Notiz / Note

Synthesis of Homobenzoctamine [9,10-Dihydro-9-(1-methylaminomethyl)-9,10-propanoanthracene] and Homomaprotiline [9,10-Dihydro-9-(3-methylaminopropyl)-9,10-propanoanthracene]

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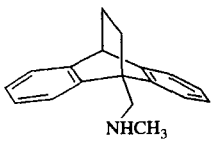
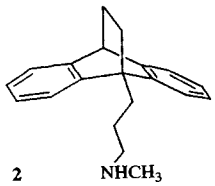
The synthesis of homobenzoctamine (**10**) and homomaprotiline (**19**) is described.

Benzoctamine (Tacitin®) (**1**) and maprotiline (Ludiomil®) (**2**) are neuroleptics which are used clinically for the treatment of mental disorders such as schizophrenia and depression[1,2]. We outline a simple and flexible route to the corresponding homologues **10** and **19**.

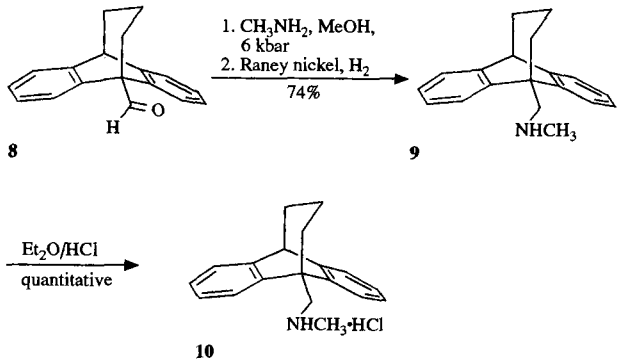


1



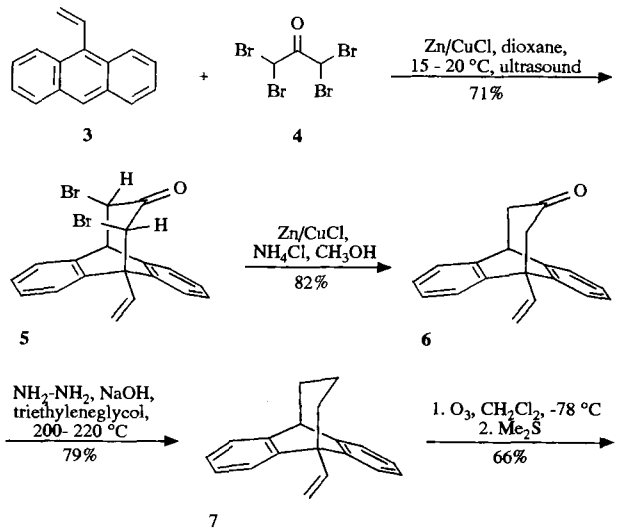
2

By following model studies[3] the cycloadduct **5** was prepared and debrominated reductively to the ketone **6**. Wolff-Kishner reduction[4] gave the tetracyclic hydrocarbon **7**, which was ozonolyzed to the crystalline aldehyde **8**. Treatment of **8** with methylamine at 6 kbar (formation of imine) and hydrogenation in situ afforded the secondary amine **9**, which was converted into the crystalline hydrochloride **10**. The overall yield of the 5-step synthesis was 23% (Scheme 1).



8 **9** **10**

Scheme 1



The synthesis of **19**, previously prepared by a Japanese group[5], is self-explanatory (Scheme 2). Hydroboration-oxidation of the tetracyclic compound **14** with $BH_3 \cdot THF$ was only moderately regioselective (**15**:**16** = 9:1). While a sterically more demanding dialkylborane was not tested, the two alcohols **15** and **16** were easily separable by chromatography. The primary alcohol **15** was converted into the chloride **17**, and methylamine (5 equiv.) was again introduced at high pressure (200 atm, 90°C, EtOH).

