Synthesis of Long-Chain 3-Alkylpyrroles Bearing Terminal Carboxy or Amino Groups

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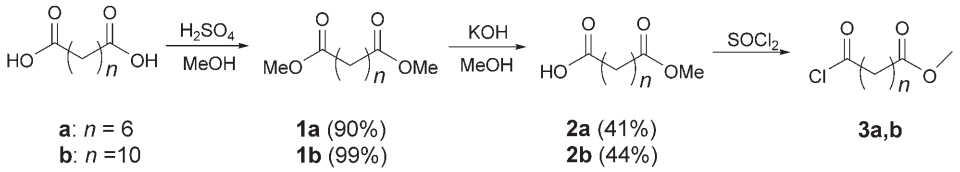
Two new ω-(1*H*-pyrrol-3-yl)alkanoic acids **8a**,**b** and the corresponding amines **9a**,**b** were prepared on large scale in 41–51 and 27–39% overall yield, respectively, starting from *N*-phenylsulfonyl-protected pyrrole. The target compounds contain the desired functional groups for attachment of biomolecules such as proteins. During synthesis, an unprecedented partial reduction of the pyrrole ring with $NaBH_3CN$ in glacial AcOH was observed, for which a plausible mechanism is proposed (*Scheme 3*).

Introduction. – Tailoring of conducting polymers has been explored for several applications, including the preparation of new electro-catalytic materials and the construction of biosensors [1]. Derivatives of 3-alkylpyrroles bearing a long alkyl chain (C_8–C_{12}) with a reactive end group constitute valuable monomers for the formation of conducting polymers. When such polymers are used to immobilize biomolecules, the alkyl chain can increase the stability and activity of, *e.g.*, proteins [2]. Synthetic methods for the construction of terminally functionalized 3-alkylpyrroles have been developed only for compounds with *short* alkyl chains comprising three to five C-atoms. Hence, in this paper, we report a facile and versatile synthesis of extended 3-alkylpyrroles with terminal COOH and NH_2 groups, respectively.

Results and Discussion. – We were interested in developing a synthesis of pyrrole derivatives in very high yields, avoiding lengthy purification procedures, and the possibility to use it for large-scale preparations.

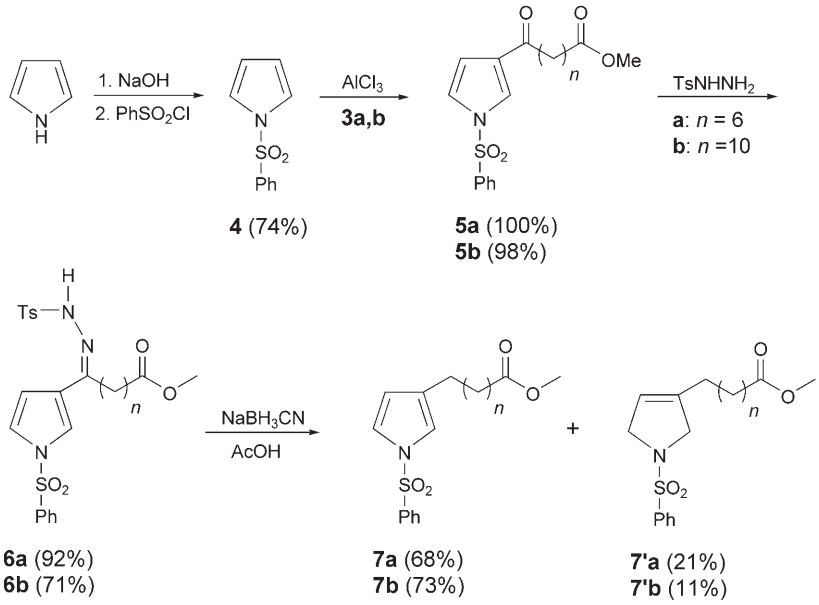
The introduction of long alkyl chains in the pyrrole required the preparation of monoacyl chlorides from the corresponding diacids (*Scheme 1*). Thus, suberic acid (= octanedioic acid; $n = 6$) and dodecanedioic acid ($n = 10$) were transformed into their respective dimethyl esters **1a**,**b** in 90–99% yield. Partial hydrolysis in the presence of $Ba(OH)_2$ [3] or KOH gave the mono-acids **2a**,**b**. Higher yields of mono-acid (*ca.* 40%) were obtained by treatment with 0.7–0.8M KOH solution for 3–4 h. The mono- and diacids were separated by repeated washing with hexanes, the diacids being virtually insoluble in this solvent, in contrast to the mono-acids, which are partially soluble. Both the diesters and the diacids could be recovered and used again, which makes the overall process more efficient. Finally, reaction of **2a**,**b** with 2 equiv. of thionyl chloride afforded the corresponding acid chlorides **3a**,**b**, which were not isolated, but used immediately after workup in a *Friedel–Crafts* reaction (see below). Attempts to obtain **2a** directly from suberic acid by mono-esterification [4] were not successful.

Scheme 1



The desired alkyl chain was introduced at the 3-position of pyrrole by *Friedel–Crafts* acylation [5] of 1-(phenylsulfonyl)-1*H*-pyrrole (**4**). The latter was obtained in 74% yield (after recrystallization) by an extremely exothermic reaction accomplished by overnight treatment of pyrrole with phenylsulfonyl chloride in a suspension of NaOH (3 equiv.) in CH_2Cl_2 (*Scheme 2*). The reaction took place in the absence of a phase-transfer catalyst [6], and could be used for the preparation of quantities of 200 g of **4**.

Scheme 2



Acylation of **4** with **3a** (1.5 equiv.) and $AlCl_3$ (3 equiv.) gave rise to quantitative conversion to methyl 8-oxo-8-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]octanoate (**5a**; *Scheme 2*). According to *Kakushima et al.* [7], the amount of $AlCl_3$ is crucial to achieve complete conversion, and a lower regioselectivity was obtained with other *Lewis* acid catalysts. The regioselective 3-acylation of **4** was confirmed by 1D and 2D ^{1}H-NMR spectroscopic analysis (*Figure*). In the case of **5a**, a strong coupling between the two vicinal pyrrole H-atoms at δ(H) 7.15 (*dd*, $J = 2, 2$, H–C(5)) and 6.69 (*dd*, $J = 2.2, 1.7$, H–C(4)) was observed, together with weak couplings with the less-shielded H-atom at δ(H) 7.72–7.75 (*m*, H–C(2)).

