Synthesis of bishomobenzoctamine 2-(9,10-dihydro-9,10-propanoanthracen-9-yl)-*N*-methylethanamine

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Tetracyclic bishomobenzoctamine as a homologue of benzoctamine **1** was synthesised. The key intermediate 9-(prop-2-en-1-yl)-9,10-dihydro-9,10-propanoanthracen-12-one was successfully synthesised via [3+4] cycloaddition of tetrabromoacetone on 9-allylanthracene by using ultrasonication at 15–20 °C followed by debromination.

Keywords: benzoctamine, homologue, antidepressant, synthesis, cycloaddition

Benzoctamine 1-(9,10-dihydro-9,10-ethanoanthracen-9-yl)-*N*-methylmethanamine **1** has been synthesised and developed into a clinically useful drug for the treatment of anxiety and tension by the Ciba-Geigy research group.[1] The key step was [4+2] cycloaddition of ethylene on anthracene-9-carboxaldehyde.

No study on the corresponding bishomobenzoctamine 2-(9,10-dihydro-9,10-propanoanthracen-9-yl)-*N*-methylethanamine **2** has yet been reported.

It is assumed from molecular model studies that the ring fold angle in bishomobenzoctamine **2** is different from benzoctamine **1**, and such a difference might be reflected in its pharmacological activities.

We outline a simple and flexible route to the corresponding bishomobenzoctamine **2** via [3+4] cycloaddition[2] by using ultrasonication at 15–20 °C. The cycloadduct **5** was prepared via [3+4] cycloaddition of 2,2,4,4-tetrabromo-acetone on allylanthracene **4**, which was obtained by the reaction of anthrone **3** with allylmagnesium bromide followed by dehydration using P_4O_{10}. The cycloadduct **5** was debrominated reductively without isolation to yield ketone **6** as key intermediate.

Wolff–Kishner reduction[3–5] of the ketone **6** gave the tetracyclic hydrocarbon **7**, which was ozonolysed to the crystalline aldehyde **8**. Reductive amination of the aldehyde **8** using a combination of the commercially available solution of methylamine in methanol, titanium(IV) isopropoxide and sodium borohydride[6] afforded the bishomobenzoctamine **2**.

Conclusion

In conclusion, we have described a simple and flexible seven-step formal synthesis of the novel compound bishomobenzoctamine **2**, from simple starting materials. The key cyclisation step was accomplished through the comparatively mild ultrasonic cycloaddition of tetrabromoacetone on allyl anthracene.

Experimental

General

IR spectra were recorded on a Perkin-Elmer 883 spectrophotometer and expressed as ν cm^{-1} NMR spectra were recorded on JEOL ECP 400 (400 MHz) in $CDCl_3$ and chemical shifts are expressed as δ ppm, and coupling constants (*J*) were given in Hz. MS spectra and HRMS were performed at the Department of Organic Chemistry of the University of Hannover-Germany using EI at 70 eV. The ultrasonic reaction was carried out using Sonerex 200, 50 W power and frequency 35 kHz.

