**New NO-Donors with Antithrombotic and Vasodilating Activities, I:**

# 3-Arylalkyl-*N*-nitroso-5-sydnone Imines

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Nine nitrosimino title compounds were prepared. They inhibit the aggregation of human platelets induced by collagen with an $IC_{50}$ = 0.7 - 33 µmol/L. The most active substance is the 3-phenylethyl derivative **6b**. The *in vitro* effect is mediated by an active metabolite which is formed by a photochemical reaction in the aggregometer. As the corresponding and so far unknown sydnone-5-cyanimines have no effect on platelets the metabolite is most certainly a NO-species. The activity of the sydnone-5-nitrimine **5b** is in the same order of magnitude ($IC_{50}$ = 7.5 µmol/L) as in the nitrosimines of type **6**. The most active compound **6b** was investigated for antithrombotic properties in a thrombosis model, where the thrombus formation was induced by a laserbeam. 2 h after oral administration of 60 mg/kg of **6b** to rats in venoles a 28% inhibition of thrombin formation was found. In arterioles this effect is more evident and a 48% inhibition is seen (the thrombus formation index is 2.6 and 3.9, respectively). These results suggest that the active metabolite is formed as well *in vivo*.

**Neue NO-Pharmaka mit antithrombotischen und gefäßerweiternden Eigenschaften, 1. Mitt.: 3-Arylalkyl-*N*-nitroso-5-sydnonimine**

Neun Nitrosoiminoverbindungen wurden dargestellt. Sie vermögen die durch Collagen ausgelöste Aggregation von Humanthrombocyten (*Born*-Test) in Konzentrationen zwischen 0.7 und 33 µmol/L halbmaximal zu hemmen. Die aktivste Verbindung ist das Phenylethylderivat **6b**. Die Aktivität ist *in vitro* auf die photolytische Bildung eines aktiven Metaboliten zurückzuführen. Hierbei handelt es sich um eine NO-Verbindung, da zu Vergleichszwecken dargestellte Cyanimine wirkungslos sind. Hingegen liegt die Aktivität des Nitrimins **5b** mit $IC_{50}$ = 7.5 µmol/L in der Größenordnung der Nitrosoiminoverbindungen **6**. Verbindung **6b** wurde in einem Thrombosemodell nach oraler Gabe an Ratten geprüft. In Venolen wurde ein 28 proz., in Arteriolen eine 48 proz. Hemmung der durch Laserstrahl ausgelösten Thrombusbildung gefunden (TBI 2.6 bzw. 3.9). Dies wird darauf zurückgeführt, daß auch *in vivo* ein aktiver Metabolit gebildet wird.

The most outstanding feature of nitrosimines is their instability. Especially in polar solvents *i.e.* DMSO they decompose to the corresponding carbonyl compounds evolving $N_2$. This seems to be the reason why this chemical class - in contrast to nitrosamines - has received very little attention.

*Akiba*[1] in 1977 was able to summarize this field thoroughly on 30 pages. Since then not much has changed. *Döpp*[2] recently could even cover this topic on 27 sheets. So it is not astonishing that no pharmacological data had been reported when *Kämpfe*[3] synthesized several sydnone nitrosimines in 1985. They were designed as intermediates for dihydrazine derivatives. Those can be prepared *via* sydnones of type **7** (Fig. 1)[4].

We recognized the unusual stability of sydnone nitrosimines. It was sufficient for assaying them in the *Born*-test which is performed routinely in our laboratory. We were very much surprised to find an inhibition of the aggregation of human platelets in concentrations of some µmol/L. We then started an extended program*) to study this effect more exactly. After some preliminary presentations[5-7] we now report our results in detail in a series of communications.

For the synthesis of the 3-arylalkyl-sydnone imines (3) we used the method of *Daeniker* and *Druey*[8]. Compounds **3** were nitrosated with $NaNO_2$ in aqueous solution[9,10]. The cyanoimines **4** and the nitrimine **5** were synthesized to investigate whether the nitroso group could be replaced by other groups with electron withdrawing properties. As no cyanosydnone imines have been described so far we had to develop a suitable method for their synthesis: finally we were successful in reacting **3** with BrCN at pH 9. For the nitrimine 5 the method of *Brookes* and *Walker*[11] was modified.

Structures **3** - **7** are supported by several typical spectral data (Table 1).

**Tab. 1:** Characteristic spectral data of sydnone imine derivatives

| Type | NMR 4-H [ppm] | IR [cm$^{-1}$] other typical bands | IR [cm$^{-1}$] C=X double bond | UV $\lambda_{max}$ [nm] | UV log ε |
|---|---|---|---|---|---|
| **3** | 8.2-8.1 | | 1670-1700 | 295-293 | 3.9 |
| **4** | 8.0 | 2180 | 1620-1650 | 330 | 4.0 |
| **5** | 8.85 | 1274/1460/1420 | 1584 | 335 | 4.29 |
| **6** | 8.9-8.8 | 1380/1420 | 1560-1570 | 335/485 | 4.3/1.9 |
| **7** | 7.0 | | 1720 | 277 | 4.5 |

In the $^1$H-NMR spectra each class of compounds can be assigned by the chemical shift of 4-H. In the IR-spectrum the valence vibration for the C=X double bond is significant for each structure type. Furthermore in the nitrosimine series **6** the N-NO bond gives rise to two strong absorptions at 1380 and 1420 cm$^{-1}$. For the cyanimines **4** $\nu_{C\equiv N}$ is found at 2180 cm$^{-1}$. The electronic spectra of the nitrosimines are characterized by two absorption bands at 335 and 485 nm. The latter is responsible for the attractive bright yellow til orange colour of these compounds.

