Platelet Aggregation Inhibiting and Anticoagulant Effects of Oligoamines, XIX:

4,4'-Phenylene-bis-sydnone Imines

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Fourteen 4,4'-*m*-phenylene- and two 4,4'-*p*-phenylene-bis-sydnone imine hydrochlorides have been synthesized. All compounds exhibited good solubility in water. In the *m*-series the 3-(3-phenylpropyl)-derivative **5c** and the 3-hexyl compound **5l** showed antiplatelet activities at or below 10 µmol/L (IC_{50}, *Born*-test with collagen). The corresponding *p*-compounds had the same (**6l**) or slightly lower (**6c**) activity. No effect on the fibrin formation (*Quick*-test) could be observed.

Antiaggregatorische und anticoagulante Eigenschaften von Oligoaminen, 19. Mitt.: 4,4'-Phenylen-bis-sydnonimine

Vierzehn 4,4'-*m*-Phenylen- und zwei 4,4'-*p*-Phenylen-bis-sydnoniminhydrochloride wurden dargestellt. Alle Verbindungen zeigten die gewünschte gute Löslichkeit in Wasser. In der *m*-Reihe waren das 3-(3-Phenylpropyl)-derivat **5c** sowie die 3-Hexylverbindung **5l** in der Lage, die Thrombocytenaggregation in Konzentrationen von 10 µmol/L oder darunter halbmaximal zu hemmen (*Born*-Test, Collagen). Die entspr. *p*-Verbindungen wiesen gleiche (**6l**) oder etwas geringere (**6c**) Hemmeffekte auf. In keinem Fall wurde die Fibrinbildung (*Quick*-Test) beeinflußt.

In previous papers of this series we have reported on the structure activity relationships of oligoamines concerning their antiplatelet and anticoagulant activities[1]. All compounds were designed following the lead structure R-$(CH_2)_n$-NH-$(CH_2)_m$-carbon bridge-$(CH_2)_m$-NH-$(CH_2)_n$-R. The most active derivatives obtained so far, were secondary amines with very lipophilic properties in spite of their basic nitrogen function being protonated under physiological conditions. These properties were accompanied by long biological half lives which have been determined in animal experiments[2].

To avoid the danger of accumulation in lipophilic tissue compartments it was desirable to synthesize oligoamines with more hydrophilic properties but nevertheless comprising the essential lipophilic parts of the structure. To unite these contradictory requirements we prepared a series of bissydnone imines. Such compounds contain the essential structural features so far elucidated: firstly at least two basic amino functions which are protonated at pH 7.4; secondly a carbon bridge between these functions and thirdly the necessary lipophilic aliphatic or aromatic hydrocarbon moieties near these functions. On the other hand we knew that sydnone imines are extremely good soluble in water.

All known bissydnone imines[3-5] are connected *via* their 3-position. By reaction of diamines, KCN, formaldehyde and $NaNO_2$ *N*-nitrosoaminoacetonitriles are prepared, which are cyclized with acids to form the 3,3'-bissydnone imines. Our attempts to apply this route for the synthesis of 3,3'-bissydnone imines with an additional arylalkyl substituent in 4-position were unsuccesful. These compounds were extremely unstable and decomposed during their isolation. We therefore inverted the principle of synthesis stated above for the preparation of 4,4'-bissydnone imines, which have not yet been described so far. As shown in fig. 1 the starting material now is an aromatic dialdehyde.

For instance isophthalaldehyde (**1**), an amine hydrochloride (**2**), and KCN are stirred until a yellow oil separates (**3**). The solution is acidified and MeOH added until homogeneity is reached. Now $NaNO_2$ is added and the solution stirred until again an oil seperates (**4**). This is extracted with ether. After drying and removal of the solvent the cyclization to the sydnone mines **5** proceeds with HCl in methanol.

