Platelet Aggregation Inhibiting and Anticoagulant Effects of Oligoamines, XXI[1]:

4,4'-Alkylene-bis-sydnone Imines

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Two methylene-, seven ethylene-, eleven propylene- and two 4,4'-butylene-bis-sydnone imines have been synthesized and tested for their antiplatelet (*Born*-test, collagen) and anticoagulant (*Quick*-test) activity *in vitro*. The most active compounds were found in the ethylene and propylene series. The most favourable substituents in 3-position of the sydnone were hexyl to octyl or phenylethyl to phenylbutyl groups. Six compounds exhibit an $IC_{50} \leq 10$ µmol/L against platelet aggregation. Three compounds showed an $IC_{75} \leq 200$ µmol/L concerning the fibrin formation (Quick $\Delta t \geq 7$ s).

Antiaggregatorische und anticoagulante Eigenschaften von Oligoaminen, 21. Mitt.[1]: 4,4'-Alkylen-bis-sydnonimine

Zwei Methylen-, sieben Ethylen-, elf Propylen- und zwei 4,4'-Butylen-bis-sydnonimine wurden dargestellt und auf ihre Fähigkeit zur Hemmung der Thrombocytenaggregation (*Born*-Test, Collagen) und zur Hemmung der Fibrinbildung (*Quick*-Test) geprüft. Die wirkungsstärksten Verbindungen wurden in der Ethylen- und Propylen-Reihe gefunden. Die günstigsten Substituenten in 3-Stellung des Sydnonimins waren Hexyl- bis Octyl- und Phenylethyl-bis Phenylbutylreste. Sechs Verbindungen hemmten die Thrombocytenaggregation halbmaximal in Konzentrationen von 10 µmol/L oder weniger. Drei Verbindungen hemmten die Fibrinbildung bei $c \leq 200$ µmol/L zu mehr als 75% (Quick $\Delta t \geq 7$ s).

Recently we reported on antiplatelet activities of 4,4'-phenylene-bis-sydnone imines[1]; these actions are due not to the sydnone imine moiety itself like in 3-amino derivatives of sydnone imines[2] but to the presence of two intact basic imino functions and a suitable lipophilic hydrocarbon group in 3-position of the sydnone imine. As a few 3,4-dialkyl derivatives of sydnone imines are known[3], we were encouraged to undertake the synthesis of the so far unknown 4,4'-alkylene-bis-sydnone imines. The scheme of synthesis is compiled in fig. 1. Starting material are the aliphatic dialdehydes **1** (m = 1 - 4). Malondialdehyde (m = 1) was obtained from 1,1,3,3-tetramethoxypropane by acidic cleavage and was used *in situ* after neutralization of the aqueous solution. The same procedure was used to get succinaldehyde (m = 2) from 2,5-dimethoxytetrahydrofurane[4]. Glutaraldehyde (m = 3) can be bought as a 25% aqueous solution. Adipinaldehyde (m = 4) was synthesized from cyclohexane-1,2-diol by reaction with periodate on Amberlite^R IRA 904[5]. The aminoacetonitriles **3** were got by reaction of the amines **2** with KCN. Their solubility in water and/or methanol decreases with increasing lipophilicity, i.e. rising number of methylene groups in the molecules of **3**. In these cases the nitrosation was carried out either in suspension of **3** in methanol/water or in a two-phase-system ($CHCl_3/H_2O$). The structures of compounds **5** were assured by spectroscopic data, e.g. in table 1 (for details see Experimental Part).

The most significant indicator of the successful synthesis is the ^{1}H-NMR signal for the methylene group adjacent to the 4-position of the sydnone imine. This signal easily can differentiate between the four series (m = 1 - 4) of alkylene derivatives. The signal for the iminium group clearly shows the influence of one sydnone moiety on the other. All ^{1}H- and ^{13}C-NMR-Signals could be assigned without doubt by DEPT and ^{1}H/^{13}C-COSY-techniques.

Tab. 1: Spectroscopic properties of selected 4,4'-alkylene-bis-sydnone imines

		^{1}H-NMR: δ (ppm)			IR [cm^{-1}]	UV [nm]
		syd(3)-CH_2	syd(4)-CH_2	NH_2	C=N	λ_{max}
5x	(m = 4)	4.62	2.89	9.79	1667	206, 302
5d	(m = 3)	4.72	3.06	10.00	1668	208, 300
5r	(m = 2)	4.76	3.30	10.11	1667	206, 302
5o	(m = 1)	4.72	5.19	10.24	1667	206, 302

For instance in **5k** the ^{13}C-absorption at 24.8 ppm corresponds with the C-atom in the middle of the propylene bridge while the two other C-atoms resonate at 20.0 ppm. This result reflects the rather high electron density in the 4-position of sydnone imines. The results of the pharmacological *in vitro* tests are as well summarized in Scheme 1. In general the antiplatelet activity varies sharply with the length of the alkylene bridge. If we compare **5o** (m = 1), **5r** (m = 2), **5d** (m = 3), and **5x** (m = 4) or **5p** (m = 1), **5o** (m = 2), **5k**, and **5z** we clearly recognize that only for m = 2 and m = 3 a strong inhibition of the platelet aggregation ($IC_{50} \leq 10$ µmol/L) is observed.