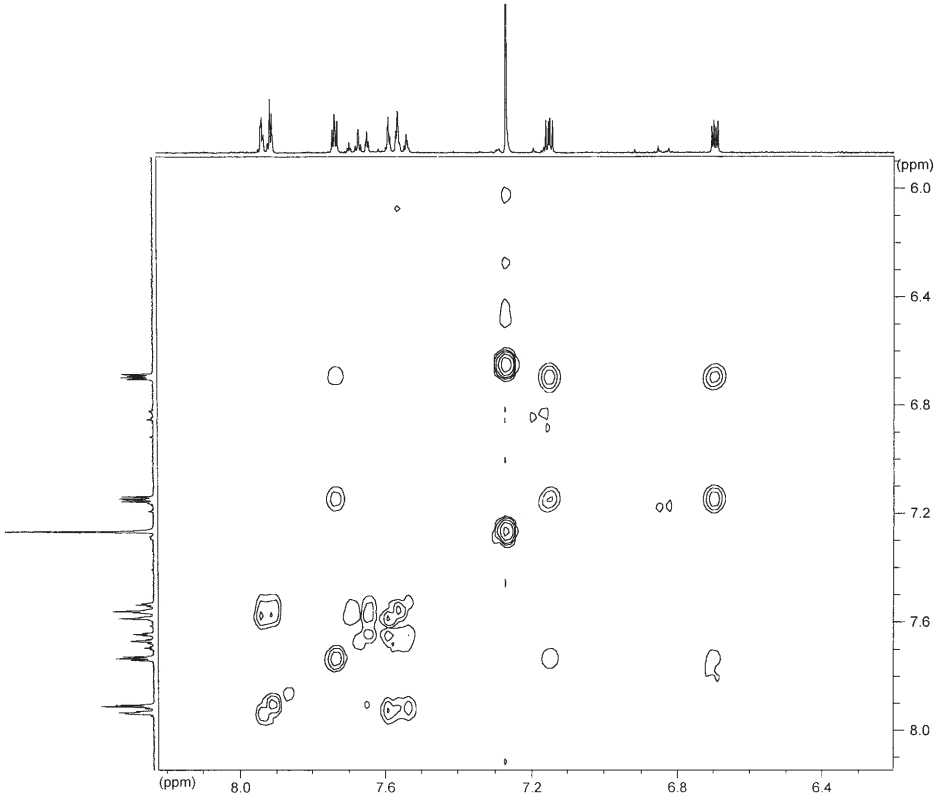
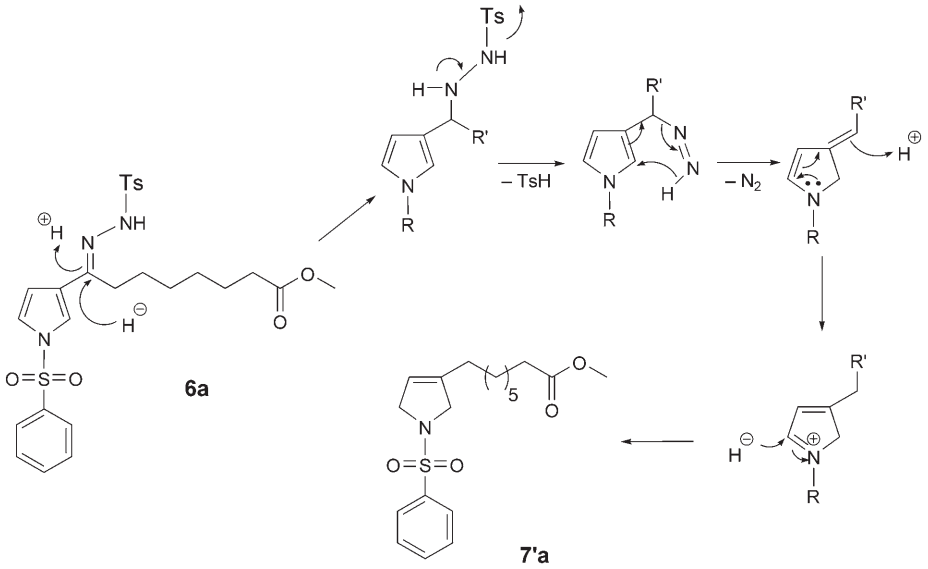


Figure. *Two-dimensional ^{1}H-NMR spectrum of* **5a** (300 MHz, $CDCl_3$)

The tosylhydrazone **6a** was obtained in 92% yield by treatment of **5a** with 1-[(4-methylphenyl)sulfonyl]hydrazine (1.2 equiv.) in anhydrous EtOH. This transformation was envisaged since tosylhydrazones can be selectively reduced under considerably milder conditions than C=O groups [8]. Reduction of **6a** was then carried out in glacial AcOH with $NaBH_3CN$ (3 equiv.) to afford the desired octanoate **7a** in 68% yield after column chromatography, together with 21% of the side product **7′a** due to simultaneous, partial pyrrole-ring reduction. Similarly, in the reaction sequence with $n = 10$, the corresponding 2,5-dihydro-1*H*-pyrrole derivative **7′b** was also observed (11% yield; by ^{1}H-NMR) upon reduction of **6b**, which yielded **7b** as the main product (*Scheme 2*).

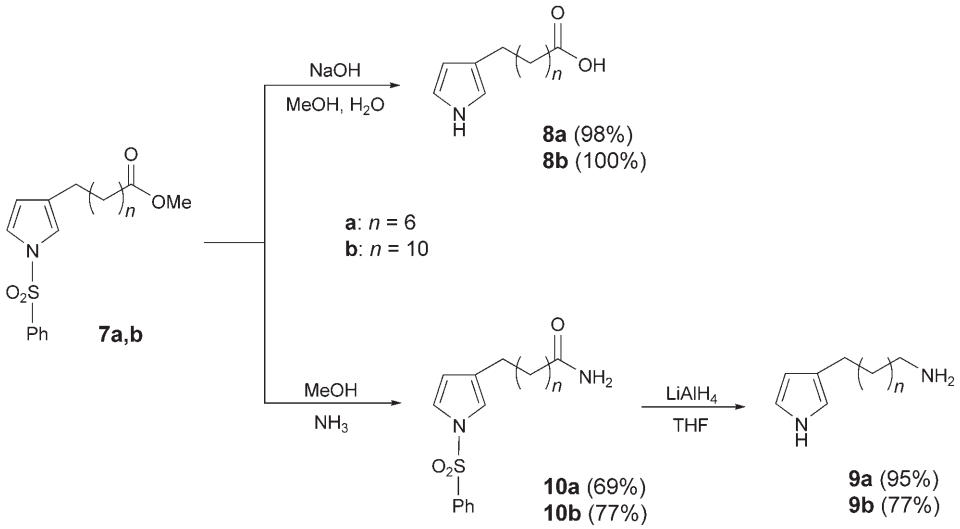
Whereas migration of C=C bonds to the site of the carbonyl C-atom has been observed in the reduction of α,β-unsaturated tosylhydrazones [9], the simultaneous reduction of pyrrole rings has not been reported, to our knowledge. A possible mechanism for the formation of **7′a** is depicted in *Scheme 3*. Interestingly, this side reaction could not be suppressed by lowering the temperature or by shortening the reaction time.