The structure of the sydnone imines could be ascertained especially by the ^{1}H-NMR spectra. The rather low field signal of the methylene group adjacent to the N-3-position at ~ 4.6 ppm is very characteristic and corresponds to the low electron density at this nitrogen. The same is true for the ^{13}C-5 signal at 168 ppm (**5l**). The ^{13}C-4 signal at 112 ppm is typical for the high electron density at this carbon atom. Furthermore by fast atom bombardement mass spectrometry the $[M+H]^+$ peak could be obtained in all cases.

Compounds **5** all showed the desired solubility in water or hepes buffer. More important, with three compounds the half maximal inhibition of platelet aggregation already was achieved in concentrations at or below 10 µmol/L.

In oligoamines with secondary aliphatic amino groups the optimal substituent was a 4-phenylbutyl or octyl chain. Not quite unexpected in the sydnone imines the maximum activities were found at slightly shorter hydrocarbons, namely a 3-phenylbutyl or hexyl moiety. These correspond to nearly the same interatomic distances between the basic imino group and the end of lipophilic substituent. No compound of the 5 series showed any important inhibition of the fibrin formation (*Quick*-test), *i.e.* a complete separation of antiplatelet and anticoagulant activities has been achieved.

In order to further investigate the influence of the aromatic bridge on the antiplatelet activity two *p*-phenylene compounds were synthesized (**6c**: n = 3, R = Ph, IC_{50} = 21 µmol/L; **6l**: n = 6, R = H, IC_{50} = 10 µmol/L). Compound **6c** has a slightly lower potency than **5c** which corresponds to

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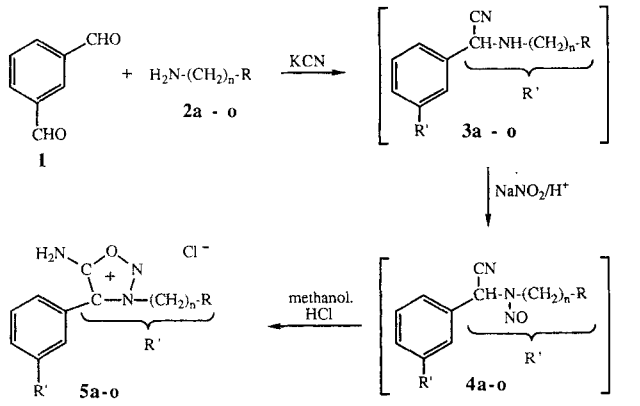

5	a	b	c	d	e	f	g	h	i	k	l	m	n	o
n	2	2	3	4	1	2	0	3	4	5	6	7	8	10
R	Ph	4-Cl-Ph	Ph	Ph	H	H	Allyl	H	H	H	H	H	H	H
IC_{50} [µmol/L]	21	18	7,5	20	220	275	170	90	90	21	10	57	41	175

Fig. 1: Synthesis of 4,4'-m-phenylene-bis-sydnone imines and their antiplatelet activity (Born-test with collagen). - Compounds **6**: see cpds. **3-5** with a *para*-substitution pattern.

previous results in secondary oligoamines with *p*-phenylene bridges. Surprisingly substance **6l** had the same antiplatelet activity as **5l**. Again no anticoagulant activities were observed.

Experimental Part

The apparatus used and the pharmacologic tests were identical with those of the previous communication[1,2].- Temp. in °C.

Phenylene-bis-sydnone imine hydrochlorides, general procedure

50 mmol amine hydrochloride and 3.25 g KCN are dissolved in 30 ml H_2O. The solution is cooled in an ice-bath and 3.35 g dialdehyde dissolved in 40 ml MeOH are added dropwise. After stirring for 2 h at rt in most cases a yellow oil separates. The mixture is cooled again with ice. Now 20 ml 4 N HCl are added. If necessary MeOH is added until homogeneity is achieved (if there is poor solubility of the intermediate aminoacetonitrile hydrochlorides in water, the aqueous phase is removed and only the oil is dissolved in MeOH). The flask is kept in ice and a solution of 3.45 g $NaNO_2$ in 10 ml H_2O is dropped in. After stirring for 1 h at rt the upper phase is discarded. The oil is washed with water, dissolved in ether (*p*-compounds: $CHCl_3$), dried with Na_2SO_4, and the solvent removed. The residue is cooled, 75 ml cold MeOH saturated with gaseous HCl are added and the solution is kept at 5° for 12 h. Then the solvent is removed by evaporation *in vacuo*. The residue is washed with ether and recrystallized.

