Synthesis and Conformational Analysis of 1-Substituted-4a-(4-chlorophenyl)-1,2,3,4-tetrahydropyrimido[6,1-*a*]isoindol-9(4a*H*)-one

Marcel K. Eberle,*† Leszek Brzechffa, and Michael J. Shapiro

Sandoz Research Institute, Department of Chemistry, East Hanover, New Jersey 07936

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The anion of 1-(4-chlorophenyl)-3-ethoxy-1*H*-isoindole was alkylated with chloroacetonitrile. Hydrolysis under acidic conditions gave 1-(4-chlorophenyl)-2,3-dihydro-3-oxo-1*H*-isoindole-1-acetonitrile in 67% yield over two steps. Catalytic hydrogenation allowed the reduction of the nitrile to 3-(2-aminoethyl)-3-(4-chlorophenyl)-2,3-dihydro-1*H*-isoindol-1-one. Heating with *p*-chlorobenzaldehyde led to the formation of 1,4a-bis(4-chlorophenyl)-1,2,3,4-tetrahydropyrimido[6,1-*a*]isoindol-9(4a*H*)-one. NMR studies revealed the stereochemistry of this compound to be cis with respect to the two 4-chlorophenyl substituents and that these were arranged in a 1,3-coaxial fashion (**4a**). Analogous observations were made for the reaction with acetaldehyde which led to the formation of 4a-(4-chlorophenyl)-1-methyl-1,2,3,4-tetrahydropyrimido[6,1-*a*]isoindol-9(4a*H*)-one.

We have reported the rearrangement[1] of 1-(4-chlorophenyl)-3-ethoxy-1*H*-isoindole (**1**) to 1-amino-4-phenylphthalazine in the presence of hydrazine and alkylations of **1** with alkylating agents like alkyl halides,[2] phenacyl bromide, and methyl chloroacetate,[3] respectively. We now describe the preparation of some novel heterocycles starting with the cyanomethylation of **1**.

In analogy to the alkylation with methyl chloroacetate, the carbanion prepared from the imino ether **1** in the presence of sodium hydride in absolute dimethylformamide was alkylated with chloroacetonitrile. Following acidic hydrolysis the 3-substituted isoindolone[4] **2** was obtained in 67% yield as a crystalline product. Catalytic hydrogenation over platinum catalyst allowed the reduction of the nitrile to the primary amine **3**.

Heating the free amine **3** with *p*-chlorobenzaldehyde in refluxing toluene gave **4** in 20% yield. We are aware of only one recent reference[5] to this ring system.[6] On the basis of ^1H and ^{13}C NMR spectroscopy a single diastereoisomer was obtained. The nonequivalency of the nonaromatic protons in the NMR spectrum of **4** provided strong evidence for a cyclic structure. This was confirmed by the DEPT ^{13}C NMR spectrum of **4** where the observed signal at 63.9 ppm was shown to be due to the C1 carbon.[7]

Minimum energy calculations on the SYBYL Molecular Modeling System (Tripos Associates) identified **4a** (see Figure 1) with the two *p*-chloro-substituted phenyl groups on the saturated pyrimidine ring in a 1,3-diaxial arrangement as the lowest energy conformation. This calculated lowest energy conformation was supported by NMR evidence observed for **4**. The low field signal at 6.6 ppm was attributed to the C1 proton. This chemical shift can be accounted for by the 1,3-periplanarity between the C1 proton and the carbonyl group.[9] Experiments using difference nuclear Overhauser effects were used to show the relative stereochemistry of **4**. It was observed that there is a negative nuclear Overhauser effect between the C1–H and the protons meta to the chlorine of the *p*-chlorophenyl ring attached to the same C1 carbon. Now that the *p*-chloro-substituted phenyl rings could be distinguished, a second experiment resulted in negative nuclear Overhauser effects between the hydrogens meta to the chlorine of the phenyl group attached to the C1 carbon (7.2 ppm) and the following hydrogens: (1) its two neighbors on the same aromatic ring (7.0 ppm), (2) the axial proton on C3 (3.4 ppm), (3) the proton on C1 (6.6 ppm), and (4) most importantly, the doublet at 6.8 ppm arising from the two equivalent hydrogens meta to the chlorine of the aromatic ring attached to C4a. This implies that the two chlorinated phenyl rings are arranged in a coaxial fashion. The observed equivalency for the 2,6 positions and 3,5 positions, respectively, in each of the two chlorinated aromatic rings indicates free rotation of these rings on the NMR time scale.