Scheme 3. *Proposed Mechanism for the Observed Reduction of* **6a** *to* **7'a** *by* $NaBH_3CN$



With compounds **7a**,**b** at hand, the syntheses of the corresponding carboxylic acids **8a**,**b** (by hydrolysis) and amines **9a**,**b** (by reduction of the corresponding amides) were straightforward (*Scheme 4*). The acids **9a**,**b** were obtained nearly quantitatively upon basic hydrolysis of **7a**,**b**. The overall yield of **9a** from pyrrole proper was 41%, and that of **9b** was 51%.

Scheme 4



Amide formation was carried out by bubbling NH_3 through a solution of **7a** or **7b** in MeOH for 10 min at 0°, and by further stirring at room temperature after sealing the reaction flask [10]. Addition of NH_3 was repeated every 2 d, until no ester could be detected by TLC. After 10 d, the amide **10a** was obtained in 69% yield. Reduction with an excess (10 equiv.) of $LiAlH_4$ in THF finally gave the desired 8-(pyrrol-3-yl)octanamine (**9a**) in 95% yield. Although $BH_3 \cdot HF$ and $BH_3 \cdot Me_2S$ are the reagents of choice for most reductions of amides [11], in the present case, the simultaneous removal of the phenylsulfonyl protecting group could be effected with $LiAlH_4$, avoiding an additional deprotection step. The conversion of pyrrole proper to **9a** was achieved in an overall yield of 27%, and the chain-elongated congener **9b** was prepared in 39% overall yield.

Conclusions. – An efficient synthesis of 3-alkylpyrroles with C_8 and C_{12} alkyl chains and COOH or NH_2 functions in ω-position has been developed. The protocol is suitable for large-scale preparations, yielding compounds of high purity and in high yields, with only few steps requiring purification. In the $NaBH_3CN$ reduction of **6a**,**b** to **7a**,**b**, the unexpected, partially ring-hydrogenated side products **7′a**,**b**, respectively, were observed, a reaction that has not been reported so far.

J. M. F. gratefully acknowledges financial support of his Ph.D. work by *Fundação para a Ciência e Tecnologia*.

Experimental Part

General. All reactions were carried out, unless mentioned, in open flasks. Technical solvents were distilled and dried prior to use. All chemicals were purchased in *puriss.* or anal. quality from *Fluka*, *Sigma*, or *Aldrich*, and used as received, unless stated otherwise. Column chromatography (CC): silica gel *60* (0.04–0.063 mm; *Fluka*). Thin layer chromatography (TLC): silica-gel *Alugram SIL G/UV$_{254}$* sheets (*Macherey-Nagel*); visualization under UV light (254 nm) and/or by spraying with ninhydrin soln. (10% in EtOH) or phosphomolybdic acid soln. (10% in EtOH), or cerium(IV) sulfate/phosphomolybdic acid soln. (made from 10.5 g cerium(IV) sulfate hydrate, 21 g phosphomolybdic acid, 60 ml conc. H_2SO_4, and 900 ml H_2O). IR: *Biorad FTS 25* apparatus; in cm^{-1}. NMR spectra: *Bruker AC-300*, at 300 and 75 MHz for ^1H and ^{13}C, resp., in $CDCl_3$; chemical shifts δ in ppm rel. to residual solvent peaks; ^{13}C-NMR multiplicities determined by DEPT; coupling constants *J* in Hz. Mass spectra were provided by the Service of Mass Spectrometry, Department of Chemistry and Biochemistry, University of Berne.

Dimethyl Octanedioate (**1a**). To a soln. of suberic acid (10 g, 57.4 mmol) in MeOH (45 ml) was added H_2SO_4 (1 ml), and the mixture was refluxed overnight. The soln. was concentrated *in vacuo*. The resulting precipitate was poured on ice, and extracted with Et_2O (3 × 40 ml). The combined org. extracts were washed with 10% aq. $NaHCO_3$ soln. and brine, and dried ($MgSO_4$). Evaporation under reduced pressure gave **1a** as an oil (10.4 g, 90%). ^1H-NMR: 3.67 (*s*, 2 CO_2Me); 2.31 (*dd*, *J* = 7.4, 7.7, 2 CH_2CO_2Me); 1.69–1.56 (*m*, 2 $CH_2CH_2CO_2Me$); 1.39–1.24 (*m*, 2 CH_2).

Dimethyl Dodecanedioate (**1b**). Prepared in analogy to **1a**, but starting from dodecanedioic acid. The title compound was isolated as a colorless solid in 99% yield. ^1H-NMR: 3.67 (*s*, 2 CO_2Me); 2.30 (*t*, *J* = 7.5, 2 CH_2CO_2Me); 1.68–1.53 (*m*, 2 $CH_2CH_2CO_2Me$); 1.36–1.21 (*m*, 6 CH_2).

Octanedioic Acid Monomethyl Ester (**2a**). To a soln. of KOH (2.07 g, 37 mmol) in MeOH (45 ml), **1a** (7.5 g, 37 mmol) was added, and the mixture was stirred for 4 h at r.t. The solvent was then removed, and Et_2O and H_2O were added. The org. layer was separated, washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford **1a** as an oil (2.57 g, 34%). The aq. layer was acidified with conc. HCl to pH 3, and extracted with Et_2O (2 × 100 ml). The combined org. extracts were washed with brine and dried ($MgSO_4$). The solvent was removed to give a mixture of a colorless solid and an oil. Extensive washing with hexane removed the suberic acid monomethyl ester, the acid being virtually insolubility in hexane. Evaporation of the washings gave the title compound **2a** as an oil (2.73 g, 41%). ^1H-NMR: 3.67 (*s*, CO_2Me); 2.41–2.27 (*m*, 2 CH_2CO_2); 1.72–1.56 (*m*, 2 $CH_2CH_2CO_2R$); 1.44–1.25 (*m*, 2 CH_2).

Dodecanedioic Acid Monomethyl Ester (**2b**). Prepared in analogy to **2a**, but starting from **1b**. The title compound was isolated as a colorless solid in 44% yield. ^{1}H-NMR: 3.67 (*s*, CO_2Me); 2.41–2.26 (*m*, 2 CH_2CO_2); 1.70–1.55 (*m*, 2 $CH_2CH_2CO_2$); 1.40–1.21 (*m*, 6 CH_2).

Methyl 8-Chloro-8-oxooctanoate (**3a**). A soln. of **2a** (1 g, 5.32 mmol) in $SOCl_2$ (1 ml, 14 mmol) was stirred at 55° for 3 h. The $SOCl_2$ was removed under reduced pressure to afford an orange oil, which was used immediately in the next step.