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Experimental

Column chromatography (silica gel, 0.02–0.63 mm, Merck) was carried out under weak positive pressure. – TLC: Precoated plates, Macherey-Nagel, Merck. – Gas chromatography: FID, N_2, Varian A 1400; glass capillary column (25 m, type OV 1 CB) and SE 54 CB (25 m fused silica, widebore). – Melting points: Büchi apparatus. – Optical rotations: Perkin-Elmer polarimeter 241. – IR: Electrophotometer 580 and FT spectrometer 1710, Perkin-Elmer. – ^1H NMR: WP 80, WH 90, WP 200 SY and AM 300, Bruker. – ^{13}C NMR: WP 200 SY, AM 300, Bruker. – MS: Spectrometer MAT 312, Finnigan. – Elementary analyses: Microanalytical lab-

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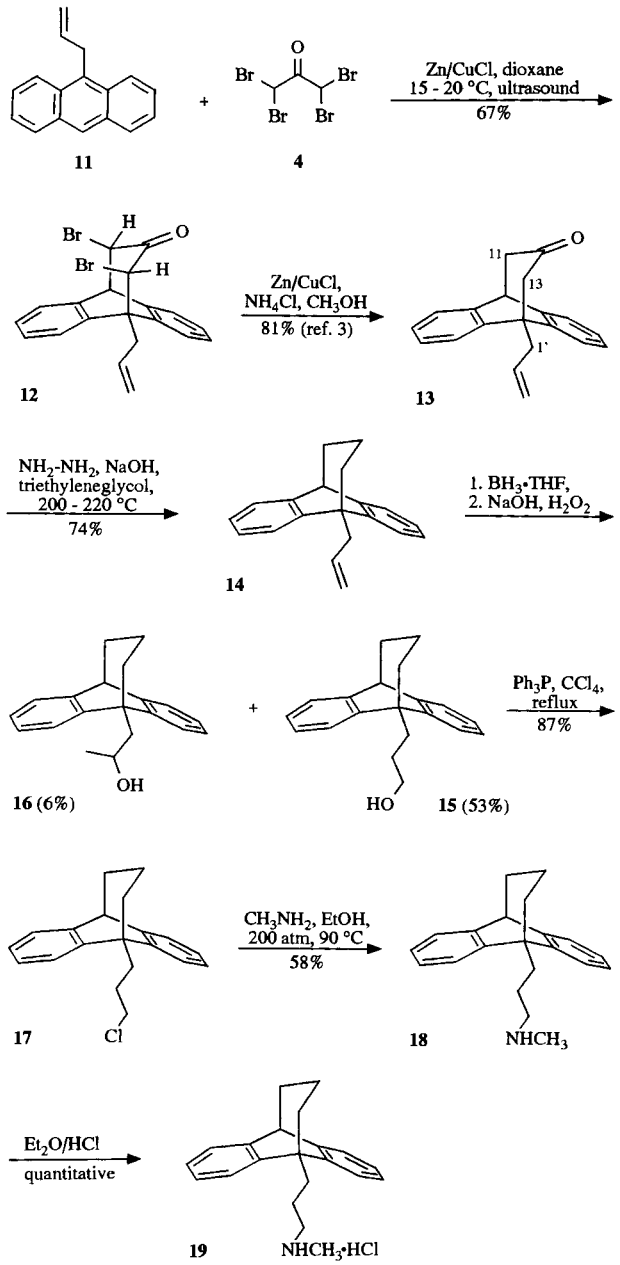
Scheme 2



oratory of the Department of Organic Chemistry. – PE: Petroleum ether. – The cycloadducts **5** and **12** were prepared as described[3].

