102 (100), 43 (86).

3-Amino-4-benzyl-1,2,4-oxadiazol-5-one (**6f**)

Crystals (DMF/H_2O), mp 169 °C (dec.), yield 2.51 g (67 %).– Anal. $C_9H_9N_3O_2$.– IR (KBr): 3371 cm^{-1} (NH_2), 1743 (C=O), 1645 (C=N).– ^{1}H-NMR ([D6]DMSO): δ = 4.74 (s, 2H, CH_2), 6.74 (s, 2H, D_2O exchange, NH_2), 7.29–7.40 (m, 5H, aromatic H).– MS (70 eV): *m/z* (%) = 191 (8) [M^+], 91 (100) [tropylium].

3-Amino-4-cyclohexylmethyl-1,2,4-oxadiazol-5-one (**6g**)

Crystals (isopropanol), mp 206 °C (dec.), yield 0.66 g (20 %).– Anal. $C_9H_{15}N_3O_2$.– IR (KBr): 3381 cm^{-1} (NH_2), 1746 (C=O), 1642 (C=N).– ^{1}H-NMR ([D$_6$]DMSO): δ = 0.94 (m, 2H), 1.14 (m, 4H), 1.45–1.66 (m, 7H), 3.32 (m, 2H, NCH_2), 6.57 (s, 2H, D_2O exchange, NH_2).– MS (70 eV): *m/z* (%) = 197 (31) [M^+], 101 (19) [**b**], 96 (13) [**a**], 55 (100).

3-Amino-4-(4-chlorobenzyl)-1,2,4-oxadiazol-5-one (**6h**)

Crystals (CH_3OH), mp 172 °C, yield 1.51 g (24 %).– Anal. $C_9H_8ClN_3O_2$.– IR (KBr): 3380 cm^{-1} (NH_2), 1745 (C=O), 1646 (C=N).– ^{1}H-NMR ([D$_6$]DMSO): δ = 4.75 (s, 2H, CH_2), 6.75 (s, 2H, D_2O exchange, NH_2), 7.33 ("d", *J* = 8 Hz, 2H, aromatic 3-H, 5-H), 7.45 ("d", *J* = 8 Hz, aromatic 2-H, 6-H).– MS (70 eV): *m/z* (%) = 227 (3), 225 (14) [M^+], 127 (37), 125 (100) [tropylium].

3-Amino-4-(4-nitrobenzyl)-1,2,4-oxadiazol-5-one (**6i**)

Yellowish crystals (DMF/H_2O), mp 143 °C (dec.), yield 2.51 g (42 %).– Anal. $C_9H_8N_4O_4$.– IR (KBr): 3331 cm^{-1} (NH_2), 1752 (C=O), 1648 (C=N).– ^{1}H-NMR ([D$_6$] acetone): δ = 5.02 (s, 2H, CH_2), 6.04 (s, 2H, D_2O exchange, NH_2), 7.66 ("d", *J* = 8 Hz, 2H, aromatic 2-H, 6-H), 8.27 ("d", *J* = 8 Hz, 2H, aromatic 3-H, 5-H).– MS (70 eV): *m/z* (%) = 236 (49), [M^+], 136 (100) [tropylium].

3-Amino-4-(2-phenylethyl)-1,2,4-oxadiazol-5-one (**6j**)

Crystals (CH_3OH), mp 207 °C, yield 2.01 g (54 %).– Anal. $C_{10}H_{11}N_3O_2$.– IR (KBr): 3365 cm^{-1}, 1749 (C=O), 1646 (C=N).– ^{1}H-NMR ([D$_6$]DMSO): δ = 2.91 (t, *J* = 8 Hz, 2H, ph-CH_2), 3.72 (t, *J* = 8 Hz, 2H, NCH_2), 6.64 (s, 2H, D_2O exchange, NH_2), 7.20–7.33 (m, 5H, aromatic H).– MS (70 eV): *m/z* (%) = 205 (5) [M^+], 104 (100), 91 (26) [tropylium].