The antiplatelet activities of **3** - **6** are summarized in Table 2. The imines **3** show no activity. This is in contrast to the well known activity of the molsidomine metabolite SIN 1 (3-(4-morpholinyl)-5-sydnone imine) whose $IC_{50}$ in our test system was 1 µmol/L. As it is known that this activity stems from the release of NO-species[12] from the

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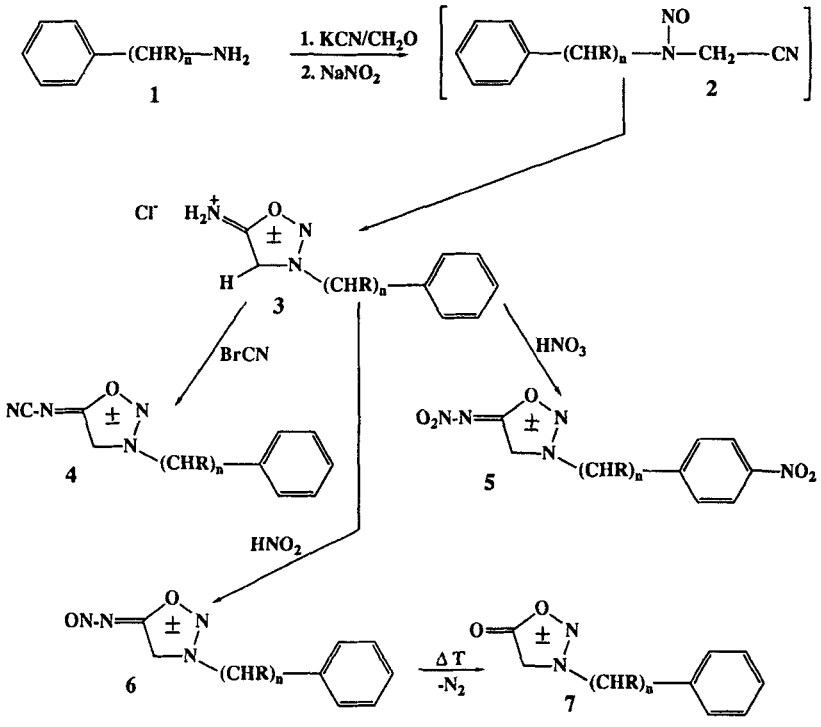
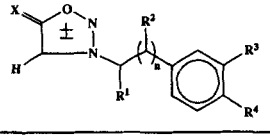


Fig. 1: Synthesis of nitroso-, nitro- and cyano derivatives of sydnone-5-imines

sydnone moiety by hydrolysis, the lack of activity of the compounds **3** reflects their hydrolytic stability under the conditions of the *Born*-test. Strong antiplatelet activities were found in the nitrosimine series **6**. The $IC_{50}$ ranges from 0.7 - 33 µmol.

Tab. 2: Inhibition of platelet aggregation by sydnone-5-imine derivatives (Born-test with collagen, an asterix means that 1.5% DMSO was present in the test tube) $R^1$ - $R^4$ and n are valid for cpds. 3 - 7.



| Compound number | X | $R^1$ | $R^2$ | $R^3$ | $R^4$ | n | $IC_{50}$ [µmol/L] |
|---|---|---|---|---|---|---|---|
| **3a** | $NH_2^+Cl^-$ | H | - | H | H | 0 | 180 |
| **6a** | NNO | H | - | H | H | 0 | 12 |
| **3b** | $NH_2^+Cl^-$ | H | H | H | H | 1 | > 500 |
| **6b** | NNO | H | H | H | H | 1 | 0.7 |
| **6c** | NNO | H | H | H | Cl | 1 | 3 |
| **6d** | NNO | H | H | $OCH_3$ | $OCH_3$ | 1 | 1.5 |
| **6e** | NNO | H | Ph | H | H | 1 | 7.5 |
| **6f** | NNO | H | OH | H | H | 1 | 1.3 |
| **6g** | NNO | $CH_3$ | OH | H | H | 1 | 10 |
| **5b** | $NNO_2$ | H | H | H | $NO_2$ | 1 | 5.3 |
| **3h** | $NH^+{}_2Cl^-$ | H | H | H | H | 2 | > 500 |
| **4h** | NCN | H | H | H | H | 2 | > 87* |
| **6h** | NNO | H | H | H | H | 2 | 3 |
| **3i** | $NH^+{}_2Cl^-$ | H | H | H | H | 3 | 250 |
| **4i** | NCN | H | H | H | H | 3 | > 87* |
| **6i** | NNO | H | H | H | H | 3 | 33 |

*) We thank Dr. *M. Just*, Cassella AG, Frankfurt for this suggestion.

As the highest activity was seen for the 3-phenyl*ethyl* derivative **6b** we substituted the phenylring according to suggestions of *Topliss*[13]. Unfortunately a twofold (**6d**) or fivefold (**6c**) decrease in activity with either substitution was achieved. The modification of the ethyl chain (**6e-g**) as well was not favourable. The cyanimines **4h** and **4i** clearly show that the antiplatelet effect is connected with the exo-nitroso group. The $IC_{50}$ of 87 µmol/L only shows the antiplatelet effect of DMSO, which had to be added for solubility reasons. Only a nitro group is able to replace the nitroso group as it is shown by the nitrimine **5b**.

During our work we noticed stronger activities in some compounds which were reinvestigated after replacement of an old lamp of our Elvi-aggregometer. We followed that hint by assaying some nitrosimines in a PAP 3 aggregometer*), where the change of transmission in platelet rich plasma is recorded with a lamp of $\lambda$ = 698 nm. Here much lower activities than in the Elvi aggregometer were observed. When the whole assay finally was handled in a darkened room no activity remained. It, therefore, was clear that the activities found are due to a photolytically released metabolite, presumably a NO-species. As the electronic absorption spectra of **6a**, **6b**, **6i** and **6k** are identical, the differences in activity seem to reflect the different ability of the molecules to bind to or to penetrate the platelet membrane. In this view the activity of the nitrimine **5b** could be due to a photochemical rearrangement from $-NO_2$ to -O-NO as it is known for nitro groups[14].