9,10-Dihydro-9-vinyl-9,10-propanoanthracen-12-one (**6**): A flame-dried apparatus was charged with zinc powder (9.35 g, 143 mmol), CuCl (1.40 g, 14.3 mmol) and NH_4Cl (2.86 g) in absol. MeOH (30 ml). The cycloadduct **5**[3] (6.00 g, 14.3 mmol) in absol. MeOH (70 ml) was added dropwise at room temperature. After stirring for ca. 12 h, the reaction mixture was filtered through silica gel. The residue was washed with Et_2O, the combined filtrates were extracted with water, dried ($MgSO_4$) and evaporated. The crude product was purified by chromatography to give **6**; yield 3.00 g (82%) of crystals, m.p. 145°C. – IR (KBr): $\tilde{\nu}$ = 2927 cm^{-1}, 1693, 1474, 1453, 1402, 1181. – ^1H NMR ($CDCl_3$): δ = 2.80 (d, J = 4 Hz, 2H, 11-H), 2.85 (s, 2H, 13-H), 4.27 (t, 1H, 10-H), 5.50 (d, J_{trans} = 18 Hz, 1H, CH=C*H*H), 5.73 (d, J_{cis} = 11 Hz, 1H, CH=CH*H*), 6.37 (dd, J = 18 Hz, J = 11 Hz, 1H, C*H*=CH_2), 7.19–7.42 (m, 8H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 43.33 (d, C-10), 47.0 (s, C-9), 50.51, 53.09 (t, C-11, C-13), 116.4 (t, CH=CH_2), 125.2–129.32 (d, arom. C), 139.64 (d, *C*H=CH_2), 141.19, 142.67 (s, arom. C), 208.33 (s, C=O). – MS: m/z (%) = 260 (26) [M^+], 230 (15), 245 (20), 203 (100), 202 (49).

$C_{19}H_{16}O$ Calcd. 260.1201 Found 260.1200 (MS)

9,10-Dihydro-9-vinyl-9,10-propanoanthracen-12-one (**7**): A mixture of ketone **6** (2.30 g, 8.84 mmol), KOH (1.47 g), hydrazine hydrate (3.53 g, 88.3 mmol, 80% solution) and triethyleneglycol[4] was stirred at 150°C for 7 h. Then the water was removed by a Dean-Stark separator, and the reaction mixture was heated for a further 8 h to 200–210°C. After cooling to room temperature, the reaction mixture was treated with dild. HCl (pH = 2 should be reached). The aqueous layer was extracted with toluene, and the combined organic phases were washed with brine. After drying ($MgSO_4$) and removal of the solvent, the crude product was purified by chromatography [silica gel, Et_2O/PE (1:5)] to give **7**; yield 1.65 g (76%) of a light yellow oil. – IR ($CHCl_3$): $\tilde{\nu}$ = 3017 cm^{-1}, 2931, 1639, 1470, 1455, 1290, 1225, 1160. – ^1H NMR ($CDCl_3$): δ = 1.20–1.39 (m, 2H, 12-H), 1.68–1.79 (m, 2H, 11-H), 1.79 (t, J = 6 Hz, 2H, 13-H), 4.02 (t, J = 4 Hz, 1H, 10-H), 5.47 (dd, J_{trans} = 18 Hz, ^2J = 2 Hz, 1H, CH=CH*H*), 5.66 (dd, J_{cis} = 10 Hz, ^2J = 2 Hz, 1H, CH=C*H*H), 6.34 (dd, J_{trans} = 18 Hz, J_{cis} = 10 Hz, 1H, C*H*=CH_2), 7.14–7.34 (8H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 22.77, 29.79, 31.43 (C-11, C-12, C-13), 46.33, 49.29 (d, C-10), 49.29 (s, C-9), 115.53 (t, C-2'), 124.75–126.37 (arom. C), 142.89 (d, C-1'), 142.94, 144.1 (s, arom. C). – MS: m/z (%) = 246 (100) [M^+], 231 (24), 217 (41), 204 (45), 203 (98), 191 (12), 178 (11).

