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6,7,14,15-Tetrahydro[1,5]diazocino[1,2-*a*:6,5-*a*′]diindole. Synthesis of a novel pentacyclic ring system

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Abstract—In search of new lead structures for potent allosteric enhancers of antagonist binding to muscarinic M_2 receptors, the first representative of a novel heterocyclic ring system, 6,7,14,15-tetrahydro[1,5]diazocino[1,2-*a*:6,5-*a*′]diindole, has been synthesized. The new pentacyclic ring skeleton is obtained from [3-(2-dibenzylaminoethyl)indol-2-yl]-acetic acid methyl ester in three steps. © 2003 Published by Elsevier Science Ltd.

1. Introduction

Many structurally different compounds belonging to various pharmacological groups have been reported to retard the dissociation of antagonists from the muscarinic acetylcholine receptor.[1,2] This effect is based on an allosteric modulation of the antagonist-receptor complex caused by a modulator occupying a site apart from the common antagonist binding area.[3,4] The inhibition of ligand dissociation may result in a receptor subtype-specific increase of ligand binding which opens various therapeutic perspectives such as for the therapy of dementia or pain.[1]

Bisquaternary analogs of the *Strychnos* alkaloid caracurine V are among the most potent allosteric modulators of muscarinic M_2 receptors.[5] The very rigid caracurine V ring skeleton satisfies the pharmacophore model of two positively charged nitrogens at a distance of ca. 10 Å surrounded by two aromatic ring systems.[6,7]

Reduction of the caracurine V skeleton to structural features responsible for good allosteric potency provides the following pentacyclic ring system (Fig. 1).

This novel ring skeleton could become a new lead structure in search of muscarinic active compounds.

Retrosynthetic analysis suggested that the desired heterocyclic ring system could be formed by intermolecular *N*-alkylation of bromoethylindole, which should be easily obtained from the corresponding methylacetate after reduction to an alcohol. An alternative route for the critical dimerization step involves the intermolecular lactame formation from the corresponding acid (Fig. 2).

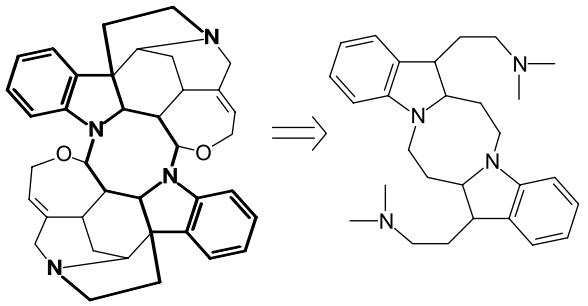

Figure 1. Structural relationship between caracurine V and the desired ring system.

2. Results and discussion

In this article we describe the synthesis of the first representative of the novel ring system employing the double alkylation strategy.

The synthesis pathway of the desired ring system is illustrated in Scheme 1.

The starting material was the known ester **1**, which was prepared according to the procedure described previously by Kuehne.[8] Thus, chlorination of *N*,*N*-dibenzyltryptamine and reaction of the resulting chloroimine with thallium dimethyl malonate, followed by monodecarbomethoxylation with lithium iodide hydrate in dimethylacetamide led to ester **1** in an overall yield of 42%. Reduction of **1** was

Keywords: 6,7,14,15-tetrahydro[1,5]diazocino[1,2-*a*:6,5-*a*′]diindole; novel pentacyclic ring system; muscarinic active compounds; dimerization of bromoethylindole.

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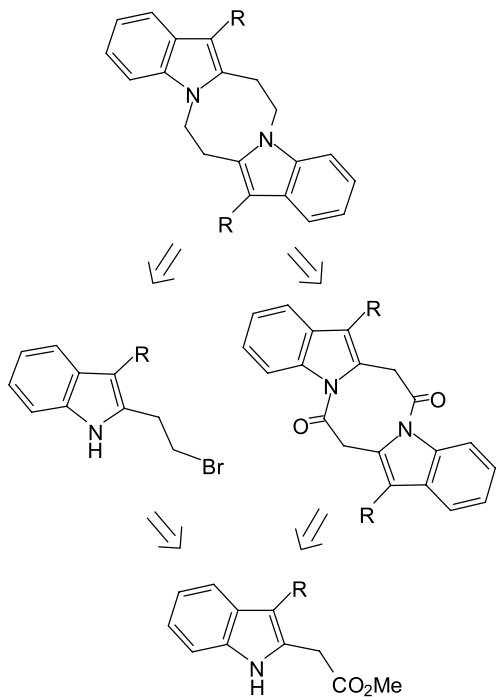


Figure 2. Retrosynthetic analysis of the desired ring system.

