Electrophilic substitution of indoles: Part XXI – Further investigation on the formation of the benzazepinone skeleton

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An interesting observation was made during the electrophilic substitution of indole with 5,5-dimethyl cyclohexane 1,3-dione resulting in the synthesis of 2,3,4,5,10,11-hexahydro-3,3-dimethyl-11-(indo-3-yl)-dibenz-[b,f]azepin-1-one system.

The reactions with 2-methyl- and 3-methyl indoles resulted in the formation of only the 1:1 product. The structures of the products have been settled on the basis of their UV, IR, 1H and 13C NMR spectral studies and MS analysis.

Trieb’s et al. had reported¹ the synthesis of an interesting product, 3 from indole 1a and cyclohexane-1,3-dione 2a using 47% hydrobromic acid¹. As this product appeared unusual, a reinvestigation of the reaction under identical conditions was carried out by Banerji et al.². Surprisingly, Trieb’s product could neither be detected nor isolated from the reaction mixture. Product 4 was obtained. The reaction mixture on treatment with 10% aqueous caustic soda solution afforded product 5a which was identified as 2,3,4,5,10,11-hexahydro-11-(indol-3-yl)-dibenz-[b,f]azepin-1-one 5a. The same product 5a was directly obtained when 47% HBr was replaced with boron trifluoride etherate³. To explore the possibility of the application of this reaction for the synthesis of benzazepinone derivatives, studies with several substrates using the same reagents were undertaken. We now report our observations with indole 1a, 2-methylindole 1b and 3-methylindole 1c with 5,5-dimethylcyclohexene-1,3-dione (dimidone).

Indole 1a reacted with 5,5-dimethylcyclohexene-1,3-dione 2b leading to the interesting benzazepinone skeleton 2,3,4,5,10,11-hexahydro-3,3’-dimethyl-11-(indol-3-yl)dibenz-[b,f]azepin-1-one 5b thereby proving that the indoleninium cation or the indole dimer 6, which must have been generated in situ, was the reactive electrophilic species.

Interestingly, unlike indole 1a, neither 2-methylindole 1b nor 3-methylindole 1c afforded the benzazepinone skeleton. Both these compounds reacted with 5,5-dimethyl-cyclohexene-1,3-dione in the first step rather than undergoing dimerisation. The structures of the products were settled from detailed spectral analysis and correlation studies.

The structure of the product was confirmed as 5b from the 75.5 MHz 13C NMR spectrum, including DEPT experiments and correlation studies. The spectrum confirmed twenty four signals representing all the twenty four carbons present in the compound.

The probable mechanism of formation of such a skeleton has been discussed earlier⁴.

| Table 1 — Reactions with 5,5-dimethylcyclohexene-1,3-dione |
|-----------------|-----------------|-----------------|
| Indole (1 g)    | Dimidone² (600 mg) | 47% Hydrobromic acid (1 mL) |
| 2-Methylindole (1 g) | Dimidone² (1.07 g) | 47% Hydrobromic acid (1 mL) |
| 3-Methylindole (1 g) | Dimidone² (1.01 g) | 47% Hydrobromic acid (1 mL) |
With 2-methylindole 1b the indolyl unit underwent electrophilic substitution yielding product 7a, C_{17}H_{19}NO (M⁺ 253), m.p. 110°C (EtOH) in 60% yield. The 75.5 MHz \(^1\)C NMR spectrum, including DEPT experiment, confirmed the structure as 7a.

Unlike the reaction of 3-methylindole with cyclohexane-1,3-dione, with 5,5-dimethylcyclohexane-1,3-dione no benzazepinone skeleton was obtained. From detailed investigation and spectral analyses it was observed that the reaction yielded a Plancher rearrangement product 7b, C_{17}H_{18}NO, M⁺ 352, m.p. 140°C (benzene-ethyl acetate 4:1) in 30% yield. The structure of the compound could be confirmed from its 75.5 MHz \(^1\)C NMR spectrum.

**Experimental Section**

All melting points are uncorrected. UV spectra (in 95% aldehyde free ethanol) were recorded using a Hitachi U-2000 spectrophotometer; IR spectra in KBr in a Perkin-Elmer 782 spectrophotometer; \(^1\)H and
\[ \text{13C NMR spectra in a Bruker AM 300L spectrometer and mass spectra on a Jeol D-300 spectrometer.} \]

Column chromatographic analysis was carried out using basic grade alumina standardized according to Brockmann (BDH). TLC analysis was carried out using 60G neutral alumina (Type-E). The spots were detected with iodine vapour. Analytical samples were routinely dried \textit{in vacuo}. Anhydrous sodium sulphate was used for drying the organic extracts.

