New NO-Donors with Antithrombotic and Vasodilating Activities, XII:

Mesoionic Oxatriazoles and Related Noncyclic Nitrosohydrazine Derivatives

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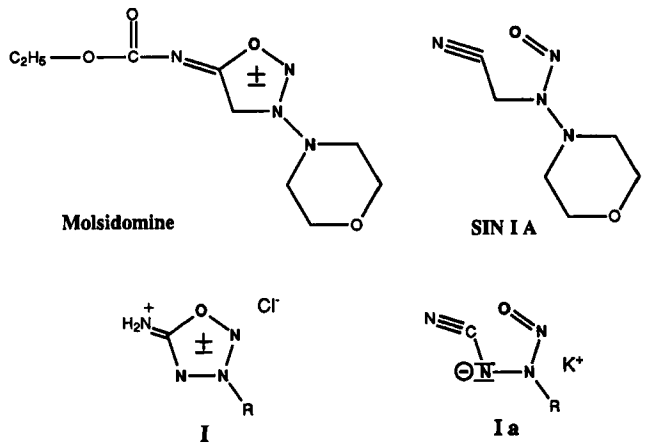
Mesoionic 1,2,3,4-oxatriazolimines and the corresponding oxatriazolones were prepared and tested for their antiplatelet and antithrombotic activities. In the *Born*-test 5-amino-3-phenyl-1,2,3,4-oxatriazolimine chloride inhibited the platelet aggregation halfmaximally in a concentration of 50 nmol/L. Its *N*-ethoxycarbonyl derivative inhibited thrombus formation in arterioles of rats by 48% (10 mg/kg, 2 h after p.o. administration). These effects appear to be related to the formation of intermediate nitrosohydrazine derivatives. This aspect was supported by the activities in noncyclic nitrosohydrazines (2 compds.), nitrosohydrazones (2) and nitrosohydrazides (11). Five of them exhibited an IC_{50} < 100 nmol/L in the *Born*-test. In a thrombotic model strong inhibition of thrombus formation was observed after intravenous application. The 1-nitroso-1-benzylhydrazine even exhibited strong inhibitory effects after oral administration.

Neue NO-Pharmaka mit antithrombotischen und gefäßerweiternden Eigenschaften, 12. Mitt.:

Mesoionische Oxatriazole und verwandte acyclische Nitrosohydrazine

Mesoionische 1,2,3,4-Oxatriazolimine und analoge Oxatriazolone wurden dargestellt und auf thrombocyteninhibitorische und antithrombotische Eigenschaften geprüft. Im *Born*-Test hemmte 5-Amino-3-phenyl-1,2,3,4-oxatriazolium-chlorid die Aggregation der Blutplättchen in einer Konzentration von 50 nmol/L halbmaximal. Sein *N*-Ethoxycarbonylderivat zeigte in Rattenarteriolen eine 48 proz. Hemmung der Thrombusbildung (10 mg/kg, 2 h nach p.o. Gabe). Diese Wirkungen sind offenbar mit der intermediären Bildung von Nitrosohydrazinderivaten verknüpft. Diese Ansicht wird gestützt durch die Aktivität von acyclischen Nitrosohydrazinen (2 Verbindungen), Nitrosohydrazonen (2) und Nitrosohydraziden (11). Fünf dieser Verbindungen weisen eine IC_{50} < 100 nmol/L im *Born*-Test auf. Im Thrombosemodell wurde bei diesen Verbindungen eine starke Hemmung der Thrombusbildung nach i.v. Verabreichung beobachtet. Das 1-Nitroso-1-benzylhydrazin wirkte überraschenderweise auch nach oraler Gabe stark antithrombotisch.

Molsidomine is one of the best known drugs which develops its pharmacologic actions by release of nitric oxide.



Scheme 1: Ring opening in sydnone imines and oxatriazolimines.

The chemical entity which is most prone to this reaction is the active metabolite SIN 1A (Scheme 1) which is formed by enzymatic hydrolysis of molsidomine followed by cleavage of the mesoionic ring system. Its instability obviously is due to a nitrosohydrazine substructure.

*) Part of the PhD thesis *P. König*, FU Berlin, 1993

This prompted us to investigate systematically compounds with hydrazine structures for their ability to develop antithrombotic and vasodilating effects. We firstly recognized that mesoionic oxatriazolimines of type I[1] which comprise a nitrosohydrazine structure totally disguised in the ring system, show a ring opening reaction similar to SIN 1A (type Ia)[2].

Recently we have reported on the NO releasing properties of sydnone-5-nitrosimines[3,4]. When we tried to synthesize the corresponding oxatriazole-5-nitrosimines of type II (Scheme 2) we found them very unstable decomposing immediately to type III oxatriazolones by expulsion of N_2. For this class of compounds blood pressure lowering properties have been reported[5,6,7] and antianginal as well as antithrombotic properties have been claimed (no data)[8]. We supposed that these effects are as well due to a mechanism involving the release of a NO species.

We, therefore, prepared the oxatriazole derivatives compiled in Tab. 1 and assayed them for their antiplatelet and antithrombotic properties.