Methyl 12-Chloro-12-oxododecanoate (**3b**). Prepared in analogy to **3a**, but starting from **2b**.

*1-(Phenylsulfonyl)-1*H*-pyrrole* (**4**). Freshly distilled pyrrole (87.4 g, 1.30 mol) was added to a well-agitated suspension of crushed NaOH (161 g, 4.03 mol) pellets in CH_2Cl_2 (900 ml). This mixture was cooled to 0° (ice bath), and stirred for 25 min. Then, a soln. of phenylsulfonyl chloride (263 g, 1.49 mol) in CH_2Cl_2 (180 ml) was added dropwise over a period of 90 min. The mixture was stirred for 4 h at 0°, and then at r.t. overnight. The reaction was quenched with distilled H_2O (2.60 l). The org. phase was separated, and the aq. layer was extracted with CH_2Cl_2 (3 × 180 ml). The combined org. extracts were washed neutral with distilled H_2O, dried ($MgSO_4$), and concentrated to a grey solid. Recrystallization from MeOH afforded **4** as a white crystalline solid (198 g, 74%). ^{1}H-NMR: 7.90–7.83 (*m*, 2 H of Ph); 7.64–7.57 (*m*, H of Ph); 7.55–7.47 (*m*, 2 H of Ph); 7.22–7.14 (*m*, H–C(2,5)); 6.35–6.28 (*m*, H–C(3,5)).

*Methyl 8-Oxo-8-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]octanoate* (**5a**). To a well-agitated suspension of $AlCl_3$ (34 g, 0.25 mol) in CH_2Cl_2 (150 ml) cooled to 0° (ice bath), **3a** was slowly added, followed by dropwise addition of **4** (18 g, 87 mmol) in CH_2Cl_2 (100 ml). The mixture was allowed to warm to r.t., stirred for 2.5 h, and then poured on ice-cold, distilled H_2O (600 ml). The org. layer was separated, and the aq. layer was extracted with CH_2Cl_2 (3 × 40 ml). The combined org. extracts were washed with sat. aq. $NaHCO_3$ soln. and H_2O, dried ($MgSO_4$), and concentrated under reduced pressure to afford **5a** (32.8 g, 100%) as a colorless, soapy solid. TLC (hexanes/AcOEt 7:3): R_f 0.50. IR (KBr): 3433*w*, 3130*m*, 3065*w*, 2932*m*, 2890*w*, 2866*w*, 2851*w*, 2360*w*, 2341*w*, 1731*s*, 1684*s*, 1541*m*, 1473*s*, 1449*m*, 1379*s*, 1338*w*, 1300*m*, 1261*w*, 1221*s*, 1175*s*, 1118*s*, 1066*s*, 912*m*, 823*w*, 797*m*, 753*m*, 726*s*, 682*m*, 615*s*, 591*s*, 559*m*. ^{1}H-NMR: 7.95–7.90 (*m*, 2 H of Ph); 7.75–7.72 (*m*, H–C(2) of pyrrole); 7.70–7.64 (*ttt*, *J* = 1.3, 2.2, 1.3, H of Ph); 7.60–7.53 (*m*, 2 H of Ph); 7.15 (*dd*, *J* = 2.2, 2.2, H–C(5) of pyrrole); 6.69 (*dd*, *J* = 2.2, 1.7, H–C(4) of pyrrole); 3.67 (*s*, CO_2Me); 2.77–2.67 (*m*, $CH_2C(O)C$); 2.31 (*t*, *J* = 7.5, CH_2CO_2Me); 1.75–1.55 (*m*, 2 CH_2CH_2COR); 1.43–1.28 (*m*, 2 CH_2). ^{13}C-NMR: 195.38 (*s*, C=O); 174.16 (*s*, CO_2Me); 138.24 (*s*, arom. C); 134.54 (*d*, arom. CH); 129.71 (*d*, arom. CH); 129.23 (*s*, C(3) of pyrrole); 127.14 (*d*, arom. CH); 124.08 (*d*, C(2) of pyrrole); 121.59 (*d*, C(5) of pyrrole); 112.53 (*d*, C(4) of pyrrole); 51.44 (*q*, CO_2Me); 39.61 (*t*, $CH_2C(O)C$); 33.97 (*t*, CH_2CO_2Me); 28.88 (*t*, CH_2); 24.72 (*t*, $CH_2CH_2C(O)C$); 24.02 (*t*, $CH_2CH_2CO_2Me$). MS: 377 (3.6, M^+), 249 (100), 234 (87), 141 (48), 94 (33), 77 (88). HR-MS: 377.129760 (M^+, $C_{19}H_{23}NO_5S^+$; calc. 377.129695).

*Methyl 12-Oxo-12-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]dodecanoate* (**5b**). Prepared in analogy to **5a**, but starting from **3b**. The title compound was isolated as a colorless, soapy solid in 98% yield. TLC (hexanes/AcOEt 8:2): R_f 0.33. IR (KBr): 3442*w*, 3350*w*, 3132*m*, 3089*w*, 3063*m*, 2926*s*, 2850*s*, 1732*s*, 1685*s*, 1583*w*, 1541*s*, 1474*s*, 1450*s*, 1422*m*, 1376*s*, 1336*m*, 1317*m*, 1279*m*, 1260*m*, 1205*s*, 1174*s*, 1122*s*, 1103*s*, 1062*s*, 912*m*, 819*m*, 797*m*, 758*m*, 727*s*, 705*m*, 681*s*, 609*s*, 592*s*, 558*s*. ^{1}H-NMR: 7.95–7.89 (*m*, 2 H of Ph); 7.75–7.72 (*m*, H–C(2) of pyrrole); 7.71–7.64 (*ttt*, *J* = 1.3, 2.3, 1.3, H of Ph); 7.60–7.53 (*m*, 2 H of Ph); 7.17–7.14 (*dd*, *J* = 2.3, 2.3, H–C(5) of pyrrole); 6.72–6.68 (*m*, H–C(4) of pyrrole); 3.67 (*s*, CO_2Me); 2.76–2.68 (*m*, $CH_2C(O)C$); 2.31 (*t*, *J* = 2.3, CH_2CO_2Me); 1.73–1.55 (*m*, 2 $CH_2CH_2C(O)C$); 1.39–1.21 (*m*, 6 CH_2). ^{13}C-NMR: 195.61 (*s*, C=O); 174.31 (*s*, CO_2Me); 138.22 (*s*, arom. C); 134.53 (*d*, arom. CH); 129.70 (*d*, arom. CH); 129.20 (*s*, C(3) of pyrrole); 127.13 (*d*, arom. CH); 124.06 (d, C(2) of pyrrole); 121.55 (*d*, C(5) of pyrrole); 112.56 (*d*, C(4) of pyrrole); 51.42 (*q*, CO_2Me); 39.80 (*t*, $CH_2C(O)$–pyrrole); 34.10 (*t*, CH_2CO_2Me); 29.37 (*t*, CH_2); 29.37 (*t*, CH_2); 29.35 (*t*, CH_2); 29.29 (*t*, CH_2); 29.20 (*t*, CH_2); 29.11 (*t*, CH_2); 24.93 (*t*, $CH_2CH_2C(O)C$); 24.30 (*t*, $CH_2CH_2CO_2Me$). MS: 433 (4.1, M^+), 249 (100), 234 (48), 141 (23), 94 (49), 77 (62). HR-MS: 433.191860 (M^+, $C_{23}H_{31}NO_5S^+$; calc. 433.192295).