In order to investigate whether the active metabolite can as well be formed *in vivo*, the most active nitrosimine **6b**

was assayed in our thrombosis model[15]. Here, 2 h after oral administration of 60 mg/kg **6b** to rats in venoles a 28 ± 4% ($p \leq 0.002$) inhibition of thrombosis was observed (thrombus formation index TFI = 2.6). In arterioles this effect was even more pronounced: a 48 ± 7% p (≤ 0.002) inhibition (TFI = 3.9) was found. It, therefore, has become evident that the 3-arylalkyl-N-nitroso-5-sydnone imines form a new class of useful antithrombotic NO-compounds.

We thank *G. Dreke*, *G. Grelbig*, *K. Leitzow*, *J. Lindemann*, *U. Ostwald*, and *A. Peuker* for spectra and CHN analyses.- The *in vitro* experiments were handled skilfully by *S. Leißring*, *K. Fischer* (†), *C. Schwarze*, and *B. Zeisig*. We are indebted to Dr. *T. Ciborski* for the animal experiments.

## Experimental part

*Aggregometry*

Elvi 840[16] or PAP 3 (Fa. BioDate). Procedure: Platelet rich plasma (PRP) and platelet poor plasma (PPP) are prepared as usual[16]. One test tube is filled with 0.5 ml PPP, the other with 0.45 ml PRP. A magnetic core is added to the PRP tube. Then the tubes are warmed to 37°C and inserted. The aggregometer is calibrated automatically and the 0% baseline recorded. Simultaneously appears at the screen: Add reagent to PRP. Now 0.05 ml collagen Horm® is added. The threshold concentration which just induces maximum aggregation is used. The procedure is stopped automatically after 6 min. The light shield is closed. While the aggregation proceeds the light transmission curve is recorded. The percentage of aggregation may be read from the screen at the same time.

*Physical data*

Mp.: Mettler FP-1 (uncorrected), rise in temp. 2°C/min.- Element analysis: Perkin-Elmer element analyzer 240 B and 240 C.- IR-spectra: Perkin-Elmer spectralphotometer 1420 with DS 7300.- $^1$H-NMR-spectra: Bruker ACE 300 or WM 250 in the solvent stated.- Mass spectra: Varian MAT 711 (80 eV) or CH 7 A (70 eV).- PI-FAB: Varian MAT CH 5 D[***] DMSO/glycerol matrix.

*Chemistry*

The method of *Daeniker*[8] was used for the preparation of the sydnone imines **3**.

*3-Benzyl-5-sydnone imine hydrochloride* (**3a**)

Crystals (isopropanol), mp. 123°C (Lit.[8]: 124-125°C). Yield 45%.- IR (KBr): 3211; 3111; 3045; 1667; 1493; 1467; 1454; 1402; 1193; 1149; 1070; 950; 912; 749; 716; 700; 615 cm$^{-1}$.- UV ($CH_3OH$): λ max (log ε) = 204 (4.22), 294 nm (3.88).- $^1$H-NMR/250 MHz ([$D_6$]DMSO): δ (ppm) = 10.01 (bs, 2 H, =$NH_2^+$, $D_2O$ exchange), 8.25 (s, 1 H, syd-H), 7.6-7.4 (m, 5 H aromat.), 5.98 (s, 2 H, N-$CH_2$).- MS (120°C): m/z = 175 (15%, $M^{+\cdot}$), 128 (17), 126 (49), 105 (52), 104 (41), 92 (67), 91 (100), 67 (34), 65 (92), 63 (49).

*3-(2-Phenylethyl)-5-sydnone imine hydrochloride* (**3b**)

Crystals (ethanol/ether), mp. 154°C (Lit.[8]: 155-158°C). Yield 53%.- $C_{10}H_{12}ClN_3O$ (225.7) Calcd. C 53.2 H 5.36 N 18.6 Found C 53.2 H 5.45 N 18.6.- IR (KBr): 3416; 3016; 2660; 1680; 1666; 1576; 1489; 1467; 1452; 1439; 1402; 1342; 1225; 1176; 1153; 1077; 1029; 992; 950; 938; 916; 777; 763; 747; 695; 625 cm$^{-1}$.- UV ($CH_3OH$): λ max (log ε) = 206 (4.26), 293 nm (3.90).- $^1$H-NMR/300 MHz ([$D_6$]DMSO): δ (ppm) = 9.83 (bs, 2 H, =$NH_2^+$, $D_2O$ exchange), 8.15 (s, 1 H, syd-H), 7.36-7.25 (m, 5 H aromat.), 4.93 (t, J = 7.3 Hz, 2 H, N-$CH_2$), 3.30 (t, 2 H, Ph-$CH_2$).- MS (70°C): m/z = 189 (4%, $M^{+\cdot}$), 132 (8), 105 (52), 104 (22), 91 (100), 77 (12), 65 (15), 36 (22).

*3-[2-(4-Chlorphenyl)-ethyl]-5-sydnone imine hydrochloride* (**3c**)

Crystals (ethanol), mp. 169°C. Yield 57%.- $C_{10}H_{11}Cl_2N_3O$ (260.1) Calcd. C 46.2 H 4.26 N 16.2 Found C 46.1 H 4.25 N 16.2.- IR (KBr): 3146; 3031; 2647; 1699; 1685; 1568; 1489; 1455; 1442; 1408; 1328; 1226; 1172; 1158; 1102; 1086; 1014; 1001; 938; 907; 851; 815; 779; 751; 732; 715; 654; 628 cm$^{-1}$.- UV ($CH_3OH$): λ max (log ε) = 205 (4.40), 293 nm (3.92).- $^1$H-NMR/300 MHz ([$D_6$]DMSO): δ (ppm) = 9.89 (s, 2 H, =$NH_2^+$, $D_2O$ exchange), 8.17 (s, 1 H, syd-H), 7.40 (d, J = 8.5 Hz, 2 H aromat., Ph-3-H and -5-H), 7.35 (d, J = 8.5 Hz, 2 H aromat., Ph-2-H and -6-H), 4.93 (t, J = 7.2 Hz, 2 H, N-$CH_2$), 3.31 (t, 2 H, Ph-$CH_2$).- MS (+FAB/DMSO/m-$NO_2$-benzyl alcohol): m/z = 226 (23%, [M+H]$^+$[$^{37}$Cl]), 224 (71, [M+H]$^+$[$^{35}$Cl]), 141 (30), 140 (10), 139 (100), 103 (31), 89 (9), 77 (13).

