The Synthesis of 1,2,3,3a,4,5,6,11-Octahydro-6,11a-methano-11a*H*-benzo[4,5]cycloocta[1,2-*c*]pyrroles. A New Heterocyclic Ring System

Engelbert Ciganek*[1], Ann S. Wright [2], and Gregory A. Nemeth

Chemical and Physical Sciences, The DuPont Merck Pharmaceutical Co.,
Experimental Station Box 80353, Wilmington DE 19880-0353 USA

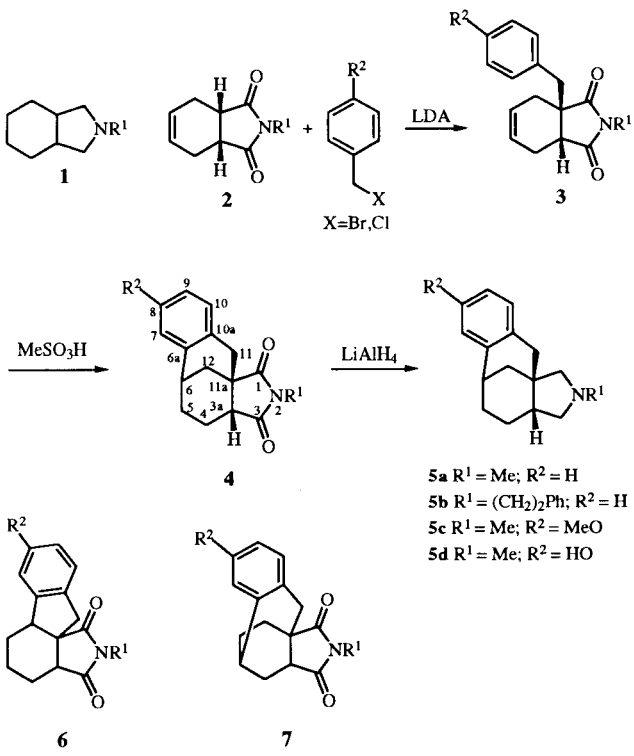
Received June 22, 1995

The synthesis of the novel 1,2,3,3a,4,5,6,11-octahydro-6,11a-methano-11a*H*-benzo[4,5]cycloocta[1,2-*c*]-pyrrole system by acid-catalyzed cyclization of *cis*-3a-benzyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-diones is described.

J. Heterocyclic Chem., **32**, 1637 (1995).

In the course of a project directed at the preparation of sigma antagonists as antipsychotics [3] it became of interest to synthesize rigidized analogs of the selective sigma ligands **1** [4]. To this end we carried out the synthesis of the novel 1,2,3,3a,4,5,6,11-octahydro-6,11a-methano-11a*H*-benzo[4,5]cycloocta[1,2-*c*]pyrrole ring system as outlined in Scheme I. Alkylation of imides **2** with the appropriate benzyl halide in the presence of lithium diisopropylamide gave the substituted imides **3**. Treatment of these with methanesulfonic acid produced the tetracyclic imides **4**. The structure was determined by a detailed nmr study of isomer **4c** (see Experimental) which excluded the possible alternate structures **6** and **7** for the cyclization product. Reduction of the imides **4** with lithium aluminum hydride produced the target compounds **5**. Demethylation of the ether **5c** with potassium methylmercaptide gave the phenol **5d** which was of interest as a potential analgesic because of its distant structural relationship to morphine.

Scheme I



EXPERIMENTAL

The ^1H (300 MHz) and ^{13}C (75 MHz) nmr spectra were determined in deuteriochloroform unless otherwise specified. For imide **4c**, spectra were acquired at 399.95 and 100.59 MHz, respectively. Mass spectra were obtained by chemical ionization (ammonia of methane) or by electron ionization. Melting points were measured in unsealed capillary tubes and are uncorrected. The tetrahydrofuran used was EM Science anhydrous grade (stored over 4Å sieves). Magnesium sulfate was used throughout for drying solutions in organic solvents.

8-Methoxy-2-methyl-4,5,6,11-tetrahydro-6,11a-methano-11a*H*-benzo[4,5]cycloocta[1,2-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (**4c**). General Procedure.