In vitro compound **1** by far is the most active derivative. This corresponds to the ease of ring opening as stated by *Christopher et al.*[2]. Comparison with **4** strongly suggests that this is facilitated by substituents in 3-position which have electron withdrawing properties. This conclusion is supported further by the observation that **2** lacks any *in*

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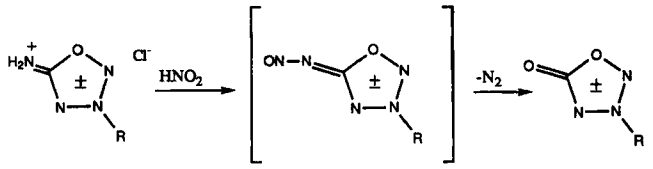


I II III

Scheme 2: Formation of oxatriazolones **III** from oxatriazolimines **I** *via* nitrosimines **II**.

vitro activity: similar to molsidomine the acylation of the 5-imino group gives compounds which *in vitro* at physiological conditions are stable against hydrolysis. Compound **3** *in vitro* inhibited platelet aggregation with medium activity suggesting that the ring opening reaction and hence the release of NO is slower than in **1**.

In vivo **1** and **4** after p.o. administration show no antithrombotic effects. That might be due to the fact that they are not only inner but as well outer salts of which the absorption from the gastrointestinal tract should be more difficult. At least in **1** this is accompanied by decomposition, so that no sufficient blood levels are achieved. The different activity of **1** and **4** after *i.v.* injection again reflects the influence of electron withdrawing substituents in 3-position and results in a strong dose dependent or small inhibition of thrombus formation [**1**], respectively.

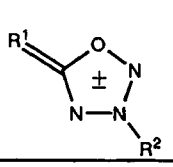
The relation between **1** and **2** corresponds to that of SIN 1 and molsidomine. With this respect **2** is a suitable prodrug for oral administration which *in vivo* exhibits - depending on the dose - strong antithrombotic activities. Compound **3** which as well solely is an inner salt, obviously is absorbed after p.o. administration. *In vivo* it seems to decompose rather slowly so that, depending on the dose, after 2 h still medium or strong inhibition of laser induced thrombus formation is observed.

In the oxatriazole series (**1**, **3**, **4**) we were not able to isolate the ring-open nitrosonitriles (from **1** and **4**) or nitrosocarboxylic acids (from **3**) sufficiently pure for the *Born*-test. This corresponds to the observation that during the synthesis of **1** or **4** appropriate nitrosonitrile - intermediates are cyclized *in situ* without prior isolation. We, therefore, were interested in non-cyclic nitrosohydrazines in order to determine the above activities of such "intermediate" compounds. With this respect nitrosohydrazines (**5**, **12**), nitrosohydrazides (**6** - **11** and **13** - **17**) and nitrosohydrazones (**18**, **19**) were prepared mostly according to methods published (Experim. Part).

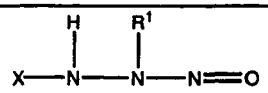
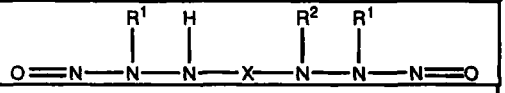
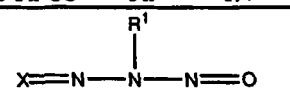
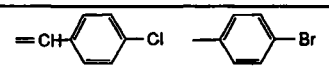
The results obtained in the *Born*-test are compiled in Tab. 2. The rather small effects of **5** and **12** show that a substituent with electron withdrawing properties at either nitrogen of the hydrazine moiety is essential for strong inhibition of the platelet aggregation. It seems not to be purely by chance that the most potent compounds (*i.e.* **10**, **11**, **13**, **14**, **16**) are exactly as active as **1** (Tab. 1) and fulfil the criteria for strong effects pointed out above.

Medium activities, therefore, are observed in compounds with substituents (**9**, **18**, **19**) of medium electron withdrawing properties. This is stressed by comparison of **9** and **10**: Substitution of the carboxamide **9** with two phenyl groups enhances the activity by one order of magnitude. Not surprisingly the sulfonic acid group in **11** gives rise to a compound of strong antiplatelet activity. In general the results of Tab. 2 support the view that non-cyclic nitrosohydra-

Tab. 1: *In vitro* antiplatelet (*Born*-test with collagen) and *in vivo* (rats) antithrombotic properties of mesoionic type **I** and **II** oxatriazoles

Compound		Inhibition of platelet aggregation IC_{50} [µmol/L]	% inhibition of thrombus formation x ± Sx/α	
			venoles	arterioles
1	$R^1 = NH_2^+Cl^-$ R^2 = Ph	0.05		
	20 min after 3 mg/kg i. v.		13 ± 3/0.002	26 ± 5/0.002
	10 mg/kg i. v.		26 ± 10/0.002	44 ± 9/0.002
2	$R^1 = NCOOC_2H_5$ R^2 = Ph	-		
	2 h after 5 mg/kg p. o.		12 ± 7/0.2	15 ± 8/0.2
	10 mg/kg p. o.		17 ± 10/0.01	48 ± 6/ 0.002
3	R^1 =O R^2 = Ph	3		
	2 h after 5 mg/kg p. o.		19 ± 4/0.002	24 ± 10/0.02
	10 mg/kg p. o.		26 ± 2/0.002	55 ± 12/0.2
4	$R^1 = NH_2^+Cl^-$ $R^2 = (CH_2)_3$-Ph	90		
	10 min after 60 mg/kg i. v.		4 ± 1/0.2	18 ± 2/0.2