Within these series the optimal substituent in 3-position of the sydnone imine is hexyl or 3-phenylpropyl. This corresponds to the results obtained for other non heterocyclic oligoamines. In contrast to oligoimines with an 4,4'-aryl-bridge[1,6] in the 4,4'-alkylene sydnone imines fibrin formation is inhibited. Maximal activities are found in **5e**, **5f**, **5i**, and **5w**. All these compounds are very lipophilic. This corresponds to former experiences in the oligoamine series. Surprisingly the antiplatelet and anticoagulant effects do run

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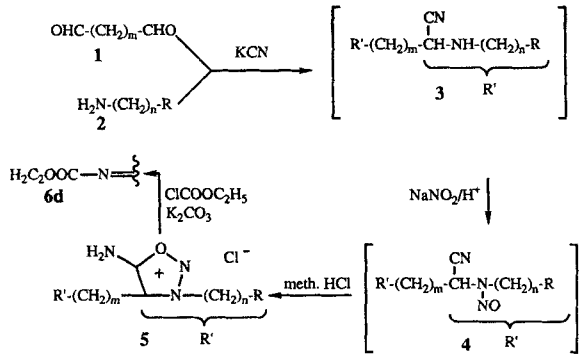

5	a	b	c	d	e	f	g	h	i	k	l
m	3	3	3	3	3	3	3	3	3	3	3
R	H	H	H	H	H	H	H	Ph	4-Cl-Ph	Ph	Ph
n	3	4	5	6	7	8	10	2	2	3	4
IC_{50} [µmol/L]	>250	145	35	3	12	8	21	11	12	5	14
Quick Δt [s]	0	0	2	4	38	36	5	0	34	13	13

5	o	p	q	r	s	t	u	v	w	x	z
m	1	1	2	2	2	2	2	2	2	4	4
R	H	Ph	H	H	H	H	Ph	Ph	Ph	H	Ph
n	6	3	5	6	7	8	2	3	4	6	3
IC_{50} [µmol/L]	57	62	40	10	13	11	8	8	11	20	62
Quick Δt [s]	4	2	2	13	13	13	4	9	29	6	2

Scheme 1: Synthesis of 4,4'-alkylene-bis-sydnone imines, their antiplatelet (*Born*-test, collagen) and anticoagulant (Qick, Δt at 400 µmol/L) activities

nearly parallel in the alkylene sydnone imines. This seems to reflect a balance between hydrophilic, i.e. good solubility in water, and lipophilic properties in these compounds. With **5e** (Δt = 13 s), **5f** (Δt = 14 s), and **5i** (Δt = 7 s) even in concentration of 200 µmol/L more than 75% inhibition (Δt = 7 s) was measured.

The most active compound **5d** was transformed into a prodrug suitable for oral application in rats. The ethoxycarbonyl derivative **6d** was obtained by reaction of **5d** with ethyl chloroformate (Scheme 1). However, even with a dose of 60 mg/kg no antithrombotic effect occurs in rats. It is known that ethoxycarbonylsydnone imines are well absorbed from the gastrointestinal tract and cleaved enzymatically[7] to give the parent compound (i.e. **5d**). We therefore assume that the lack of activity has pharmacokinetic reasons. The good solubility of **5d** in water suggests a quick renal clearance so that the steady state concentrations necessary for antithrombotic effects are not reached.

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Experimental Part

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

Preparation of **5a-l**

A solution of 50 mmol amine hydrochloride and 3.25 g KCN in 30 ml H_2O is cooled with ice while 10 ml of an aqueous solution of glutaraldehyde (25%) is dropped in. The mixture is stirred 2 h at room temp. (rt) while an oil precipitates. The upper layer is discarded and the oil dissolved in 50 ml MeOH. While cooling 20 ml 4 N HCl are added. A suspension forms. In the case of **5a-c** it dissolves by addition of MeOH. Now 3.45 g $NaNO_2$ in 10 ml H_2O are dropped in with cooling. The mixture is stirred 2 h at rt whilst an oil or a solid precipitates. It is extracted with ether, dried, and the ether is removed. The residue is mixed with 75 ml cold MeOH saturated with gaseous HCl and kept at 5° overnight.- The solvent is evaporated, the residue washed with ether and little isopropanol and recrystallized.

4,4'-Propylene-bis-3-propylsydnone imine hydrochloride (**5a**)

Crystals (methanol/ether), mp. 181° (degr.). Yield 30%.- $C_{13}H_{22}N_6O_2 \cdot 2$ HCl (367.3) Calc. C 42.5 H 6.59 N 22.9 Found C 42.6 H 6.88 N 22.9.- IR (KBr): 2964; 2934; 2627; 1673; 1667; 1599; 1502; 1451; 1371; 1329; 1284; 1217; 1135; 1112; 1016; 945; 885; 802; 753; 722; 629 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.06), 302 nm (4.12).- ^{1}H-NMR/250 MHz ([D_6]-DMSO): δ (ppm) = 9.98 (s, 4H, NH_2^+, D_2O exchange), 4.70 (t, J = 7 Hz, 4H, syd(3)-CH_2), 3.05 (t, J = 7 Hz, 4H, syd(4)-CH_2), 1.94 (tq, J = 7/7 Hz, 4H, syd(3)-CH_2-CH_2), 1.79 (bs, 2H, syd(4)-CH_2-CH_2), 0.99 (t, J = 7 Hz, 6H, CH_3).- ^{13}C-NMR/75 MHz ([D_6]-DMSO): δ (ppm) = 167.2 (s, syd-C5), 113.5 (syd-C4), 52.7 (syd(3)-CH_2), 24.7 (syd(4)-CH_2-CH_2), 21.6 (CH_3-CH_2), 19.9 (syd(4)-CH_2), 10.5 (CH_3).- MS (+ FAB/DMSO-glycerol): m/z = 295 (100%, $[M+H]^+$), 223 (8), 137 (10), 108 (13).

4,4'-Propylene-bis-3-butylsydnone imine hydrochloride (**5b**)

Crystals (ethanol/ether), mp. 177° (degr.). Yield 50%.- $C_{15}H_{26}N_6O_2 \cdot 2$ HCl·0.5 H_2O (404.3) Calc. C 44.6 H 7.23 N 20.8 Found C 44.1 H 7.34 N 20.5.- IR (KBr): 3410; 2956; 1668; 1502; 1453; 1276; 1202; 1133; 930 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.06), 302 nm (4.09).- ^{1}H-NMR/250 MHz ([D_6]-DMSO): δ (ppm) = 10.05 (s, 4H, NH_2^+, D_2O exchange), 4.75 (t, J = 7 Hz, 4H, syd(3)-CH_2), 3.08 (t, J = 7 Hz, 4H, syd(4)-CH_2), 1.90-1.87 (m, 6H, syd(3)-CH_2-CH_2 and syd(4)-CH_2-CH_2), 1.43 (m, 4H, CH_3-CH_2), 0.94 (t, J = 7 Hz, 6H, CH_3).- MS (+ FAB/DMSO-glycerol): m/z = 323 (43% $[M+H]^+$), 310 (2), 255 (6), 237 (8), 108 (20), 67 (28), 57 (100).

