

Electrophilic Substitution in Indoles. Part-I: Reaction of 3-Methyl Indole with Sulphuryl Chloride[§]

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Skatole (I) on treatment with sulphuryl chloride in presence of acetic acid underwent interesting substitution and rearrangement reactions to afford four new oxindole compounds, 3,5,7-trichloro-3-methyl oxindole (II), 3,5-dichloro-3-methyl oxindole (III), 3-hydroxy-5,7-dichloro-3-methyl oxindole (IV) and 3-hydroxy-5-chloro-3-methyl oxindole (V).

IN continuation of our work¹⁻³ on the electrophilic substitution of indoles we studied the reaction of 3-methyl indole (skatole) with sulphuryl chloride in acetic acid. Substitution reactions and interesting rearrangements were observed.

Acheson *et al*⁴ had earlier reported the formation of ethyl-3-methyl oxindole-3-carboxylate from ethyl-3-methyl-indole-2-carboxylate by the action of sulphuryl chloride in acetic acid. No chlorine atom was incorporated in the aromatic nucleus or in the pyrrole ring. However, we found that skatole (I) under similar conditions underwent substitution with chlorine both on the aromatic nucleus and the pyrrole ring yielding products (II-V). The products could be successfully resolved into pure components on Tswett column (over silica gel).

Compound (II), $C_9H_8NOCl_3$, m.p. 160° (petrol : benzene=1 : 1), showed three molecular ion peaks at M^+ 253, 251 and 249 corresponding to the isotopic chlorine atoms. The 1H nmr spectrum (d_6 -acetone) of II exhibited chemical shifts at $\delta 7.48$ (d, 1H, $J_m=1.9$ Hz) for the C_4-H , $\delta 7.37$ (d, 1H, $J_m=1.9$ Hz) for C_6-H , $\delta 1.85$ (s, 3H) for the methyl protons at C_3 and $\delta 10.06$ (1H, disappearing on deuteration) for indole $>NH$. The electronic spectra displayed significant light absorption at 264 (log $\epsilon=3.88$) and 315 nm (3.24), the latter being characteristic of a chlorine substituted aromatic nucleus. The structure could therefore be established as 3,5,7-trichloro-3-methyl oxindole (II).

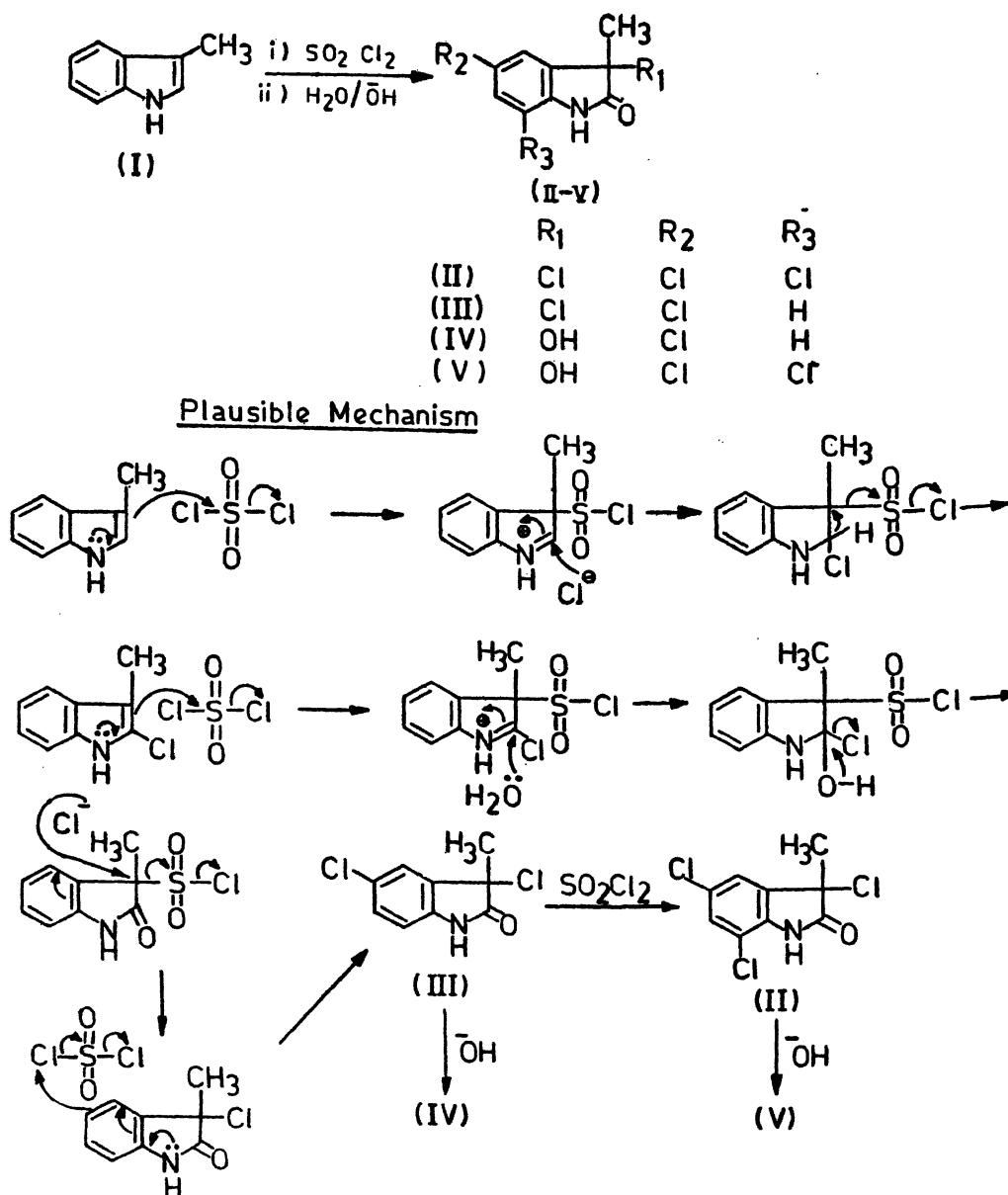
The compound (III), $C_9H_7NOCl_2$, m.p. 150° (petrol : benzene=1 : 2) showed two molecular ion peaks at M^+ 215 and 217 due to the presence of chlorine atom in the molecule. Strong absorption peaks were observed in the electronic spectra at 311 (log $\epsilon=3.07$), 260 (3.87) and 218 nm (4.92). The 1H nmr spectrum (d_6 -DMSO) confirmed the