$C_{19}H_{18}$ Calcd. 246.1409 Found 246.1408 (MS)

9,10-Dihydro-9,10-propanoanthracene-9-carbaldehyde (**8**): The tetracyclic alkene **7** (1.50 g, 6.09 mmol) was dissolved in CH_2Cl_2 (ca. 8 ml) and ozonolyzed at –78°C. After complete reaction (blue color), Me_2S (6 equiv.) was added, and the reaction mixture was stirred for 18 h at –50°C. After warming to room temperature, the volatile components were removed under reduced pressure (12 Torr). The residue was purified by chromatography [silica gel, Et_2O/PE (1:10)] to give **8**; yield 1.00 g (66%) of crystals, m.p. 96°C. – IR (KBr): $\tilde{\nu}$ = 2924 cm^{-1}, 1723, 1474, 1453, 1290. – ^1H NMR ($CDCl_3$): δ = 1.30 (m, 2H, 12-H), 1.73 (dt, J = 6 Hz, J = 4 Hz, 1H, 11-H), 1.88 (t, J = 4 Hz, 1H, 10-H), 6.80–7.33 (m, 8H, arom. H), 10.14 (s, 1H, CH=O). – ^{13}C NMR ($CDCl_3$): δ = 22.66, 28.32 (d, C-11, C-12), 29.93 (t, C-13), 45.69 (d, C-10), 123.77, 126.35, 126.45, 127.28 (d, arom. C), 139.07, 143.20 (s, arom. C), 202.16 (d, C=O). – MS: m/z (%) = 248 (20) [M^+], 220 (43), 219 (100), 192 (38), 191 (67), 189 (30), 177 (36).

$C_{18}H_{16}O$ (248.1) Calcd. C 87.77 H 5.72
Found C 87.58 H 6.0

Calcd. 248.1201 Found 248.1202 (MS)

9,10-Dihydro-9-(1-methylaminomethyl)-9,10-propanoanthracene (**9**): Methylamine (ca. 1.00 ml, ca. 8 mmol, 8.03 M solution in MeOH) was added to the aldehyde **8** (0.60 g, 2.40 mmol) in absol. MeOH (15 ml). After 48 h at 6 kbar, the solvent was evaporated. The solid residue was dissolved in MeOH (10 ml) and hydrogenated at atmospheric pressure by using Raney nickel (0.20 g). After filtration and removal of the solvent, the mixture was diluted with ice-cold half-concentrated HCl. The aqueous layer was washed with $CHCl_3$ (2×), then the aqueous layer was treated with solid KOH to reach pH = 12, saturated with NaCl and extracted with $CHCl_3$ (2×). The combined organic phases were washed with brine and dried (K_2CO_3). Removal of the solvent gave the amine **9**; yield 0.47 g

(74%). – IR ($CHCl_3$): $\tilde{\nu}$ = 3069 cm^{-1}, 3013, 2931, 2856, 1475, 1262, 1099. – ^1H NMR ($CDCl_3$): δ = 1.20–1.32 (m, 2H, 12-H), 1.48 (t, J = 6 Hz, 2H, 13-H), 1.63–1.73 (m, 2H, 11-H), 2.00 (s, 1H, NH), 2.59 (s, 3H, CH_3), 3.42 (s, 2H, 1′-H), 3.98 (t, J = 5 Hz, 1H, 10-H), 7.15–7.40 (m, 8H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 22.65, 29.59, 36.63 (t, C-11, C-12, C-13), 36.94 (q, CH_3), 46.39 (d, C-10), 46.91 (s, C-9), 55.58 (t, C-1′), 123.54, 125.87, 126.11, 126.16 (d, arom. C), 142.48, 143.57 (s, arom. C). – MS: m/z (%) = 263 (6) [M^+], 261 (29), 248 (19), 233 (18), 220 (36), 219 (100), 218 (22), 192 (32), 191 (60), 189 (24), 178 (35).