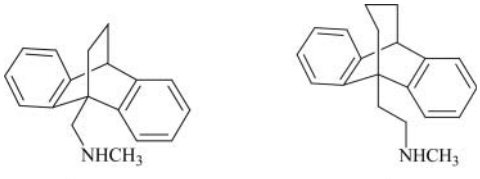
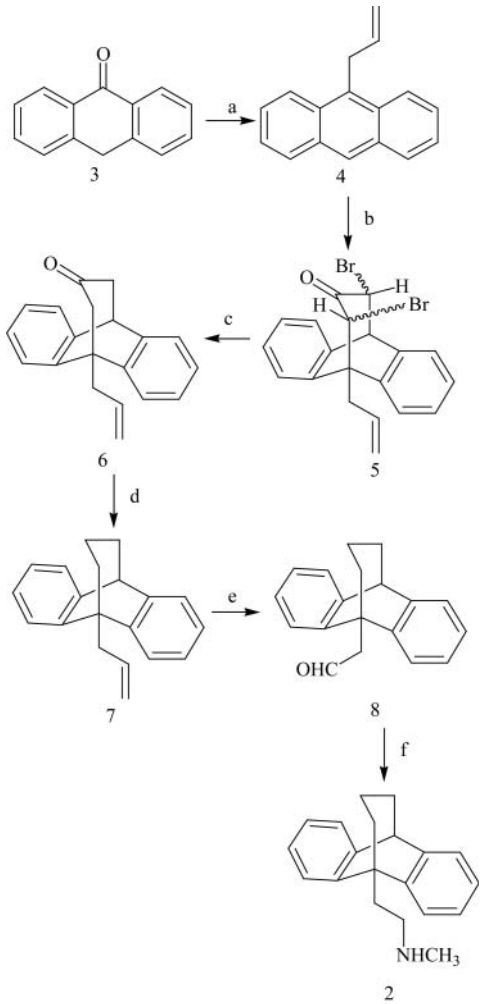


Fig. 1 Benzoctamine and bishomobenzoctamine.



Scheme 1 Reagents and conditions: (a) **1**. Allylmagnesium bromide, THF, r.t., 8h; 2. C_6H_6, P_2O_5, r.t., 6h; (b) tetrabromoacetone, Zn/CuCl, $(CH_3)_3SiCl$, dioxane, 15–20 °C, ultrasound, 8h; (c) Zn/CuCl, NH_4Cl, methanol, r.t., 6h; (d) 85% $H_2N–NH_2$, KOH, triethylene glycol 150 °C, 5h, 200–220 °C, 5h; (e) 1. O_3, CH_2Cl_2, –78 °C, 0.5 h; 2. $(CH_3)_2S$, 4 h, r.t; f) 1. CH_3NH_2, CH_3OH, r.t., 4h; 2. $NaBH_4$, r.t, 6h.

Allylanthracene (**4**): Anthrone solution (5.01 g, 25.8 mmol) in 100 mL anhydrous THF was slowly added to allyl magnesium bromide (33 mL, 33 mol, 1M solution, Aldrich). The mixture was stirred for 8 h at room temperature. The reaction mixture was subsequently acidified with 10% HCl, the organic layer was separated, and the

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aqueous layer was extracted with ether (2 × 50 mL). The combined organic layer was washed with water, dried over Na_2SO_4 and the solvent was evaporated. To the crude product was added 25 mL benzene, 6g P_2O_5 and stirred for 6 h at room temperature. P_2O_5 was filtered off and the benzene was removed under vacuum. The crude product was purified by flash column chromatography (hexane-dichloromethene 1:1 to give 6 (4.6 g, 82 %) as a yellow solid, m.p. 46 °C. IR (KBr): ν = 3047, 2945, 1620, 1444, 729 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.37 (d; *J* = 5.48 Hz, 2H, H-1′), 4.97 (dd; *J* = 1.48 Hz, *J* = 10.24 Hz, 1H, H-3′), 5.06 (dd; *J* = 1.48 Hz, *J* = 16.84 Hz, 1H, H-3′), 6.21–6.28 (m; 1H, H-2′), 7.28- 7.60 (m; 9H, Aromatic -H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ = 32.00 (C-1'), 116.00 (C-3′) 136.50 (C-2′), 124.58, 124.89, 125.36, 126.25, 127.20, 128.20, 129.08, 129.19, 130.06, 131.56, 131.71, 133.55, 134.05, 134.05. MS (EI) *m/z* (%) = 218 (100) [M^+], 203 (54), 191 (27), 176 (5), 165 (7), HRMS (EI) Calcd for $C_{17}H_{14}$ [M^+] 218.1096. Found 218.1097.

