Synthesis of 3-(4-Piperidylidene)-1,3-dihydro-2*H*-indol-2-one Derivatives

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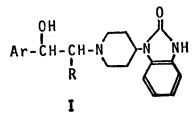
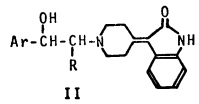
Synopsis. 3-[1-(2-Aryl-2-hydroxyethyl)-4-piperidylidene]-1,3-dihydro-2*H*-indol-2-one with structure **II**, as potential antihypertensive agent was synthesized. The intermediates, 3-[1-(2-aryl-2-oxoethyl)-4-piperidylidene]-1,3-dihydro-2*H*-indol-2-one (**5**) were prepared from 4-piperidone *via* 4 steps. Selective reduction of carbonyl group in **5** was realized using diisobutyl aluminium hydride to afford compound **II**.

As part of a research program aimed at the development of new antihypertensive agents we have investigated compounds showing a selective inhibitory activity against α-adrenoreceptor, and reported recently syntheses of 4-piperidylbenzimidazolinones (**I**), and their antihypertensive activities.[1-2] As an extension of our studies, we have attempted to modify I by replacing the benzimidazol-2-one group with other heterocycles. This paper describes the synthesis of compounds **II**, in which benzimidazole nitrogen is replaced by an sp^2 carbon atom.

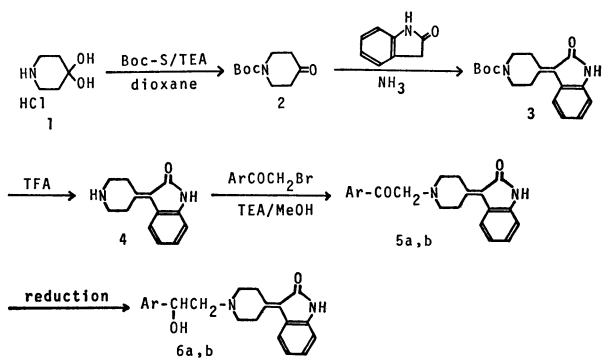


I



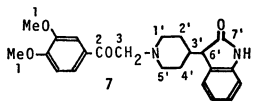
II

The target compounds were synthesized by the route indicated in the following chart. 4-Piperidone hydrate hydrochloride (**1**) reacted with *t*-butyl *s*-(4,6-dimethylpyrimidin-2-yl)thiocarbonate (Boc–S) in the presence of triethylamine (TEA) in dioxane to give 1-t-butoxycarbonyl-4-piperidone (**2**) in 81% yield.

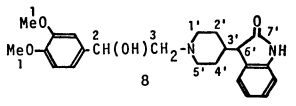


Boc : t-butoxycarbonyl
Ar : a=3,4-dimethoxyphenyl, b=3,4-methylenedioxyphenyl

Base-catalyzed condensation[3] of **2** with 2-oxindole afforded 68% of 3-(1-*t*-butoxycarbonyl-4-piperidylidene)-1,3-dihydro-2*H*-indol-2-one (**3**), which was treated with trifluoroacetic acid to produce 3-(4-piperidylidene)-1,3-dihydro-2*H*-indol-2-one (**4**) in an excellent yield. Bromoacetophenone derivatives were condensed with **4** in a similar manner as previously reported[1] to yield aminoketones **5**. It has been observed that the 3-exo double bond in 2-oxindole is reducible by several reducing agents.[3-6] Therefore, some studies were made on the selective reduction of carbonyl group in **5a**. Aminoketone **5a** was reduced with sodium cyanoborohydride in the presence of acetic acid in MeOH to afford 3-[1-[2-(3,4-dimethoxyphenyl)-2-oxoethyl]piperidin-4-yl]-1,3-dihydro-2*H*-indol-2-one (**7**) in 68% yield. [free **7**: oil, IR($CHCl_3$) 1705, 1680 (sh) cm^{-1}; **7** ·fumarate: mp 190—192 °C