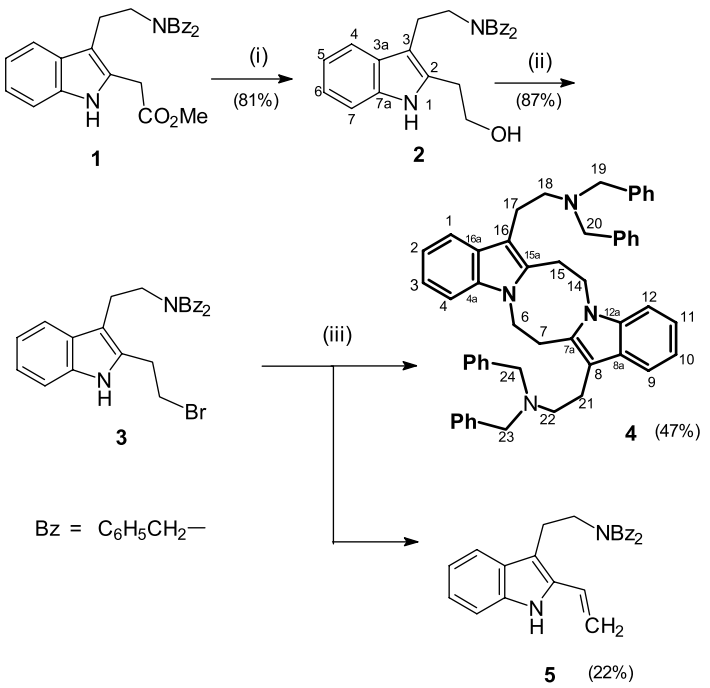
carried out with lithium aluminium hydride in THF giving alcohol **2** in 81% yield. Conversion of **2** to the corresponding alkyl bromide **3** could be achieved using carbontetrabromide (CBr_4) and tris-(dimethylamino)phosphine in 87% yield. The targeted ring system was prepared via dimerization of **3** in DMF with sodium hydride as base giving the bis(dibenzylethylamine) analog **4** in 47%. A side-reaction involving a HBr elimination from **3** gave 2-vinylindole **5** in 22% yield. Compounds **4** and **5** could be separated by column chromatography on silica gel. Another possible four-ring by-product resulting from the intramolecular *N*-alkylation of **3** could not be observed.

We also investigated the other route for building the title ring system via the corresponding eight-membered ring dilactame. After saponification of ester **1** to the corresponding acid, several coupling attempts were made to obtain the desired dilactame. Unfortunately, no dimerization product could be isolated after treatment of the acid with DCC, Mukaiyama's reagent,[9] 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ)[10] and 1[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI)/(dimethylamino)pyridine (DMAP).[11] Finally, we reduced the indole double bond of **1** with $NaBH_4$, CF_3COOH, expecting that the increased nucleophilic character of the indole nitrogen would facilitate the lactame formation.

Disappointingly, no cyclization product could be observed after coupling attempts of the corresponding indoline acid with coupling reagents mentioned above.

All new compounds were characterized by IR, ^1H NMR, ^{13}C NMR and MS. The NMR assignments were made using H,H-COSY and HMQC experiments. For the compound **4**, HMBC and ROESY experiments were necessary for a complete assignment.

Unlike caracurine V which is a highly symmetrical ring system with a 2-fold symmetry axis,[7] the novel ring skeleton showed no symmetry, as indicated by NMR spectroscopy. Both ^1H and ^{13}C NMR spectra of compound **4** revealed double sets of signals, each for half the molecule. Furthermore, methylene hydrogen atoms at C-6, C-7, C-14, C-17, C-19, C-20, C-21, C-22, C-23 and C-24 appeared as two, widely separated resonances. The non-equivalence of the



Scheme 1. (i) $LiAlH_4$, dry THF, room temperature, 3 h, (ii) CBr_4, $P(NMe_2)_3$, dry CH_2Cl_2, room temperature, 16 h, (iii) NaH, dry DMF, 0°C, 15 min, room temperature, 20 min.

methylene hydrogen atoms suggested a high rigidity of the novel ring system.