9-(Prop-2-en-1-yl)-9,10-dihydro-9,10-propanoanthracen-12-one (**6**)*:* (3.16 g, 48.32 mmol) powdered zinc, (1.35 g, 13.64 mmol) CuCl and a small amount of absol. dioxane was placed into a flame-dried flask filled. The flask was suspended into a water-filled sonicator (15 20 °C). A solution of (2.65 mL) Me_3SiCl and (5.1 g, 13.65 mmol) tetrabromo-acetone was slowly added, followed by a solution of 9-allylanthracene (2.6 g, 11.93) in 3 mL absol. dioxane. After the mixture had been sonicated for 8 h, the dioxane was evaporated and (20 mL) MeOH, (1.8 g, 7.52 mmol) zinc powder, (1.35 g, 13.64 mmol) CuCl and (4 g) NH_4Cl was added. After stirring for 6 h at room temperature, the reaction mixture was filtered through silica gel. The residue was washed with CH_2Cl_2, washed with water saturated aqueous NH_4Cl, H_2O and brine, dried with $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate 10:1 to give 9 (1.31 g, 70%) as a white solid, m.p. 128 °C. IR (KBr): ν = 3070, 2912, 1683, 1475, 1448, 717cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.61 (s; 2H, H-13), 2.75 (d; *J* = 3.68 Hz, 2H, H-11), 3. 25 (d; *J* = 5.84 Hz, 2H, H-1′), 4.27 (t; *J* = 3.68 Hz, 1H, H-10), 5.15 (dd; *J* = 1.84 Hz, *J* = 10.28 Hz, 1H, H-3′), 5.30 (dd; *J* = 1.84 Hz, *J* = 17.6 Hz, 1H, H-3′), 5.69 (m; 1H, H-2′), 7.20–7.23 (m; 8H, Aromatic-H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ = 37.62, 43.56, 43.62, 50.26, 59.42, 118.25 134.60 (aliphatic carbons), 124.98, 126.31, 126.91, 127.11, 142.01, 208.88 MS (EI) *m/z* (%) = 274 (100) [M^+], 275 (23), 231 (28), 217 (41), 216 (19), 215 (38), 203 (20), 202 (27), 191 (43), 189 (24). HRMS (EI) Calcd for $C_{20}H_{18}O$ [M^+] 274.1359. Found 274.1358.

9-(Prop-2-en-1-yl)-9,10-dihydro-9,10-propanoanthracene (**7**): A mixture of (0.88 g, 3.21 mmol) ketone 6, (0.72g, 12.83 mmol) KOH, (2.285 g, 45.7 mmol) hydrazine hydrate and (4 mL) triethyleneglycol was stirred at 150 C for 5 h. Then the water was removed by a Dean-Stark separator, and the reaction mixture was heated for a further 5 h to 200–210 °C. After cooling to room temperature, the reaction mixture was treated with dil. HCl (pH = 2 was reached). The aqueous layer was extracted with toluene, and the combined organic phases were washed with brine, dried with $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate 5:1) to give 10 (0.63 g, 57%) as a yellow oil. IR ($CDCl_3$): ν = 3068, 3016, 2958, 2926, 1473, 1452, 752cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.25–1.29 (m; 2H, H-12), 1.31 (t; *J* = 6.6 Hz, 2H, H-13), 1.63 (t; *J* = 5.88 2H, H-11), 3.19 (t; *J* = 2.58 Hz, 2H, H-1′), 3.99 (t; *J* = 3.68 Hz, 1H, H-10), 5.17 (m; 1H, H-3′), 5.27 (m; Hz, 1H, H-3′), 5.79 (m; 1H, H-2′), 7.22–7.29 (m; 8H, aromatic-H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ = 23.53, 29.86, 30.15, 39.22, 39.39, 45.71, 46.70, 46.98, 117.42, 136.70 (aliphatic carbons), 124.45, 124.85, 125.31, 126.08, 126.32, 126.37, 126.47, 143.25, 143.45, 143.85, 143.94. MS (EI) *m/z* (%) = 260 (61) [M^+], 232 (19), 231 (42), 220 (27), 219 (85), 218 (55), 217 (53), 204 (18), 203 (53), 202 (60), 192 (29), 191 (100), 189 (61), 178 (44), 176 (15),165 (36), 152 (16). HRMS (EI) Calcd for $C_{20}H_{20}$ [M^+] 260.1563. Found 260.1565.