3-Amino-4-(3-phenylpropyl)-1,2,4-oxadiazol-5-one (**6k**)

Leaves (DMF/H_2O), mp 148 °C, yield 1.41 g (71 %).– Anal. $C_{11}H_{13}N_3O_2$.– IR (KBr): 3386 cm^{-1} (NH_2), 1735 (C=O), 1640 (C=N).– ^{1}H-NMR ([D$_6$]DMSO): δ = 1.85 (m, 2H, CH_2-CH_2-CH_2), 2.58 (t, *J* = 8 Hz, 2H, phCH_2), 3.54 (t, *J* = 7 Hz, 2H, NCH_2), 6.64 (s, 2H, D_2O exchange, NH_2), 7.16 (m, 5H, aromatic H).– MS (70 eV): *m/z* (%) = 219 (62) [M^+, $C_{11}H_{13}N_3O_2$], 91 (100).

3-Amino-4-(3-cyclohexylpropyl)-1,2,4-oxadiazol-5-one (**6l**)

Leaves (CH_3OH/H_2O), mp 167 °C (dec.), yield 3.06 g (54 %).– Anal. $C_{11}H_{19}N_3O_2$.– IR (KBr): 3376 cm^{-1} (NH_2), 1751 (C=O), 1644 (C=N).– ^{1}H-NMR ([D$_6$]DMSO): δ = 0.78–0.89 (m, 2H), 1.09–1.21 (m, 6H), 1.50–1.67 (m, 7H), 3.46 (t, *J* = 7 Hz, 2H, NCH_2), 6.59 (s, 2H, D_2O exchange, NH_2).– MS (70 eV): *m/z* (%) = 225 (32) [M^+, $C_{11}H_{19}N_3O_2$], 166 (100) [$C_{10}H_{16}NO$, **c**], 101 (36) [$C_2H_3N_3O_2$, **b**].

3-Amino-4-[3-(N-phthalimidyl)-propyl]-1,2,4-oxadiazol-5-one (**6m**)

Crystals (CH_3OH), mp 185–188 °C (dec.), yield 1.43 g (34%).– Anal. $C_{13}H_{12}N_4O_4$.– IR (KBr): 3394 cm^{-1} (NH_2), 1760 (5-C=O), 1710 (phthal-C=O), 1644 (C=N).– ^{1}H-NMR ([D$_6$]DMSO): δ = 1.91 (tt, *J* = 7/7 Hz, 2H, CH_2-CH_2-CH_2), 3.54 (t, *J* = 8 Hz, 2H, oxadiazole NCH_2), 3.62 (t, *J* = 7 Hz, 2H, phthal-NCH_2), 6.66 (s, 2H, D_2O exchange, NH_2), 7.82–7.90 (m, 4H, aromatic H).– MS (70 eV): *m/z* (%) = 288 (56) [M^+], 160 (100) [phthal = N^+ = CH_2].

3-Amino-4-(2-naphthylmethyl)-1,2,4-oxadiazol-5-one (**6n**)

Colorless light crystals (CH_3OH), mp 218 °C, yield 0.61 g (36 %).– Anal. $C_{13}H_{11}N_3O_2$.– IR (KBr): 3366 cm^{-1} (NH_2), 1750 (C=O), 1645 (C=N).– ^{1}H-NMR ([D$_6$]DMSO): δ = 4.93 (s, 2H, CH_2), 6.78 (s, 2H, D_2O exchange, NH_2), 7.45 (d, *J* = 9 Hz, 1H, aromatic 3-H), 7.53 (m, 2H, aromatic 6-H, 7-H), 7.80 (s, 1H, aromatic 1-H), 7.93 (m, 3H, aromatic 4-H, 5-H, 8-H).– MS (70 eV): *m/z* (%) = 241 (15) [M^+], 141 (100) [naphthylium].