4,4'-m-Phenylene-bis-3-(2-phenylethyl)-sydnone imine hydrochloride (**5a**)

Crystals (isopropanol), mp. 160° (degr.). Yield 50 %.- $C_{26}H_{24}N_6O_2 \cdot 2$ HCl (525.5) Calc. C 59.4 H 4.99 N 16.0 Found C 59.2 H 5.03 N 15.5.- IR (KBr): 3410; 3019; 1671; 1509; 1453; 1243; 1172; 1081; 1029; 953; 814; 751; 701 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.32), 244 (3.86), 310 nm (3.99).- ^{1}H-NMR / 300 MHz ([D_6]DMSO): δ (ppm) = 10.11 (s, 4 H, NH_2^+, D_2O exchange), 7.91-7.88 (m, 4 H aromat.), 7.26-7.14 (m, 10 H aromat.), 4.87 (t, J = 7 Hz, 4 H, syd-CH_2), 3.07 (t, J = 7 Hz, 4 H, Ph-CH_2).- MS (+ FAB/DMSO-glycerol): m/z = 453 (6 %, [M+H]$^+$), 165 (2), 131 (2), 106 (11), 105 (100), 91 (15), 79 (10).

4,4'-m-Phenylene-bis-3-[2-(4-chlorophenyl)-ethyl]-sydnone imine hydrochloride (**5b**)

Crystals (ethanol/ether), mp. 171° (degr.). Yield 60 %.- $C_{26}H_{22}N_6O_2Cl_2 \cdot 2$ HCl (594.3) Calc. C 52.5 H 4.07 N 14.1 Found C 52.6 H 4.08 N 14.0.- IR (KBr): 3416; 3016; 1669; 1510; 1490; 1468; 1409; 1242; 1170; 1091; 1014; 956; 812; 698 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 202 (4.56), 218 (4.46), 243 (4.13), 308 nm (4.24).- ^{1}H-NMR / 250 MHz ([D_6]DMSO): δ (ppm) = 10.24 (s, 4 H, NH_2^+, D_2O exchange), 7.98-7.86 (m, 4 H aromat.), 7.31 and 7.23 (two dd, J = 7/2 Hz, each 4 H aromat., C_6H_4Cl), 4.90 (t, J = 7 Hz, 4 H, syd-CH_2), 3.11 (t, J = 7 Hz, 4 H, Ph-CH_2).- MS (+ FAB/DMSO-glycerol): m/z = 525 (0.3 %), 523 (1.8), 521 (2.6 [M+H]$^+$; 2 · ^{35}Cl), 373 (0.6), 371 (2), 141 (43), 139 (100), 127 (8), 125 (18), 115 (10), 103 (45), 91 (9), 77 (21).

4,4'-m-Phenylene-bis-(3-phenylpropyl)-sydnone imine hydrochloride (**5c**)

Crystals (isopropanol/ether), mp. 137°. Yield 60%.- $C_{28}G_{28}N_6O_2 \cdot 2$ HCl (553.5) Calc. C 60.8 H 5.46 N 15.2 Found C 60.5 H 5.50 N 15.1.- IR (KBr): 3396; 3019; 1668; 1512; 1496; 1453; 1365; 1267; 1166; 1085; 953; 797; 750; 700 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 205 (4.47), 244 (4.04), 307 (4.18).- ^{1}H-NMR / 250 MHz ([D_6]DMSO): δ (ppm) = 10.13 (bs, 4 H, NH_2^+, D_2O exchange), 8.0-7.8 (m, 4 H, aromat.), 7.4-7.0 (m, 10 H, aromat.), 4.60 (t, J = 7 Hz, 4 H, syd-CH_2), 2.59 (t, J = 7 Hz, 4 H, Ph-CH_2), 2.02 (tt, J = 7/7 Hz, 4 H, syd-CH_2-$\underline{CH_2}$).- ^{13}C-NMR / 62.89 MHz ([D_6]DMSO): δ (ppm) = 166.8 (s, syd-C 5), 139.8, 134-126, 121.7 (C arom.), 112.2 (s, syd-C 4), 51.9 (t, syd-CH_2), 31.2 (t, Ph-CH_2), 28.4 (t, syd-CH_2-$\underline{CH_2}$).- MS (+FAB/DMSO-glycerol): m/z = 481 (16%, [M+H]$^+$), 450 (2), 346 (4), 91 (100).