4,4'-Propylene-bis-3-pentylsydnone imine hydrochloride (**5c**)

Crystals (ethanol/ether), mp. 193° (degr.). Yield 40%.- $C_{17}H_{30}N_6O_2 \cdot 2$ HCl·0.5 H_2O (432.4) Calc. C 47.2 H 7.69 N 19.4 Found C 47.4 H 7.92 N 19.3.- IR (KBr): 3408; 2950; 2926; 2870; 2622; 1671; 1599; 1505; 1451; 1259; 1195; 1134; 947; 725; 643 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.11), 302 nm (4.07).- ^{1}H-NMR/300 MHz ([D_6]-DMSO): δ (ppm) = 10.00 (s, 4H, NH_2^+, D_2O exchange), 4.72 (t, J = 7 Hz, 4H, syd(3)-CH_2), 3.06 (t, J = 7 Hz, 4H, syd(4)-CH_2), 1.89 (tt, J = 7/7 Hz, 4H, syd(3)-CH_2-CH_2), 1.79 (bs, 2H, syd(4)-CH_2-CH_2), 1.35 (m, 8H, CH_3-(CH_2)$_2$), 0.88 (t, J = 7 Hz, 6H, CH_3).- MS (+ FAB/DMSO-glycerol): m/z = 351 (100%, $[M+H]^+$), 251 (5), 223 (3), 137 (9), 108 (18), 95 (12), 80 (17).

4,4'-Propylene-bis-3-hexylsydnone imine hydrochloride (**5d**)

Crystals (ethanol/ether), mp. 184° (degr.). Yield 50%.- $C_{19}H_{34}N_6O_2 \cdot 2$ HCl (451.4) Calc. C 50.6 H 8.04 N 18.6 Found C 50.6 H 8.19 N 18.6.- IR (KBr): 3434; 3196; 2992; 2958; 2925; 2855, 1668, 1503; 1449; 1430; 1411; 1331; 1293; 1208; 1187; 1136; 964; 933; 793; 727 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 208 (4.18), 300 nm (4.27).- ^{1}H-NMR/300 MHz ([D_6]-DMSO): δ (ppm) = 10.00 (s, 4H, NH_2^+, D_2O exchange), 4.72 (t, J = 7 Hz, 4H, syd(3)-CH_2), 3.06 (t, J = 7 Hz, 4H, syd(4)-CH_2), 1.90 (t, J = 7 Hz, 4H, syd(3)-CH_2-CH_2), 1.80 (bs, 2H, syd(4)-CH_2-CH_2), 1.37 (m, 4H,

syd(3)-$(CH_2)_2$-C$\underline{H}_2$), 1.29 (m, 8H, CH_3-(C$\underline{H}_2$)$_2$), 0.87 (t, J = 7 Hz, 6H, CH_3).- MS (+ FAB/DMSO-glycerol): m/z = 379 (32%, $[M+H]^+$), 265 (10), 138 (18), 108 (28), 95 (28), 82 (25), 67 (43), 55 (100).

4,4'-Propylene-bis-3-heptylsydnone imine hydrochloride (**5e**)

Crystals (isopropanol), mp. 185° (degr.). Yield 55%.- $C_{21}H_{38}N_6O_2 \cdot 2$ HCl·1 H_2O (497.5) Calc. C 50.7 H 8.50 N 16.9 Found C 50.4 H 8.51 N 16.8.- IR (KBr): 3412; 2951; 2923; 2856; 1671; 1504; 1451; 1278; 1136; 949; 801; 725 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.10), 302 nm (4.10).- ^{1}H-NMR/250 MHz ([D_6]-DMSO): δ (ppm) = 10.00 (s, 4H, NH_2^+, D_2O exchange), 4.72 (t, J = 7 Hz, 4H, syd(3)-CH_2), 3.06 (t, J = 7 Hz, 4H, syd(4)-CH_2), 1.91-1.79 (m, 6H, syd(3)-CH_2-C$\underline{H}_2$ and syd(4)-CH_2-C$\underline{H}_2$), 1.44-1.26 (m, 16 H, CH_3-(C$\underline{H}_2$)$_4$), 0.87 (t, J = 7 Hz, 6H, CH_3).- MS (+ FAB/DMSO-glycerol): m/z = 407 (7%, $[M+H]^+$), 279 (3), 197 (3), 151 (3), 108 (12), 95 (10), 77 (5), 57 (100).

4,4'-Propylene-bis-3-octylsydnone imine hydrochloride (**5f**)

Crystals (methanol/ether), mp. 185° (degr.). Yield 50%.- $C_{23}H_{42}N_6O_2 \cdot 2$ HCl (507.5) Calc. C 54.4 H 8.74 N 16.6 Found C 54.5 H 9.31 N 16.7.- IR (KBr): 2922; 2854; 1671; 1505; 1452; 1230; 940; 724 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.09), 302 nm (4.11).- ^{1}H-NMR/250 MHz ([D_6]-DMSO): δ (ppm) = 10.03 (s, 4H, NH_2^+, D_2O exchange), 4.86 (t, J = 7 Hz, 4H, syd(3)-CH_2), 3.06 (t, J = 7 Hz, 4H, syd(4)-CH_2), 1.95-1.81 (m, 6H, syd(3)-CH_2-C$\underline{H}_2$ and syd(4)-CH_2-C$\underline{H}_2$), 1.39-1.18 (m, 20 H, CH_3-(C$\underline{H}_2$)$_5$), 0.87 (t, J = 7 Hz, 6H, CH_3).- MS (+ FAB/DMSO-glycerol): m/z = 435 (10%, $[M+H]^+$), 293 (3), 108 (13), 95 (16), 71 (34), 57 (100).