3-Amino-4-cinnamyl-1,2,4-oxadiazol-5-one (**6o**)

Bright leaves (CH_3OH), mp 175–179 °C (dec.), yield 1.68 g (66 %).– Anal. $C_{11}H_{11}N_3O_2$.– IR (KBr): 3401 cm^{-1} (NH_2), 1748 (C=O), 1643 (C=N).– ^{1}H-NMR ([D$_6$] DMSO): δ = 4.31 (d, *J* = 6 Hz, 2H, CH_2), 6.27 (dt, *J* = 16/6 Hz, 1H, ph-CH = C*H*-CH_2), 6.56 (d, *J* = 16 Hz, 1H, ph-C*H* = CH), 6.68 (s, 2H, D_2O exchange, NH_2), 7.30 (m, 3H, aromatic 3-H, 4-H, 5-H), 7.45 (d, *J* = 7 Hz, 2H, aromatic 2-H, 6-H).– MS (70 eV):*m/z* (%) = 217 (100) [M^+], 117 (49) [ph-CH = $CH-CH_2^+$].

5-(3-Amino-4,5-dihydro-5-oxo-1,2,4-oxadiazol-4-yl)-pentanoic acid ethyl ester (**6p**)

Waxy material. Purification by distillation (bp 120 °C, 5.3 Pa). The residue (!) is further purified by rotational chromatography (ethyl acetate/$CHCl_3$ 1:1). Mp 49 °C, yield 0.6 g (11 %).– Anal. $C_9H_{15}N_3O_4$.– IR (KBr): 3391 cm^{-1} (NH_2), 1740 (C=O), 1643 (C=N).– ^{1}H-NMR ([D$_6$]DMSO): δ = 1.20 (t, *J* = 7 Hz, 3H, CH_3), 1.53 (m, 4H, CH_2-CH_2-CH_2-CH_2), 2.32 (t, *J* = 7 Hz, 2H, OCO-CH_2), 3.50 (t, *J* = 7 Hz, 2H, NCH_2), 4.04 (q, *J* = 7 Hz, 2H, OCH_2), 6.61 (s, 2H, D_2O exchange, NH_2).– MS (70 eV): *m/z* (%) = 229 (43) [M^+], 184 (100) [M^+-OC_2H_5-CO], 128 (12) [**a**]. 101 (69) [**b**]. 29 (56).

5-(3-Amino-4,5-dihydro-5-oxo-1,2,4-oxadiazol-4-yl)-2-acetylamino-pentanoic acid methyl ester (**6r**)

From **4r** and hydroxylamine in ethanol (!). Purification by rotational chromatography (ethyl acetate/ethanol 4 : 1). Crystals, mp 117 °C, yield 0.17 g (11 %).– IR (KBr): 3318 cm^{-1} (NH_2), 1753 (C=O), 1646 (C=O).– ^{1}H-NMR ([D$_6$]acetone): δ = 1.69–1.91 (m, 4H, N-CH_2-(CH_2)$_2$), 1.95 (s, 3H, NHCOCH_3), 3.61–3.68 (m, 5H, NCH_2, OCH_3), 4.52 (m, 1H, CH_2-C*H*-$COOCH_3$), 5.96 (s, 2H, D_2O exchange, NH_2) 7.55 (d, *J* = 8 Hz, CONH).– MS ([+]-FAB, DMSO/glycerol): *m/z* (%) = 273 (100) [M + H]$^+$, 231 (70), 171 (33) [**a**], 43 (90) [CH_3CO].

3-Amino-4-(3-aminopropyl)-1,2,4-oxadiazol-5-one hydrochloride (**6q**)

2.75 g (9.54 mmol) **6m** are suspended in 50 mL methanol and an excess of hydrazine monohydrate and some mL conc. HCl added. The suspension is boiled for some min, and concentrated *in vacuo*. The phthalic acid hydrazide which has formed is sucked off. The solution is kept overnight in the refrigerator. The crystals which have formed are sucked off, dissolved in ethanol, and precipitated with ethereal hydrochloric acid.