4,4'-m-Phenylene-bis-4-phenylbutyl-sydnone imine hydrochloride (**5d**)

Crystals (methanol/ether) mp. 160°. Yield 70%.- $C_{30}H_{32}N_6O_2 \cdot 2$ HCl (581.5) Calc. C 62.0 H 5.89 N 14.5 Found C 61.9 H 5.93 N 14.7.- IR (KBr): 3420; 2980; 2940; 1665; 1515; 1495; 1470; 1450; 1425; 745; 695 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 204 (4.54), 143 (4.04), 306 (4.23).- ^{1}H-NMR / 250 MHz ([D_6]DMSO): δ (ppm) = 10.09 (bs, 4 H, NH_2^+, D_2O exchange), 8.0-7.8 (m, 4 H, aromat.), 7.3-7.1 (m, 10 H, aromat.), 4.60 (t, J = 7 Hz, 4 H, syd-CH_2), 2.50 (t, J = 7 Hz, 4 H, Ph-CH_2), 1.75 (tt, J = 7/7 Hz, 4 H, syd-CH_2-$\underline{CH_2}$), 1.57 (tt, J = 7/7 Hz, 4 H, Ph-CH_2-$\underline{CH_2}$).- MS (+FAB/DMSO-glycerol): m/z = 509 (5%, [M+H]$^+$), 360 (1), 131 (9), 105 (11), 91 (100).

4,4'-m-Phenylene-bis-3-methylsydnone imine hydrochloride (**5e**)

Crystals (methanol/isopropanol/ether), mp. 168° (degr.). Yield 65%.- $C_{12}H_{12}N_6O_2 \cdot 2$ HCl · 0.5 H_2O (354.2) Calc. C 40.7 H 4.27 N 23.7 Found C 40.4 H 4.07 N 23.4.- IR (KBr): 3409; 3003; 1667; 1512; 1475; 1437; 1324; 1104; 954; 827; 758; 695; 607 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.27), 246 (3.97), 308 nm (4.12).- ^{1}H-NMR / 300 MHz ([D_6]DMSO): δ (ppm) = 10.06 (bs, 4 H, NH_2^+, D_2O exchange), 7.91-7.88 (m, 4 H aromat.), 4.27 (s, 6 H, CH_3).- ^{13}C-NMR / 75 MHz (CD_3OD): δ (ppm) = 168.7 (syd-C 5), 134.7-132.5 (C aromat.), 123.5 (Ph-C 1 u. C 3), 114.2 (syd-C 4), 39.6 (CH_3).- MS (+FAB/DMSO-glycerol): m/z = 273 (9% [M+H]$^+$), 260 (2), 241 (3), 93 (100, glycerol-H$^+$), 91 (2).

4,4'-m-Phenylene-bis-3-ethylsydnone imine hydrochloride (**5f**)

Crystals (ethanol/ether), mp. 155° (degr.). Yield 80%.- $C_{14}H_{16}N_6O_2 \cdot 2$ HCl (373.2) Calc. C 45.1 H 4.86 N 22.5 Found C 45.3 H 5.19 N 22.2.- IR (KBr): 3454; 3394; 2959; 1672; 1505; 1459; 1424; 1349; 1246; 1118; 979;

936; 825; 753; 702 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.25), 244 (3.85), 306 nm (4.04).- ^{1}H-NMR / 300 MHz ([D_6]DMSO): δ (ppm) = 10.08 (s, 4 H, NH_2^+, D_2O exchange), 7.95-7.84 (m, 4 H aromat.), 4.63 (q, J = 7 Hz, 4 H, CH_2), 1.43 (t, J = 7 Hz, 6 H, CH_3).- MS (+FAB/DMSO-glycerol): m/z = 301 (8% $[M+H]^+$), 288 (3), 261 (5), 241 (4), 93 (100, glycerol-H^+), 91 (2).