To a solution of 4.5 ml (3.12 g, 31 mmoles) of diisopropylamine in 45 ml of tetrahydrofuran was added below -30° 6 ml of 2.5 *M n*-butyllithium (15 mmoles), the mixture was cooled to -65° and a solution of 4.95 g (28 mmoles) of *cis*-2-methyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (**2a**) in 15 ml of tetrahydrofuran was added. The mixture was stirred at -65° for 30 minutes, 5.70 g (35.8 mmoles) of 4-methoxybenzyl chloride in 15 ml of tetrahydrofuran was added, the cooling bath was removed and stirring was continued for 18 hours. Toluene (100 ml) and water (50 ml) were added, the aqueous phase was extracted with two 30-ml portions of toluene, and the combined organic phases were washed with 5% hydrochloric acid, water, and 10% aqueous sodium carbonate solution, and dried. Removal of the solvents from the dried solution and short-path distillation of the residue (6.42 g) gave a fraction (2.31 g, 29%) distilling at 200-230° bath temperature/0.002 mm, which was essentially pure *cis*-3a-(4-methoxybenzyl)-2-methyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (**3c**) and which was used in the next step without further purification; ^1H nmr had δ 7.0 (d, J = 9 Hz, 2 H), 6.8 (d, J = 9 Hz, 2 H), 5.9 (m, 2 H), 3.8 (s, 3 H), 3.2 (d, J = 13.5 Hz, 1 H), 3.0 (m, 1 H), 2.8 (s, 3 H), 2.7 (d, J = 13.5 Hz, 1 H), 2.6-2,7 (m, 2 H), 2.0-2.2 (m, 2 H); ^{13}C nmr: δ 24.1, 25.6, 32.0, 42.3, 43.3, 50.6, 55.5, 114.0, 114.3, 128.1, 128.3, 131.3, 159.1, 179.7, 182.6.

A mixture of 2.10 g of imide **3c** and 20 ml of methanesulfonic acid was stirred at room temperature for 8 hours (or 1 hour at 60°), 100 ml of methylene chloride was added, and the cooled mixture was made basic with 15% aqueous sodium hydroxide solution.

Removal of the solvent from the dried organic phase gave 2.19 g (104%) of essentially pure title compound as an oil; ^{1}H nmr: δ 7.08 (d, J = 8.4 Hz, 1 H, H_{10}), 6.78 (d/d, J = 8.4/2.8 Hz, 1 H, H_9), 6.68 (d, J = 2.8 Hz, 1 H, H_7), 3.83 (s, 3 H, OMe), 3.53 (d, J = 16.5 Hz, 1 H, H_{11}), 3.14-3.19 (m, 1 H, H_6), 3.07 (s, 3 H, NMe), 2.68 (d/d, J = 16.5, 2.3 Hz, 1 H, H_{11}), 2.66 (d/d, J = 8.0/3.4 Hz, 1 H, H_{3a}), 2.04-2.16 (m, 1 H, H_{12}), 2.06-2.12 (m, 1 H, H_4), 1.75-1.83 (m, 2 H, H_5), 1.65 (d/d/d, J = 12.8/2.3/2.3 Hz, 1 H, H_{12}), 1.39-1.50 (m, 1 H, H_4). The structure was confirmed by COSY, heteronuclear multiple quantum 2D (HMQC) and multiple bond heteronuclear multiple quantum (HMBC) experiments. These were run using the pulse sequences provided by Varian Associates which are based on the work of Summers *et al.* [5]. The HMQC data set, 2048 x 512 x 2, was collected using a 2-second relaxation delay and a J value of 140 Hz for the one-bond proton-carbon coupling. The data were processed in a phase-sensitive mode in t_2 and in absolute value mode in t_1. The data set was zero filled to give 2048 x 4096 points after transforming. The HMBC data set, 2048 x 512 x 2, was collected using a 2-second relaxaion delay and a value of 140 Hz for the one-bond, and 7 Hz for the multiple-bond proton-carbon coupling constants. The data were processed in absolute value mode in both t_1 and t_2. Zero filling was used to give a data set of 2048 x 4096 points. Proton-proton correlated 2D (COSY) spectra were acquired with a 45° observed pulse with 4096 x 512 points. These data were processed in absolute value mode and zero filled to give a final data set of 4096 x 2048 points. The COSY shows that the C_{3a} methine proton couples to only one of the C_4 methylene protons. These are in turn coupled to the C_5 methylene protons. Likewise, the C_6 methine proton shows coupling to only one of the protons on each of the C_5 and C_{12} methylenes. The points of attachment of the aromatic ring were determined using the HMBC data. The C_{10} proton shows long-range couplings to carbons 8, 6a, and 11, and the C_{11} protons show long-range couplings to the C_1 carbonyl as well as carbons 6a, 10, 10a, 3a, and 11a. This confirms one point of attachment. The other was confirmed *via* both the C_5 and C_{12} methylenes showing a long-range coupling to the 6a carbon, placing the point of attachment of the 6a carbon to be on the C_6 methine carbon.

8-Methoxy-2-methyl-1,2,3,3a,4,5,6,11-octahydro-6,11a-methano-11a*H*-benzo[4,5]cycloocta[1,2-*c*]pyrrole (**5c**).