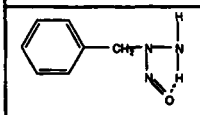
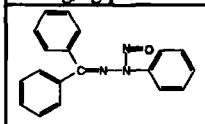
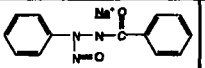
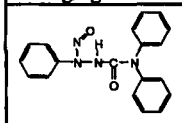
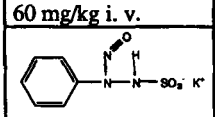
Tab. 2: Antiplatelet activities of nitrosohydrazines, -hydrazides and -hydrazones (*Born*-test, collagen)

Type			
IV			
Compound	X	R^1	IC_{50} [µmol/L]
5	H	Ph-CH_2	180
6	CO-Ph	Ph	0.6
7	CO-$COOC_2H_5$	Ph	0.5
8	CO-CO-NH-C_2H_5	Ph	0.2
9	CO-NH_2	Ph	1
10	CO-N-$(Ph)_2$	PH	0.08
11	$SO_3^-K^+$	Ph	0.06
V			
	X	R^1	IC_{50} [µmol/L]
12	CH_2	Ph-CH_2	9
13	CO-CO	Ph	0.08
14	CO-CH_2-CO	Ph	0.04
15	CO-$(CH_2)_3$-CO	Ph	0.1
16	CO-$(CH_2)_4$-CO	Ph	0.06
17	1,2-CO-Ph-CO	Ph	1.4
VI			
	X	R^1	IC_{50} [µmol/L]
18			1
19	=C(Ph)$_2$	Ph	1.8

zines do function as intermediates in the NO releasing process of mesoionic oxatriazole compounds.

Selected compounds of Tab. 2 were submitted to an *in vivo* thrombosis model. The results are summarized in Tab. 3. Only compound **5** exhibited a strong antithrombotic effect after p.o. administration. A 60% inhibition of thrombus formation in arterioles is near the maximum effect achievable in this hard thrombosis model. The difference to the poor *in vitro* result is rather typical. It suggests a good absorption after p.o. administration and enzyme dependent alteration of **5** probably involving the liver. Compounds **6** and **10** which possess strong platelet inhibiting properties *in vitro* are inactive when applied orally. This result shows that the compounds are decomposed prior to absorption from the g.i. tract. When the absorption barriers are bypassed by i.v. injection such "unstable" nitrosohydrazines exhibit extremely strong antithrombotic activities (*e.g.* **6a** which had been chosen instead of **6** on account of its good solubility in water, and **11**). So typical rules for NO-donors are reinforced by these results: Compounds with strong *in vitro* activity are poor with concern to long

Tab. 3: *In vitro* antiplatelet (*Born*-test with collagen) and *in vivo* (rats) antithrombotic properties of non-cyclic nitrosohydrazines, nitrosohydrazides, and nitrosohydrazones, n.s. = not significant

	% inhibition of thrombosis formation $x \pm S_x/\alpha$		
Compound	venoles	arterioles	inhibition of platelet aggregation IC_{50} [µmol/L]
 5 2 h after 60 mg/kg p.o.	29 ± 1/0.002	60 ± 3/0.002	180
 6 2h after 60 mg/kg p.o.	0 ± 1/n.s.	0 ± 2/n.s.	2
 6a 10 min after 60 mg/kg i.v.	56 ± 2/0.002	72 ± 6/0.002	0.2
 10 2 h after 60 mg/kg i. v.	3 ± 1/0.1	1 ± 2/n.s.	0.08
 11 10 min after 60 mg/kg i. v.	7 ± 5/0.2	47 ± 1/0.002	0.06

term p.o. prohibition of thrombosis. On the other hand compounds with suitable structures which are inactive *in vitro* (*e.g.* **5**) are promising candidates for *in vitro p.o.* investigations.

Experimental Part

IR spectra: KBr.- ^{1}H-NMR spectra: [D_6]DMSO at 300 MHz, unless otherwise stated.- Further analytical details have been communicated[13]. Platelet aggregation and animal experiments were carried out as usual[3,23].

5-Amino-3-phenyl-1,2,3,4-oxatriazolium chloride (**1**)

Crystals, mp. 189° (dec.) (ref.[1]: 191°).- $C_7H_6N_4O \cdot HCl$ (198.6).- Calcd. C 42.3 H 3.55 N 28.2. Found C 42.2 H 3.40 N 28.1.