*3-[2-(3,4-Dimethoxyphenyl)-ethyl]-5-sydnone imine hydrochloride* (**3d**)

Light yellow powder (ethanol/isopropanol), mp. 162°C (dec.). Yield 32%.- $C_{12}H_{16}ClN_3O_3$ (285.7) Calcd. C 50.4 H 5.64 N 14.7 Found C 50.1 H 5.65 N 14.8.- IR (KBr): 3326; 3291; 3235; 3160; 3017; 2607; 1669; 1573; 1516; 1468; 1456; 1422; 1342; 1292; 1258; 1238; 1184; 1157; 1135; 1080; 1044; 1026; 1012; 948; 855; 827; 805; 783; 764; 755; 668; 633 cm$^{-1}$.- UV ($CH_3OH$): λ max (log ε) = 207 (4.25), 229 (3.92), 286 nm (3.89).- $^1$H-NMR/300 MHz ([$D_6$]DMSO): δ (ppm) = 9.84 (s, 2 H, =$NH_2^+$, $D_2O$ exchange), 8.13 (s, 1 H, syd-H), 6.96 (d, J = 1.6 Hz, 1 H aromat., Ph-2-H), 6.88 (d, J = 8.2 Hz, 1 H aromat., Ph-5-H), 6.76 (dd, J = 8.2/1.6 Hz, 1 H, Ph-6-H), 4.90 (t, J = 7.2 Hz, 2 H, N-$CH_2$), 3.74 (s, 3 H, $OCH_3$), 3.71 (s, 3 H, $OCH_3$), 3.22 (t, J = 7 Hz, 2 H, Ph-$CH_2$).- MS (+FAB/DMSO/glycerol): m/z = 250 (95%, [M+H]$^+$), 166 (50), 165 (100), 164 (25), 151 (61), 150 (27), 135 (22), 121 (19), 105 (19), 91 (30), 77 (16), 76 (27).

*3-(1,2-Diphenylethyl)-5-sydnone imine hydrochloride* (**3e**)

Crystals (isopropanol), mp. 91°C. Yield 31%.- $C_{16}H_{16}ClN_3O$ (301.9) Calcd. C 63.6 H 5.3 N 13.9 Found C 63.3 H 5.27 N 13.9.- IR (KBr): 3403; 3158; 3021; 2103; 1686; 1673; 1494; 1467; 1453; 1247; 1158; 1073; 955; 747; 697 cm$^{-1}$.- UV ($CH_3OH$): λ max (log ε) = 206 (4.40), 297 nm (3.90).- $^1$H-NMR/300 MHz ([$D_6$]DMSO): δ (ppm) = 9.98 (s, 2 H, =$NH_2^+$, $D_2O$ exchange), 8.38 (s, 1 H, syd-H), 7.74-7.18 (m, 10 H aromat.), 6.65 (dd, J = 8.8/7.6 Hz, 1 H, Ph-CH [X-part]), 3.85 ("dd", J = 14/8.8 Hz, 1 H, Ph-$CH_2$ [A-part]), 3.82 (dd, J = 14/7.6 Hz, 1 H, Ph-$CH_2$ [M-part]).- MS (+FAB/DMSO/glycerol): m/z = 266 (3%, [M+H]$^+$), 182 (17), 181 (100), 165 (5), 115 (4), 104 (4), 103 (5), 91 (10), 85 (9).

*[2-(5-Imino-sydnone-3-yl)-phenyl]-ethanol hydrochloride* (**3f**)

Needles (ethanol/aceton), mp. 176°C (decompn.). Yield 54%.- $C_{10}H_{12}ClN_3O_2$ (241.7) Calcd. C 49.7 H 5.00 N 17.4 Found C 49.8 H 5.03 N 17.5.- IR (KBr): 3259; 3173; 3020; 2650; 1680; 1665; 1565; 1491; 1470; 1451; 1417; 1349; 1330; 1300; 1282; 1256; 1218; 1179; 1170; 1157; 1091; 1063; 1026; 1003; 979; 942; 923; 895; 841; 744; 724; 702; 686; 619 cm$^{-1}$.- UV ($CH_3OH$): λ max/nm (log ε) = 205 (4.28), 295 (3.98).- $^1$H-NMR/300 MHz ([$D_6$]DMSO): δ (ppm) = 9.84 (bs, 2 H, =$NH_2^+$, $D_2O$ exchange), 8.18 (s, 1 H, syd-H), 7.51 (d, J = 7.1 Hz, 2 H, Ph-2-H and 6-H), 7.42-7.31 (m, 3 H aromat.), 6.35 (d, J = 4.7 Hz, 1 H, -OH, [X-part] $D_2O$ exchange), 5.22 (m, 1 H, -CH(OH) [M-part]), 4.92 (dd, J = 13/3 Hz, 1 H, N-$CH_2$ [A-part]), 4.70 (dd, J = 13/9.2 Hz, 1 H, N-$CH_2$ [B-part]).- MS (150°C): m/z = 215 (0.35%, $M^{+\cdot}$), 107 (99), 105 (10), 79 (100), 77 (51), 69 (40), 51 (12), 36 (22).

[***] We thank Dr. *G. Holzmann* for discussion of these mass spectra.