structure of this compound (III) as 3,5-dichloro-3-methyl oxindole. While aromatic C_4-H proton resonated at $\delta 7.54$ (d, 1H, $J_m=2.12$ Hz), the other two aromatic protons at C_6 and C_7 were discernible at $\delta 7.28$ (dd, 1H, $J_o=8.29$, $J_m=2.12$ Hz) and $\delta 6.87$ (d, 1H, $J_o=8.29$ Hz) respectively. The C_3 -methyl protons were observed at $\delta 1.79$ (s, 3H) and the $>NH$ proton appeared at $\delta 10.88$ as a singlet which disappeared on deuteration.

Compound (IV), $C_9H_8NO_2Cl$ (M^+ 197 and 199), m.p. 240° (ethylacetate : benzene=3 : 1) was characterised as 3-hydroxy-5-chloro-3-methyl oxindole from its spectral data. The electronic spectrum showed absorption maxima at 313 (log $\epsilon=4.15$), 298 (3.09) and 258 nm (3.93) characteristic of a chlorinated oxindole compound. The 1H nmr spectrum, when recorded in d_6 -DMSO, also substantiated this observation. Characteristic peaks were discernible in the 1H nmr spectrum at $\delta 7.28$ (dd, 1H, $J_m=2.2$, $J_p=0.4$ Hz; C_6-H), $\delta 7.21$ (dd, 1H, $J_o=9.0$, $J_m=2.2$ Hz, C_7-H), $\delta 6.78$ (dd, 1H, $J_o=9.0$, $J_p=0.4$ Hz, C_4-H), $\delta 1.33$ (s, 3H, C_3-CH_3), $\delta 10.29$ (s, 1H, $>NH$, disappearing on deuteration) and $\delta 5.95$ (s, 1H, C_3-OH , exchangeable with D_2O).

The compound (V), $C_9H_7NO_2Cl_2$ (M^+ 231 and 233), m.p. 225° (benzene : ethyl acetate=4 : 1), λ_{max} in nm : 304 (log $\epsilon=3.17$), 259 (3.94) and 216 (4.31), was characterised as 3-hydroxy-5,7-dichloro-3-methyl oxindole. The 1H nmr (d_6 -DMSO) showed characteristic signals for the C_6-H at $\delta 7.38$ (d, 1H, $J_m=1.75$ Hz), C_4-H at $\delta 7.30$ (d, 1H, $J_m=1.75$ Hz), C_3-CH_3 at $\delta 1.36$ (s, 3H) and an exchangeable proton at $\delta 10.78$ for $>NH$ (s, 1H). Unfortunately the C_3 -hydroxyl proton could not be detected, possibly it underwent deuteration in d_6 -DMSO. The presence of C_3-OH in the compound (V) could be confirmed from mass spectrum and ^{13}C nmr spectrum analysis.

[§]Dedicated to Professor N. R. Dhar on the occasion of his 90th birthday.