5-(N-Ethoxycarbonylimino)-3-phenyl-1,2,3,4-oxatriazol (inner salt) (**2**)

300 mg (1.5 mmol) **1** are dissolved in little water, cooled, 1.5 mmol K_2CO_3 and some ml of $CHCl_3$ are added. Then 2.2 mmol ethylchlorofor-

mate are added and again 1.5 mmol K_2CO_3-solution is dropped in. The mixture is stirred for 1 h, the org. layer separated and the aqueous layer extracted twice with $CHCl_3$. The combined $CHCl_3$ extracts are dried (Na_2SO_4), and the solvent is removed at room temp.: Powder, mp. 113° (dec.), yield 85%.- $C_{10}H_{10}N_4O_3$ (234.2) Calcd. C 51.3 H 4.31 N 23.9 Found C 50.7 H 4.10 N 24.2.- IR: 3079; 2978; 2907; 1795; 1719; 1684; 1644; 1621; 1525; 1484; 1470; 1451; 1365; 1348; 1305; 1288; 1201; 1175; 1161; 1125; 1071; 1020; 948; 876; 796; 778; 758; 682 cm^{-1}.- ^{1}H-NMR: δ (ppm) = 8.14 (d, J = 7.8 Hz, 2H aromat., 2-H, 6-H), 7.89-7.77 (m, 3H aromat., 3-H, 4-H, 5-H), 4.07 (q, J = 7.1 Hz, 2H, O-CH_2), 1.22 (t, J = 7.1 Hz, 3H, $CH_2C\underline{H}_3$).- MS (60°): m/z = 234 ($M^{+\cdot}$, 1%), 189 (20), 105 (19), 77 (100), 51 (18), 29 (27).

Phenyl-1,2,3,4-oxatriazol-5-one (inner salt) (**3**)

Red powder, mp. 76° (dec.) (ref.[9] 76-78°), yield 80%.- $C_7H_5N_3O_2$ (163.2) Calcd. C 51.4 H 3.08 N 25.8 Found C 51.6 H 2.80 N 25.6.- MS (CI, 80°, isobutane): m/z = 164 ([M + H]$^+$, 100%).

N^1-Nitroso-N^1-phenylpropyl-aminoguanidine

0.1 mol N^1-phenylpropylaminoguanidine hydrochloride is dissolved in 40 ml water. The solution is adjusted to pH 4 with HCl conc. and at 10-15° 0.1 mol $NaNO_2$ are slowly added. After 1 h of stirring 50% NaOH until pH 8 is added. While a colourless compound precipitates the mixture is stirred for one more h at 0° and kept for 24 h in a refrigerator. The precipitate is sucked off and recrystallized from water: Crystals, mp. 66° (dec.), yield 50%.- $C_{10}H_{15}N_5O$ (221.3) Calcd. C 54.3 H 6.78 N 31.7 Found C 54.3 H 6.87 N 31.6.- IR: 3416; 3328; 3219; 3019; 2931; 2854; 1628; 1583; 1480; 1457; 1260; 1232; 1153; 1079; 1028; 968; 884; 822; 745; 700 cm^{-1}.- ^{1}H-NMR: δ (ppm) = 7.29 (dd, J = 7.4/7.4 Hz, 2H aromat., 3-H and 5-H), 7.22-7.16 (m, 3H aromat., 2-H, 4-H, 6-H), 5.72 (s, 2H, NH_2, *Z*-rotamere, 4%, D_2O exchange), 5.53 (s, 2H, NH_2, *Z*-rotamere, 4%, D_2O exchange), 5.44 (s, 2H, NH_2, *E*-rotamere, 96%, D_2O exchange), 5.16 (s, 2H, NH_2, *E*-rotamere, 96%, D_2O exchange), 3.99 (t, J = 6.95 Hz, 2H, N-CH_2, *E*-rotamere, 96%), 3.66 (t, J = 7 Hz, 2H, N-CH_2, *Z*-rotamere, 4%), 2.62 (t, J = 7.7 Hz, 2H, Ph-CH_2-, *E*-rotamere, 96%), 2.4 (overlap with solvent signal, *Z*-rotamere), 2.02-1.92 (m, 2H, $CH_2C\underline{H}_2CH_2$, *E*-rotamere, 96%), 1.8-1.7 (m, 2H, $CH_2C\underline{H}_2CH_2$, *Z*-rotamere, 4%).- MS (160°): m/z = 191 ([M - NO•]$^+$, 17%), 91 (73), 87 (18), 70 (104), 65 (14), 59 (116), 43 (100), 30 (10), 18 (27).

5-Amino-3-phenylpropyl-1,2,3,4-oxatriazolium chloride (inner salt) (**4**)

0.1 mol N^1-nitroso-N^1-phenylpropyl-aminoguanidine is dissolved in 50 ml of conc. HCl and the solution kept icecold for 24 h. The surplus of HCl is removed in vacuo. To the residue a satd. solution of $NaHCO_3$ is added, the mixture is extracted with ethereal HCl and the solid obtained after evaporation is recrystallized from ether/ethanol: crystals, mp. 131° (dec.), yield 45%.- $C_{10}H_{12}N_4O \cdot HCl$ (240.7) Calcd. C 49.9 H 5.42 N 23.3 Found C 50.3 H 5.48 N 23.2.- IR: 3373; 2990; 2640; 1728; 1690; 1629; 1578; 1493; 1452; 1444; 1431; 1314; 1271; 1205; 1166; 1096; 1039; 986; 967; 797; 743; 699 cm^{-1}.- ^{1}H-NMR: δ (ppm) = 10.99 (bs, 2H, $=NH_2^+$, D_2O exchange), 7.32 (dd, J = 7.4/7.4 Hz, 2H aromat., 3-H and 5-H), 7.26-7.2 (m, 3H aromat., 2-H, 4-H, 6-H), 4.9 (t, J = 6.8 Hz, 2H, N-CH_2), 2.78 (t, J = 7.25 Hz, 2H, Ph-CH_2), 2.34-2.24 (m, 2H, $CH_2C\underline{H}_2CH_2$).- MS (CI, 100°, isobutane): m/z = 205 ([M + H]$^+$, 100%), 161 (19), 155 (10), 119 (59), 91 (84), 87 (21).