A solution of imide **4c** (2.20 g, 7.4 mmoles) in 20 ml of tetrahydrofuran was treated under ice cooling with 20 ml of 1 *M* lithium aluminum hydride in tetrahydrofuran (20 mmoles) and the mixture was heated under reflux for 8 hours. Sequential addition of 0.8 ml of water, 0.8 ml of 15% sodium hydroxide solution, and 2.2 ml of water and concentration of the filtered mixture gave 1.64 g of crude **5c** containing *ca.* 20% of a second product. Short-path distillation (180-205°, 0.002 mm), treatment of the distillate with hydrogen chloride in ether, and crystallization of the precipitate from ethanol gave 0.85 g (39%) of the hydrochloride of the title compound, mp 239-240° dec.

Anal. Calcd. for $C_{17}H_{24}ClNO$: C, 69.49; H, 8.23; N, 4.77. Found: C, 69.34; H, 8.18; N, 4.70.

The free base had ^{1}H nmr: δ 7.0 (d, J = 8 Hz, 1 H), 6.7 (d/d, J = 8/3 Hz, 1 H), 6.6 (d, J = 3 Hz, 1 H), 3.8 (s, 3 H), 3.0 (m, 1 H), 2.5-2.8 (m, 6 H), 2.4 (s, 3 H), 1.2-2.0 (m, 7 H).

2-Methyl-1,2,3,3a,4,5,6,11-octahydro-6,11a-methano-11a*H*-benzo-[4,5]cycloocta[1,2-*c*]pyrrol-8-ol (**5d**).

A mixture of 0.89 g (3.1 mmoles) of crude amine **5c**, 1.5 g (17.4 mmoles) of potassium methylmercaptide, and 8 ml of dry dimethylformamide was stirred under nitrogen in a 140° oil bath for 12 hours, 10% hydrochloric acid (10 ml) was added with cooling, and the mixture was made basic with concentrated ammonium hydroxide solution after stirring for 15 minutes. Extraction with methylene chloride, conversion of the crude base into the hydrochloride, and crystallization from methanol gave 0.26 g (20% from imide **4c**) of **5d** hydrochloride, mp 270-272°.

Anal. Calcd. for $C_{16}H_{22}ClNO$: C, 68.68; H, 7.93; N, 5.01. Found: C, 68.62; H, 8.03; N, 4.91.

The free base had ^{1}H nmr: δ 6.9 (d, J = 8 Hz, 1 H), 6.6 (d/d, J = 8/3 Hz, 1 H), 6.5 (d, J = 3 Hz, 1 H), 2.5-3.0 (m, 7H), 2.4 (s, 3 H), 1.2-2.1 (m, 7 H)

2-Methyl-1,2,3,3a,4,5,6,11-octahydro-6,11a-methano-11a*H*-benzo[4,5]cycloocta[1,2-*c*]pyrrole (**5a**).

The hydrochloride of **5a** was obtained in 63% yield from imide **4a** after crystallization from 99% ethanol, mp 194-195°.

Anal. Calcd. for $C_{16}H_{22}ClN$: C, 72.85; H, 8.41; N, 5.31. Found: C, 72.69; H, 8.47; N, 5.29.

The free base had ^{1}H nmr: δ 7.0-7.2 (m, 4 H), 3.1 (m, 1 H), 2.5-2.9 (m, 6 H), 2.4 (s, 3 H), 1.2-2.1 (m, 7 H).

1,2,3,3a,4,5,6,11-Octahydro-2-(2-phenylethyl)-6,11a-methano-11a*H*-benzo[4,5]cycloocta[1,2-*c*]pyrrole (**5b**).

The hydrochloride of **5b** was obtained in 41% yield from imide **4b** after crystallization from benzene/hexane, mp 251° dec.

Anal. Calcd. for $C_{23}H_{28}ClN$: C, 78.05; H, 7.97; Cl, 10.02; N, 3.96. Found: C, 78.34; H, 7.90; Cl, 9.67; N, 3.58.

The free base had ^{1}H nmr: δ 7.2-7.4 (m, 5 H), 7.0-7.1 (m, 4 H), 3.1 (m, 1 H), 2.5-3.0 (m, 10 H), 1.2-2.1 (m, 7 H).and ^{13}C nmr: δ 19.7, 29.0, 33.6; 35.3, 35.8; 38.9, 40.7, 43.3, 57.8, 59.5, 67.4, 125.6, 125.7, 125.9, 128.2, 128.3, 128.5, 128.6, 137.0, 140.5, 140.6.

REFERENCES AND NOTES

[1] Current Address: 121 Spring House Way, Kennett Square PA 19348, USA.

[2] Current address: Pfizer Central Research, Groton CT

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