7



8

(EtOH)]. The structure of **7** is based on its ^{13}C NMR spectrum,[7] in which **7** exhibited peaks at δ 195.0 (C-2 carbon), δ 140.6 (C-3′ carbon) and 156.6 (C-6′ carbon). Starting material **5a** was recovered in the Meerwein-Pondorf-Verley reduction despite of extensive examination of reducting conditions. Although certain compounds such as enolizable β-keto esters, β-diketones and sterically hindered ketones are known to be resistant to aluminium isopropoxide reduction,[8] no reduction of β-amino-ketones by this method has been reported yet. Since aluminium hydride (AlH_3) was found to be the most selective reagent for the reduction of α,β-unsaturated carbonyl group,[9] this reagent was tried. When **5a** was reduced with 3 mol equiv. of AlH_3, it afforded 3-[1-[2-(3,4-dimethoxyphenyl)-2-hydroxyethyl]piperdin-4-yl]-1-,3-dihydro-2*H*-indol-2-one (**8**) [free **8**: oil, IR ($CHCl_3$) 1705 cm^{-1}, ^1H NMR (DMSO-d_6) δ 4.60 (t, 1H, ArCHOH); **8** ·succinate: mp 166—167 °C (from EtOH)]. The structure of **8** is based on its ^{13}C NMR spectrum (δ 38.3 for C-3′ carbon, δ 50.0 for C-6′ carbon and δ 69.4 for C-2 carbon) and elemental analyses. Reduction with 1.5 mol equiv. of AlH_3 afforded a mixture of four products which were separated by preparative TLC to give **6a** (15%), **7** (7%), and **8** (26%) together with starting material **5a** (35%). In the ^1H NMR spectrum of **6a**, the C-2 proton signal was observed at δ 4.72 as a triplet, and the C-3′ and C-6′ carbon signals at δ 140.6 and 157.3, respectively in the ^{13}C NMR spectrum. In the infrared spectra, **6a** absorbed strongly at 1697 cm^{-1} due to a conjugated CONH group, while **8** absorbed at 1705 cm^{-1} due to an isolated CONH group. Although **6a** was obtained by this procedure, the yield was low and the isolation of the product was troublesome. Consequently, reduction using diisobutyl aluminium hydride ((DIBAH)[10] was further studied. The reaction with 3.5 mol equiv. of DIBAH at room temperature in CH_2Cl_2 gave a 6:4 mixture of **6a** and **8**. However, the reaction carried out at low temperatures (−10—−20 °C) afforded **6a** almost exclusively. In this manner we succeeded in the practical synthesis of **6a** in a fairly good yield. Compound **6b** was also obtained by this procedure from **5b** in 56.3% yield.

Experimental

Infrared spectra were recorded on a Hitachi 215 grating infrared spectrometer. ^{1}H NMR spectra were measured on a JNM-PFT-100 spectrometer. ^{13}C NMR spectra were obtained at 25.1 MHz on a JNM-FX-100 spectrometer, operating in the Fourier transform mode with Me_4Si as an internal standard.

1-t-Butoxycarbonyl-4-piperidone (2). A solution of 4-piperidone hydrate hydrochloride (**1**, 9.3 g, 0.061 mol), triethylamine (12.5 g, 0.124 mol), and Boc–S (14.8 g, 0.062 mol) in 100 ml of dioxane and 30 ml of water was stirred at 20 °C for 6 h and concentrated under reduced pressure. The residue was extracted with AcOEt. The extract was worked up as usual to give crude crystals, which were recrystallized from petroleum ether to give 9.8 g (81.3%) of **2** ; mp 70—72 °C. IR (KBr) 1730 (sh), 1720, 1695 cm^{-1}. Found: C, 60.38; H, 8,78; N, 6.92%. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03%.

3-[1-(t-Butoxycarbonyl)-4-piperidylidene]-1,3-dihydro-2H-indol-2-one (3). NH_3 (2.4 g, 0.14 mol), **2** (1.51 g, 7,58 mmol), and oxindole (1.01 g, 7.59 mmol) in 25 ml of EtOH were made to react according to the reported procedure[3] to afford 1.62 g (67.9%) of **3**; mp 204—205 °C (EtOH). IR (KBr) 1700, 1690 (sh), 1670 cm^{-1}. Found: C, 68.66; H, 7.05; N, 8.82%. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91%.