3. Conclusion

In conclusion, we have presented a short route towards the new 6,7,14,15-tetrahydro[1,5]diazocino[1,2-*a*:6,5-*a*′]-diindole ring skeleton. Starting from the known [3-(2-dibenzylaminoethyl)indol-2-yl]-acetic acid methyl ester, the first member of this new heterocyclic class could be achieved in three steps in an overall yield of 33%. This method opens an easy route to many new analogs with various *N*-substituents.

4. Experimental

4.1. General

All melting points were determined using a capillary melting point apparatus (Gallenkamp, Sanyo) and are uncorrected. Column chromatography was carried out on silica gel 60 (0.063–0.200 mm) obtained from Merck. A Bruker AV-400 spectrometer was used to obtain ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra, respectively. The ^{1}H NMR spectrum of **4** was recorded at 600 MHz on Bruker AV-600 spectrometer. The chemical shifts (δ) are reported in ppm relative to $CDCl_3$ (7.24 for ^{1}H, 77.0 for ^{13}C). Mass spectra were determined on a Finnigan MAT 8200 spectrometer. IR spectra, recorded as ATR, were obtained by using a Bio Rad, PharmalyzIR instrument. Elemental analyses were performed by the microanalytical section of the Institute of Anorganic Chemistry, University of Würzburg.

4.2. Materials

Starting materials and reagents were obtained from commercial suppliers. Ester **1** was prepared according to the procedure of Kuehne.[8]

4.2.1. 2-[3-(2-Dibenzylaminoethyl)indol-2-yl]ethanol (2). The solution of ester **1** (1.72 g, 4.2 mmol) in dry THF (20 ml) was added dropwise to the suspension of $LiAlH_4$ (0.23 g, 6.3 mmol) in dry THF (30 ml) at 0°C under argon. The mixture was stirred at room temperature for 3 h. After cooling to 0°C, 2 ml of water was slowly added, followed by the careful addition of 2 ml of 15% NaOH and 4 ml of water. The reaction mixture was stirred at room temperature for 1 h and filtered. The precipitant was washed with THF and the combined THF solutions were dried over anhydrous Na_2SO_4 and evaporated. Purification by column chromatography (SiO_2, $CHCl_3$/MeOH, 10/1), gave 1.30 g (81%) of alcohol **2** as a pale yellow solid. Crystallization from ether/hexane afforded an analytical sample: mp 77–78°C; TLC R_f=0.56 (SiO_2, $CHCl_3$/MeOH, 10/1); FT-IR (ATR) ν (cm^{-1}) 3348, 3052, 2889, 1456, 1356, 1063, 1015, 735, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (br, 1H, NH), 7.40–6.97 (m, 14H), 3.72 (s, 4H, 2×–CH_2–Ph), 3.71 (t, 2H, J=5.8 Hz, –CH_2–CH_2–OH), 2.87 (m, 2H, –CH_2–CH_2–N), 2.75 (t, 2H, J=5.8 Hz, –CH_2–CH_2–OH), 2.67 (m, 2H, –CH_2–CH_2–N), 1.79 (br, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5 (C-7a), 135.3 (C-3a), 133.0 (C-2), 128.92, 128.94, 128.7, 128.1 (benzene rings), 126.8 (C-3), 121.1 (C-5), 118.9 (C-4), 118.1 (C-6), 110.3 (C-7), 62.3 (–CH_2–CH_2–OH), 58.5 (2×–CH_2–Ph), 54.0 (–CH_2–CH_2–N), 28.8 (–CH_2–CH_2–OH), 22.1 (–CH_2–CH_2–N); MS (EI, 70 eV) *m*/*z* (rel. int) 384 [M^+] (1), 210 (60), 91 (100). Anal. calcd for $C_{26}H_{28}N_2O$: C, 81.21; H, 7.34; N, 7.29. Found: C, 81.06; H, 7.02; N, 7.22.