4,4'-Propylene-bis-3-decylsydnone imine hydrochloride (**5g**)

Crystals (methanol/ether), mp. 182° (degr.). Yield 40%.- $C_{27}H_{50}N_6O_2 \cdot 2$ HCl (563.7) Calc. C 57.5 H 9.30 N 14.9 Found C 57.6 H 9.44 N 15.0.- IR (KBr): 3413; 2951; 2919; 2852; 1672; 1668; 1503; 1452; 1377; 1229; 1138; 936; 723 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 203 (4.25), 300 nm (4.22).- ^{1}H-NMR/250 MHz ([D_6]-DMSO): δ (ppm) = 9.94 (s, 4H, NH_2^+, D_2O exchange), 4.69 (t, J = 7 Hz, 4H, syd(3)-CH_2), 3.05 (t, J = 7 Hz, 4H, syd(4)-CH_2), 1.91-1.80 (m, 6H, syd(3)-CH_2-C$\underline{H}_2$ and syd(4)-CH_2-C$\underline{H}_2$), 1.42-1.25 (m, 28 H, CH_3-(C$\underline{H}_2$)$_7$), 0.86 (t, J = 7 Hz, 6H, CH_3).- MS (+ FAB/DMSO-glycerol): m/z = 491 (8%, $[M+H]^+$), 321 (5), 138 (13), 108 (24), 95 (23), 57 (63), 55 (53), 43 (100).

4,4'-Propylene-bis-3-(2-phenylethyl)-sydnone imine hydrochloride (**5h**)

Crystals (methanol/ether), mp. 194° (degr.). Yield 45%.- $C_{23}H_{26}N_6O_2 \cdot 2$ HCl·0.5 H_2O (500.4) Calc. C 55.2 H 5.84 N 16.8 Found C 55.4 H 5.69 N 16.9.- IR (KBr): 3410; 3020; 2990; 1666; 1499; 1475; 1322; 1257; 1174; 1081; 941; 753; 708 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.45), 306 nm (4.18).- ^{1}H-NMR/300 MHz ([D_6]-DMSO): δ (ppm) = 10.01 (s, 4H, NH_2^+, D_2O exchange), 7.33-7.28 (m, 10 H aromat.), 5.00 (t, J = 7 Hz, 4H, syd(3)-CH_2), 3.28 (t, J = 7 Hz, 4H, syd(4)-CH_2), 2.97 (t, J = 7 Hz, 4H, Ph-CH_2), 1.66 (bs, 2H, syd(4)-CH_2-C$\underline{H}_2$).- MS (+ FAB/DMSO-glycerol): m/z = 419 (6%, $[M+H]^+$), 303 (1), 285 (2), 218 (1), 203 (2), 137 (5), 105 (100), 91 (13), 78 (8).

4,4'-Propylene-bis-3-[2-(4-chlorophenyl)-ethyl]-sydnone imine hydrochloride (**5i**)

Crystals (methanol/ether), mp. 212° (degr.). Yield 40%.- $C_{23}H_{24}N_6O_2Cl_2 \cdot 2$ HCl (560.3) Calc. C 49.3 H 4.67 N 15.0 Found C 48.8 H 4.60 N 14.9.- IR (KBr): 3412; 3013; 1670; 1598; 1491; 1447; 1410; 1314; 1254; 1166; 1091; 1014; 939; 818; 779; 721; 629 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 210 (4.29), 306 nm (4.05).- ^{1}H-NMR/300 MHz ([D_6]-DMSO): δ (ppm) = 10.08 (s, 4H, NH_2^+, D_2O exchange), 7.41-7.35 (m, 8H aromat.), 5.04 (t, J = 7 Hz, 4H, syd(3)-CH_2), 3.30 (t, J = 7 Hz, 4H, syd(4)-CH_2), 3.03 (t, J = 7 Hz, 4H, Ph-CH_2), 1.65 (bs, 2H, syd(4)-CH_2-C$\underline{H}_2$).- MS (+ FAB/DMSO-glycerol): m/z = 489 (2.4%), 487 (3.5, $[M+H]^+$), 141 (32), 139 (100), 103 (64), 77 (19).

4,4'-Propylene-bis-3-(3-phenylpropyl)-sydnone imine hydrochloride (**5k**)

Crystals (ethanol/ether), mp. 189° (degr.). Yield 40%.- $C_{25}H_{30}N_6O_2 \cdot 2$ HCl (519.5) Calc. C 57.8 H 6.21 N 16.2 Found C 57.9 H 6.41 N 16.0.- IR (KBr): 3430; 3196; 3002; 1667; 1497; 1449; 1324; 1288; 1208; 1163; 981; 947; 802; 750; 701 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 205 (4.50), 301 nm (4.19).- ^{1}H-NMR/300 MHz ([D_6]-DMSO): δ (ppm) = 10.02 (s, 4H, NH_2^+, D_2O exchange), 7.33-7.17 (m, 10 H aromat.), 4.77 (t, J = 7 Hz, 4H, syd(3)-CH_2), 3.11 (t, J = 7 Hz, 4H, syd(4)-CH_2), 2.78 (t, J = 7 Hz, 4H, Ph-CH_2), 2.20 (tt, J = 7/7 Hz, Ph-CH_2-C$\underline{H}_2$), 1.80 (bs, 2H, syd(4)-CH_2-C$\underline{H}_2$).- ^{13}C-NMR/75 MHz ([D_6]-DMSO): δ (ppm) = 167.3 (syd-C5), 140.3 (Ph-C 1), 128.3-126.0 (C aromat.), 113.7 (syd-C4), 51.0 (syd(3)-C$\underline{H}_2$), 31.3 (Ph-CH_2), 29.8 (Ph-CH_2-C$\underline{H}_2$), 24.8 (syd(4)-CH_2-C$\underline{H}_2$), 20.0 (syd(4)-C$\underline{H}_2$).- MS (+ FAB/DMSO-glycerol): m/z = 447 (4%, $[M+H]^+$), 299 (2), 119 (8), 117 (10), 115 (6), 91 (100), 79 (9), 41 (9).