4,4'-m-Phenylene-bis-3-allylsydnone imine hydrochloride (**5g**)

Crystals (isopropanol), mp. 121° (degr.). Yield 60%.- $C_{16}H_{16}N_6O_2 \cdot 2$ HCl · 0.5 H_2O (406.3) Calc. C 47.3 H 4.71 N 20.7 Found C 47.1 H 4.84 N 20.7.- IR (KBr): 3436; 3400; 2942; 1672; 1636; 1520; 1507; 1417; 1379; 1353; 1243; 1208; 981; 942; 819; 698 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.30), 2.46 (4.03), 308 (4.16).- ^{1}H-NMR / 300 MHz ([D_6]DMSO): δ (ppm) = 10.10 (s, 4 H, NH_2^+, D_2O exchange), 7.91-7.81 (m, 4 H aromat.), 5.97-5.84 (m, 2 H, CH), 5.43-5.29 (m, 8 H, $-CH_2-$, $=CH_2$).- MS (+FAB/DMSO-glycerol): m/z = 325 (1% $[M+H]^+$), 312 (1), 273 (2), 93 (glycerol-H^+), 75 (29).

4,4'-m-Phenylene-bis-3-propylsydnone imine hydrochloride (**5h**)

Crystals (methanol/isopropanol), mp. 145° (degr.). Yield 70%.- $C_{16}H_{20}N_6O_2 \cdot 2$ HCl · 0.5 H_2O (410.3) Calc. C 46.8 H 5.65 N 20.5 Found C 47.2 H 5.71 N 20.4.- IR (KBr): 3464; 3422; 2964; 2934; 2876; 1680; 1583; 1509; 1467; 1422; 1391; 1360; 1329; 1268; 1239; 1121; 954; 912; 809; 701; 644 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.32), 246 (3.99), 306 nm (4.20).- ^{1}H-NMR / 300 MHz ([D_6]DMSO): δ (ppm) = 10.12 (s, 4 H, NH_2^+, D_2O exchange), 7.95-7.84 (m, 4 H aromat.), 4.57 (t, J = 7 Hz, 4 H, syd-CH_2), 1.76 (tq, J = 7/7 Hz, 4 H, syd-CH_2-$C\underline{H}_2$), 0.86 (t, J = 7 Hz, 6 H, CH_3).- MS (+FAB/DMSO-glycerol): m/z = 329 (5% $[M+H]^+$), 316 (3), 297 (1), 275 (4), 241 (11), 93 (100, glycerol-H^+), 91 (2).

4,4'-m-Phenylene-bis-3-butylsydnone imine hydrochloride (**5i**)

Crystals (methanol/isopropanol/ether), mp. 153° (degr.). Yield 60%.- $C_{18}H_{24}N_6O_2 \cdot 2$ HCl · 1 H_2O (447.4) Calc. C 48.3 H 6.30 N 18.8 Found C 48.6 H 6.46 N 18.8.- IR (KBr): 3423; 3008; 2956; 2872; 1678; 1580; 1509; 1462; 1422; 1358; 1282; 1243; 1205; 1124; 958; 811; 700; 644 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.15), 244 (3.96), 306 nm (4.16).- ^{1}H-NMR / 300 MHz ([D_6]DMSO): δ (ppm) = 10.06 (s, 4 H, NH_2^+, D_2O exchange), 7.95-7.86 (m, 4 H aromat.), 4.60 (t, J = 7 Hz, 4 H, syd-CH_2), 1.70 (tt, J = 7/7 Hz, 4 H, syd-CH_2-$C\underline{H}_2$), 1.28 (tq, J = 7/7 Hz, 4 H, CH_3-$C\underline{H}_2$), 0.79 (t, J = 7 Hz, 6 H, CH_3).- MS (+FAB/DMSO-glycerol): m/z = 357 (100% $[M+H]^+$), 289 (11), 284 (12), 245 (13), 243 (13), 144 (17), 131 (28), 116 (13), 104 (13), 91 (22).