4.2.2. 2-(2-Bromoethyl)-3-(2-dibenzylaminoethyl)indole (3). The solution of $P(NMe_2)_3$ (2.61 g, 16 mmol) in dry CH_2Cl_2 (30 ml) was added dropwise to the mixture of alcohol **2** (1.52 g, 4.0 mmol) and CBr_4 (2.62 g, 8.0 mmol) in dry CH_2Cl_2 (60 ml) at 0°C. After stirring for 16 h at room temperature, the reaction mixture was washed with water (3×50 ml) and brine 30 ml, dried over anhydrous Na_2SO_4 and evaporated. Purification by column chromatography (SiO_2, EtOAc/hexane, 1/5), gave the compound **3** (1.55 g, 87%) as a pale yellow solid. Crystallization from ether/hexane afforded an analytical sample: mp 130°C; TLC R_f=0.32 (SiO_2, EtOAc/hexane, 1/5); FT-IR (ATR) ν (cm^{-1}) 3221, 2900, 1456, 750, 698, 654; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (br, 1H, NH), 7.61–6.95 (m, 14H), 3.75 (s, 4H, 2×–CH_2–Ph), 3.34 (t, 2H, J=7.1 Hz, –CH_2–CH_2–Br), 3.10 (t, 2H, J=7.1 Hz –CH_2–CH_2–Br), 2.85 (m, 2H, –CH_2–CH_2–N), 2.67 (m, 2H, –CH_2–CH_2–N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4 (C-7a), 133.2 (C-3a), 129.3, 129.0, 128.9, 128.3 (benzene rings), 127.2 (C-2), 121.6 (C-5), 119.2 (C-4), 118.4 (C-6), 110.6 (C-7), 108.0 (C-3), 59.1 (2×–CH_2–Ph), 54.4 (–CH_2–CH_2–N), 32.0 (–CH_2–CH_2–Br), 30.1 (–CH_2–CH_2–Br), 22.5 (–CH_2–CH_2–N); MS (CI, NH_3 gas, 150 eV) *m*/*z* (rel. int) 449 (10), 447 (9) $[M+1]^+$ (8), MS (EI, 70 eV) *m*/*z* (rel. int) 367 (6), 210 (100), 91 (92). Anal. calcd for $C_{26}H_{27}BrN_2$: C, 69.48; H, 6.50; N, 6.23. Found: C, 69.22; H, 6.42; N, 5.82.

4.2.3. 8,16-Bis-(2-dibenzylaminoethyl)-6,7,14,15-tetrahydro[1,5]diazocino[1,2-*a*:6,5-*a*′]diindole (4) and 2-vinyl-3-(2-dibenzylaminoethyl)-indole (5). The suspension of NaH (0.07 g, 2.9 mmol) in dry DMF (10 ml) was added dropwise to the solution of **3** (0.5 g, 1.1 mmol) in dry DMF (20 ml) at 0°C. The reaction mixture was stirred for 20 min at 0°C and then for 15 min at room temperature. Diethylether (30 ml) and cold water (30 ml) were added and the aqueous phase was extracted with diethylether (2×30 ml). The combined ether extracts were washed with water (2×15 ml) and brine (15 ml), dried over anhydrous Na_2SO_4 and evaporated. Purification by column chromatography (SiO_2, EtOAc/hexane, 1/3), gave the desired dimer compound **4** (0.2 g, 47%) as a colorless solid and compound **5** (0.09 g, 22%) as a yellow solid. Crystallization of **4** from ether/hexane afforded an analytical sample: mp 130°C; TLC R_f=0.56 (SiO_2, EtOAc/hexane, 1/3); FT-IR (ATR) ν (cm^{-1}) 3221, 2900, 1456, 750, 698, 654; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (d, 1H, J=8.5 Hz, H-4), 7.36 (d, 4H, J=7.0 Hz), 7.23–7.09 (m, 14H), 7.03 (ddd, 1H, J=8.3, 7.1, 1.0 Hz, H-11), 7.00–6.97 (m, 5H), 6.49 (d, 1H, J=8.3 Hz, H-12), 6.48 (dd, 1H, J=7.2, 1.0 Hz, H-9), 6.43 (t, 1H, J=7.2 Hz, H-10), 3.79–3.72 (m, 2H, H^b-14 and H^b-6), 3.70 (d, 2H, J=13.7 Hz, H^b-19 and H^b-20), 3.63 (d, 2H, J=13.7 Hz, H^a-19 and H^a-20), 3.17 (ddd, 1H, J=13.8, 12.1, 3.3 Hz, H^a-14), 2.90 (d, 2H, J=13.9 Hz, H^b-23 and H^b-24), 2.81 (ddd, 1H, J=13.9, 10.1, 6.1 Hz, H^b-17), 2.74