*(±)-erythro-[2-(5-Imino-sydnone-3-yl)-phenyl]-propanol hydrochloride* (**3g**)

From *rac*-norephedrine-HCl. Powder (ethanol/ether), mp. 172°C (Lit.[17]: 168°C). Yield 40%.- $C_{11}H_{14}ClN_3O_2$ (255.7) Calcd. C 51.7 H 5.52 N 16.4 Found C 51.4 H 5.59 N 16.5.- IR (KBr): 3359; 3159; 3058; 2629; 1703; 1583; 1496; 1468; 1448; 1410; 1379; 1325; 1266; 1242; 1197; 1174; 1118; 1104; 1063; 1034; 1000; 986; 935; 869; 747; 701; 662 $cm^{-1}$.- UV ($CH_3OH$): λ max (log ε) = 206 (4.09), 295 nm (3.87).- $^1$H-NMR/300 MHz ([$D_6$]DMSO): δ (ppm) = 9.82 (s, 2 H, $=NH_2^+$, $D_2O$ exchange), 8.27 (s, 1 H, syd-H), 7.46 (d, J = 7.2 Hz, 2 H aromat., Ph-2-H and 6-H), 7.40-7.28 (m, 3 H aromat., Ph-3-H, 4-H, 5-H), 6.36 (d, J = 4.7 Hz, 1 H, OH, $D_2O$ exchange), 5.28 (m, 1 H, N-CH($CH_3$)), 5.18 (dd, 1 H, Ph-CH(OH)), 1.40 (d, J = 6.8 Hz, 3 H, $CH_3$).- MS (+FAB/DMSO/glycerol): m/z = 220 (90%, $[M+H]^+$), 135 (18), 117 (9), 86 (100), 75 (14).- MS (140°C): m/z = 219 (4%, $M^{+\cdot}$), 107 (100), 105 (25), 83 (37), 79 (49), 77 (27).

*3-(3-Phenylpropyl)-5-sydnone imine hydrochloride* (**3h**)

Crystals (isopropanol), mp. 166°C (decompn.). Yield 60%.- $C_{11}H_{13}N_3O \cdot HCl$ (239.7) Calcd. C 55.1 H 5.89 N 17.5 Found C 55.0 H 6.02 N 17.5.- IR (KBr): 3162; 3068; 3017; 2920; 2654; 2612; 1702; 1601; 1573; 1493; 1482; 1462; 1451; 1414; 1355; 1296; 1215; 1161; 1088; 1039; 1007; 975; 932; 914; 783; 746; 729 $cm^{-1}$.- UV ($CH_3OH$): λ max (log ε) = 204 (4.20), 293 nm (3.91).- $^1$H-NMR/250 MHz ([$D_6$]DMSO): δ (ppm) = 9.76 (bs, 2 H, $=NH_2^+$, $D_2O$ exchange), 8.13 (s, 1 H, syd-H), 7.4-7.1 (m, 5 H aromat.), 4.65 (t, J = 7 Hz, N-$CH_2$), 2.69 (t, J = 7 Hz, 2 H, Ph-$CH_2$), 2.27 (tt, J = 7/7 Hz, 2 H, $CH_2$-$C\underline{H}_2$-$CH_2$).- MS (150°C): 203 (5%, $M^{+\cdot}$), 186 (19), 173 (28), 146 (91), 118 (18), 105 (100), 104 (63), 91 (100), 79 (33), 77 (50), 69 (60).

*3-(4-Phenylbutyl)-5-sydnone imine hydrochloride* (**3i**)

Crystals (isopropanol), mp. 165°C. Yield 55%.- $C_{12}H_{15}N_3O$ Calcd. C 56.8 H 6.36 N 16.6 Found C 56.6 H 6.34 N 16.5.- IR (KBr): 3160; 3030; 1680; 1670; 1580; 1485; 1450; 1185; 1090; 1005; 945; 750; 700 $cm^{-1}$.- UV ($CH_3OH$): λ max (log ε) = 204 (4.21), 293 nm (3.93).- $^1$H-NMR/250 MHz ([$D_6$]DMSO): δ (ppm) = 9.95 (bs, 2 H, $=NH_2^+$, $D_2O$ exchange), 8.16 (s, 1 H, syd-H), 7.4- 7.1 (m, 5 H aromat.), 4.70 (t, J = 7 Hz, 2 H, N-$CH_2$), 2.63 (t, J = 7 Hz, 2 H, Ph-$CH_2$), 1.96 (tt, J = 7 Hz, Ph-$CH_2$-$CH_2$-$C\underline{H}_2$-$CH_2$), 1.64 (tt, J = 7/7 Hz, 2 H, Ph-$CH_2$-$C\underline{H}_2$-$CH_2$).- MS (130°C): m/z = 217 (2%, $M^{+\cdot}$), 200 (26), 187 (18), 186 (16), 173 (10), 160 (14), 131 (43), 117 (13), 91 (100), 69 (38).

The method of *Kholodov* and *Yashunskii*[10] was used for the preparation of the nitrososydnone imines **6**.

*3-Benzyl-N-nitroso-5-sydnone imine* (**6a**)

Yellow crystals (DMF/ether), mp. 117.5°C (Lit.[9]: 117°C). Yield 75%.- IR (KBr): 3443; 3070; 3002; 1625; 1587; 1565; 1495; 1457; 1417; 1382; 1331; 1326; 1288; 1236; 1168; 1088; 1077; 1064; 1020; 1001; 968; 935; 877; 800; 719; 703; 686 $cm^{-1}$.- UV ($CH_3OH$): λ max (log ε) = 204 (4.08), 263 (3.54), 330 nm (4.15).- $^1$H-NMR/250 MHz ([$D_6$]DMSO): δ (ppm) = 8.83 (s, 1 H, syd-H), 7.7-7.4 (m, 5 H, aromat.), 5.97 (s, 2 H, Ph-$CH_2$).- MS (+FAB/DMSO/glycerol): m/z = 205 (7%, $[M+H]^+$), 105 (4), 91 (100).