*Methyl 8-{[(4-Methylphenyl)sulfonyl]hydrazono}-8-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]octanoate* (**6a**). 1-[(4-Methylphenyl)sulfonyl]hydrazine (10.6 g, 57 mmol) was added to a soln. of **5a** (18 g, 48 mmol) in anh. EtOH (60 ml). The mixture was heated at reflux for 30 min. The solvent was removed to afford a brown solid, which was washed with cold Et_2O, and dried *in vacuo* to give **6a** as a colorless solid (23.5 g, 92%). IR (KBr): 3434 (br.), 3221*m*, 3137*w*, 2936*m*, 2860*w*, 2361*s*, 2342*s*, 1739*s*, 1654*w*, 1592*w*, 1559*w*, 1496*w*, 1449*m*, 1375*s*, 1332*s*, 1274*w*, 1240*w*, 1183*s*, 1163*s*, 1120*w*, 1064*s*, 954*w*, 921*w*, 869*w*, 817*w*, 728*m*, 687*m*, 669*m*, 633*m*, 618*m*, 590*s*, 553*m*, 458*w*, 419*w*. ^{1}H-NMR: 7.91–7.82 (*m*, 5 arom. H); 7.68–7.58 (*m*, arom. H); 7.57–7.47 (*m*, 2 arom. H); 7.34–7.28 (*m*, 2 arom. H, H–C(2) of pyrrole); 7.08 (*t*, *J* = 2.6, H–C(5) of pyrrole); 6.61–6.57 (*dd*, *J* = 1.3, 1.3, H–C(4) of pyrrole); 3.69 (*s*, CO_2Me); 2.45–2.23 (*m*, CH_2CO_2Me, $CH_2C{=}N$, Ph*Me*); 1.71–1.49 (*m*, $CH_2CH_2CO_2Me$); 1.48–1.36 (*m*, $CH_2CH_2C{=}N$); 1.19–1.35 (*m*, 2 CH_2). ^{13}C-NMR: 174.18 (*s*, C=O); 151.15 (*s*, arom. C); 144.10 (*s*,

arom. C); 138.60 (*s*, arom. C); 134.18 (*d*, arom. CH); 129.54 (*d*, arom. CH); 128.07 (*d*, arom. CH); 127.94 (*s*, C(3) of pyrrole); 126.84 (*d*, arom. CH); 121.75 (d, C(2) of pyrrole); 119.54 (*d*, C(5) of pyrrole); 112.15 (*d*, C(4) of pyrrole); 51.59 (*q*, CO_2Me); 33.73 (*t*, CH_2CO_2Me); 29.07 (*t*, $CH_2C{=}N$); 28.45 (*t*, CH_2); 27.55 (*t*, CH_2); 25.40 (*t*, $CH_2CH_2C{=}N$); 24.17 (*t*, $CH_2CH_2CO_2Me$); 21.59 (*q*, Ph*Me*). MS: 545 (0.3, M^+), 361 (32), 246 (42), 220 (31), 141 (33), 106 (30), 91 (71), 77 (100). HR-MS: 545.165040 (M^+, $C_{26}H_{31}N_3O_6S_2^+$; calc. 545.165430).

*Methyl 12-{[(4-Methylphenyl)sulfonyl]hydrazono}-12-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]dodecanoate* (**6b**). Prepared in analogy to **6a**, but starting from **5b**. The title compound was isolated as a colorless solid in 71% yield. IR (KBr): 3443 (br.), 3256*m*, 3208*m*, 3137*m*, 3067*w*, 2977*s*, 2853*m*, 2360*w*, 2341*w*, 1734*s*, 1599*m*, 1495*m*, 1449*m*, 1366*s*, 1334*s*, 1175*s*, 1097*m*, 1068*s*, 917*m*, 813*m*, 728*s*, 685*m*, 623*s*, 590*s*, 561*m*. ^{1}H-NMR: 7.88–7.82 (*m*, 4 arom. H); 7.67–7.60 (*m*, arom. H); 7.56–7.49 (*m*, 2 arom. H); 7.42–7.39 (*m*, H); 7.33–7.28 (*m*, 2 arom. H, H–C(2) of pyrrole); 7.11–7.08 (*dd*, $J = 2.2$, 2.2, H–C(5) of pyrrole); 6.60 (*q*, $J = 1.7$, H–C(4) of pyrrole); 3.68 (*s*, CO_2Me); 2.41 (*s*, Ph*Me*); 2.38–2.28 (*m*, CH_2CO_2Me, $CH_2C{=}N$); 1.69–1.59 (*m*, $CH_2CH_2C{=}N$); 1.47–1.16 (*m*, 7 CH_2). MS: 601 (2.1, M^+), 417 (39), 276 (63), 246 (72), 221 (42), 141 (39), 106 (56), 91 (76), 80 (59), 77 (100). HR-MS: 601.227910 (M^+, $C_{30}H_{39}N_3O_6S_2^+$; calc. 601.228030.

*Methyl 8-[1-(Phenylsulfonyl)-1*H*-pyrrol-3-yl]octanoate* (**7a**) *and Methyl 8-[2,5-Dihydro-1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]octanoate* (**7′a**). $NaBH_3CN$ (1.15 g, 18 mmol) was added to a soln. of **6a** (3.34 g, 6 mmol) in glacial AcOH (60 ml), and the mixture was stirred at 40° for 80 min. The reaction was quenched with ice-cold, distilled H_2O (150 ml), and the mixture was extracted with Et_2O (3 × 120 ml). The combined org. extracts were washed with sat. aq. $NaHCO_3$ soln. (strong gas evolution!) and H_2O, until neutral, dried ($MgSO_4$), and concentrated on a rotatory evaporator. The resulting oil was purified by CC (SiO_2; AcOEt/hexanes 1:9) to afford **7a** (1.51 g, 68%) as a colorless, soapy solid, together with the side product **7′a** (21%).