4,4'-Propylene-bis-3-(4-phenylbutyl)-sydnone imine hydrochloride (**5l**)

Crystals (methanol/ether), mp. 187° (degr.). Yield 40%.- $C_{27}H_{34}N_6O_2 \cdot 2$ HCl (547.5) Calc. C 59.2 H 6.63 N 15.4 Found C 59.1 H 6.80 N 15.1.- IR (KBr): 3016; 2987; 2934; 2621; 1666; 1601; 1503; 1452; 1411; 1356; 1326; 1270; 1248; 1204; 1151; 1088; 1028; 981; 936; 794; 748; 727; 700 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 208 (4.37), 302 nm (4.13).- ^{1}H-NMR/300 MHz ([D_6]-DMSO): δ (ppm) = 10.00 (s, 4H, NH_2^+, D_2O exchange), 7.27-7.17 (m, 10 H aromat.), 4.75 (t, J = 7 Hz, 4H, syd(3)-CH_2), 3.04 (t, J = 7 Hz, 4H, syd(4)-CH_2), 2.63 (t, J = 7 Hz, 4H, Ph-CH_2), 1.92 (m, 4H, syd(3)-CH_2-C$\underline{H}_2$), 1.73 (m, 6H, syd(4)-CH_2-C$\underline{H}_2$ und Ph-CH_2-C$\underline{H}_2$).- MS (+ FAB/DMSO-glycerol): m/z = 475 (6%, $[M+H]^+$), 313 (2), 242 (2), 131 (5), 117 (6), 105 (9), 91 (100).

Synthesis of **5o** *and* **5p**

4.1 g (25 mmol) 1,1,3,3-Tetramethoxypropane are warmed (40°) in 20 ml 0.6 N HCl for 1 min. The solution is neutralized with $NaHCO_3$ and dropped immediately to an ice cold solution of 50 mmol amine hydrochloride and 3.25 g KCN in 25 ml H_2O. The mixture is stirred for 2 h at rt. An oil separates. The upper layer is discarded and the oil dissolved in 50 ml MeOH. With cooling 20 ml 4 N HCl are added. A solution of 3.45 g $NaNO_2$ in 10 ml is dropped in while cooling. After additional stirring for 2 h at rt a brown oil forms. The upper layer is discarded. For **5o** the oil is dissolved in ether (**5p**: $CHCl_3$) and dried with Na_2SO_4. The solvent is removed. 75 ml cold MeOH, saturated with gaseous HCl, is added and the mixture kept at 5° overnight. The solvent is removed. The residue is washed with ether and aceton and recrystallized from the solvent stated.

4,4'-Methylene-bis-3-hexylsydnone imine hydrochloride (**5o**)

Crystals (isopropanol), mp. 172° (degr.). Yield 15%.- $C_{17}H_{30}N_6O_2 \cdot 2$ HCl (423.4) Calc. C 48.2 H 7.62 N 19.9 Found C 48.1 H 8.01 N 19.6.- IR (KBr): 2947; 2917; 2900; 2870; 2856; 1667; 1494; 1458; 1437; 1399; 1377; 1332; 1264; 1233; 1122; 1063; 952; 805; 737; 685; 649 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.12), 302 nm (4.09).- ^{1}H-NMR/300 MHz ([D_6]-DMSO): δ (ppm) = 10.24 (s, 4H, NH_2^+, D_2O exchange), 5.19 (s, 2H, syd(4)-CH_2, D_2O exchange), 4.72 (t, J = 7 Hz, 4H, syd(3)-CH_2), 1.92 (tt, J = 7/7 Hz, 4H, syd(3)-CH_2-C$\underline{H}_2$), 1.40-1.30 (m, 12 H, CH_3-(-C$\underline{H}_2$-)$_3$), 0.88 (t, J = 7 Hz, 6H, CH_3).- MS (+ FAB/DMSO-glycerol): m/z = 351 (100%, $[M+H]^+$), 222 (18), 179 (14), 138 (20), 123 (13), 110 (24), 97 (22), 81 (27).

4,4'-Methylene-bis-3-(3-phenylpropyl)-sydnone imine hydrochloride (**5p**)

Crystals (isopropanol), mp. 169° (degr.). Yield 15%.- $C_{23}H_{26}N_6O_2 \cdot 2$ HCl·2 H_2O (527.4) Calc. C 52.4 H 6.11 N 15.9 Found C 52.4 H 6.16 N 15.5.- IR (KBr): 3406; 3047; 3017; 2992; 2971; 1658; 1589; 1489; 1441; 1392; 1345; 1333; 1293; 1257; 1239; 1179; 1113; 1087; 1033; 972; 762; 706; 674; 610 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 208 (4.08), 302 nm (3.78).- ^{1}H-NMR/300 MHz ([D_6]-DMSO): δ (ppm) = 10.34 (s, 4H, NH_2^+, D_2O exchange), 7.56-7.29 (m, 10 H aromat.), 5.25 (s, 2H, syd(4)-CH_2, D_2O exchange), 4.76 (t, J = 7 Hz, 4H, syd(3)-CH_2), 2.78 (t, J = 7 Hz, 4H, Ph-CH_2), 2.24 (tt, J = 7/7 Hz, 4H, syd(3)-CH_2-C<u>H</u>$_2$).- MS (+ FAB/DMSO-glycerol): m/z = 419 (14%, $[M+H]^+$), 380 (10), 325 (13), 117 (16), 91 (100), 76 (8).