$C_{19}H_{21}N$ Calcd. 263.1674 Found 263.1674 (MS)

9,10-Dihydro-9-(1-methylaminomethyl)-9,10-propanoanthracene Hydrochloride (**10**): The amine **9** was treated with ethereal HCl to give quantitatively the hydrochloride, m.p. 246°C. – IR (KBr): $\tilde{\nu}$ = 3426 cm^{-1}, 2923, 2855, 1578, 1478, 1403, 1381, 1154, 1124. – ^1H NMR (CD_3OD): δ = 1.16 (m, 2H, 12-H), 1.55 (t, J = 6 Hz, 2H, 13-H), 1.60–1.71 (m, 2H, 11-H), 2.96 (s, 3H, CH_3), 4.10–4.15 (m, 3H, 1′-H, 10-H), 7.30–7.45 (m, 8H, arom. H). – MS: m/z (%) = 221 (47), 220 (15), 204 (13), 192 (33), 191 (100), 189 (55), 179 (31), 178 (73), 177 (37).

$C_{19}H_{22}ClN$ (299.9) Calcd. C 76.11 H 7.40 N 4.67
Found C 75.74 H 7.28 N 4.90

9,10-Dihydro-9-(2-propenyl)-9,10-propanoanthracen-12-one (**13**): The cycloadduct **12**[3] (6.50 g, 15.7 mmol) was debrominated as described for compound **6** to give **13**; yield 3.48 g (81%) of crystals, m.p. 133°C. – IR (KBr): $\tilde{\nu}$ = 2925 cm^{-1}, 1687, 1403, 1262, 1102. – ^1H NMR ($CDCl_3$): δ = 2.63 (s, 2H, 13-H), 2.77 (d, J = 4 Hz, 2H, 11-H), 3.29 (m, 2H, 1′-H), 4.29 (t, J = 4 Hz, 1H, 10-H), 5.14–5.38 (m, 2H, CH=CH_2), 5.62–5.82 (m, 1H, CH=CH_2), 7.2–7.48 (m, 8H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 37.6, 50.4, 59.4 (t, C-1′, C-11, C-13), 43.6 (s, C-9), 43.8 (d, C-10), 118.0 (t, CH=CH_2), 134.4 (d, CH=CH_2), 141.6, 142.0 (s, arom. C), 145.0, 146.1, 146.4, 146.8 (d, arom. C), 218.6 (s, C=O). – MS: m/z (%) = 274 (89) [M^+], 230 (25), 217 (44), 202 (33), 190 (35).

$C_{20}H_{18}O$ Calcd. C 274.1358 Found 274.1356 (MS)

9,10-Dihydro-9-(2-propenyl)-9,10-propanoanthracen-12-one (**14**): The ketone **13** (2.00 g, 7.30 mmol) was reduced as described for compound **7** to give **14**; yield 1.32 g (69%) of a light yellow oil. – IR ($CHCl_3$): $\tilde{\nu}$ = 3074 cm^{-1}, 3019, 2930, 1636, 1474, 1454, 1123, 1041. – ^1H NMR ($CDCl_3$): δ = 1.15–1.30 (m, 2H, 12-H), 1.54 (t, J = 6 Hz, 2H, 13-H), 1.16–1.73 (m, 2H, 11-H), 3.15 (dt, J = 6 Hz, J = 1 Hz, 2H, 1′-H), 3.98 (t, J = 4 Hz, 1H, 10-H), 5.07–5.31 (m, 2H, CH=CH_2), 5.62–5.85 (m, 1H, CH=CH_2), 7.12–7.40 (m, 8H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 23.06, 29.43, 39.83, 39.97 (t, C-1′, C-11, C-12, C-13), 45.33 (s, C-9), 46.62 (d, C-10), 116.89 (t, CH=CH_2), 124.24–126.17 (d, arom. C), 136.26 (d, CH=CH_2), 143.17, 143.57 (s, arom. C). – MS: m/z (%) = 260 (83) [M^+], 232 (26), 231 (58), 219 (98), 218 (66), 217 (72), 216 (39), 215 (63), 202 (68), 191 (100), 178 (74).