Data of **7a**. TLC (hexanes/AcOEt 9:1): R_f 0.25. IR (KBr): 3439*w*, 3126*m*, 3076*w*, 3031*w*, 3006*w*, 2922*s*, 2847*s*, 2533*w*, 2358*w*, 1904*w*, 1732*s*, 1584*w*, 1477*m*, 1445*m*, 1366*s*, 1307*m*, 1253*s*, 1221*m*, 1183*s*, 1107*s*, 1060*s*, 952*w*, 885*w*, 848*w*, 799*m*, 756*m*, 731*s*, 690*s*, 639*s*, 623*m*, 588*s*, 558*s*, 485*w*, 411*w*. ^{1}H-NMR: 7.87–7.79 (*m*, 2 arom. H); 7.63–7.55 (*m*, arom. H); 7.53–7.45 (*m*, 2 arom. H); 7.10–7.05 (*dd*, $J = 2.4$, 2.4, H–C(2) of pyrrole); 6.92–6.87 (*m*, H–C(5) of pyrrole); 6.17–6.12 (*m*, H–C(4) of pyrrole); 3.67 (*s*, CO_2Me); 2.40–2.25 (*m*, CH_2CO_2Me, $CH_2C(C){=}C$); 1.67–1.42 (*m*, $CH_2CH_2CO_2Me$, $CH_2CH_2C(C){=}C$); 1.35–1.20 (*m*, 3 CH_2). ^{13}C-NMR: 174.26 (*s*, C=O); 139.26 (*s*, arom. C); 133.56 (*d*, arom. CH); 130.09 (*s*, C(3) of pyrrole); 129.24 (*d*, arom. CH); 126.63 (*d*, arom. CH); 120.92 (*d*, C(2) of pyrrole); 117.24 (*d*, C(5) of pyrrole); 114.88 (*d*, C(4) of pyrrole); 51.44 (*q*, CO_2Me); 34.04 (*t*, CH_2CO_2Me); 29.82 (*t*, $CH_2C(C){=}C$); 29.02 (*t*, CH_2); 28.96 (*t*, CH_2); 26.68 (*t*, $CH_2CH_2C(C){=}C$); 24.87 (*t*, $CH_2CH_2CO_2Me$). MS: 363 (18, M^+), 221 (100), 141 (34), 80 (72), 77 (82). HR-MS: 363.150420 (M^+, $C_{19}H_{25}NO_4S^+$; calc. 363.150430).

Data of **7′a**. TLC (hexanes/AcOEt 9:1): R_f 0.16. ^{1}H-NMR: 7.88–7.80 (*m*, 2 arom. H); 7.63–7.48 (*m*, 3 arom. H); 5.28–5.22 (*m*, CH=C); 4.14–4.06 (*m*, $NCH_2CH{=}C$); 4.04–3.96 (*m*, $NCH_2C(C){=}C$); 3.67 (*s*, CO_2Me); 2.30 (*t*, $J = 7.5$, CH_2CO_2Me); 2.01–1.91 (*m*, $CH_2C(C){=}C$); 1.66–1.50 (*m*, $CH_2CH_2CO_2Me$); 1.43–1.14 (*m*, 4 CH_2). ^{13}C-NMR: 174.24 (*s*, C=O); 139.66 (*s*, arom. C); 137.26 (*s*, CH=*C*); 132.59 (*d*, arom. CH); 129.10 (*d*, arom. CH); 127.35 (*d*, arom. CH); 117.85 (*d*, *C*H=C); 56.49 (*t*, $NCH_2C(C){=}C$); 55.05 (*t*, $NCH_2CH{=}C$); 51.48 (*q*, CO_2Me); 34.01 (*t*, CH_2CO_2Me); 28.96 (*t*, $CH_2C(C){=}C$); 28.94 (*t*, CH_2); 28.55 (*t*, CH_2); 27.08 (*t*, $CH_2CH_2C(C){=}C$); 24.84 (*t*, $CH_2CH_2CO_2Me$). MS: 365 (0.9, M^+), 224 (95), 208 (51), 192 (45), 141 (51), 94 (33), 80 (92), 77 (100).

*Methyl 12-[1-(Phenylsulfonyl)-1*H*-pyrrol-3-yl]dodecanoate* (**7b**). Prepared as described for **7a**, but starting from **6b**. The title compound **7b** was isolated as a colorless, soapy solid in 73% yield. The side product **7′b** (11%) was detected by ^{1}H-NMR, but not isolated. TLC (hexanes/AcOEt 8:2): R_f 0.65. IR (KBr): 3438*w*, 3164*w*, 3127*m*, 3077*w*, 3032*w*, 3007*w*, 2914*s*, 2847*s*, 2532*w*, 2361*w*, 1905*w*, 1731*s*, 1630*w*, 1570*w*, 1537*w*, 1477*m*, 1444*s*, 1367*s*, 1316*m*, 1287*m*, 1262*s*, 1230*s*, 1207s, 1183*s*, 1167*s*, 1108*s*, 1061*s*, 953*m*, 887*w*, 799*m*, 756*m*, 731*s*, 691*s*, 639*s*, 623*s*, 588*s*, 559*s*. ^{1}H-NMR: 7.86–7.80 (*m*, 2 arom. H); 7.63–7.56 (*ttt*, $J = 1.3$, 2.4, 1.3, arom. H); 7.53–7.45 (*m*, 2 arom. H); 7.09–7.06 (*dd*, $J = 2.2$, 2.2, H–C(2) of pyrrole); 6.92–6.88 (*m*, H–C(5) of pyrrole); 6.18–6.14 (*dd*, $J = 1.7$, 1.7, H–C(4) of pyrrole); 3.67 (*s*, CO_2Me); 2.41–2.28 (*tt*, $J = 7.5$, 7.5, CH_2CO_2Me, $CH_2C(C){=}C$); 1.69–1.58 (*m*, $CH_2CH_2CO_2Me$); 1.56–1.43 (*m*, $CH_2CH_2C(C){=}C$); 1.37–1.18 (*m*, 7 CH_2). ^{13}C-NMR: 174.35 (*s*, C=O); 139.24 (*s*, arom. C); 133.55 (*d*, arom. CH); 130.22 (*s*, C(3) of pyrrole); 129.23 (*d*, arom. CH); 126.62 (*d*, arom. CH); 120.88 (*d*, C(2) of pyrrole); 117.22 (*d*, C(5) of pyrrole); 114.93 (*d*, C(4) of pyrrole); 51.44 (*q*, CO_2Me); 34.09 (*t*, CH_2CO_2Me); 29.90 (*t*, $CH_2C(C){=}C$); 29.51 (*t*, CH_2); 29.40 (*t*, CH_2); 29.35 (*t*, CH_2); 29.22 (*t*, CH_2); 29.18 (*t*, CH_2); 29.12 (t, CH_2); 26.72 (*t*, $CH_2CH_2C(C){=}C$); 24.92 (*t*, $CH_2CH_2CO_2Me$). MS: 419 (22, M^+), 278 (81), 221 (100), 141 (71), 80 (90), 77 (89). HR-MS: 419.214020 (M^+, $C_{23}H_{33}NO_4S^+$; calc. 419.213031).

