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UNUSUAL OXIDATION OF 2 (OR 3)-METHYLINDOLE DERIVATIVES WITH ACTIVE MANGANESE DIOXIDE

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ABSTRACT: Oxidation of 5-methoxy-1-phenylsulfonyl-2-methyl indole-3-aldehyde (**3**) with active manganese dioxide to the corresponding indole-2,3-dialdehyde (**4**) and similar reactions are reported.

In continuation of our studies related to carbazole containing natural products[1], we required large amounts of various indole aldehydes. During the synthesis of indole aldehydes, we found the unusal oxidation of the indole-methyl group with active manganese dioxide. There is only one report[2] of oxidation of methylene group with active manganese dioxide to the corresponding ketone. To the best of our knowledge there is no other report of either activated methylene or methyl group in an indole ring being oxidized with active manganese dioxide. The indole aldehydes are proved to be useful intermediates for the synthesis of various medicinally important alkaloids[3] and

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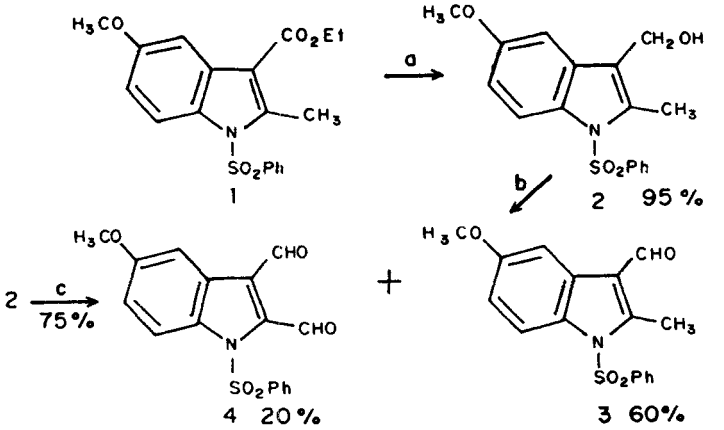
carbolines[4,5]. Generally the activity of the manganese dioxide depends upon its method of preparation[6]. Recently the oxidation of naphthols with active manganese dioxide to the respective naphthaquinone was reported[7]. More recently yadav et al reported[8] the regioselective synthesis of hydroxy butenolides with active manganese dioxide. These reports prompted us to develop a new synthetic methodology for indole - 2,3-dialdehyde, potential intermediate for the synthesis of pyridazino[4,5-b]indole[9].

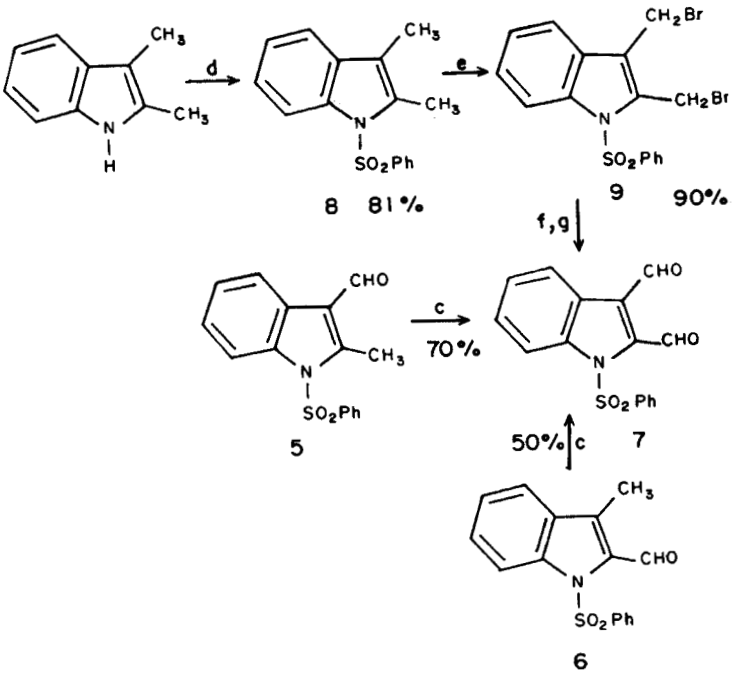
The known indole (**1**) was reduced by LAH at rt without cleaving the phenylsulfonyl group to give the alcohol (**2**). The alcohol (**2**) was refluxed with active manganese dioxide in dichloromethane to give a



a) LAH/THF, rt, 95% b) $MnO_2/CH_2Cl_2,\Delta$ c) $MnO_2/ClCH_2CH_2Cl,\Delta$ 75%

mixture of monoaldehyde (**3**) and dialdehyde (**4**) in 60% and 20% yield respectively. When the same oxidation was repeated in boiling 1,2-dichloroethane the dialdehyde (**4**) was obtained as the sole product in

