An Efficient Synthesis of Streptindole

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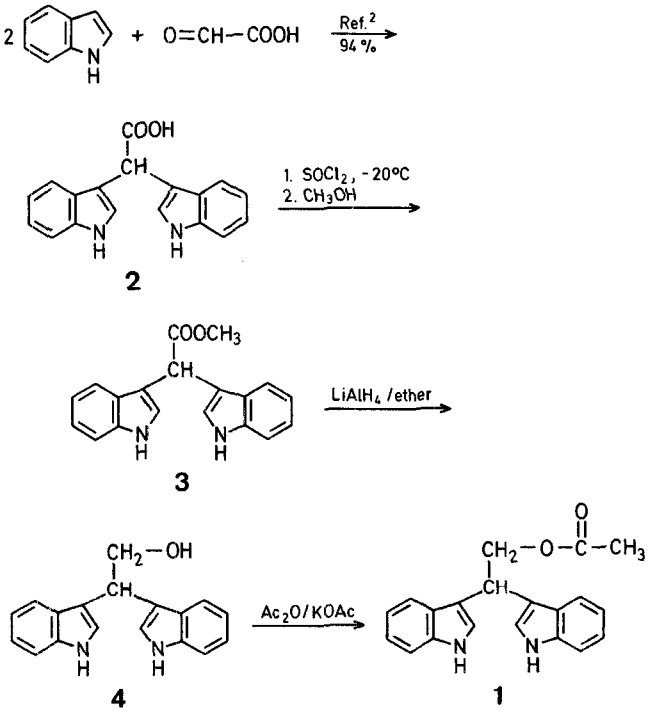
A recent report[1] described the isolation of streptindole **(1)** which is metabolised by human intestinal bacteria. This compound is the first genotoxic diindolylethane metabolite to be isolated from cultures of human bacteria and as proof of structure it was synthesised by the reaction of acetoxyacetaldehyde and indole. The yield was only 2%.



Since streptindole may be implicated in the development of colonic cancers it is of importance to have sufficient of it to enable meaningful biological tests to be conducted. Thus, we have devised an efficient, although conventional, synthesis of the compound which requires firstly the reaction of indole with glyoxylic acid to give diindolylacetic acid **(2)** which, as the methyl ester **(3)**, is reduced to the corresponding alcohol **(4)** by the action of lithium aluminium hydride. Finally, the alcohol **4** is *O*-acetylated to afford steptindole **(1)**. Although four steps are required each works well and the overall yield of pure metabolite is 50%.

Streptindole (1):

Methyl Bis[3-indolyl]-acetate **(3)**: To bis[3-indolyl]-acetic acid[2] (**2**; 2.5 g, 17.2 mmol), thionyl chloride (6 g, 51 mmol) is added dropwise, with stirring at −20 °C, followed by the addition of methanol (75 ml); the solvent and reagent are then removed by evaporation under reduced pressure affording an oil. This product is column-chromatographed on silica gel using dichloromethane as eluent; yield: 3.3 g (63%); pale yellow oil (Ref.[3], m.p. 45–50 °C).

2,2-Bis[3-indolyl]-ethanol **(4)**: A solution of the ester **3** (3 g, 9.9 mmol) in dry ether (50 ml) is added dropwise to a stirred suspension of lithium aluminium hydride (3 g, 7.9 mmol) in ether (50 ml) at 0 °C. After the addition, the temperature of the mixture is raised to ~ 20 °C, and 20 min later, saturated aqueous sodium potassium tartrate solution (10 ml) is introduced. The organic layer is separated and the residue extracted with chloroform (2 × 50 ml). The combined organic phases are washed with water (25 ml), dried with magnesium sulphate, and evaporated to give alcohol **4** as a gum. After chromatography on a short-path silica gel column, the pure alcohol **4** is obtained as a colourless crystalline solid; yield: 2.2 g (81%); m.p. 50 °C (60–80 °C petrol/toluene).

$C_{18}H_{16}N_2O$	calc.	C 78.23	H 5.84	N 10.14
(276.3)	found	78.1	5.8	10.2

Streptindole **(1)**: A mixture of alcohol **4** (0.80 g, 2.9 mmol), potassium acetate (1 g), and acetic anhydride (5 ml) is stirred at room temperature for 17 h. Ethyl acetate (20 ml) and ethanol (3 ml) are added and the mixture is stirred overnight. The solution is then washed with water (3 × 2 ml), 5% sodium hydrogen carbonate solution (3 × 2 ml), and dried with magnesium sulphate. The solvent is then evaporated to give the product as a colourless oil [T.L.C.: $R_f = 0.66$, silica, 5% ethyl acetate/dichloromethane]; yield: 0.80 g (87%); indefinite low m.p.

$C_{20}H_{18}N_2O_2$ (318.1368)

M.S.: *m/e* = 318.1374.

I.R. ($CHCl_3$): $\nu = 3400, 1730, 1620\ cm^{-1}$.

U.V. (ethanol): $\lambda_{max} = 273, 283, 290$ nm.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 1.93$ (s, 3H); 4.72 (d, 2H, $J = 6.9$ Hz); 4.93 (t, 2H, $J = 6.9$ Hz); 6.96 (d, d, 2H, $J_1 = 7.8$ Hz, $J_2 = 6.8$ Hz); 7.08 (d, d, 2H, $J_3 = 8.3$ Hz, $J_2 = 6.8$ Hz); 7.23 (s, 1H); 7.40 (d, 2H, $J_3 = 8.3$ Hz); 7.62 ppm (d, 2H, $J_1 = 7.8$ Hz).

The spectral data of compound **1** given here correspond almost exactly to those reported[1] for the natural product.

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