2-(9,10-Dihydro)-9,10-propanoanthracen-9-yl)ethanal (**8**): The tetracyclic alkene 7 (0.3 g, 1.15 mmol) was dissolved in CH_2Cl_2 (ca. 9 mL) and ozonolysed at –78 °C. After complete the reaction (blue colour), Me_2S (6 equiv.) was added, and the reaction mixture was stirred for further 4 h at to room temperature, the volatile components were removed under vacuum. The crude product was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate 15:1) to give 11 (0.18 g, 60%) as a white solid, m.p. 94 °C. IR ($CDCl_3$): ν = 3064, 3018, 2931, 2856, 1728, 1477, 1452, 754 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.22–1.26 (m; 2H, H-12), 1.67 (t; *J* = 4.4 Hz, 2H, H-13), 1.72–1.72 (m; 2H, H-11), 2.81 (dd; *J* = 3.68 Hz, *J* = 16.88 Hz 1H, H-1′), 2.94 (dd; *J* = 2.96 Hz, *J* = 16.88 Hz, 1H, H-1′), 3.99 (t; *J* = 3.68 Hz, 1H, H-10), 6.96–7.23 (m; 8H, aromatic-H), 10.14 (S; H-C=O).^{13}C NMR ($CDCl_3$, 400 MHz) δ = 22.10, 22.98, 29.15, 29.30, 37.84, 37.91, 45.94, 46.53, 57.94 (aliphatic carbons), 123.35, 126.08, 126.22, 126.37, 126.51, 139.03, 142.46, 142.59, 143.21, 143.35, 202.48. MS (EI) *m/z* (%) = 262 (38) [M^+], 234(37), 233(56), 220(44), 219(80), 218(67), 205(42), 204(26), 203(31), 202(32), 192(55), 191(100), 189(53), 178(44.85), 176(17), 165(33), 152(25). HRMS (EI) Calcd for $C_{19}H_{18}O$ [M^+] 262.1359. Found 262.1358.

2-(9,10-Dihydro-9,10-propanoanthracen-9-yl)-N-methylethanamine (**2**): Titanium(IV) isopropoxide (0.1 mL, 0,25 mmol) was added to a commercially available solution of methylamine in methanol (2M, 7.5 mL) followed by the addition of the aldehyde (0.22 mL, 0.22 mmol). The reaction mixture was stirred at ambient temperature for 4h, after which sodium borohydride (7.7 mg, 0.19 mmol) was added and the resulting mixture was further stirred for another period of 4h. The reaction was then quenched by the addition of water (0.1 mL), the resulting inorganic precipitate was filtered and washed with diethyl ether (2 mL). The organic layer was separated and the aqueous part was further extracted with diethyl ether (2 × 4 mL). The combined ether extracts were dried over K_2CO_3. Removal of the solvent under vacuum gave bishomobenzoctamine **2** in high purity 0.04 g, (57%). IR ($CDCl_3$): ν = 3448, 3338, 2962, 2926, 2852, 1598, 1475, 1450, 1261, 1093, 1020, 800 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.09 (t; *J* = 6.6 Hz, 2H, H-13), 1.19–1.62 (m, 6H, H1′, H11, H-12), 2.24 (S; 3H, CH_3), 2.51–2.28 (m; 2H, H-2′), 2.32 (S; 1H, NH), 3.97 (t; *J* = 4.4 Hz, 1H, H-10), 7.19–7.40 (m; 8H, aromatic-H).MS (EI) *m/z* (%) = 277 (33) [M^+], 262 (33), 234 (16), 233 (26), 220(22), 219 (84), 218 (23), 205 (16), 203 (19), 202 (20), 192 (25), 191 (100), 189 (29), 178 (19). HRMS (EI) Calcd for $C_{20}H_{23}N$ [M^+] 277.1829. Found 277.1830.

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