75% yield. Separate oxidation of (**3**) in boiling 1,2-dichloroethane also gave (**4**). The method seems to be general as the monoaldehyde (**5**) also underwent smooth oxidation under the same condition to give the dialdehyde (**7**) in 70% yield. But the isomeric mono aldehyde (**6**) requires



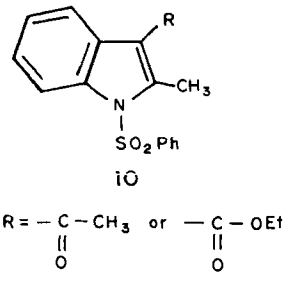
d) NaH/THF, $PhSO_2Cl$,81% e) 2eq.NBS/CCl_4,Δ,90%

f) $NaHCO_3/CH_3CN$-H_2O,Δ g) $MnO_2/ClCH_2CH_2Cl$,Δ,80%

longer reaction time and larger quantities of manganese dioxide and also the yield of the dialdehyde was only 50%. The dialdehyde (**7**) was prepared independently from N-benzenesulfonyl-2,3-dimethylindole (**8**)[10]. The compound (**8**) was converted into the corresponding 2,3-

bis(bromomethyl)N-phenylsulfonylindole (**9**). The latter was converted to the diol viz. 2,3-bis(hydroxymethyl)N-phenylsulfonyl indole by using $NaHCO_3$ in CH_3CN-H_2O. The diol was oxidised by MnO_2 under similar conditions to give (**7**).

Surprisingly compound (**10**) or N-free compound of (**3**) or (**5**) failed to give the expected dialdehydes. Similarly our attempts to oxdize 4-hydroxy-3-substituted carbazoles[11] (**11**) to the corresponding quinones were also in vain. It is envisaged that compound (**4**) and (**7**) may serve as intermediates for several carbazole alkaloids and pyridazino [4,5-b] indole. Further work is in progress towards extending this oxidation to various indole derivatives.



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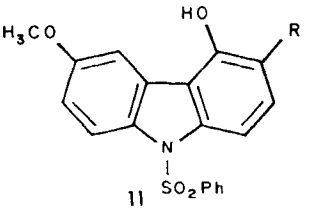
R = −C(=O)−CH3 or −C(=O)−OEt



11

R = −CH(=O) , −C(=O)−CH3 or −C(=O)−OEt

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 598 spectrophotometer. PMR spectra were recorded on a Varian-EM-390 instrument and the chemical shifts are given in ppm downfield from the internal TMS. Elemental Analyses were performed using Perkin-Elmer 240 B elemental analyser. TLC was developed on

glass plates coated with silica gel (ACME) of 0.25mm thickness and visualized with iodine. Chromatographic separations were performed on silica gel (100-200 mesh). The active manganese dioxide was prepared[6] by adding a solution of potassium permanganate to manganese sulfate solution at 80°C.

5-methoxy-1-phenylsulfonyl-3-hydroxymethyl-2-methylindole (2): To a well stirred suspension of LAH (570mg, 15mmol) in dry THF (50mL), the ester **1** (7.5g, 20mmol) in the same solvent (150mL) was slowly added and stirred under N_2 for lh. Then the excess LAH was destroyed (CH_3OH) and 10% NaOH (2mL) was added and stirred. The THF solution was decanted, the residue was washed with THF (3X20mL). The combined THF portion was dried (K_2CO_3) and the solvent removed to give the alcohol **2**; Yield 5.96 g (95%); mp 114°C (benzene-hexane); **^{1}H NMR**($CDCl_3$/TMS) δ 1.7 (s, 1 H, -CH_2OH), 2.5 (s, 3 H, -CH_3), 3.7 (s, 3 H, -OCH_3), 4.5 (s, 2 H, - CH_2OH) 6.7-8 (s, 8 H, Ar-H).