Preparation of **5q** - **5w**

2.64 g (25 mmol) 2,5-Dimethoxytetrahydrofurane in 20 ml 0.6 N HCl are warmed (40°) until complete dissolution which takes some min. The solution is neutralized with $NaHCO_3$ and dropped in an ice cold solution of 50 mmol amine hydrochloride and 3.25 g KCN in 25 ml H_2O. While stirring for 2 h at rt a precipitate forms. Then 20 ml 4 N HCl and 20 ml MeOH are added. To this suspension (ice bath) 3.45 g $NaNO_2$ in 10 ml H_2O are added dropwise and stirring is continued for 2 h at rt. The precipitate is sucked off and extracted with ether. The ether is dried with Na_2SO_4 and the solvent is removed. 75 ml cold MeOH saturated with HCl are added. The mixture is kept at 5° overnight. The solvent is removed, the residue washed with ether and aceton and recrystallized.

4,4'-Ethylene-bis-3-pentylsydnone imine hydrochloride (**5q**)

Crystals (isopropanol), mp. 164° (degr.). Yield 30%.- $C_{16}H_{28}N_6O_2 \cdot 2$ HCl·0.5 H_2O (418.3) Calc. C 45.9 H 7.47 N 20.1 Found C 45.9 H 7.64 N 20.3.- IR (KBr): 3406; 2952; 2923; 1667; 1494; 1438; 1380; 1326; 1258; 1114; 1058; 967; 807; 736; 684; 648 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.12), 302 nm (4.16).- ^{1}H-NMR/300 MHz ([D_6]-DMSO): δ (ppm) = 10.07 (s, 4H, NH_2^+, D_2O exchange), 4.73 (t, J = 7 Hz, 4H, syd(3)-CH_2), 3.27 (s, 4H, syd(4)-CH_2), 1.92 (tt, J = 7/7 Hz, 4H, syd(3)-CH_2-C<u>H</u>$_2$), 1.36 (m, 8H, CH_3-(-C<u>H</u>$_2$-)$_2$), 0.89 (t, J = 7 Hz, 6H, CH_3).- MS (+ FAB/DMSO-glycerol): m/z = 337 (64%, $[M+H]^+$), 229 (60), 160 (56), 136 (100), 115 (21), 109 (81), 91 (44), 84 (41), 81 (46), 79 (58).

4,4'-Ethylene-bis-3-hexylsydnone imine hydrochloride (**5r**)

Crystals (isopropanol), mp. 177° (degr.). Yield 25%.- $C_{18}H_{32}N_6O_2 \cdot 2$ HCl (437.4) Calc. C 49.4 H 7.83 N 19.2 Found C 49.2 H 8.21 N 19.0.- IR (KBr): 3197; 2954; 2934; 2870; 1667; 1489; 1457; 1436; 1377; 1291; 1248; 1129; 1061; 974; 804; 735; 681; 647 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.16), 302 nm (4.19).- ^{1}H-NMR/300 MHz ([D_6]-DMSO): δ (ppm) = 10.11 (s, 4H, NH_2^+, D_2O exchange), 4.76 (t, J = 7 Hz, 4H, syd(3)-CH_2), 3.30 (s, 4H, syd(4)-CH_2), 1.92 (tt, J = 7/7 Hz, 4H, syd(3)-CH_2-C<u>H</u>$_2$), 1.40-1.29 (m, 12 H, CH_3-(-C<u>H</u>$_2$-)$_3$), 0.88 (t, J = 7 Hz, 6H, CH_3).- MS (+ FAB/DMSO-glycerol): m/z = 365 (100%, $[M+H]^+$), 122 (42), 96 (77), 80 (65), 78 (64), 76 (42), 70 (67).

4,4'-Ethylene-bis-3-heptylsydnone imine hydrochloride (**5s**)

Crystals (isopropanol), mp. 171° (degr.). Yield 20%.- $C_{20}H_{36}N_6O_2 \cdot 2$ HCl (465.5) Calc. C 51.6 H 8.23 N 18.1 Found C 51.6 H 8.72 N 18.2.- IR (KBr): 3411; 2947; 2917; 2870; 1670; 1494; 1456; 1436; 1377; 1326; 1240; 1203; 1127; 1061; 964; 806; 736; 684; 648 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.10), 300 nm (4.14).- ^{1}H-NMR/300 MHz ([D_6]-DMSO): δ (ppm) = 10.10 (s, 4H, NH_2^+, D_2O exchange), 4.74 (t, J = 7 Hz, 4H, syd(3)-CH_2), 3.29 (s, 4H, syd(4)-CH_2), 1.91 (tt, J = 7/7 Hz, 4H, syd(3)-CH_2-C<u>H</u>$_2$), 1.36-1.27 (m, 16 H, CH_3-(-C<u>H</u>$_2$-)$_4$), 0.87 (t, J = 7 Hz, 6H, CH_3).- MS (+ FAB/DMSO-glycerol): m/z = 393 (100%, $[M+H]^+$), 265 (18), 122 (32), 111 (21), 96 (46), 94 (40), 81 (38).

4,4'-Ethylene-bis-3-octylsydnone imine hydrochloride (**5t**)

Crystals (isopropanol), mp. 177° (degr.). Yield 15%.- $C_{22}H_{40}N_6O_2 \cdot 2$ HCl (493.5) Calc. C 53.5 H 8.58 N 17.0 Found C 55.1 H 8.66 N 17.0.- IR (KBr): 3417; 3113; 2966, 2951; 2910; 2623; 1664; 1491; 1464; 1417; 1379; 1338; 1315; 1263; 1225; 1092; 1036; 982; 906; 812; 725; 618 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.12), 302 nm (4.15).- ^{1}H-NMR/300 MHz ([D_6]-DMSO): δ (ppm) = 10.10 (s, 4H, NH_2^+, D_2O exchange), 4.74 (t, J = 7 Hz, 4H, syd(3)-CH_2), 3.29 (s, 4H, syd(4)-CH_2), 1.91 (tt, J = 7/7 Hz, 4H, syd(3)-CH_2-C<u>H</u>$_2$), 1.26 (m, 20 H, CH_3-(-C<u>H</u>$_2$-)$_5$), 0.86 (t, J = 7 Hz, 6H, CH_3).- MS (+ FAB/DMSO-glycerol): m/z = 421 (69%, $[M+H]^+$), 279 (38), 250 (11), 165 (9), 152 (9), 137 (20), 122 (36), 111 (32), 96 (58), 81 (64), 70 (100).