4,4'-m-Phenylene-bis-3-pentylsydnone imine hydrochloride (**5k**)

Crystals (methanol/aceton/ether), mp. 152° (degr.). Yield 70%.- $C_{20}H_{28}N_6O_2 \cdot 2$ HCl (457.4) Calc. C 52.5 H 6.61 N 18.4 Found C 52.6 H 6.65 N 18.2.- IR (KBr): 3416; 2951; 2929; 2867; 1670; 1509; 1465; 1423; 1367; 1266; 1194; 1127; 951; 815; 699 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.35), 246 (4.03), 3.06 nm (4.24).- ^{1}H-NMR / 300 MHz ([D_6]DMSO): δ (ppm) = 10.07 (s, 4 H, NH_2^+, D_2O exchange), 7.92-7.89 (m, 4 H aromat.), 4.59 (t, J = 7 Hz, 4 H, syd-CH_2), 1.71 (tt, J = 7/7 Hz, 4 H, syd-CH_2-$C\underline{H}_2$), 1.27-1.16 (m, 8 H, CH_3-$(C\underline{H}_2)_2$), 0.78 (t, J = 7 Hz, 6 H, CH_3).- MS (+FAB/DMSO-glycerol): m/z = 385 (18% $[M+H]^+$), 372 (8), 303 (12), 290 (4), 241 (4), 93 (100, glycerol-H^+), 91 (5).

4,4'-m-Phenylene-bis-3-hexylsydnone imine hydrochloride (**5l**)

Crystals (methanol/ether), mp. 138° (degr.). Yield 55%.- $C_{22}H_{32}N_6O_2 \cdot 2$ HCl · 0.5 H_2O (494.5) Calc. C 53.4 H 7.13 N 17.0 Found C 53.5 H 7.14 N 16.9.- IR (KBr): 3400; 2951; 2925; 2868; 2080; 1666; 1514; 1468; 1425; 1370; 1337; 1248; 1230; 1181; 1138; 1084; 952; 871; 793; 729; 696; 606 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 203 (4.35), 243 (4.05), 305 nm (4.19).- ^{1}H-NMR / 250 MHz ([D_6]DMSO): δ (ppm) = 10.20 (s, 4 H, NH_2^+, D_2O exchange), 7.99-7.84 (m, 4 H, aromat.), 4.61 (t, J = 7 Hz, 4 H, syd-CH_2), 1.70 (tt, J = 7/7 Hz, 4 H, syd-CH_2-$C\underline{H}_2$), 1.26-1.18 (m, 12 H, CH_3-$(C\underline{H}_2)_3$), 0.81 (t, J = 7 Hz, 6 H, CH_3).- ^{13}C-NMR / 75 MHz ([D_6]DMSO broad band decouple): δ (ppm) = 166.7 (syd-C 5), 133.1-130.5 (C aromat.), 121.8 (Ph-C 1 and C 3), 112.0 (syd-C 4), 52.2 (syd(3)-$C\underline{H}_2$), 30.3 (syd(3)-CH_2-$C\underline{H}_2$), 26.7 (syd-$(CH_2)_2$-$C\underline{H}_2$), 24.9 (syd-$(CH_2)_3$-$C\underline{H}_2$), 21.6 (syd-$(CH_2)_4$-$C\underline{H}_2$), 13.6 (CH_3).- MS (+FAB/DMSO-glycerol): m/z = 413 (26% $[M+H]^+$), 356 (8), 317 (13), 215 (11), 159 (29), 144 (25), 131 (32), 116 (24), 104 (33), 91 (18), 77 (17), 57 (24), 55 (30), 43 (100).