9,10-Dihydro-9-(3-hydroxypropyl)-9,10-propanoanthracene (**15**) *and 9,10-Dihydro-9-(2-hydroxypropyl)-9,10-propanoanthracene* (**16**): BH_3 · THF (1.70 ml, 1.70 mmol, 1.00 M solution in THF) was added dropwise to a well-stirred solution of **14** (1.05 g, 4.03 mmol) in THF (10 ml) at 0°C. After stirring the mixture for 12 h at room temperature, water (2 ml), 3 M NaOH (2 ml) and H_2O_2 (2 ml) were added, and stirring was continued for further 8 h. The reaction mixture was diluted with water and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was purified by chromatography [silica gel, Et_2O/PE (1:1)] to give **15** and **16**.

15: Yield 0.60 g (53%) of an oil. – IR ($CHCl_3$): $\tilde{\nu}$ = 3610 cm^{-1}, 3085, 2920, 1485, 1450, 1139, 1150. – ^1H NMR ($CDCl_3$): δ = 1.08 (m, 2H, 12-H), 1.50 (t, J = 6 Hz, 2H, 13-H), 1.53–1.79 (m, 4H, 1′-H, 11-H), 2.26–2.39 (m, 2H, 2′-H), 3.72 (t, J = 6 Hz, 2H, 3′-H), 3.95 (t, J = 5 Hz, 1H, 10-H), 7.10–7.39 (m, 8H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 22.91, 27.57, 29.65, 31.55, 39.26 (t, C-1′, C-2′, C-11, C-12, C-13), 45.86 (s, C-9), 46.31 (d, C-10), 63.42 (t, C-3′), 123.95–125.94 (d, arom. C), 142.90, 143.44 (s, arom. C). – MS: m/z (%) = 278 (8) [M^+], 260 (7), 232 (12), 219 (59), 205 (14), 191 (100), 189 (29), 178 (23).

$C_{20}H_{22}O$ Calcd. 278.1671 Found 278.1671 (MS)

16: Yield 0.07 g (6%) of an oil. – IR ($CHCl_3$): $\tilde{\nu}$ = 3500 cm^{-1}, 3190, 2950, 2890, 1490, 1470, 1450, 1250, 1150. – ^1H NMR ($CDCl_3$): δ = 1.12–1.24 (m, 2H, 12-H), 1.37 (d, J = 6 Hz, 3H, CH_3), 1.51–1.65 (m, 4H, 11-H, 13-H), 1.75 (s, 1H, OH), 2.37 (dd, J = 18 Hz, J = 4 Hz, 1H, 1′-H), 2.62 (dd, J = 18 Hz, J = 7 Hz, 1H, 1′-H), 4.12–4.27 (m, 1H, 2′-H), 7.12–7.36 (m, 8H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 22.53 (q, CH_3), 22.84, 26.91, 44.62 (t, C-11, C-12, C-13), 46.44 (d, C-10), 46.60 (s, C-9), 65.44 (d, C-2′), 67.81 (t, C-1′), 123.69–126.13 (d, arom. C), 143.12, 143.70 (s, arom. C). – MS: m/z (%) = 278 (5) [M^+], 261 (4), 260 (14), 231 (12), 220 (21), 204 (13), 192 (100), 178 (15).