*8-(1*H*-Pyrrol-3-yl)octanoic Acid* (**8a**). A soln. of **7a** (1.74 g, 4.8 mmol) in a 2:1 (*v*/*v*) mixture (60 ml) of MeOH and 5M aq. NaOH was refluxed for 1.5 h, and then allowed to cool to r.t. The MeOH was removed under

reduced pressure, and the aq. mixture was acidified with HCl to pH 3, and then extracted with Et_2O (3×20 ml). The combined org. extracts were washed neutral with H_2O, dried ($MgSO_4$), and concentrated under reduced pressure to afford **8a** as a colorless solid (0.98 g, 98%). IR (KBr): 3383*s*, 3042 (br.), 2920*s*, 2849*s*, 2703*w*, 2651*w*, 2610*w*, 1697s, 1549*w*, 1493*w*, 1465*m*, 1441*m*, 1400*m*, 1342*m*, 1309*m*, 1275*m*, 1238*s*, 1211*m*, 1185*m*, 1160*w*, 1074*m*, 1007*w*, 961*w*, 912*m*, 776*s*, 737*m*, 716*m*, 681*m*, 624*w*, 582*m*. ^{1}H-NMR: 8.12–7.88 (*m*, NH); 6.76–6.70 (*dd*, $J = 2.6$, 2.6, H–C(2) of pyrrole); 6.61–6.55 (*m*, H–C(5) of pyrrole); 6.12–6.08 (*dd*, $J = 2.6$, 2.6, H–C(4) of pyrrole); 2.53–2.44 (*m*, $CH_2C(C)=C$); 2.34 (*t*, $J = 7.5$, CH_2CO_2H); 1.71–1.51 (*m*, $CH_2CH_2CO_2H$, $CH_2CH_2C(C)=C$); 1.43–1.30 (*m*, 3 CH_2). ^{13}C-NMR: 178.68 (*s*, C=O); 117.59 (*d*, C(2) of pyrrole); 114.81 (*d*, C(5) of pyrrole); 108.55 (*d*, C(4) of pyrrole); 33.80 (*t*, CH_2CO_2H); 31.10 (*t*, $CH_2C(C)=C$); 29.24 (*t*, CH_2); 29.11 (*t*, CH_2); 29.03 (*t*, CH_2); 26.88 (*t*, $CH_2CH_2C(C)=C$); 24.69 (*t*, $CH_2CH_2CO_2H$). MS: 209 (9, M^+), 94 (25), 80 (100). HR-MS: 209.141590 (M^+, $C_{12}H_{19}NO_2^+$; calc. 209.141579).

*12-(1*H*-Pyrrol-3-yl)dodecanoic Acid* (**8b**). Prepared in analogy to **8a**, but starting from **7b**. The title compound was isolated as a colorless solid in quant. yield. IR (KBr): 3390*s*, 3041*m*, 2919*s*, 2848*s*, 1693*s*, 1543*w*, 1494*w*, 1467*m*, 1438*m*, 1405*m*, 1341*m*, 1317*m*, 1293*m*, 1265*m*, 1244*m*, 1222*s*, 1202*m*, 1183*m*, 1161*w*, 1074*m*, 1017*w*, 961*m*, 909*m*, 766*s*, 579*m*. ^{1}H-NMR: 8.10–7.91 (*m*, NH); 6.75–6.71 (*dd*, $J = 2.6$, 2.6, H–C(2) of pyrrole); 6.60–6.56 (*m*, H–C(5) of pyrrole); 6.12–6.08 (*m*, H–C(4)); 2.53–2.44 (*m*, $CH_2C(C)=C$); 2.36 (*t*, $J = 7.5$, CH_2CO_2H); 1.70–1.50 (*m*, $CH_2CH_2CO_2H$, $CH_2CH_2C(C)=C$); 1.41–1.19 (*m*, 8 CH_2). ^{13}C-NMR: 179.09 (*s*, C=O); 124.66 (*s*, C(3) of pyrrole); 117.53 (*d*, C(2) of pyrrole); 114.79 (*d*, C(5) of pyrrole); 108.54 (*d*, C(4) of pyrrole); 33.87 (*t*, CH_2CO_2H); 31.20 (*t*, $CH_2C(C)=C$); 29.58 (*t*, CH_2); 29.55 (*t*, CH_2); 29.51 (*t*, CH_2); 29.41 (*t*, CH_2); 29.22 (*t*, CH_2); 29.04 (*t*, CH_2); 26.92 (*t*, $CH_2CH_2C(C)=C$); 24.67 (*t*, CH_2CH_2COOH). MS: 265 (17, M^+), 94 (24), 80 (100). HR-MS: 265.204160 (M^+, $C_{16}H_{27}NO_2^+$; calc. 265.204179).

*8-[1-(Phenylsulfonyl)-1*H*-pyrrol-3-yl]octanamide* (**10a**). A soln. of **7a** (7 g, 19 mmol) in MeOH (50 ml) was cooled to 0° (ice bath), and NH_3 was bubbled through this soln. for 10 min. The reaction flask was sealed with a septum, and the mixture was stirred at r.t. Every second day, the mixture was cooled again to 0°, and NH_3 was bubbled through the soln. for 10 min, before the flask was sealed again. After 10 d, the resulting colorless precipitate was filtered off, washed with cold Et_2O, and dried *in vacuo* to afford **10a** (4.66 g, 69%). TLC (hexanes/AcOEt 7:3): R_f 0.08. IR (KBr): 3433*s*, 3395*m*, 3337*m*, 3220*m*, 3116*m*, 3101*w*, 3057*w*, 3006*w*, 2924*m*, 2908*m*, 2849*m*, 2579*w*, 2488*w*, 2421*w*, 2362*w*, 1658*s*, 1618*m*, 1584*w*, 15.27*w*, 1471*m*, 1448*m*, 1415*m*, 1369*s*, 1323*w*, 1285*w*, 1261*m*, 1216*w*, 1169*s*, 1111*s*, 1060*s*, 791*m*, 732*s*, 681*m*, 622*s*, 582*s*, 554*m*. ^{1}H-NMR: 7.88–7.80 (*m*, 2 arom. H); 7.63–7.56 (*m*, arom. H); 7.54–7.46 (*m*, 2 arom. H); 7.11–7.05 (*m*, H–C(2) of pyrrole); 6.93–6.88 (*m*, H–C(5) of pyrrole); 6.18–6.14 (*dd*, $J = 1.7$, 1.7, H–C(4) of pyrrole); 5.58–5.14 (*m*, NH_2); 2.41–2.32 (*m*, $CH_2C(C)=C$); 2.18–2.25 (*m*, CH_2CONH_2); 1.69–1.61 (*m*, $CH_2CH_2CONH_2$); 1.56–1.44 (*m*, $CH_2CH_2C(C)=C$); 1.37–1.20 (*m*, 3 CH_2). ^{13}C-NMR: 133.60 (*d*, arom. CH); 130.07 (*s*, C(3) of pyrrole); 129.27 (*d*, arom. CH); 126.64 (*d*, arom. CH); 120.91 (*d*, C(2) of pyrrole); 117.22 (*d*, C(5) of pyrrole); 114.89 (*d*, C(4) of pyrrole); 35.79 (*t*, CH_2CONH_2); 29.79 (*t*, $CH_2C(C)=C$); 29.07 (*t*, CH_2); 29.01 (*t*, CH_2); 28.94 (*t*, CH_2); 26.66 (*t*, $CH_2CH_2C(C)=C$); 25.39 (*t*, $CH_2CH_2CONH_2$). MS: 348 (0.8, M^+), 77 (100). HR-MS: 349.1579 (M^+, $C_{18}H_{24}N_2O_3S^+$; calc. 349.1585).

