A Facile Preparation of 1-(6-Hydroxyindol-1-yl)-2,2-dimethylpropan-1-one

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An effective synthesis of 1-(6-hydroxyindol-1-yl)-2,2-dimethylpropan-1-one (4) was developed starting from 1*H*-indole (2). The key step involved suitable utilization of 4-(1-pyrrolidino)pyridine for the removal of the chloroacetyl moiety from chloroacetic acid 1-(2,2-dimethylpropionyl)-1*H*-indol-6-yl ester (3); a possible mechanism is, also, presented. Compound 4 might lead to selectively substituted derivatives, either on the phenolic-O*H* or the indolyl-N*H*, with putative biological interest. In this respect, we found that the core structure of 1*H*-indol-6-ol (1) possesses a degree of aldose reductase inhibitory potential, at a concentration of 100 μM.

Key words 4-(1-pyrrolidino)pyridine; chloroacetyl removal; 1*H*-indol-6-ol; aldose reductase

It has been suggested that the oxygen function in the benzene portion of the indole derivatives plays a significant role in expression of biological activities.[1)]

In the present work, 1*H*-indol-6-ol[2)] (**1**) was investigated for its aldose reductase inhibitory potential. Subsequently, a suitable protected derivative of compound **1** was synthesized, as a putative scaffold for selective functionalization of either its phenolic-O*H* or indolyl-N*H* moieties.

The inhibition of the aldose reductase enzyme (AR, ALR2, E.C. 1.1.1.21) was selected to be investigated as an indicative biological property, because the activation of this enzyme is implicated in a number of pathological conditions: I) in diabetic patients, for the development of the long term complications of the disease,[3)] and II) in non diabetic individuals, for the ischemic myocardial injury,[4)] for the abnormal proliferation of vascular smooth muscle cells,[5)] and for bipolar and unipolar mood disorders.[6)] Furthermore, about 29% of human liver cancers overexpress AR which might contribute to their resistance to chemotherapy.[7)]

1*H*-indol-6-ol (**1**) was tested *in vitro* for its ability to inhibit rat lens AR. The performed assay was based on the spectrophotometric monitoring of NADPH oxidation, which is proven to be a quite reliable method.[8)] It was found that compound **1** exhibits, although week, an inhibitory activity at a concentration of 100 μM (23%, S.E.M.=5, n=3).

The synthesis of a N-protected 1*H*-indol-6-ol derivative (*i.e.* 1-benzenesulfonyl-1*H*-indol-6-ol) has been previously reported.[1)] However, it involved a seven steps sequence starting from 1-benzenesulfonyl-1*H*-pyrrole. More recently,[2)] a three steps preparation of chloroacetic acid 1-(2,2-dimethylpropionyl)-1*H*-indol-6-yl ester (**3**) from 1*H*-indole (**2**), has been reported. We considered that this compound could be converted to 1-(6-hydroxyindol-1-yl)-2,2-dimethylpropan-1-one (**4**) by the action of an appropriate nucleophile under non hydrolytic conditions (Chart 1). Although compound **1** is of interest, because it shows activity as an AR inhibitor (ARI), we consider compound **4** interesting too, because it possesses a structure which is amenable to appropriate chemical modifications which could lead to selectively substituted derivatives either on the phenolic-O*H* or the indolyl-N*H*. These types of compounds could have a putative better ARI activity (or other biological properties) than compound **1**.

For the preparation of **4**, the action of a series of tertiary amines on **3** was investigated, and representative results are shown in Table 1 (runs 1—6). A main point derived from these data is that a factor that influences the ability of the tertiary amines studied to remove the chloroacetyl moiety was their nucleophilic character. This is supported a) from the different yields obtained after the use of the 4-dimethylaminopyridine (run 2) and after the use of the 2-dimethylaminopyridine (run 4), and b) from the fact that the best overall result (*i.e.* yield in combination with reaction time) was obtained with the use of the hypernucleophilic[9,10)] catalyst 4-(1-pyrrolidino)pyridine. This compound exhibits a relatively higher nucleophilicity compared with the rest four amines referred in Table 1. As indices of nucleophilicity[11)] we used appropriately calculated[12)] $E_{(HOMO)}$ values. These values (expressed in hartees) were for the 4-(1-pyrrolidino)pyridine −0.303019, for the 4-dimethylaminopyridine −0.313050, for the 1,8-diazabicyclo[5.4.0]undec-7-ene −0.314187, for the 2-dimethylaminopyridine −0.339156 and for the triethylamine −0.352981.

The formation of a substantial amount of product **4** in the presence of triethylamine (run 6), which has comparatively

Table 1. Results from the Reaction of Certain Nucleophiles with **3**

Run	Nucleophile (mol eq)	Time (h)	Yield of **4** (%)
1	4-(1-Pyrrolidino)pyridine (3.6)	24	79[a)]
2	4-Dimethylaminopyridine (3.6)	48	51[a)]
3	1,8-Diazabicyclo[5.4.0]undec-7-ene (3.6)	48	69[a)]
4	2-Dimethylaminopyridine (7)	48	—[b)]
5	Triethylamine (3.6)	48	—[b)]
6	Triethylamine (22)	144	40[a)]

a) No starting material **3** was detected by TLC. *b*) Predominantly starting material **3**, based on TLC.