4,4'-Ethylene-bis-3-(2-phenylethyl)-sydnone imine hydrochloride (**5u**)

Crystals (ethanol), mp. 198° (degr.). Yield 20%.- $C_{22}H_{24}N_6O_2 \cdot 2$ HCl·0.5 H_2O (486.4) Calc. C 54.3 H 5.59 N 17.3 Found C 54.2 H 5.49 N 17.3.- IR (KBr): 3434; 2951; 2934; 2839; 1669; 1595; 1490; 1444; 1355; 1322; 1284; 1235; 1167; 1078; 1033; 994; 968; 935; 843; 742; 699; 640; 614 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 208 (4.36), 302 nm (4.16).- ^{1}H-NMR/300 MHz ([D_6]-DMSO): δ (ppm) = 10.12 (bs, 4H, NH_2^+, D_2O exchange), 7.34-7.29 (m, 10 H aromat.), 5.04 (t, J = 7 Hz, 4H, syd(3)-CH_2), 3.31 (t, J = 7 Hz, 4H, Ph-CH_2), 3.08 (s, 4H, syd(4)-CH_2).- MS (+ FAB/DMSO-glycerol): m/z = 405 (17%, $[M+H]^+$), 315 (1), 271 (2), 115 (2), 105 (100), 91 (9), 79 (9).

4,4'-Ethylene-bis-3-(3-phenylpropyl)-sydnone imine hydrochloride (**5v**)

Crystals (ethanol), mp. 184° (degr.). Yield 15%.- $C_{24}H_{28}N_6O_2 \cdot 2$ HCl (505.5) Calc. C 57.0 H 5.98 N 16.6 Found C 57.1 H 6.09 N 16.6.- IR (KBr): 3422; 2995; 1666; 1492; 1452; 1433; 1335; 1272; 1201; 1150; 988; 944; 800; 748; 699; 636 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 208 (4.41), 302 nm (4.15).- ^{1}H-NMR/300 MHz ([D_6]-DMSO): δ (ppm) = 10.06 (s, 4H, NH_2^+, D_2O exchange), 7.32-7.20 (m, 10 H aromat.), 4.74 (t, J = 7 Hz, 4H, syd(3)-CH_2), 3.26 (s, 4H, syd(4)-CH_2), 2.73 (t, J = 7 Hz, 4H, Ph-CH_2), 2.20 (tt, J = 7/7 Hz, 4H, syd(3)-CH_2-C<u>H</u>$_2$).- MS (+ FAB/DMSO-glycerol): m/z = 433 (20%, $[M+H]^+$), 404 (2), 285 (5), 117 (7), 91 (100), 69 (5).

4,4'-Ethylene-bis-3-(4-phenylbutyl)-sydnone imine hydrochloride (**5w**)

Crystals (ethanol), mp. 179° (degr.). Yield 15%.- $C_{26}H_{32}N_6O_2 \cdot 2$ HCl·0.5 H_2O (542.5) Calc. C 57.6 H 6.50 N 15.5 Found C 57.6 H 6.49 N 15.6.- IR (KBr): 3434; 2977; 2955; 1667; 1600; 1492; 1451; 1438; 1396; 1310; 1279; 1248; 1164; 1077; 1027; 969; 805; 743; 699; 621 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 208 (4.43), 302 nm (4.16).- ^{1}H-NMR/300 MHz ([D_6]-DMSO): δ (ppm) = 10.02 (bs, 4H, NH_2^+, D_2O exchange), 7.30-7.15 (m, 10 H aromat.), 4.74 (t, J = 7 Hz, 4H, syd(3)-CH_2), 3.23 (s, 4H, syd(4)-CH_2), 2.63 (t, J = 7/7 Hz, 4H, Ph-CH_2), 1.92 (tt, J = 7/7 Hz, 4H, syd(3)-CH_2-C<u>H</u>$_2$), 1.70 (tt, J = 7/7 Hz, Ph-CH_2-C<u>H</u>$_2$).- MS (+ FAB/DMSO-glycerol): m/z = 492 (16%, $[M+H]^+$), 299 (4), 157 (19), 131 (5), 117 (3), 105 (6), 91 (100), 79 (36).

Preparation of **5x** *and* **5z**

40 mmol amine hydrochloride and 2.6 g KCN are dissolved in 20 ml H_2O. The crude hexanedial from 2.5 g (22 mmol) cyclohexane-1,2-diol[5] in 20 ml MeOH is dropped in while cooling with ice. The mixture is stirred for 2 h at rt. A yellow oil forms. The mixture is cooled and 15 ml 4 N HCl are added. A colorless precipitate forms, which is sucked off and

resuspended in 150 ml $CHCl_3$. Again 15 ml 4 N HCl and 30 ml H_2O are added. A solution of 2.8 g $NaNO_2$ in 10 ml H_2O is dropped in (cooling!). This two-phase-system is stirred overnight at rt. The remaining solid is sucked off and discarded. The org. layer is separated, washed twice with H_2O, dried with Na_2SO_4, and the chloroform is evaporated. A yellow oil remains. It is dissolved in 60 ml cold MeOH which is saturated with gaseous HCl and kept at 5° overnight. The precipitate is sucked off and discarded. The solution is evaporated. The residue is washed with ether and aceton and recrystallized.