4,4'-m-Phenylene-bis-3-heptylsydnone imine hydrochloride (**5m**)

Crystals (ethanol/ether), mp. 137° (degr.). Yield 50%.- $C_{24}H_{36}N_6O_2 \cdot 2$ HCl (513.5) Calc. C 56.1 H 7.46 N 16.4 Found C 55.8 H 7.60 N 16.6.- IR (KBr): 3402; 2951; 2924; 2856; 1671; 1512; 1466; 1377; 1277; 1243; 1178; 1127; 955; 814; 700 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 203 (4.37), 244 (4.05), 305 nm (4.22).- ^{1}H-NMR / 250 MHz ([D_6]DMSO): δ (ppm) = 10.14 (s, 4 H, NH_2^+, D_2O exchange), 7.97-7.88 (m, 4 H aromat.), 4.60 (t, J = 7 Hz, 4 H, syd-CH_2), 1.70 (tt, J = 7/7 Hz, 4 H, syd-CH_2-$C\underline{H}_2$), 1.23 (m, 16 H, CH_3-$(C\underline{H}_2)_4$), 0.83 (t, J = 7 Hz, 6 H, CH_3).- MS (+FAB/DMSO-glycerol): m/z = 441 (100% $[M+H]^+$), 326 (14), 287 (13), 285 (15), 172 (16), 170 (14), 159 (16), 144 (18), 131 (32), 116 (15), 104 (13), 91 (11).

4,4'-m-Phenylene-bis-3-octylsydnone imine hydrochloride (**5n**)

Crystals (ethanol/ether), mp. 126° (degr.). Yield 45%.- $C_{26}H_{40}N_6O_2 \cdot 2$ HCl (541.6) Calc. C 57.7 H 7.82 N 15.5 Found C 57.9 H 8.08 N 15.5.- IR (KBr): 3056; 3047; 2954; 2948; 2923; 2918; 2854; 2342; 1666; 1602; 1516; 1465; 1425; 1375; 1267; 1181; 1131; 1088; 956; 887; 795; 722; 695; 647 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.16), 244 (3.90), 306 nm (4.05).- ^{1}H-NMR / 250 MHz ([D_6]DMSO): δ (ppm) = 10.11 (s, 4 H, NH_2^+, D_2O exchange), 7.97-7.84 (m, 4 H aromat.), 4.59 (t, J = 7 Hz, 4 H, syd-CH_2), 1.68 (tt, J = 7/7 Hz, 4 H, syd-CH_2-$C\underline{H}_2$), 1.26-1.18 (m, 20 H, CH_3-$(C\underline{H}_2)_5$), 0.83 (t, J = 7 Hz, 6 H, CH_3).- MS (+FAB/DMSO-glycerol): m/z = 469 (6% $[M+H]^+$), 131 (17), 78 (19), 71 (39), 69 (29), 67 (13), 63 (20), 61 (22), 57 (100), 55 (63).

4,4'-m-Phenylene-bis-3-decylsydnone imine hydrochloride (**5o**)

Crystals (methanol/ether), mp. 142° (degr.). Yield 60%.- $C_{30}H_{48}N_6O_2 \cdot 2$ HCl (597.7) Calc. C 60.3 H 8.43 N 14.1 Found C 60.1 H 8.41 N 14.1.- IR (KBr): 2914; 2848; 1666; 1517; 1467; 1421; 1366; 948; 793; 698 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.31), 244 (4.04), 308 nm (4.21).- ^{1}H-NMR / 300 MHz ([D_6]DMSO): δ (ppm) = 10.16 (s, 4 H, NH_2^+, D_2O exchange), 7.98-7.84 (m, 4 H aromat.), 4.61 (t, J = 7 Hz, 4 H, syd-CH_2), 1.69 (tt, J = 7/7 Hz, 4 H, syd-CH_2-$C\underline{H}_2$), 1.21-1.18 (m, 28 H, CH_3-$(C\underline{H}_2)_7$), 0.85 (t, J = 7 Hz, 6 H, CH_3).- MS (+FAB/DMSO-glycerol): m/z = 525 (74% $[M+H]^+$), 373 (15), 327 (17), 172 (35), 159 (32), 144 (36), 131 (61), 116 (31), 104 (33), 84 (49), 70 (84), 68 (100), 66 (54).