Heating the free amine **3** with acetaldehyde in refluxing toluene resulted in the formation of **5**. This was isolated as a 4:1 mixture of diastereoisomers with the major isomer having the methyl and the *p*-chlorophenyl groups in a coaxial arrangement. In the NMR spectrum of this compound there were two signals due to the methyl group and two signals due to the nonaromatic methine group. The major isomer gave rise to a doublet at 1.1 ppm and to a quartet at 5.7 ppm. In this case the methyl group is subject to a shielding effect by the *p*-chlorophenyl group and is observed at higher field while the methine proton is subject to deshielding by the carbonyl group and is observed at lower field. For the minor isomer the corresponding signals were observed at 2.0 and 4.2 ppm, respectively. These assignments were confirmed by using difference nuclear Overhauser effects as described above.

Rotational restrictions in such 1,3-interactions of phenyl rings have initially been studied in 1,8-disubstituted naphthalenes by House et al.[10] and by J. D. Roberts et al.[11]

† Present address: Preclinical Research, Department of Chemistry, Sandoz Ltd., Basel 4002, Switzerland.

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(6) Compound of different oxidation stage and with different substitution pattern.
(7) For the numbering of compound **4**, see Figure 1.
(8) Computer-generated (SYBYL) energy minimum.
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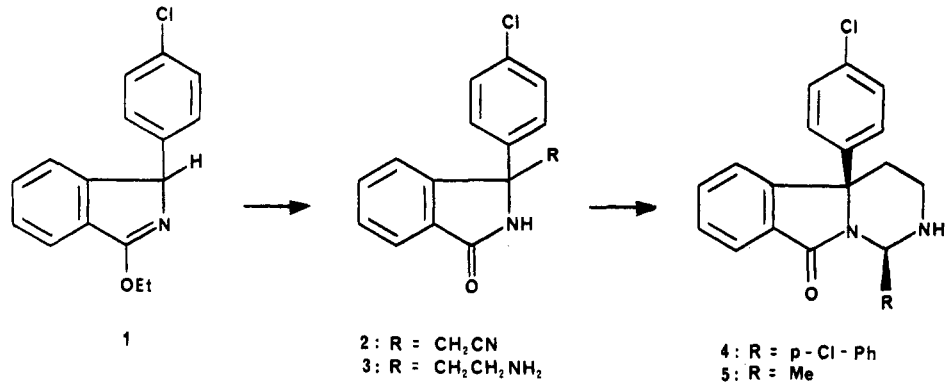
Scheme I



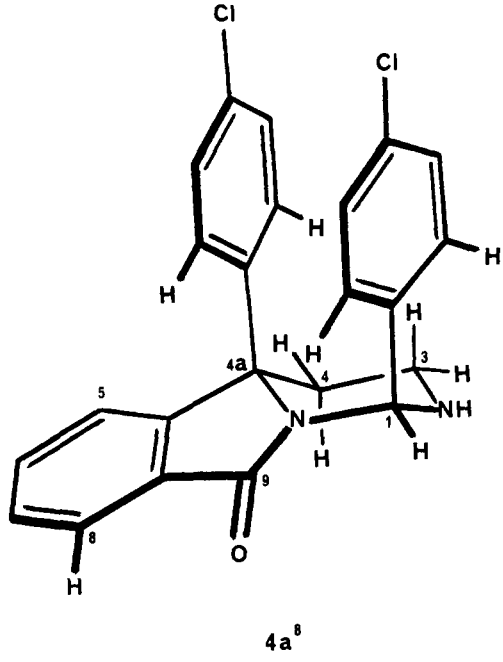


Figure 1.

Experimental Section

Proton magnetic resonance spectra were obtained on a JEOL FX 200 spectrometer and, where indicated, on a Bruker 500-MHz instrument and are recorded in hertz or δ values (parts per million) relative to TMS (tetramethylsilane) as internal standard. Infrared spectra were recorded on an Analect Instrument FX-6200 FTIR. Thin layer chromatography (TLC) was carried out on glass plates coated with silica gel HF-254, E. Merck AG. Mass spectra were measured on a LKB 9000 (low resolution) or on a VG 7070E (high resolution) mass spectrometer.

1-(4-Chlorophenyl)-2,3-dihydro-3-oxo-1*H*-isoindole-1-acetonitrile (2). To the suspension of 8.7 g (0.36 mol) of NaH in 100 mL of absolute DMF was added slowly a solution of 82 g (0.3 mol) of imino ether 1 in 600 mL of DMF. After the addition, the mixture was stirred at room temperature for 2 h under an atmosphere of nitrogen. Then 25 g (0.37 mol) of chloroacetonitrile dissolved in 100 mL of DMF was added. The mixture was stirred overnight. The solvent was evaporated under high vacuum and the residue was extracted with methylene chloride, washed with water, and dried over Na_2SO_4. The solvent was evaporated and the residue heated for 3 h with 200 mL of ethanol and 50 mL of 2 N HCl solution. The cooled solution was concentrated. The solid product was filtered off and recrystallized from ethanol/water, giving 57.0 g of the product, yield 67%, mp 172–174 °C. An analytical sample had mp 178–180 °C: MS, *m/e* 282 [M^+]; NMR 3.33 (s, 2, CH_2) 7.2–7.7 (m, 7, Ar H) 7.8–8.1 (m, 2, 1 exchangeable in D_2O, 1 Ar H + NH); IR (KBr) 1700 (C=O), 2240 (CN), 3400 (NH) cm^{-1}. Anal. Calcd for $C_{16}H_{11}ClN_2O$ (282.7): C, 68.0; H, 3.9; N, 9.9; Cl, 12.5. Found: C, 67.8; H, 3.8; N, 9.8; Cl, 12.7.