Crystals (ethanol), mp 173 °C (dec.), yield 1.11 g (91 %).– Anal. $C_5H_{11}ClN_4O_2$.– IR (KBr): 3380 cm^{-1} (NH_2), 1738 (C=O), 1647 (C=N).– ^{1}H-NMR ([D$_6$]DMSO): δ = 1.89 (m, 2H, CH_2-CH_2-CH_2), 2.80 (m, 2H, $CH_2N^+H_3$), 3.64 (t, *J* = 7 Hz, 2H, oxadiazole-NCH_2), 6.80 (s, 2H, D_2O exchange, NH_2), 8.04 (s, 3H, D_2O exchange NH_3^+).– MS (70 eV): *m/z* (%) = 158 (23) [M^+], 101 (26) [**b**], 57 (28) [**a**], 30 (100) [$CH_2 = NH_2^+$].

4,4'-Hexamethylene-bis-(3-amino-1,2,4-oxadiazol-5-one) (**6s**)

Crystals (DMF/H_2O), mp 213 °C (dec.), yield 1.29 g (42 %).– Anal. $C_{10}H_{16}N_6O_4$.– IR (KBr): 3393 cm^{-1} (NH_2), 1741 (C=O), 1645 (C=N).– ^{1}H-NMR ([D$_6$]DMSO): δ = 1.24 (s, 4H, N(CH_2)$_2$-CH_2), 1.52 (m, 4H, N-CH_2-CH_2), 3.47 (t, *J* = 7 Hz, 4H, NCH_2), 6.60 (s, 4H, D_2O exchange, NH_2).– MS (70 eV): *m/z* (%) = 284 (3), [M^+], 73 (73), 44 (100).

2-Alkyl and 2-arylalkyl-3-amino-1,2,4-oxadiazol-5-ones (**10**)

1.36 g (10 mmol) *N*-cyanocarbamic acid ethyl ester and 0.7 g (10 mmol) hydroxylamine hydrochloride are dissolved in methanol and stirred 48 h at room temp. The solvent is removed at room temp. The residue is suspended in cold water, sucked off, and washed with ice water and dried. The crude product (3-amino-2,5-dihydro-1,2,4-oxadiazol-5-one) is dissolved in as little DMF as possible. Now 10 mmol alkyl bromide and 10 mmol triethylamine are added. After addition of a catalytic amount of KI the mixture is stirred 4 h at room temp. After addition of little water crystals are formed, which are sucked off and recrystallized.

3-Amino-2-pentyl-1,2,4-oxadiazol-5-one (**10c**)

From 1.94 g (12.84 mmol) bromopentane. Crystals (DMF/H_2O), mp 179 °C (dec.), yield 0.19 g (9 %).– Anal. $C_7H_{13}N_3O_2$.– IR (KBr): 3319 cm^{-1} (NH_2), 1742 (C=O), 1662 (C=N).– ^{1}H-NMR ([D_6]DMSO): δ = 0.87 (t, *J* = 7 Hz, 3H, CH_3), 1.28 (m, 4H, H_3C-(CH_2)$_2$, 1.54 (m, 2H, N-CH_2-CH_2), 3.60 (t, *J* = 7 Hz, 2H, NCH_2), 8.02 (s, 2H, D_2O exchange, NH_2).– MS (70 eV): *m/z* (%) = 171 (14) [M^+], 154 (100) [M^+-NH_3].

3-Amino-2-benzyl-1,2,4-oxadiazol-5-one (**10f**)

From 1.30 g (7.60 mmol) benzyl bromide. Crystals (DMF/H_2O), mp 117–124 °C (dec.), yield 0.38 g (26 %).– Anal. $C_9H_9N_3O_2$.– IR (KBr): 3317 cm^{-1} (NH_2), 1756 (C=O), 1667 (C=N).– ^{1}H-NMR ([D_6]DMSO): δ = 4.84 (s, 2H, CH_2), 7.31–7.43 (m, 5H, aromatic H), 8.29 (s, 2H, D_2O exchange, NH_2).– MS ([+]FAB, DMSO/glycerol): *m/z* (%) = 192 (59) [M + H^+], 91 (100) [tropylium].

Biology

The thrombosis experiments were carried out as usual[12].

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