The reaction mixture was poured into crushed ice, allowed to settle for 1 hr, extracted with methylene chloride and the organic layer was washed with 2% NaHCO\(_3\) solution and subsequently with water till the washings tested neutral to pH paper and dried over anhydrous sodium sulphate. The concentrate was subjected to column chromatography using basic aluminium oxide using solvents of increasing polarity as eluates.

\textbf{Compound 5b:} It was obtained from indole (1 g), dimidone (600 mg) and 47% HBr (1 mL) as orange crystals from the earlier fractions of benzene : ethyl acetate 4:1, eluate yield 70%, m.p. 268° (d); UV \(\lambda_{\text{max}}\) (EtOH) : 331, 392, 224 and 203 nm in EtOH (log \(\epsilon\) = 4.26, 3.87, 4.48 and 4.46 respectively); \(^1\text{H NMR (DMSO-d}_6\) : \(\delta\) 10.31, 8.87 (1H, each, NH protons at N-1 and H-5'); 1.08, 1.06 (3H, each for 2-Me groups of the dimidone unit), 2.65 and 2.19 (2H, s each; \(\text{C}_2\)- and \(\text{C}_4\)-methylene protons); 5.21 (1H, d, \(J = 6.0\) Hz, doubly allylic \(\text{C}_1\)-proton), 3.34 (1H, dd, \(J = 13.4; 6.0\) Hz and 3.03 (1H, d, \(J = 13.4\) Hz) for the pair of non-equivalent methylene protons \(\text{H}_1\) and \(\text{H}_6\); 6.25 (1H, d,
$J = 1.3$ Hz; C-2' indolyl proton); 7.70 and 7.18 (1H, d, each; $J = 8.7$ Hz; C-9 and C-4 protons). 7.07-6.89 (4H, multiplet); MS : $m/z$ 356 (Found : C, 80.80; H, 6.72; N, 7.80, $C_{24}H_{20}N_{2}$O requires C, 80.89; H, 6.74; N, 7.86%).

**Compound 7a** : It was obtained from 2-methylindole (1 g), dimidone (1.07 g) and 47% HBr (1 mL). It was isolated from the later fraction of the benzene : ethyl acetate (4:1) eluate as green crystals, yield 60%, m.p. 400 (ErOH); UV: $\lambda_{max}$ (EtOH) : 361.5, 280, 222.5 nm (log $\varepsilon$ = 4.16, 3.88 and 4.34 respectively); IR (KBr) : 3250, 2980, 1640, 1580, 1465, 1440, 1320 and 750 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$) : $\delta$ 11.50 (1H, br.s, >NH); 1.04 (6H, s, gem-dimethyls at C-3'); 2.47 (3H, s, CH$_3$ group at C-3); 2.72 and 2.22 (2H, s each; four methylene protons at C-2' and C-4'), 7.58 and 7.32 (1H, d, each $J = 7.3$ Hz; C-7 and C-4 protons), 7.09-6.99 (2H, m; C-5 and C-6 protons), 6.03 (1H, s, C$_6$' H).

**Compound 7b** : It was obtained from 3-methylindole (1 g), dimidone (1.01 g) and 47% HBr (1 mL). It was obtained from the earlier fractions of benzene : ethyl acetate (1:1) eluate as orange crystals, yield 30%, m.p. 140° (benzene-ethyl acetate 4:1); UV : $\lambda_{max}$ (EtOH) : 365, 260.5 and 205 nm (log $\varepsilon$ = 4.29, 4.02 and 4.70 respectively); IR (KBr) : 3920, 1610, 1500, 1360, 1220 and 840 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$) $\delta$ 11.2 (indole >NH proton); 1.04 (6H, s, 2 methyl groups of the dimidone unit at C-3'), 2.24 (3H, s; CH$_3$ group at C-3); 2.73 and 2.40 (4 methylene protons at C-2' and C-4' (2H, s each), 7.53 and 7.30 (1H, d, each; $J = 7.8$ Hz; C-4 and C-7 protons), 7.13 and 6.99 (1H, t, $J_1 = 7.2$ and 7.5 Hz for C-6 and C-5 protons respectively), MS : $m/z$ 253 (M$^+$) (Found : C, 82.00; H, 5.60; N, 5.00, $C_{17}H_{19}NO$ requires C, 82.5; H, 5.64, N, 5.64%).

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**References**