4,4'-Butylene-bis-3-hexylsydnone imine hydrochloride (**5x**)

Crystals (ethanol/ether), mp. 172° (degr.). Yield 60%.- $C_{20}H_{36}N_6O_2 \cdot 2$ HCl·1 H_2O (483.5) Calc. C 49.7 H 8.34 N 17.4 Found C 49.5 H 8.16 N 17.5.- IR (KBr): 3390; 3191; 3009; 2952; 2928; 2853; 1667; 1503; 1457; 1334; 1240; 1129; 949; 799; 723 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (3.90), 302 nm (3.93).- ^{1}H-NMR/300 MHz ([D_6]-DMSO): δ (ppm) = 9.79 (s, 4H, NH_2^+, D_2O exchange), 4.62 (t, J = 7 Hz, 4H, syd(3)-CH_2), 2.89 (bs, 4H, syd(4)-CH_2), 1.89 (tt, J = 7/7 Hz, 4H, syd(3)-CH_2-C$\underline{H}_2$), 1.64 (bs, 4H, syd(4)-CH_2-C$\underline{H}_2$), 1.40-1.28 (m, 12 H, CH_3-(-C$\underline{H}_2$-)$_3$), 0.87 (t, J = 7 Hz, 6H, CH_3).- MS (+ FAB/DMSO-glycerol): m/z = 393 (100%, $[M+H]^+$), 301 (8), 283 (6), 121 (17), 89 (20), 76 (41).

4,4'-Butylene-bis-3-(3-phenylpropyl)-sydnone imine hydrochloride (**5z**)

Crystals (ethanol/ether), mp. 172° (degr.). Yield 40%.- $C_{26}H_{32}N_6O_2 \cdot 2$ HCl·1 H_2O (551.5) Calc. C 56.6 H 6.58 N 15.2 Found C 56.9 H 6.36 N 15.2.- IR (KBr): 3400; 3186; 2980; 2941; 2925; 1666; 1507; 1449; 1347; 1301; 1204; 1152; 947; 750; 701; 629 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 210 (4.37), 302 nm (4.19).- ^{1}H-NMR/250 MHz ([D_6]-DMSO): δ (ppm) = 9.85 (s, 4H, NH_2^+, D_2O exchange), 7.34-7.18 (m, 10 H aromat.), 4.66 (t, J = 7 Hz, 4H, syd(3)-CH_2), 2.89 (bs, 4H, syd(4)-CH_2), 2.75 (t, J = 7 Hz, 4H, Ph-CH_2), 2.21 (tt, J = 7/7 Hz, 4H, syd(3)-CH_2-C$\underline{H}_2$), 1.63 (bs, 4H, syd(4)-CH_2-C$\underline{H}_2$).- MS (+ FAB/DMSO-glycerol): m/z = 461 (11%, $[M+H]^+$), 448 (1), 331 (3), 93 (glycerol-H^+), 91 (81).

4,4'-Propylene-bis-N-ethoxycarbonyl-3-hexyl-sydnone imine (**6d**)

5.9 g of **5d** are dissolved in 150 ml H_2O and 4.9 g ethyl chloroformate are added. While cooling with ice a solution of 4.6 g K_2CO_3 in 50 ml H_2O is dropped in during 2 h. The mixture is stirred overnight. A brown oil forms. The aqueous layer is discarded, the oil dissolved in CH_2Cl_2, dried with Na_2SO_4, and the solvent is removed. The residue is purified by rotational chromatography (Chromatotron; $CHCl_3$/EtOH 9:1). The solvent is evaporated and the oily product dried i. vac. It crystallizes in the refrigerator after some days.

Crystals, mp. 62° (degr.). Yield 75%.- $C_{25}H_{42}N_6O_6$ (522.7) Calc. C 57.5 H 8.10 N 16.1 Found C 57.4 H 8.21 N 16.1.- IR (KBr): 2951; 2924; 2858; 1654; 1609; 1487; 1418; 1362; 1258; 1240; 1136; 1092; 1060; 1006; 982; 938; 889; 799 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 236 (4.38), 326 nm (4.31).- ^{1}H-NMR/300 MHz ($CDCl_3$): δ (ppm) = 4.46 (t, J = 7 Hz, 4H, syd(3)-CH_2), 4.17 (q, J = 7 Hz, 4H, CO-CH_2), 2.77 (t, J = 7 Hz, 4H, syd(4)-CH_2), 2.15 (quintett, J = 7 Hz, 2H, syd(4)-CH_2-C$\underline{H}_2$), 1.94 (tt, J = 7/7 Hz, 4H, syd(3)-CH_2-C$\underline{H}_2$), 1.34-1.26 (m, 18 H, CH_3-(-C$\underline{H}_2$-)$_3$ and CO-CH_2-C$\underline{H}_3$), 0.90 (t, J = 7 Hz, 6H, CH_3).- ^{1}H-NMR/300 MHz ([D_6]-DMSO): δ (ppm) = 4.53 (t, J = 7 Hz, 4H, syd(3)-CH_2), 3.97 (q, J = 7 Hz, 4H, CO-CH_2), 2.70 (t, J = 7 Hz, 4H, syd(4)-CH_2), 1.87 (m, 6H, syd(4)-CH_2-C$\underline{H}_2$ and syd(3)-CH_2-C$\underline{H}_2$), 1.29 (m, 12 H, CH_3-(C$\underline{H}_2$)$_3$), 1.17 (t, J = 7 Hz, 6H, CO-CH_2-C$\underline{H}_3$), 0.86 (t, J = 7 Hz, 6H, CH_3).- MS (+ FAB/DMSO-glycerol): m/z = 523 (7%, $[M+H]^+$), 477 (27), 451 (9), 449 (7), 363 (7), 272 (9), 213 (14), 136 (35), 106 (100), 89 (77), 77 (82), 60 (90).

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