1-Nitroso-1-phenylmethyl-hydrazine (**5**)

Beige crystals, mp. 65° (dec.) (ref.[10]: 71°), yield 70%.- $C_7H_9N_3O$ (150.2) Calcd. C 55.6 H 6.00 N 27.9 Found C 56.1 H 6.02 N 27.8.- IR: 3293; 3187; 3095; 1569; 1492; 1450; 1432; 1349; 1295; 1176; 1134; 1075; 1028; 1002; 949; 935; 804; 702 cm^{-1}.- ^{1}H-NMR: δ (ppm) = 7.52-7.30 (m, 5H aromat.), 7.0 (s, 2H, NH_2, D_2O exchange), 5.26 (s, 2H, CH_2).- MS (NI-FAB/DMSO-glycerol): m/z = 150 ([M - H]$^-$, 100%), 135 (58).

2'-Nitroso-2'-phenyl-benzenecarboxylic acid hydrazide (**6**)

Light yellow crystals, mp. 103° (dec.) (ref.[11,12]: 110/106°), yield 65%.- $C_{13}H_{11}N_3O_2$ (241.3) Calcd. C 64.7 H 4.60 N 17.4 Found C 64.3 H 4.29 N 17.2.- IR: 3226; 1669; 1642; 1598; 1506; 1481; 1449; 1382; 1326; 1307; 1274; 1147; 1090; 1031; 1008; 934; 863; 752; 712 cm^{-1}.- ^{1}H-NMR: δ (ppm) = 11.47 (s, 1H, CO-NH, D_2O exchange), 7.97 (d, J = 7.6 Hz, 2H, benzoyl-2-H and 6-H), 7.74-7.53 (m, 7H, Ph 2-H, 3-H, 5-H, 6-H, benzoyl-3-H, 4-H, 5-H), 7.42 (t, J = 7.1 Hz, 1H, Ph 4-H).- MS (NI-FAB/DMSO-glycerol): m/z = 241 ([M - H]$^-$, 25%), 211 (100), 120 (7).

2-(N^2-Nitroso-N^2-phenyl-hydrazo)-ethanedioic acid-ethylester (**7**)[13]

Crystals, mp. 80-81° (dec.) ref.[13]: 81°.- $C_{10}H_{11}N_3O_4$ (237.2) Calcd. C 50.6 H 4.67 N 17.7 Found C 50.3 H 4.61 N 17.3.- IR: 3264; 2978; 1734; 1717; 1593; 1481; 1451; 1367; 1295; 1186; 1118; 1034; 1014; 993; 911; 853; 791; 758; 690 cm^{-1}.- ^{1}H-NMR: δ (ppm) = 11.93 (s, 1H, CO-NH, D_2O exchange), 7.68 (d, J = 8.1 Hz, 2H aromat., 2-H, 6-H), 7.54 (dd, J = 7.8/7.8 Hz, 2H, aromat. 3-H, 5-H), 7.42 (t, J = 7.3 Hz, 1H aromat., 4-H), 4.34 (q, J = 7.1 Hz, 2H, CO-CH_2), 1.32 (t, J = 7.1 Hz, 3H, CH_2-$C\underline{H}_3$).- MS (NI-FAB/DMSO-glycerol): m/z = 236 ([M - H]$^-$, 32%), 207 (100), 206 (99), 133 (23), 116 (8).

2-(N^2-Nitroso-N^2-phenyl-hydrazo)-ethanedioic acid-ethylamide (**8**)[13]

Crystals, mp. 116° (dec.) (ref.[13]: 107/8°), yield 70%.- $C_{10}H_{12}N_4O_3$ (236.2) Calcd. C 50.8 H 5.12 N 23.7 Found C 50.6 H 5.17 N 23.2.- IR: 3286; 3221; 2979; 2930; 1705; 1674; 1666; 1593; 1543; 1500; 1485; 1453; 1381; 1359; 1307; 1287; 1216; 1177; 1149; 1124; 1091; 1071; 1041; 1028; 991; 951; 913; 894; 815; 757; 689 cm^{-1}.- ^{1}H-NMR: δ (ppm) = 11.76 (s, br., 1H, CO-NH, D_2O exchange), 9.07 (m, 1H, N$\underline{H}$-CH_2, exchange with CF_3COOD), 7.63 (d, J = 8 Hz, 2H aromat., 2-H, 6-H), 7.54 (dd, J = 7.4/7.8 Hz, 2H aromat., 3-H, 5-H), 7.41 (t, J = 7.3 Hz, 1H aromat., Ph-4-H), 3.26-3.17 (m, 2H, NH-$C\underline{H}_2$), 1.09 (t, J = 7.1 Hz, 3H, $NHCH_2C\underline{H}_3$).- MS (NI-FAB/DMSO-glycerol): m/z = 235 ([M - H]$^-$, 18%), 206 (100), 205 (80), 133 (10), 116 (9), 71 (7).