Scheme 1

TABLE I—¹³C nmr SPECTRA OF THE COMPOUND II-V

Carbon Numbers	Compound Numbers [Chemical Shifts in ppm (δ)]			
	(II) ^b	(III) ^c	(IV) ^c	(V) ^c
C-2	175.23 (s)	174.48 (s)	180.59 (s)	179.51 (s)
C-3	61.94 (s)	62.49 (s)	74.06 (s)	73.52 (s)
C-4	122.91 (d)	124.31 (d)	124.94 (d)	122.50 (d)
C-5	133.60 (s)	132.74 (s)	136.92 (s)	138.02 (s)
C-6	129.69 ^d (d)	130.02 ^e (d)	129.94 (d)	128.00 (d)
C-7	116.32 (s)	111.80 (d)	112.32 (d)	114.92 (s)
C-4a	129.04 ^d (s)	126.49 ^e (s)	127.03 (s)	126.51 (s)
C-7a	135.90 (s)	139.44 (s)	141.29 (s)	136.93 (s)
C ₈ -CH ₃	25.56 (q)	24.65 (q)	25.47 (q)	26.05 (q)

b : CDCl₃ ; δ(CDCl₃) = δ(TMS) + 76.9c : d₆-DMSO ; δ(d₆-DMSO) = δ(TMS) + 39.5

d, e : values are interchangeable.

The structures of all these products have been confirmed from their ¹³C nmr spectra (both SFORD and noise decoupled) and the plausible mechanism of their formation has been rationalised in Scheme 1.

Experimental

Melting points were recorded in a Koffler Block and are uncorrected. The uv spectra (95% aldehyde free ethanol) were recorded on a Varian Techtron 634 spectrophotometer, the ir spectra on a Beckman IR 20 spectrometer in KBr disc, the ¹H nmr (80 MHz, Internal standard : TMS) and ¹³C nmr (20 MHz) spectra were run on Varian CFT-20 and Varian FT-80A spectrophotometer. The column chromatography was carried out with silica gel (B.D.H., 60-120 mesh) and thin-layer chromato-

graphy was run using silica gel (Gouri Chemicals, Calcutta). The organic solvents were dried by using appropriate drying agents and the samples were routinely dried over P_2O_5 for 24 hr.

Preparation and isolation of 3,5,7-trichloro-3-methyl oxindole (II), 3,5-dichloro-3-methyl oxindole (III), 3-hydroxy-5-chloro-3-methyl oxindole (IV) and 3-hydroxy-5,7-dichloro-3-methyl oxindole (V): 3-Methyl indole (skatole) (5 g; 0.0427 mole) was dissolved in acetic acid (50 ml) and the mixture was warmed on a water bath until the solid dissolved. The solution was then heated to 50-60° and stirred while a mixture of SO_2Cl_2 (14 ml) in acetic acid (28 ml) was added fairly rapidly from the dropping funnel. When the addition was complete, the reaction mixture was heated to 70° and kept at this temperature for 30 min. The mixture was allowed to cool slowly with stirring and left for 36 hr at room temperature. The reaction mixture was poured into ice-water, the pH being maintained at 5 by dropwise addition of about 4N NaOH solution. The remaining acid was neutralised with $NaHCO_3$. The mixture was extracted with ether, washed with water and dried over anhydrous Na_2SO_4 . The solvent was evaporated to yield a dark brown mass which on chromatography over silica gel with solvents of increasing polarity (petrol, benzene and ethylacetate in various proportions) afforded four compounds.

The compound (II) was obtained in the petroleum-benzene (1:1) and benzene eluates, m.p. 160° (petrol: benzene=1:1), yield 21%, ν_{max}^{KBr} : 3100 (>NH), 1730 (>CO), 1610, 1580 and 1450 cm^{-1} (aromatic), m/e: 253, 251, 249, 214 (base peak), 187, 179, 151, 123, 114, 89, 76, 63 and 52.

Further elution with benzene afforded the product (III) in crude form. It was subsequently purified by rechromatography over silica gel using benzene-ethylacetate, 5:1, m.p. 150°, yield 4.5%, ν_{max}^{KBr} : 3200 (>NH), 1760, 1700 (>CO), 1625 and 1485 cm^{-1} (aromatic), m/e: 217, 215, 180 (base peak), 162, 145, 117, 89, 62, 58.

The compound (IV) was obtained from the benzene-ethylacetate, 3:1 eluate and purified by repeated crystallisation, m.p. 240°, yield 15.2%, ν_{max}^{KBr} : 3200 (>NH/-OH), 1695 (>CO), 1610 and 1470 (aromatic). The compound under electron impact showed two molecular ions at m/e 199 and 197. Further fragmentation yielded particles having m/e at 182, 171, 169, 156, 154 (base peak), 126, 99, 90, 63 and 43.

The mother liquor of the compound (IV) upon chromatography over silica gel afforded the compound (V) in the benzene: ethylacetate, 4:1 eluate, m.p. 225° (benzene: ethylacetate, 4:1), (yield 0.7%), ν_{max}^{KBr} : 3370 (>NH), 3160 (-OH), 1610 and 1450 cm^{-1} (aromatic). The mass spectrum showed two molecular ions at m/e 233, 231 respectively, other ion fragments being at m/e 205, 203, 190, 188, 160, 124, 97, 62, 61, 43 (base peak).

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