*N-Nitroso-3-(2-phenylethyl)-5-sydnone imine* (**6b**)

Ochre crystals (methanol), mp. 123°C (Lit.[10]: 119°C). Yield 85%.- $C_{10}H_{10}N_4O_2$ (218.2) Calcd. C 55.0 H 4.62 N 25.7 Found C 55.1 H 4.57 N 25.6.- IR (KBr): 3424; 3128; 1563; 1488; 1454; 1414; 1387; 1350; 1300; 1277; 1234; 1161; 1109; 1023; 1007; 949; 875; 838; 775; 761; 729; 706; 644 $cm^{-1}$.- UV ($CH_3CN$): λ max (log ε) = 268 (3.55), 334 (4.27), 486 nm (1.89).- $^1$H-NMR/250 MHz ([$D_6$]DMSO): δ (ppm) = 8.84 (s, 1 H, syd-H), 7.31 (m, 5 H aromat.), 4.98 (t, J = 7.2 Hz, 2 H, N-$CH_2$), 3.38 (t, 2 H, Ph-$CH_2$).- MS (+FAB/DMSO/glycerol): m/z = 219 (7%, $[M+H]^+$), 189 (6), 158 (8), 105 (100), 91 (18), 77 (8).

*3-[2-(4-Chlorphenyl)-ethyl]-N-nitroso-5-sydnone imine* (**6c**)

Ochre crystals (methanol), mp. 115°C (Lit.[10]: 125°C). Yield 30%.- $C_{10}H_9ClN_4O_2$ (252.7) Calcd. C 47.5 H 3.59 N 22.2 Found C 47.6 H 3.42 N 22.3.- IR (KBr): 3422; 3048; 1910; 1566; 1491; 1439; 1414; 1381; 1342; 1237; 1090; 1068; 1014; 965; 954; 917; 876; 817; 781; 715; 676; 644; 625 $cm^{-1}$.- UV ($CH_3CN$): λ max (log ε) = 218 (3.95), 269 (3.53), 334 (4.28), 487 nm (1.89).- $^1$H-NMR/300 MHz ([$D_6$]DMSO): δ (ppm) = 8.84 (s, 1 H, syd-H), 7.41 (d, J = 8.4 Hz, 2 H aromat., Ph-3-H and -5-H), 7.35 (d, 2 H aromat., Ph-2-H and -6-H), 4.98 (t, J = 7.1 Hz, 2 H, N-$CH_2$), 3.38 (t, J = 7.1 Hz, 2 H, Ph-$CH_2$).- MS (+FAB/DMSO/glycerol): m/z = 255 (14%, $[M+H]^+[^{37}Cl]$), 254 (12, $[M]^{+\cdot}[^{37}Cl]$), 253 (40, $[M+H]^+[^{35}Cl]$), 252 (25, $[M]^{+\cdot}[^{35}Cl]$), 223 (15), 192 (23), 154 (26), 140 (10), 139 (100), 136 (25), 125 (17), 107 (12), 103 (23), 90 (10), 89 (17), 79 (44), 77 (21).

*3-[2-(3,4-Dimethoxyphenyl)-ethyl]-N-nitroso-5-sydnone imine* (**6d**)

Orange powder (methanol), mp. 127°C. Yield 51%.- $C_{12}H_{14}N_4O_4$ (278.3) Calcd. C 51.8 H 5.07 N 20.1 Found C 51.6 H 5.04 N 20.2.- IR (KBr): 3441; 3120; 3096; 3006; 2929; 2831; 1590; 1560; 1513; 1454; 1441; 1415; 1386; 1347; 1302; 1289; 1260; 1238; 1189; 1182; 1157; 1139; 1088; 1038; 1024; 1009; 946; 934; 911; 873; 855; 794; 780; 692; 652; 617 $cm^{-1}$.- UV ($CH_3CN$): λ max (log ε) = 202 (4.53), 230 (3.88), 334 (4.26), 484 nm (1.90).- $^1$H-NMR/300 MHz ([$D_6$]DMSO): δ (ppm) = 8.81 (s, 1 H, syd-H), 6.94 (d, J = 1.6 Hz, 1 H aromat., Ph-2-H), 6.88 (d, J = 8.2 Hz, 1 H aromat., Ph-5-H), 6.77 (dd, J = 8.1/1.9 Hz, 1 H aromat., Ph-6-H), 4.95 (t, J = 7.1 Hz, 2 H, N-$CH_2$), 3.72 (s, 3 H, $OCH_3$), 3.71 (s, 3 H, $OCH_3$), 3.29 (t, J = 7.1 Hz, 2 H, Ph-$CH_2$).- MS (+FAB/DMSO/glycerol): m/z = 279 (11%, $[M+H]^+$), 249 (5), 218 (7), 166 (14), 165 (100), 151 (32), 135 (6), 121 (6), 105 (6), 91 (9), 78 (16).

*3-(2,2-Diphenylethyl)-N-nitroso-5-sydnone imine* (**6e**)

As the corresponding sydnone imine **3e** was very hygroscopic it was nitrosated *in situ*.- **6e**: Light yellow powder (methanol), mp. 120°C. Yield 57%.- $C_{16}H_{14}N_4O_2$ (294.3) Calcd. C 65.3 H 4.79 N 19.0 Found C 65.0 H 4.58 N 18.9.- IR (KBr): 3422; 3126; 3053; 1558; 1492; 1450; 1412; 1380; 1347; 1328; 1310; 1237; 1125; 1016; 973; 947; 878; 786; 764; 743; 727; 698; 648; 613 $cm^{-1}$.- UV ($CH_3CN$): λ max (log ε) = 268 (3.60), 336 (4.26), 489 nm (1.91).- $^1$H-NMR/300 MHz ([$D_6$]DMSO): δ (ppm) = 8.90 (s, 1 H, syd-H), 7.48 (d, J = 7.7 Hz, 4 H aromat., Ph-2-H, Ph-6-H), 7.35 (dd, 4 H aromat., Ph-3-H, Ph-5-H), 7.25 (dd, 2 H aromat., Ph-4-H), 5.53 (d, J = 8.4 Hz, 2 H, N-$CH_2$), 4.98 (t, J = 8.4 Hz, 1 H, $(Ph)_2CH$).- MS (+FAB/DMSO/glycerol): m/z = 295 (10%, $[M+H]^+$), 265 (8), 214 (13), 182 (16), 181 (100), 167 (25), 165 (16), 103 (26), 91 (17), 78 (26), 76 (12).