1-Nitroso-1-phenyl-semicarbazide (**9**)[14]

Crystals, mp. 120° (dec.) (ref.[14]: 126-127°), yield 70%.- $C_7H_8N_4O_2$ (180.2) Calcd. C 46.7 H 4.48 N 31.1 Found C 46.8 H 4.50 N 31.2.- IR: 3388; 3244; 1723; 1702; 1608; 1521; 1503; 1450; 1352; 1308; 1194; 1150; 1092; 1071; 1019; 1000; 950; 861; 786; 740; 685; 643 cm^{-1}.- ^{1}H-NMR/250 MHz: δ (ppm) = 9.04 (s, 1H, CO-NH, D_2O exchange), 7.68-7.64 (m, 2H aromat., 2-H, 6-H), 7.55-7.48 (m, 2H aromat., 3-H, 5-H), 7.40-7.34 (m, 1H aromat., 4-H), 6.47 (s, 2H, CO-NH_2, D_2O exchange).- MS (NI-FAB/DMSO-glycerol): m/z = 179 ([M - H]$^-$, 12%), 149 (100).

1-Nitroso-1,4,4-triphenyl-semicarbazide (**10**)[15]

Crystals, mp. 126° (dec.), yield 90%.- $C_{19}H_{16}N_4O_2$ (332.4) Calcd. C 68.7 H 4.87 N 16.9 Found C 68.4 H 4.66 N 16.7.- IR: 3309; 3051; 1952; 1679; 1587; 1487; 1468; 1461; 1448; 1328; 1298; 1283; 1201; 1173; 1155; 1145; 1072; 1041; 1020; 1003; 951; 913; 899; 818; 766; 760; 737; 703; 695 cm^{-1}.- ^{1}H-NMR: δ (ppm) = 9.17 (s, 1H, CO-NH, D_2O exchange), 7.67 (d, J = 7.9 Hz, 2H, Ph(1)-2-H, 6-H), 7.54-7.22 (m, 13 H, Ph(4,4')-3-H, 5-H, Ph(4,4')-2-H, 4-H, 6-H, Ph(1)-3-H, 4-H, 5-H).- MS (NI-FAB/DMSO-glycerol): m/z = 331 ([M - H]$^-$, 14%), 301 (66%), 168 (100), 133 (32).

N^2-Nitroso-N^2-phenyl-hydrazo-sulfonic acid potassium salt (**11**)[11]

Crystals, mp. 203-210° (dec.), yield 40%.- $C_6H_6KN_3O_4S$ (255.3) Calcd. C 28.2 H 2.37 N 16.4 Found C 28.2 H 2.26 N 16.3.- IR: 3168; 3050; 2912;

2285; 1593; 1494; 1470; 1451; 1311; 1273; 1253; 1241; 1232; 1219; 1148; 1114; 1101; 1061; 1017; 998; 890; 859; 759; 750; 702; 680; 657 cm^{-1}.- ^{1}H-NMR: δ (ppm) = 8.8 (s, 1H, SO_3NH, D_2O exchange), 7.78 (d, J = 7.9 Hz, 2H aromat., 2-H, 6-H), 7.46 (dd, J = 7.6/8.1 Hz, 2H aromat., 3-H, 5-H), 7.33 (t, J = 7.4 Hz, 1H aromat., 4-H).- MS (NI-FAB/DMSO-glycerol): m/z = 216 ([M - K]$^-$, 100%), 186 (76), 80 (41).

Methane-bis-2-nitroso-2-phenylmethyl-hydrazine (**12**)[16]

Crystals, mp. 105° (dec.) (ref.[17]: 103°), yield 10%.- $C_{15}H_{18}N_6O_2$ (314.3) Calcd. C 57.3 H 5.77 N 26.7 Found C 57.4 H 5.75 N 26.5.- IR: 3241; 3054; 3022; 1492; 1447; 1435; 1377; 1344; 1323; 1200; 1141; 1092; 1073; 1039; 996; 940; 780; 760; 742; 701 cm^{-1}.- ^{1}H-NMR/250 MHz: δ (ppm) = 8.17 (t, 1H, D_2O exchange, NH, *Z*-part of *EZ*-conformer, 10%), 7.97 (t, J = 6.3 Hz, 2H, NH, D_2O exchange, *Z/Z*-conformer, 90%), 7.58 (t, 1H, NH, D_2O exchange, *E*-part of *E/Z*-conformer, 10%), 7.4-7.22 (m, 10 H aromat., *Z/Z*- + *E/Z*-conformer), 7.11 (d, J = 6.3 Hz, 2H aromat., 2-H, 6-H, *E/Z*-conformer, 10%), 5.39 (s, 2H, Ph-CH_2, *E/Z*-conformer, 10%), 5.33 (s, 4H, Ph-CH_2, *Z/Z*-conformer, 90%), 4.81 (s, 2H, Ph-CH_2, *E/Z*-conformer, 10%), 4.25 (dd, J = 5 Hz, 2H, NH-C$\underline{H_2}$-NH, *E/Z*-conformer, 10%), 4.14 (dd, J = 6.2/5.2 Hz, 2H, NH-C$\underline{H_2}$-NH, *Z/Z*-conformer, 90%, after D_2O exchange signals at 4.25 and 4.14 become s).- MS [NI-FAB/DMSO-glycerol]: m/z = 313 ([M - H]$^-$, 6%), 150 (100), 135 (74).