9-(3-Chloropropyl)-9,10-dihydro-9,10-propanoanthracene (**17**): A mixture of the alcohol **15** (0.30 g, 1.08 mmol) and triphenylphosphane (0.38 g, 1.45 mmol) in CCl_4 (10 ml) was heated at reflux for 12 h. The reaction mixture was filtered, and the residue was washed with PE. After removal of the solvent, the crude product was purified by chromatography [Et_2O/PE (1:10)] to give **17**; yield 0.28 g (87%) of a light yellow oil. – IR ($CHCl_3$): $\tilde{\nu}$ = 3005 cm^{-1}, 2920, 1470, 1450, 910. – ^1H NMR ($CDCl_3$): δ = 1.15–1.90 (m, 2H, 12-H), 1.50–1.65 (m, 4H, 11-H, 13-H), 1.89–2.05, 2.40–2.51 (m, 4H, 1′-H, 2′-H), 3.72 (t, J = 5 Hz, 2H, CH_2Cl), 3.97 (t, J = 3 Hz, 1H, 10-H), 7.14–7.36 (m, 8H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 22.91, 27.33, 29.68, 32.85, 39.62 (t, C-1′, C-2′, C-11, C-12, C-13), 45.82 (s, C-9), 46.12 (t, CCl), 46.33 (d, C-10), 123.93, 125.89, 126.09, 126.15 (d, arom. C), 142.53, 143.48 (s, arom. C). – MS: m/z (%) = 296 (3) [M^+], 219 (45), 204 (10), 191 (100), 178 (18).

9,10-Dihydro-9-(3-methylaminopropyl)-9,10-propanoanthracene (**18**): The chloride **17** (0.20 g, 0.68 mmol) and methylamine (ca. 0.50 ml, ca. 3.40 mmol, 8.03 M solution in EtOH) in EtOH (5 ml) were heated under a pressure of 200 atm to 100°C for 18 h. After cooling to room temperature and removal of the solvent, the residue was worked up as described for compound **9** to give the amine **18**; yield 0.12 g (58%). – IR ($CHCl_3$): $\tilde{\nu}$ = 3072 cm^{-1}, 2931, 2801, 1667, 1475, 1452, 1378. – ^1H NMR ($CDCl_3$): δ = 1.13–1.29 (m, 2H, 12-H), 1.45–1.70 (m, 6H, 1′-H, 11-H, 13-H), 2.5 (s, 1H, NH), 2.25–2.38 (m, 2H, 2′-H), 2.46 (s, 3H, CH_3), 2.76 (t, J = 6 Hz, 2H, 3′-H), 3.96 (t, J = 4 Hz, 1H, 10-H), 7.15–7.38 (m, 8H, arom. H). – ^{13}C NMR ($CDCl_3$): δ = 22.14, 22.96, 29.70, 32.80, 39.65 (t, C-1′, C-2′, C-11, C-12, C-13), 36.44 (q, CH_3), 46.14 (d, C-10), 46.40 (s, C-9), 52.90 (t, C-3′), 123.94–126.26 (d, arom. C), 142.92, 143.48 (s, arom. C). – MS: m/z (%) = 291 (62) [M^+], 276 (2), 191 (14), 178 (9).

$C_{21}H_{25}N$ Calcd. 291.1987 Found 291.1987 (MS)

9,10-Dihydro-9-(3-methylaminopropyl)-9,10-propanoanthracene Hydrochloride (**19**): The amine **18** was treated with ethereal HCl to give quantitatively the crystalline hydrochloride **19**, m.p. 233°C. – IR (KBr): $\tilde{\nu}$ = 3436 cm^{-1}, 2927, 2853, 1636, 1474, 1452, 1116, 755. – ^1H NMR ($CDCl_3$): δ = 1.08–1.20, 1.43–1.62, 1.80, 2.30–2.42

(m, 10H, 1′-H, 2′-H, 11-H, 12-H, 13-H), 2.67 (s, 3H, CH_3), 3.29 (m, 2H, NCH_2), 3.96 (t, J = 3 Hz, 1H, 10-H). – MS: m/z (%) = 291 (75), 232 (11), 219 (16), 191 (20), 178 (7).

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[264/92]

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5: 143331-54-8 / **6**: 143858-40-6 / **7**: 143858-41-7 / **8**: 143858-42-8 / **9**: 143858-43-9 / **10**: 143858-44-0 / **12**: 143331-55-9 / **13**: 71131-15-2 / **14**: 71131-16-3 / **15**: 71131-17-4 / **16**: 143858-45-1 / **17**: 143858-46-2 / **18**: 71131-10-7 / **19**: 75264-98-1