Oxidation of 2 with manganese dioxide: To a solution of alcohol **2** (3.3g, 10mmol) in CH_2Cl_2 (200mL) was added freshly prepared MnO_2 (10g) and refluxed for 6h. The progress of the reaction was monitored by TLC and continued until the disappearence of starting material. Then the MnO_2 was filtered and washed with CH_2Cl_2 (3x20mL). The removal of solvent gave the mixture of monoaldehyde (**3**) and dialdehyde (**4**), which were separated by column chromatrography (silicagel, 50 g) using 10% benzene/hexane as eluent.

5-methoxy-1-phenylsulfonyl-2-methylindole-3-carboxaldehyde (3): 2g (60%); mp 132-134°C (benzene-hexane); **IR(KBr)** 1660 (CO), 1370 and 1170 Cm^{-1} (SO_2); **^{1}H NMR** ($CDCl_3$/TMS) 2.9 (s, 3 H, -CH_3), 3.9 (s, 3H, -OCH_3), 6.8-7.8 (m, 8 H, Ar-H), 10.4 (s, 1 H, -CHO). Anal.Calcd for $C_{17}H_{15}NO_4S$; C, 62; H, 4.6; N, 4.2. Found C, 62.2; H, 4.4; N, 4.5.

5-methoxy-1-phenylsulfonyl-indole-2,3-dialdehyde (4): 680mg (20%); mp 138-140°C (MeOH); **IR(KBr)**: 1670 (CO), 1370 and 1170 Cm^{-1} (SO_2); **^{1}H NMR** ($CDCl_3$/TMS) δ 3.9 (s, 3H, - OCH_3), 7.3-8 (m, 8 H, Ar-H), 10.5 (s, 1 H, -CHO), 10.9 (s, 1 H, -CHO). Anal. Calcd for $C_{17}H_{13}NO_5S$: C, 59.47; H, 3.82; N, 4.08. Found: C, 59.82; H, 3.93; N, 3.85.

1-(phenylsulfonyl)-2,3-dimethylindole (8)[10]. 11.5 g (81%) : mp 140°C (MeOH); **IR (KBr)** 1380 and 1140 Cm^{-1} (SO_2); **^{1}H NMR** ($CDCl_3$) δ 2 (s, 3 H, CH_3), 2.5 (S, 3 H, CH_3), 7 - 8.2 (m, 9 H, ArH).

1 (phenylsulfonyl)-2,3-dibromomethylindole (9). A solution of **8** (2.9 g, 10 mmol), NBS (3.6 g, 20 mmol) and benzoylperoxide (50 mg) in dry CCl_4 (100 mL) was refluxed for 2 h. The suspension was cooled to rt, filtered and the filtrate concentrated in vacuo to give dibromo compound **9** as brown crystal. Yield 4 g (90%); mp 138°C; **^{1}H NMR** ($CDCl_3$, 90 MHz) δ 4.9 (s, 2 H, CH_2Br), 5.2 (s, 2 H, CH_2 Br), 7.4-8.3 (m, 9 H).

1-phenylsylfonyl-indole-2,3-dicarboxaldehyde (7): To a solution of **10** (4.4 g, 10 mmol) in CH_3CN (150 mL) and H_2O (20 mL), $NaHCO_3$ (2.5 g, 30 mmol) was added and refluxed for 2 h. Then the solvent was

completely removed and the sticky residue was extracted with CH_2Cl_2 (3x30 mL), dried (Na_2SO_4) and the solvent was removed to give the diol. Oxidation of the diol was similar to that of **4**. Yield 2.5 g (80%); mp 162-164°C (EtOH); **IR(KBr)** 1680 (CO), 1370 and 1160 Cm^{-1} (SO_2); **^{1}H NMR** ($CDCl_3$) δ 7.1-8.3 (m, 9 H, ArH), 10.4 (s, 1 H, -CHO), 10.7 (s, 1 H, -CHO); Anal. Calcd for $C_{16}H_{11}NO_4S$: C, 61.33; H, 3.54; N, 4.47. Found: C, 61.52; H, 3.82; N, 4.32.

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