2',2'-Dinitroso-2',2'-diphenyl-ethanedioic acid dihydrazide (**13**)

The solution of 2',2'-Diphenyl-ethanedioic acid dihydrazide[17] (3.7 mmol) in 10 ml of glacial acetic acid is cooled with ice and a conc. solution of $NaNO_2$ (10 mmol) in water dropped in. Water is added until no more precipitate is formed. The crystals are sucked off and washed with much water. Yellow crystals, mp. 125° (dec.), yield 75%.- $C_{14}H_{12}N_6O_4$ (328.3) Calcd. C 50.9 H 4.27 N 25.4 Found C 51.6 H 3.71 N 25.0.- IR: 3234; 3052; 2974; 1685; 1591; 1484; 1453; 1325; 1315; 1290; 1185; 1159; 1109; 1093; 1068; 1031; 1008; 992; 898; 812; 758; 691; 662 cm^{-1}.- ^{1}H-NMR: δ (ppm) = 12.1 (s, 2H, CO-NH, D_2O exchange), 7.73 (d, J = 8.1 Hz, 4H aromat., 2-H, 6-H), 7.57 (dd, J = 7.5/8 Hz, 4H aromat., 3-H, 5-H), 7.44 (t, J = 7.3 Hz, 2H, Ph-4-H).- MS (NI-FAB/DMSO-glycerol): m/z = 327 ([M - H]$^-$, 21%), 297 (44), 267 (100), 175 (30), 133 (81).

2',2'-Dinitroso-2',2'-diphenyl-1,3-propanedioic acid dihydrazide (**14**)

From 2',2'-diphenyl-1,3-propanedioic acid dihydrazide (3.7 mmol) and $NaNO_2$ (5 mmol) as described for **13**.- Yellow crystals, mp. 102°, yield 70%.- $C_{15}H_{14}N_6O_4$ (342.3) Calcd. C 52.6 H 4.12 N 24.6 Found C 52.2 H 4.68 N 23.9.- IR: 3229; 2979; 1722; 1688; 1593; 1485; 1451; 1411; 1366; 1330; 1290; 1197; 1177; 1161; 1124; 1032; 986; 942; 895; 835; 750; 710; 686 cm^{-1}.- ^{1}H-NMR: δ (ppm) = 11.28 (s, 2H, CO-NH, D_2O exchange), 7.68 (d, J = 8 Hz, 4H aromat., 2-H, 6-H), 7.53 (dd, J = 7.5/8.1 Hz, 4H aromat., 3-H, 5-H), 7.39 (t, J = 7.3 Hz, 2H, Ph-4-H), 3.65 (s, 2H, CH_2).- MS (NI-FAB-/DMSO-glycerol): m/z = 341 ([M - H]$^-$, 14%), 311 (54), 281 (85), 204 (33), 191 (13), 175 (100), 148 (16), 133 (81), 77 (21).

2',2'-Dinitroso-2',2'-diphenyl-1,5-pentanedioic acid dihydrazide (**15**)

From 2',2'-diphenyl-1,5-pentanedioic acid dihydrazide[18] (3.7 mmol) and $NaNO_2$ (7.5 mmol) as described for **13**.- Yellow crystals, mp. 96° (dec.), yield 75%.- $C_{17}H_{18}N_6O_4$ (370.3) Calcd. C 55.1 H 4.90 N 22.7 Found C 54.9 H 4.79 N 21.7.- IR: 3222; 3174; 3051; 2975; 1701; 1689; 1593; 1480; 1452; 1382; 1332; 1309; 1292; 1270; 1207; 1177; 1157; 1141; 1127; 1045; 1033; 1006; 995; 982; 911; 895; 743; 682 cm^{-1}.- ^{1}H-NMR/250 MHz: δ (ppm) = 10.9 (s, 2H, CO-NH, D_2O exchange), 7.65 (d, J = 8.1 Hz, 4H aromat., 2-H, 6-H), 7.53 (dd, J = 7.4/8.1 Hz, 4H, Ph-3-H, 5-H), 7.39 (t, J = 7.2 Hz, 2H aromat., 4-H), 2.51-2.45 (t, J = 7.2 Hz, 4H, CO-CH_2), 1.9 (t, J = 7.2 Hz, 2H, $CH_2C\underline{H_2}CH_2$).- MS (NI-FAB/DMSO-glycerol): m/z = 369 ([M - H]$^-$, 17%), 339 (53), 309 (100), 220 (18), 203 (60), 175 (11), 161 (17), 148 (11), 133 (9).