3-(4-Piperidylidene)-1,3-dihydro-2H-indol-2-one (4). Compound **3** (7.5 g, 23,9 mmol) was treated with 25 ml of trifluoroacetic acid (TFA) at 0 °C. After stirring the solution for 2 h at 0 °C, TFA was removed *in vacuo* and the residue was made alkaline with 1 M NaOH. The crystals separated were collected and recrystallized from AcOEt to yield 4.4 g (85.9%) of **4**; mp 234—238 °C (decomp), IR (KBr) 1697, 1680 (sh) cm^{-1}. Found: C, 72.59; H, 6.60; N, 12,81%. Calcd for $C_{23}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08%.

3-[1-[2-(3,4-Dimethyoxyphenyl)-2-oxoethyl]-4-piperidylidene]-1,3-dihydro-2H-indol-2-one (5a). Compound **5a** was obtained by the previously reported procedure[1] in 89.5% yield from **4** and 3,4-dimethoxybromoacetophenone; mp 145—146 °C (EtOH). IR (KBr) 1690 (br) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ=3.9 (s, 2H, $COCH_2N$), 10.5 (NH). ^{13}C NMR (DMSO-d_6 δ=28.0, 31.2 (C-2′, C-4′), 53.1, 53.6 (C-1′, C-5′), 55.5, 55.7 (C-1), 62.8 (C-3), 140.6 (C-3′), 156.6 (C-6′), 168.7 (C-7′), 195.0 (C-2). Found: C, 70.20; H, 6.04; N, 7.04%. Calcd for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.16; N, 7.14%. Compound **5b** was prepared in a similar manner as **5a** in 82.2% yield; mp 167.5—171 °C decomp. IR (KBr) 1698—1680 (br) cm^{-1}. NMR (DMSO-d_6) δ=3.80 ($COCH_2N$), 6.12 (OCH_2O), 10.3 (NH). Found: C, 69.96; H, 5.29; N, 7.33%. Calcd for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44%.

Reduction of 5a with DIBAH. To a cooled solution of **5a** (2.73 g, 6.96 mmol) in 160 ml of CH_2Cl_2 was added DIBAH (5.0 g, 35.2 mmol) in 70 ml of CH_2Cl_2 at −20 °C over 2 h. The solution was stirred for additional 5 h at the same temperature. Then, 60 ml of MeOH and 200 ml of water were successively added to the solution. The organic layer was separated, washed with water, dried over $MgSO_4$, and concentrated. The residue was recrystallized from AcOEt to afford 1.3 g (47.4%) of **6a**; mp 98—99 °C. IR (KBr) 1697 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ=4.72 (t, 1H, ArCHOH), 10.4 (NH). ^{13}C NMR (DMSO-d_6) δ 28.1, 31.3 (C-2′, C-4′), 53.7, 54.0 (C-1′, C-5′), 55.4, 55.5, (C-1), 65.4 (C-3), 69.7 (C-2), 14.06 (C-3′), 157.3 (C-6′), 168.8 (C-7′). Found: C, 69.89; H, 6.82; N, 6.59%. Calcd for $C_{23}H_{26}N_2O_4$; C, 70.03; H, 6.64; H, 7.10%.

Similar treatment of **5b** with DIBAH gave 56.3% of **6b**; mp 176—178 °C (from MeOH–CH_2Cl_2). IR (KBr) 1692 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ=4.72 (t, 1H, ArCHOH), 5.95 (s, 2H, OCH_2O), 10.35 (br, 1H, NH). Found: C, 69.97; H, 5.84; N, 7.33%. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.82; H, 5.86; N, 7.40%.

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7) In the ^{1}H NMR spectra of **7** and **8** the signals assignable to C-3′ and C-6′ protons overlapped with those of piperidine ring protons. Therefore the structures were confirmed by ^{13}C NMR spectroscopy.

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