*12-[1-(Phenylsulfonyl)-1*H*-pyrrol-3-yl]dodecanamide* (**10b**). Prepared in analogy to **10a**, but starting from **7b**. The title compound was isolated as a colorless solid in 77% yield. TLC (CH_2Cl_2/MeOH 9:1): R_f 0.68. ^{1}H-NMR: 7.88–7.78 (*m*, 2 arom. H); 7.63–7.56 (*m*, arom. H); 7.54–7.46 (*m*, 2 arom. H); 7.09–7.06 (*dd*, $J = 2.2$, 2.2, H–C(2) of pyrrole); 6.93–6.88 (*m*, H–C(5) of pyrrole); 6.18–6.14 (*dd*, $J = 1.7$, 1.7, H–C(4) of pyrrole); 5.51–5.15 (*m*, NH_2); 2.41–2.32 (*m*, $CH_2C(C)=C$); 2.27–2.18 (*m*, CH_2CONH_2); 1.70–1.60 (*m* $CH_2CH_2CONH_2$); 1.55–1.43 (*m*, $CH_2CH_2C(C)=C$); 1.38–1.18 (*m*, 7 CH_2).

*8-(1*H*-Pyrrol-3-yl)octanamine* (**9a**). $LiAlH_4$ was added to a well-stirred soln. of **10a** (0.71 g, 2 mmol) in anh. THF (20 ml) over a period of 2.5 h. The mixture was heated at reflux for 16 h. The reaction was quenched with 2M aq. NaOH soln., until gas evolution ceased. Then, distilled H_2O was added, and the mixture was stirred at r.t. for 4 h. The THF was removed on a rotatory evaporator, and to the remaining 'wet' solid, distilled H_2O and CH_2Cl_2 were added. The org. layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure to afford **9a** (0.38 g, 95%) as an oil. IR (KBr): 3400*m*, 3215*m*, 2920*s*, 2850*s*, 1561*s*, 1535*s*, 1485*s*, 1469*s*, 1431*m*, 1341*m*, 1065*m*, 765*s*. ^{1}H-NMR: 8.14–7.75 (*m*, NH_2); 6.75–6.65 (*m*, H–C(2) of pyrrole); 6.60–6.50 (*m*, H–C(5) of pyrrole); 6.12–6.00 (*m*, H–C(4) of pyrrole); 2.71–2.59 (*m*, CH_2NH_2); 2.52–2.39 (*m*, $CH_2C(C)=C$); 1.64–1.51 (*m*, $CH_2CH_2NH_2$); 1.50–1.18 (*m*, 6 CH_2, $CH_2CH_2C(C)=C$). ^{13}C-NMR: 124.58 (*s*, C(3) of pyrrole); 117.53 (*d*, C(2) of pyrrole); 114.78 (*d*, C(5) of pyrrole); 108.49 (*d*, C(4) of pyrrole); 42.25 (*t*, CH_2NH_2); 33.86 (*t*, $CH_2CH_2NH_2$); 31.18 (*t*, $CH_2C(C)=C$); 29.67 (*t*, CH_2); 29.50 (*t*, CH_2); 29.45 (*t*, CH_2); 26.92 (*t*, $CH_2CH_2C(C)=C$); 26.88 (*t*, $CH_2CH_2CH_2NH_2$). MS: 194 (60, M^+), 94 (51), 80 (100). HR-MS: 195.1856 (M^+, $C_{12}H_{22}N_2^+$; calc. 195.1861).

*12-(1*H*-Pyrrol-3-yl)dodecanamine* (**9b**). Prepared in analogy to **9a**, but from **10b**. The title compound was isolated as a colorless solid in 77% yield. IR (KBr): 3399 (br.), 2918*s*, 2850*s*, 1566*m*, 1471*m*, 1070*m*, 767*m*. ^{1}H-NMR: 8.25–7.91 (*m*, NH_2); 6.73 (*q*, *J* = 2.4, H–C(2) of pyrrole); 6.61–6.50 (*m*, H–C(5) of pyrrole); 6.13–6.02 (*m*, H–C(4) of pyrrole); 2.72–2.65 (*m*, CH_2NH_2); 2.53–2.44 (*m*, $CH_2C(C)=C$); 1.66–1.52 (*m*, $CH_2CH_2NH_2$); 1.50–1.14 (*m*, 9 CH_2). ^{13}C-NMR: 124.67 (*s*, C(3) of pyrrole); 117.53 (*d*, C(2) of pyrrole); 114.79 (*d*, C(5) of pyrrole); 108.53 (*d*, C(4) of pyrrole); 42.28 (*t*, CH_2NH_2); 33.89 (*t*, $CH_2CH_2NH_2$); 31.21 (*t*, $CH_2C(C)=C$); 29.64 (*t*, CH_2); 29.62 (*t*, CH_2); 29.60 (*t*, CH_2); 29.53 (*t*, CH_2); 29.52 (*t*, CH_2); 29.50 (*t*, CH_2); 26.94 (*t*, $CH_2CH_2C(C)=C$); 26.89 (*t*, $CH_2CH_2CH_2NH_2$). MS: 250 (40, M^+), 94 (28), 80 (100). HR-MS: 250.240660 (M^+, $C_{16}H_{30}N_2^+$; calc. 250.240899).

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Received March 14, 2005