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Convenient synthesis of 7-hydroxyindole

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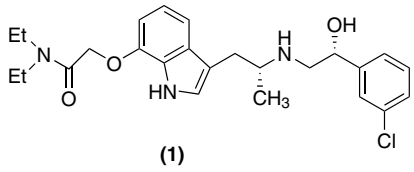
Abstract—7-Hydroxyindole, the key building block for the synthesis of AJ-9677 **1**, was prepared from indoline in six steps in 36% overall yield. AJ-9677 **1** is a potent and selective adrenaline β3-agonist being considered as a clinical candidate to treat obesity in those who are suffering from diabetes.

Regioselective syntheses of 7-hydroxyindole has been attempted by several research groups. As the 2, 3, 5 and 7 positions of the indole ring are reactive to electrophiles, the site-oriented synthesis of 7-hydroxyindole starting directly from indole is difficult.

Therefore, main approaches so far reported to the site-selectively substituted indole synthesis including 7-substituted ones started from benzene rings by constructing indole rings on them[1]. These processes afforded good yields although they need high[1d,e] or extremely low-temperature[1c,f] reaction condition using moisture-sensitive reagents. One of these methods was effectively utilized in the preparation of (*R*)-3-(2-aminopropyl)-7-benzyloxyindole which is the main component of AJ-9677 (Fig. 1) **1** by Fujii et al.[2] As for 7-hydroxyindole preparation, the Batcho–Leimgruber methods[1b] need very expensive starting materials such as 3-methyl-2-nitrophenol and dimethylformamide dimethylacetal. Also in the last step, careful control of the reduction of (*E*)-6-benzyloxy-2-nitro-β-pyrrolidinostyrene with Raney nickel and 85% hydrazine is needed.

On the other hand, there are two procedures for the synthesis of 7-substituted indoles starting from indoline[3]. Iwao and Kuraishi prepared 7-formylindoline from indoline via three steps in 50% overall yield and from which the derived 7-formyl indole is commercially available[4]. However, there is no report of 7-hydroxyindole synthesis starting from indoline.



(1)

Figure 1. Structure of AJ-9677.

In this letter we describe a convenient 6-steps synthesis of 7-hydroxyindole starting from indoline following the Scheme 1. Indoline **2** was treated with succinic anhydride in pyridine for 5 h at room temperature. 1H-Indoline-1-butanoic acid **3** was obtained in 96% yield. The acid **3** was cyclized to form azepinoindole-4,5-dione **4** in 72% yield by heating at 120 °C in PPA for 10 h. Several attempts to convert **4** to pyrrolo benzoxazine-2,5-dione **5** by Baeyer–Villiger oxidation with peracetic acid, *m*-chloroperbenzic acid, trifluoroperacetic acid, etc., were unsuccessful. However, oxidation with $K_2S_2O_8$ in 70% H_2SO_4, at −5 °C, for a few minutes gave oxidized product **5** in 75% yield.

This amide lactone **5** was hydrolyzed to 7-hydroxyindoline **6** in 3 N HCl refluxing 5 h under nitrogen gas in 87% yield. Finally, the indoline ring was oxidized to 7-hydroxyindole **7** with MnO_2 in benzene refluxing 6 h in 81% yield. Overall yield from indoline **2** was 36%. Spectroscopic data and mp of the products are shown in Ref.5. In this procedure, every reaction does not require extreme conditions or expensive reagents and the crystalline products are easy to handle for purification.

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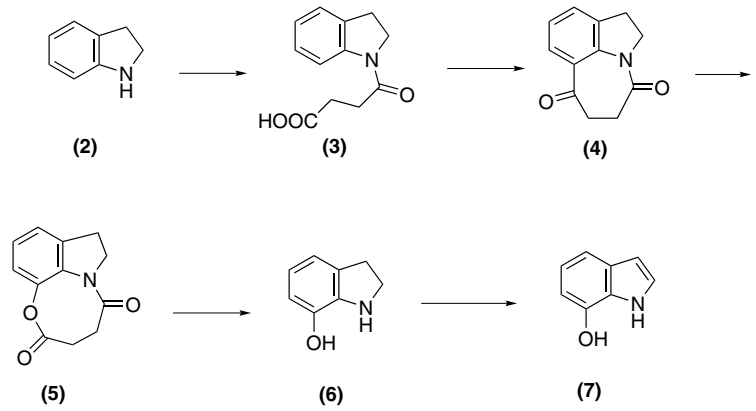

Scheme 1.

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5. (a) 1H-Indoline-1-butanoic acid **3** mp: 164 °C, IR (Nujol) ν_{max}: 1713.6, 1662.3, 1602.5, 1487.0 cm^{-1}, ^1H NMR (300 MHz, DMSO): δ 8.03 (7H, d, J = 8.1 Hz), 7.22 (4H, d, J = 7.2 Hz), 7.13 (6H, t, J = 7.2 Hz), 6.97 (5H, t, J = 7.2 Hz), 4.10 (2H, t, J = 8.4 Hz), 3.14 (3H, t, J = 8.4 Hz), 2.64–2.74 (–CO–CH_2–CH_2–CO–, m). Mass: m/z 219.0899, composition, $C_{12}H_{13}NO_3$. (b) Azepinoindole-4,7-dione **4** mp: 144 °C, IR (nujol) ν_{max}: 1679.4, 1640.9, 1606.7, 1598.2 cm^1. ^1H NMR (300 Mz, $CDCl_3$): δ 7.94 (6H, d, J = 8.1 Hz), 7.43 (4H, d, J = 6.9 Hz), 7.10 (5H, t, J = 8.1 Hz), 4.25 (2H, t, j = 7.8 Hz), 3.15 (3H, t, J = 8.4 Hz), 2.83–2.96 (–CO–CH_2–CH_2–CO–, m). Mass: m/z 201.0798, composition, $C_{12}H_{11}NO_2$. (c) Pyrrolobenzoxazine-2,5-dione **5** mp: 180–184 °C, IR (nujol) ν_{max}: 1717.9, 1640.9, 1606.7, 1576.8 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 6.98 (5H, t, J = 7.8 Hz), 6.72 (4H, d, J = 7.2 Hz), 6.64 (6H, d, J = 8.1 Hz), 4.09 (2H, t, J = 8.4 Hz), 3.10 (3H, t, J = 9.0 Hz), 2.76–2.89 (–$COCH_2CH_2CO$–, m). Mass: m/z 235.0843, composition, $C_{12}H_{11}O_3{\cdot}H_2O$ (crystallized from H_2O). (d) 7-Hydoroxyindoline **6** mp: 120–124 °C, IR (nujol) ν_{max}: 3303.6, 2598.3, 1628.1, 1593.9 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.77 (4H, d, J = 7.2 Hz), 6.67 (5H, t, J = 7.5 Hz), 6.59 (6H, d, J = 8.1 Hz), 5.30 (OH, s), 3.58 (2H, t, J = 8.1 Hz), 3.06 (3H, t, J = 8.4 Hz). Mass: m/z 135.0672, composition, C_8H_9NO. (e) 7-Hydroxyindole **7** mp: 96–99 °C, IR (nujol) ν_{max}: 3410.4, 3282.2, 1660.6, 1585.4, 1491.3, 1414.4 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.38 (NH, s), 7.23 (4H, d, J = 6.2 Hz), 7.21 (2H, t, J = 2.5 Hz),6.94 (5H, t, J = 7.9 Hz), 6.56 (6H, d, J = 6.9 Hz), 6.53 (3H, t, J = 2.1 Hz), 4.91 (OH, s). Mass: m/z 133.0531, composition C_8H_7NO.