3-(2-Aminoethyl)-3-(4-chlorophenyl)-2,3-dihydro-1*H*-isoindol-1-one (3). A mixture of 20 g (0.07 mol) of **2** and 1 g of platinum oxide was hydrogenated overnight. The filtered solution was treated with dry HCl gas to give 21 g of the product, yield 93%, mp 331–333 °C: MS, *m/e* 286 [M^+]. Anal. Calcd for $C_{16}H_{15}ClN_2O{\cdot}HCl$ (323.3): C, 59.5; H, 5.0; N, 8.7; Cl, 21.9. Found: C, 59.2; H, 5.4; N, 8.6; Cl, 22.1. The free base had mp 138–140 °C.

1,4a-Bis(4-chlorophenyl)-1,2,3,4-tetrahydropyrimido[6,1-*a*]isoindol-9(4a*H*)-one (4). A solution of 10 g (0.035 mol) of free base **3** and 5.9 g (0.04 mol) of *p*-chlorobenzaldehyde in 300 mL of toluene was heated to reflux over a Dean–Stark tube for 3 days. The crude was crystallized from CH_2Cl_2/ether/hexane to give 2.7 g (19%) of product, mp 192–195 °C. After two recrystallizations, the mp was 210–212 °C: MS, *m/e* 408 [M^+]; NMR (500) 1.65 (dt, 1, C4-H_{ax}), 2.0 (s, 1, NH), 3.0 (d, 1, C4-H_{eq}), 3.2 (md, 1, C3-H_{eq}), 3.4 (dt, 1, C3-H_{ax}), 6.6 (s, 1, C1-H), 6.8 (d, 2, 3,5-H_2 of C4a-phenyl), 6.95 (d, 2, 2,6-H_2 of C4a-phenyl), 7.0 (d, 2, 3,5-H_2 of C1-phenyl), 6.9–7.0 (m, 1, C5-H), 7.2 (d, 2, 2,6-H_2 of C1-phenyl), 7.4 (m, 2, C6-H, C7-H), 7.9 (m, 1, C8-H); ^{13}C NMR 35.7 (CH_2), 38.0 (NCH_2), 63.9 (NCHN), 64.7 (C4a), 121.5–132.6 (7 signals, Ar CH), 129.1-153.4 (6 signals, Ar C), 168.9 (C=O); IR 3340, 1690 cm^{-1}. Anal. Calcd for $C_{23}H_{18}Cl_2N_2O$ (409.3): C, 67.5; H, 4.4; N, 6.8; Cl, 17.3. Found: C, 67.6; H, 4.7; N, 6.9; Cl, 17.6.

4a-(4-Chlorophenyl)-1-methyl-1,2,3,4-tetrahydropyrimido[6,1-*a*]isoindol-9(4a*H*)-one (5). A solution of 0.75 g (2.5 mmol) of the free base **3** and 0.2 g (5 mmol) of acetaldehyde in 40 mL of toluene was heated to reflux for 18 h. The solvent was evaporated and the crude was purified on a silica gel column to give 150 mg of the product: TLC, 2 components of very similar R_f values; yield 18%; mp 158–160 °C; MS, *m/e* 313 (M + 1); NMR (500 MHz) 1.1 and 2.0 (ratio 4:1) (d, 3, J = 7.5 Hz, CH_3), 5.7 and 4.2 (q, 1, J = 7.5 Hz, NCHN), 1.4–1.7 (m, 2, NH + C4-H_{ax}), 2.8–3.4 (m, 3, NCH_2CH_{eq}), 6.9–7.5 (m, 7, Ar H), 7.9 (m, 1, C8-H). Anal. Calcd for $C_{18}H_{17}ClN_2O$ (312.8): C, 69.1; H, 5.5; N, 9.0. Found: C, 68.8; H, 5.4; N, 8.8.

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Registry No. 1, 26859-66-5; 2, 109719-96-2; 3, 109719-97-3; *cis*-4, 109719-98-4; *cis*-5, 109719-99-5; *trans*-5, 109720-00-5; ClCH_2CN, 107-14-2; *p*-ClC_6H_4CHO, 104-88-1; AcH, 75-07-0.