2',2'-Dinitroso-2',2'-diphenyl-1,6-hexanedioic acid dihydrazide (**16**)

From 2',2'-diphenyl-1,6-hexanedioic acid dihydrazide[18] (3.7 mmol) and $NaNO_2$ (7.5 mmol) (ref. **13**).- Yellow crystals, mp. 116° (dec.), yield 75%.- $C_{18}H_{20}N_6O_4$ (384.4) Calcd. C 56.2 H 5.24 N 21.9 Found C 56.3 H 5.24 N 21.8.- IR: 3235; 3054; 2945; 1688; 1595; 1481; 1451; 1371; 1308; 1290; 1254; 1180; 1133; 1116; 1033; 989; 969; 916; 884; 746; 686 cm^{-1}.- ^{1}H-NMR/250 MHz: δ (ppm) = 10.89 (s, 2H, CO-NH, D_2O exchange), 7.64 (d, J = 8.1 Hz, 4H aromat., 2-H, 6-H), 7.53 (dd, J = 7.4/8.1 Hz, 4H aromat., 3-H, 5-H), 7.4 (t, J = 7.2 Hz, 2H, Ph-4-H), 2.42 (m, 4H, CO-CH_2), 1.67 (m, 4H, $CH_2C\underline{H_2}C\underline{H_2}CH_2$).- MS (NI-FAB/DMSO-glycerol): m/z = 383 ([M - H]$^-$, 11%), 353 (25), 324 (100), 234 (13), 217 (13), 133 (14), 77 (6).

2',2'-Dinitroso-2',2'-diphenyl-1,2-benzene-dicarboxylic acid (**17**)

2',2'-Diphenyl-1,2-benzene-dicarboxylic acid[19] (3.7 mmol) is suspended in ethanol, acidified with conc. HCl, cooled with ice, and 7.5 mmol $NaNO_2$ (aqueous sol.) are dropped in.- Light yellow crystals (ethanol/water), mp. 128°, yield 85%.- $C_{20}H_{16}N_6O_4$ (404.4) Calcd. C 59.4 H 3.99 N 20.8 Found C 59.6 H 3.75 N 20.1.- IR: 3208; 1764; 1737; 1679; 1592; 1497; 1483; 1466; 1448; 1348; 1281; 1180; 1155; 1118; 1086; 1049; 1028; 986; 922; 875; 779; 753; 704; 687 cm^{-1}.- ^{1}H-NMR: δ (ppm) = 11.51 (s, 2H, CO-NH, D_2O exchange), 7.905 (d, J = 3.2 Hz, 2H, phthal-3-H, 6-H), 7.81 (m, 2H, phthal-4-H, 5-H), 7.705 (d, J = 7.9 Hz, 4H aromat., 2-H, 6-H), 7.44-7.33 (m, 6H aromat., 3-H, 4-H, 5-H).- MS (NI-FAB/DMSO-glycerol): m/z = 403 ([M - H]$^-$, 15%), 373 (44), 345 (19), 315 (15), 254 (8), 238 (85), 146 (100).

N^2-(4-Bromophenyl)-N^2-nitroso-4-chlorobenzaldehyde hydrazone (**18**)

0.32 mmol N^2-(4-bromophenyl)-4-chlorobenzaldehyde hydrazone[20] are dissolved in little glacial acetic acid, cooled with ice and 1.3 g $NaNO_2$, small crystals are added. Crystals are sucked off and washed with water. Orange red crystals, mp. 71-72° (dec.), yield 50%.- $C_{13}H_8BrClN_3O$ (337.6) Calcd. C 46.1 H 2.68 N 12.4 Found C 46.1 H 2.64 N 11.9.- IR: 3084; 1697; 1590; 1555; 1483; 1398; 1364; 1253; 1219; 1166; 1087; 1067; 1010; 975; 885; 823; 769; 750 cm^{-1}.- ^{1}H-NMR/250 MHz: δ (ppm) = 8.46 (s, CH=N), 7.98-7.41 (m, mixture of C-NO and N-NO compounds).- MS (100°): m/z = 308 ([M - NO]$^+$, 20%), 170 (21), 111 (39), 90 (16), 75 (35), 63 (13), 50 (15), 28 (12).- NI-FAB/DMSO-glycerol m/z = 337 ([M - H]$^-$, 75%), 307 (45), 170 (14), 155 (9), 127 (7), 79 (54), 338 (100).

N^2-Nitroso-1,1,N^2-triphenyl-methanon hydrazone (**19**)[21]

2 g (7.3 mmol) 1,1,N^2-Triphenylmethanon hydrazone[22] are dissolved in 25 ml glacial acetic acid. While adding 1 g $NaNO_2$ as a conc. aqueous solution the mixture is cooled to keep the temp. at 15°C. Yellow crystals precipitate. Precipitation is completed by addition of water. The crystals are sucked off and washed with much water. Bright yellow crystals, mp. 100-105° (dec.) (ref.[22]: 100-105°), yield 70%.- $C_{19}H_{15}N_3O$ (301.4) Calcd. C 75.7 H 5.02 N 13.9 Found C 75.9 H 4.91 N 13.4.- IR: 3317; 3233; 3050; 1688; 1597; 1550; 1486; 1463; 1426; 1325; 1306; 1287; 1249; 1174; 1107; 1091; 1054; 1030; 998; 967; 904; 851; 812; 784; 767; 755; 731; 699; 690 cm^{-1}.- ^{1}H-NMR/250 MHz: δ (ppm) = 7.76-7.09 (m, 13 H aromat.), 7.10 (d, J = 7 Hz, 2H aromat.).- MS (NI-FAB/DMSO-glycerol): m/z = 271 ([M - NO]$^-$, 100%), 255 (17), 237 (13), 179 (13), 165 (14), 151 (15).

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