*[2-[5-Nitrosoimino-sydnone-3-yl]-phenyl]-ethanol* (**6f**)

Yellow needles (sulfolan/methanol), mp. 157°C. Yield 64%.- $C_{10}H_{10}N_4O_3$ (234.2) Calcd. C 51.3 H 4.30 N 23.9 Found C 51.3 H 4.16 N 23.7.- IR (KBr): 3382; 3077; 3015; 2966; 1960; 1562; 1487; 1452; 1403; 1384; 1371; 1353; 1298; 1286; 1249; 1214; 1118; 1091; 1062; 1025; 1000; 968; 923; 899; 881; 835; 814; 757; 737; 709; 697; 651; 629; 614 $cm^{-1}$.- UV ($CH_3CN$): λ max/nm (log ε) = 268 (3.55), 336 (4.26), 486 (1.89).- $^1$H-NMR/300 MHz ([$D_6$]DMSO): δ (ppm) = 8.82 (s, 1 H, syd-H), 7.51 (d, J = 7.2 Hz, 2 H aromat., Ph-2-H and -6-H), 7.42 (dd, 2 H aromat., Ph-3-H and -6-H), 7.35 (dd, 1 H aromat., Ph-4-H), 6.25 (d, J = 4.7 Hz, 1 H, OH, $D_2O$ exchange), 5.29 (ddd, J = 9.3/4.7/3.1 Hz, after exchange dd, 1 H, Ph-CH(OH) [X-part]), 4.95 (dd, J = 13.1/3.1 Hz, 1 H, N-$CH_2$ [A-part]), 4.76

(dd, J = 13.1/9.3 Hz, 1 H, N-$CH_2$ [M-part]).- MS (+FAB/DMSO/glycerol): m/z = 235 (95%, $[M+H]^+$), 234 (45), 206 (44), 205 (67), 173 (22), 148 (97), 130 (15), 121 (100), 115 (17), 107 (54), 103 (92), 91 (57), 85 (27), 78 (51), 77 (20), 76 (56).

*rac-erythro-[2-[5-Nitrosoimino-sydnone-3-yl]-phenyl]-propanol* (**6g**)

Yellow plates (methanol), mp. 136°C. Yield: 45%.- $C_{11}H_{12}N_4O_3$ (248.2) Calcd. C 53.2 H 4.87 N 22.6 Found C 53.4 H 4.81 N 22.5.- IR (KBr): 3283; 3173; 3019; 2995; 2976; 2943; 2875; 1964; 1572; 1489; 1448; 1440; 1420; 1402; 1375; 1357; 1314; 1290; 1253; 1215; 1198; 1152; 1115; 1096; 1045; 1025; 994; 961; 925; 896; 880; 856; 837; 765; 755; 720; 703; 692; 641; 615 $cm^{-1}$.- UV ($CH_3CN$): λ max/nm (log ε) = 272 (3.93), 335 (4.25), 486 nm (1.93).- $^1$H-NMR/300 MHz ([$D_6$]DMSO): δ (ppm) = 8.93 (s, 1 H, syd-H), 7.46-7.29 (m, 5 H aromat.), 6.25 (d, J = 4.8 Hz, 1 H, OH, $D_2O$ exchange), 5.25 (m, 2 H, N-CH($CH_3$)-CH), 1.52 (d, J = 6.6 Hz, 3 H, $CH_3$).- MS (+FAB/DMSO/glycerol): m/z = 249 (36%, $[M+H]^+$), 219 (13), 171 (14), 157 (12), 135 (24), 117 (10), 115 (12), 93 (100%, [gly+H]$^+$), 91 (9), 79 (97), 77 (5), 75 (19).

*N-Nitroso-3-(3-phenylpropyl)-5-sydnone imine* (**6h**)

Orange crystals (aceton/ether), mp. 88°C. (decompn.). Yield 55%.- $C_{11}H_{12}N_4O_2$ (232.2) Calcd. C 56.9 H 5.21 N 24.1 Found C 57.1 H 5.17 N 24.4.- IR (KBr): 3421; 3053; 3006; 2952; 2928; 1562; 1495; 1453; 1417; 1382; 1345; 1295; 1274; 1236; 1174; 1080; 1063; 1019; 976; 946; 909; 876; 821; 776; 747; 698 $cm^{-1}$.- UV ($CH_3OH$): λ max (log ε) = 204 (4.10), 264 (3.56), 327 nm (4.27).- $^1$H-NMR/250 MHz ([$D_6$]DMSO): δ (ppm) = 8.85 (s, 1 H, syd-H), 7.4-7.2 (m, 5 H aromat.), 4.71 (t, J = 7 Hz, 2 H, N-$CH_2$-), 2.74 (t, J = 7 Hz, 2 H, Ph-$CH_2$-), 2.36 (tt, J = 7/7 Hz, 2 H, -$CH_2$-C<u>H</u>$_2$-$CH_2$-).- MS (+FAB/DMSO/glycerol): m/z = 233 (18%, $[M+H]^+$), 204 (10), 203 (11), 172 (10), 133 (12), 105 (10), 91 (100).- MS (80°C): m/z = 204 (1%, $[M-N_2]^{+\cdot}$), 117 (18), 105 (21), 91 (100), 77 (18), 68 (98).

*N-Nitroso-3-(4-phenylbutyl)-5-sydnone imine* (**6i**)

Yellow crystals (acetone/ether), mp. 94°C (dec.). Yield 70%.- $C_{12}H_{14}N_4O_4$ (246.3) Calcd. C 58.5 H 5.73 N 22.8 Found C 58.5 H 5.81 N 22.8.- IR (KBr): 3421; 3069; 2921; 1564; 1492; 1413; 1382; 1359; 1332; 1240; 1093; 1022; 984; 956; 806; 739; 700 $cm^{-1}$.- UV ($CH_3OH$): λ max (log ε) = 203 (4.09), 263 (3.41), 325 nm (4.06).- $^1$H-NMR/250 MHz ([$D_6$]DMSO): δ (ppm) = 8.82 (s, 1 H, syd-H), 7.4-7.1 (m, 5 H aromat.), 4.72 (t, J = 7 Hz, 2 H, N-$CH_2$), 1.69 (tt, J = 7 Hz, 2 H, Ph-$CH_2$-C<u>H</u>$_2$-$CH_2$).- MS (+FAB/DMSO/glycerol): m/z = 247 (8%, $[M+H]^+$), 218 (4), 217 (5), 187 (4), 133 (6), 118 (8), 91 (100).