4,4'-p-Phenylene-bis-3-(3-phenylpropyl)-sydnone imine hydrochloride (**6c**)

Crystals (methanol/ether), mp. 180° (degr.). Yield 20%.- $C_{28}H_{28}N_6O_2 \cdot 2$ HCl (553.5) Calc. C 60.8 H 5.46 N 15.2 Found C 60.5 H 5.51 N 15.0.- IR (KBr): 3424; 3096; 2939; 1666; 1599; 1539; 1494; 1479; 1451; 1368; 1339; 1303; 1258; 1175; 1158; 1091; 1034; 1009; 959; 948; 862; 841; 783; 756; 736; 705; 669 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 208 (4.36), 312 nm (4.06).- ^{1}H-NMR / 300 MHz ([D_6]DMSO): δ (ppm) = 9.84 (s, 4 H, NH_2^+, D_2O exchange), 7.84 (s, 4 H aromat.), 7.25-7.10 (m, 10 H aromat.),

4.61 (t, J = 7 Hz, 4 H, syd-CH_2), 2.60 (t, J = 7 Hz, 4 H, Ph-CH_2), 2.06 (tt, J = 7/7 Hz, 4 H, syd-CH_2-C<u>H</u>$_2$).- MS (+FAB/DMSO-glycerol): m/z = 481 (10% $[M+H]^+$), 346 (4), 307 (3), 249 (2), 157 (3), 144 (7), 129 (5), 117 (7), 105 (5), 91 (100).

4,4'-p-Phenylene-bis-3-hexylsydnone imine hydrochloride (**6l**)

Crystals (ethanol), mp. 194° (degr.). Yield 30%.- $C_{22}H_{32}N_6O_2 \cdot 2$ HCl (485.5) Calc. C 54.4 H 7.06 N 17.3 Found C 54.3 H 7.24 N 17.2.- IR (KBr): 3405; 2948; 2850; 1667; 1538; 1490; 1482; 1378; 1327; 1275; 1240; 1182; 1136; 1092; 1009; 944; 858; 660 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.22), 310 nm (4.19).- ^{1}H-NMR / 300 MHz ($[D_6]$DMSO): δ (ppm) = 9.88 (s, 4 H, NH_2^+, D_2O exchange), 7.90 (s, 4 H aromat.), 4.61 (t, J = 7 Hz, 4 H, syd-CH_2), 1.73 (tt, J = 7/7 Hz, 4 H, syd-CH_2-C<u>H</u>$_2$), 1.28-1.20 (m, 12 H, CH_3-(C<u>H</u>$_2$)$_3$), 0.82 (t, J = 7 Hz, 6 H, CH_3).- MS (+FAB/DMSO-glycerol): m/z = 413 (76% $[M+H]^+$), 400 (15), 317 (31), 312 (23), 273 (18), 131 (58), 78 (35), 74 (100, from glycerol).

References

1 K. Rehse, Drugs of the Future *13*, 941 (1988).
2 K. Rehse, A. Kesselhut, V. Schein, M. Kämpfe, B. Rose, and E. Unsöld, Arch. Pharm. (Weinheim) *324*, 301 (1991).
3 H.U. Daeniker and J. Druey, Helv. Chim. Acta *40*, 918 (1957).
4 V.G. Yashunskii and L.E. Kholodov, J. Gen. Chem. USSR (Engl. Transl.) *32*, 3592, 3661 (1962); C.A. *58*, 2444h, 13939d (1968).
5 Brit. Pat. 962.293 (1964); C.A. *61*, 9504h (1964).

[Ph31]