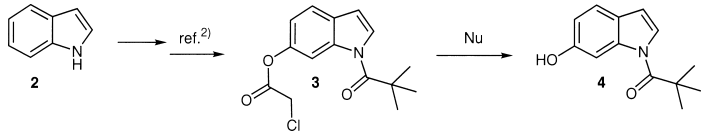

Chart 1

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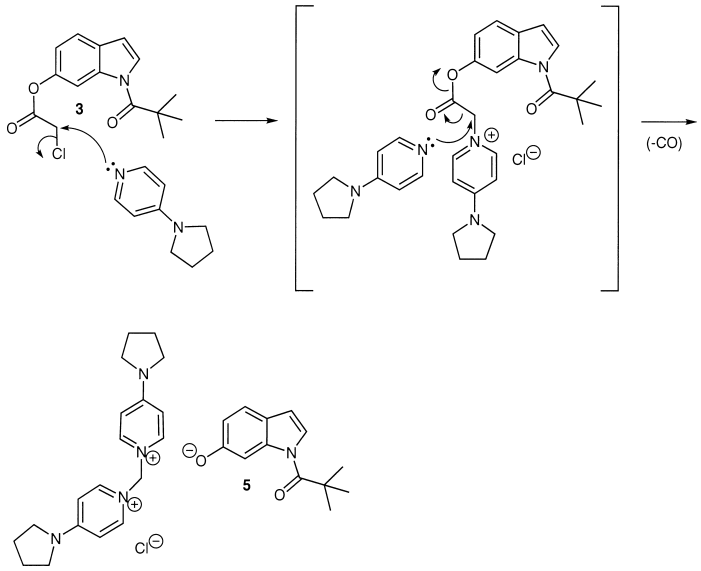

Chart 2

the lower $E_{(HOMO)}$, is probably due to the utilization of a high excess of this base, in combination with an extended reaction time period. If, instead 3.6 equivalents of triethylamine were used (run 5), only a small amount of product was formed.

A possible mechanism for the removable of the chloroacetyl moiety from **3** is shown in Chart 2. The proposed putative formation of the dimmer salt **5** could explain the necessity of the use of the amine in twice, at least, molar concentration with respect to **3** in order for the reaction to be completed. If equimolar quantities were instead used, even with the 4-(1-pyrrolidino)pyridine, the reaction always stopped approximately halfway, still after a prolonged period of time.

Experimental

Melting points are uncorrected and were determined in open glass capillaries using a Mel-Temp II apparatus. UV spectra were recorded on a Perkin-Elmer 554 spectrophotometer, IR spectra were obtained on a Perkin-Elmer 597 spectrophotometer and ^{1}H-NMR spectra on a Bruker AW-80 spectrometer with internal TMS standard. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, U.S.A.

1-(6-Hydroxyindol-1-yl)-2,2-dimethylpropan-1-one (4) A mixture of chloroacetic acid 1-(2,2-dimethylpropionyl)-1*H*-indol-6-yl ester[2] (**3**) (0.300 g, 1.02 mmol), and 4-(1-pyrrolidino)pyridine (0.546 g, 3.67 mmol) in CH_2Cl_2 (15 ml) was stirred at room temperature for 24 h, under a N_2 atmosphere. It was then poured in a mixture of CH_2Cl_2 (25 ml) and ice, acidified with a dilute aqueous HCl solution, the two phases were separated, and the aqueous was extracted with CH_2Cl_2 (2×25 ml). The combined organic layer and extracts were washed with a saturated NaCl solution, dried (Na_2SO_4), and filtered. The filtrate was mixed with silica gel (2 g), stirred at room temperature for 1 h, concentrated, and the residue was flash chromatographed on silica gel with EtOAc–petroleum ether (1 : 8) to afford the title compound (0.176 g, 79%) as a white solid, mp 130—131 °C (CH_2Cl_2–petroleum ether). ^{1}H-NMR ($CDCl_3$) δ: 1.49 (9H, s), 6.44—7.01 (3H, m), 7.39 (1H, d, J=8.4 Hz), 7.57 (1H, d, J=3.2 Hz), 8.22 (1H, s). IR (Nujol) cm^{-1}: 3580, 1685. *Anal.* Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: 71.70; 7.05; 6.45.

***In Vitro* Aldose Reductase Enzyme Assay** The test compound, 1*H*-indol-6-ol[2] (**1**), was dissolved in a 10% aqueous DMSO solution. Lenses were quickly removed from Fischer-344 rats of both sexes following euthanasia, and enzyme preparation and assay was performed as previously described.[13] The experiment was performed in triplicate.

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