(ddd, 1H, J=13.9, 9.7, 6.1 Hz, H^a-17), 2.64 (ddd, 1H, J=13.7, 10.2, 6.5 Hz, H^a-6), 2.61–2.51 (m, 4H, CH_2-15 and CH_2-18), 2.54 (d, 2H, J=13.9 Hz, H^a-23 and H^a-24), 2.40–2.48 (m, 2H, H^b-7 and H^b-21), 2.13 (ddd, 1H, J=12.5, 10.2, 6.6 Hz, H^a-7), 1.99 (ddd; 1H, J=14.1, 11.9, 4.5 Hz, H^a-21), 1.86 (ddd, 1H, J=12.5, 12.5, 4.5 Hz, H^b-22), 0.85 (m, 1H, H^a-22); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4 (C-12a), 140.0, 139.9, 128.7, 128.4, 128.2, 127.9, 126.8, 126.3 (benzene rings), 135.0 (C-4a), 134.6 (C-8a), 132.8 (C-15a), 129.3 (C-16a), 127.6 (C-11), 122.7 (C-9), 120.5 (C-3), 119.5 (C-2), 118.4 (C-1), 117.9 (C-10), 112.3 (C-4), 109.6 (C-16), 106.2 (C-12), 85.5 (C-7a), 59.7 (C-8), 58.6 (C-19 and C-20), 57.4 (C-23 and C-24), 54.0 (C-18), 48.5 (C-22), 38.4 (C-14), 35.0 (C-6), 30.7 (C-21), 29.7 (C-7), 21.9 (C-17), 21.7 (C-15); MS (CI, NH_3 gas, 150 eV) m/z (rel. int) 733 [M^+] (39), MS (EI, 70 eV) m/z (rel. int), 641 (51), 522 (33), 210 (70); 91 (100). Anal. calcd for $C_{52}H_{52}N_4$: C, 85.21; H, 7.15; N, 7.64. Found: C, 85.00; H, 7.32; N, 7.61. Crystallization of **5** from $CHCl_3$/hexane afforded an analytical sample: mp 111–113°C; TLC R_f=0.45 (SiO_2, EtOAc/hexane, 1/3); FT-IR (ATR) ν (cm^{-1}) 3411, 3010, 2818, 1450, 1026, 881, 737, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (br, 1H, NH), 7.44–6.98 (m, 14H), 6.70 (dd, 1H, J=17.5, 11.5 Hz, $-CH$=CH_2), 5.41 (d, 1H, J=17.5 Hz, $-CH$=CH^aH^b), 5.22 (d, 1H, J=11.5 Hz, $-CH$=CH^aH^b), 3.74 (s, 4H, 2×$-CH_2-$Ph), 2.98, (m, 2H, $-CH_2-CH_2-$N), 2.74 (m, 2H, $-CH_2-CH_2-$N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8 (C-7a), 136.1 (C-3a), 132.2 (C-2), 128.8, 128.7, 128.1 (benzene rings), 126.8 (C-3), 125.4 ($-CH$=CH_2), 122.9 (C-5), 119.3 (C-4), 119.0 (C-6), 110.7 ($-CH$=CH_2), 110.4 (C-7), 58.6 (2×$-CH_2-$Ph), 54.2 ($-CH_2-CH_2-$N), 22.1 ($-CH_2-CH_2-$N); MS (EI, 70 eV) m/z (rel. int) 366 [M^+] (2), 210 (100), 149 (33), 91 (97). Anal. calcd for $C_{26}H_{26}N_2$: C, 84.74; H, 7.66; N, 7.60. Found: C, 84.37; H, 7.37; N, 7.22.

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