*N-Nitro-3-[2-(4-nitrophenyl)-ethyl]-5-sydnone imine* (**5b**)

10 mmol **3b** are added to 30 ml ice-cold conc. $H_2SO_4$. Fuming nitric acid (excess!) is dropped in. After stirring for 20 min at room temp. about 50 g crushed ice is added. The precipitate is sucked off, dissolved in acetone, purified with charcoal and recrystallized. Light yellow crystals (acetone/ethanol), mp. 156°C (dec.). Yield 53%.- $C_{10}H_9N_5O_5$ (279.2) Calcd. C 43.0 H3.25 N 25.1 Found C 42.7 H 3.17 N 25.1.- IR (KBr): 3400; 3169; 3100; 3029; 2984; 2928; 2850; 1584; 1515; 1472; 1458; 1438; 1395; 1344; 1275; 1239; 1214; 1199; 1180; 1173; 1148; 1103; 1074; 1037; 1022; 1011; 971; 916; 857; 778; 769; 749; 702; 671; 645; 612 $cm^{-1}$.- UV ($CH_3CN$): λ max (log ε) = 194 (4.46), 270 (4.46), 335 nm (4.29).- $^1$H-NMR/300 MHz ([$D_6$]DMSO): δ (ppm) = 8.85 (s, 1 H, syd-H), 8.21 (d, J = 8.5 Hz, 2 H aromat., 3-H, 5-H), 7.62 (d, J = 8.5 Hz, 2 H aromat., 2-H, 6-H), 5.06 (t, J = 7.2 Hz, 2 H, N-$CH_2$), 3.52 (t, 2 H, Ph-$CH_2$).- MS (220°C): m/z = 279 (3%, $[M]^{+\cdot}$), 203 (29), 150 (23), 136 (57), 119 (13), 106 (15), 91 (18), 90 (22), 77 (30), 67 (60), 43 (61), 30 (100).- MS (+FAB/DMSO/glycerol): m/z = 280 (8%, $[M+H]^+$), 263 (2), 235 (6), 204 (4), 149 (23), 117 (14).

*General procedure for the preparation of N-Cyano-5-sydnone imines* (**4**)

15 mmol 5-sydnone imine hydrochloride and 15 mmol (1.56 g) BrCN are dissolved (if necessary MeOH is added) in 40 ml $H_2O$ and cooled with ice. During 1 h 7.5 ml 2N $NH_3$ are dropped in. The pH-value is carefully controlled and not allowed to rise over pH = 9 - 10 in order to avoid degradation of the sydnone imine. The mixture is stirred for 1 h at room temp. and kept overnight at 5°C. The yellow precipitate is recrystallized.

*N-Cyano-3-(3-phenylpropyl)-5-sydnone imine* (**4h**)

Pink plates (methanol), mp. 104°C. Yield 41%.- $C_{12}H_{12}N_4O$ (228.3) Calcd. C 63.1 H 5.29 N 24.4 Found C 62.8 H 5.28 N 24.5.- IR (KBr): 3440; 3072; 2924; 2176; 2145; 1656; 1599; 1492; 1469; 1442; 1427; 1352; 1325; 1251; 1232; 1188; 1164; 1112; 1045; 979; 960; 933; 870; 825; 764; 747; 703 $cm^{-1}$.- UV ($CH_3CN$): λ max (log ε) = 209 (4.13), 229 (4.13), 331 nm (3.96).- $^1$H-NMR/300 MHz ([$D_6$]DMSO): δ (ppm) = 8.02 (s, 1 H, syd-H), 7.32-7.18 (m, 5 H aromat.), 4.52 (t, J = 7.0 Hz, 2 H, N-$CH_2$), 2.67 (t, 2 H, Ph-$CH_2$), 2.25 (tt, 2 H, Ph-$CH_2$-C<u>H</u>$_2$-$CH_2$).- MS (100°C): m/z = 228 (4%, $M^{+\cdot}$), 117 (13), 91 (100), 77 (10), 68 (32), 65 (24), 51 (14), 41 (20).

*N-Cyano-3-(4-phenylbutyl)-5-sydnone imine* (**4i**)

Beige plates (methanol), mp. 77°C. Yield 28%.- $C_{13}H_{14}N_4O$ (242.3) Calcd. C 64.4 H 5.82 N 23.1 Found C 64.2 H 5.72 N 23.0.- IR (KBr): 3069; 2917; 2887; 2856; 2386; 2182; 1625; 1492; 1456; 1359; 1298; 1267; 1240; 1195; 1157; 1111; 1088; 1019; 984; 957; 895; 788; 776; 744; 720; 691; 641 $cm^{-1}$.- UV ($CH_3OH$): λ max (log ε) = 210 (4.16), 227 (4.13), 326 nm (3.97).- $^1$H-NMR/300 MHz ([$D_6$]DMSO): δ (ppm) = 7.98 (s, 1 H, syd-H), 7.30-7.18 (m, 5 H aromat.), 4.54 (t, J = 7.0 Hz, 2 H, N-$CH_2$), 2.61 (t, J = 7.7 Hz, 2 H, Ph-$CH_2$), 1.94 (tt, 2 H, N-$CH_2$-C<u>H</u>$_2$-$CH_2$), 1.61 (tt, 2 H, Ph-$CH_2$-C<u>H</u>$_2$-$CH_2$).- MS (200°C): m/z = 242 (4%, $M^{+\cdot}$), 91 (100), 28 (26).

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