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LEWIS ACID INDUCED ELECTROPHILIC SUBSTITUTION OF INDOLES : PART 6

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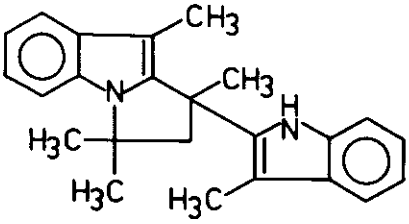
Abstract The electrophilic substitution of 3-methylindole with mesityl oxide and acetone in the presence of $BF_3.Et_2O$ has been discussed.

In an earlier paper[1] we reported the structure (1) of a new heterocycle (dimer 1) obtained by the electrophilic substitution of 3-methylindole (skatole) with mesityl oxide in the presence of $BF_3.Et_2O$. Recent studies on the effects of low power selective irradiation of the gem-dimethyl and the methylene protons on the long-range ($^2J_{CCH}$) couplings of the quaternary carbons at 37.61 and 61.60 ppm led us to revise the structure of this reaction product to (2). We also discuss in this paper the structures of two new heterocycles, designated dimers 2 and 3, which were formed by the electrophilic substitution of skatole with acetone in the presence of the same Lewis acid.

Dimer 1, $C_{24}H_{26}N_2$ (M^+ 342.2068), mp 206°C (petrol-benzene = 1:1), yield 20%, was obtained by the dimeric association of skatole around one six carbon unit derived from mesityl oxide. The ^1H-NMR spectrum[2] in $CDCl_3$ revealed the presence of eight aromatic protons and one indole $\gt N\underline{H}$ (9H m; one exchangeable with D_2O in the region δ7.10-7.65), a pair of non-equivalent methylene protons (1H, d each at δ2.80 and 3.05; J=14.0Hz), two skatole methyls (3H, s each at δ2.45 and 2.38) and three more methyls (3H, s each at δ2.20, 1.63 and 1.31). The ^{13}C-NMR data[3] have been given in Table 1.



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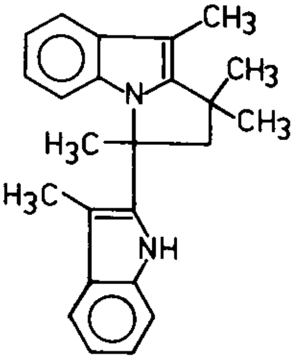


(2)

Table 1 20 MHz ^{13}C-NMR Signals of Dimer 1 in $CDCl_3$, ppm

C	CH	CH_2	CH_3
147.59	121.35	60.80	28.51
138.12	120.60		28.46
134.16	119.07		27.20
133.70	118.95		9.40
130.60	118.50		7.79
130.26	117.96		
105.00	110.64		
100.22	110.20		
61.60			
37.61			

In order to settle between the two structures (1) and (2) it was necessary to carry out low power selective irradiation of the gem-dimethyl and methylene protons. It is apparent both from Table 1 as well as from a consideration of the two possible structures (1) and (2) that the peaks of interest in these experiments would be the quaternary carbons at 61.60 and 37.61 ppm and the methylene carbon at 60.80 ppm. The chemical shift at 61.60 ppm is obviously assignable to the carbon bonded to nitrogen. So two selective experiments were carried with irradiation at 79.542220 MHz, mid-way between the gem-methyls, and at 79.542333 MHz, mid-way between the $-CH_2-$ protons, using a common power level ($\gamma H_2 = 240$ Hz). If structure (2) be correct then as a result of irradiation at 79.542220 MHz the quaternary carbon at 61.60 ppm would show coupling to both the lone methyl and the $-CH_2-$ protons whereas the carbon at 37.61 ppm would be coupled to only the $-CH_2-$ protons. In case of structure (1) the reverse situation would be met with. It was observed that the methylene carbon signal at 60.80 split into a complex pattern. The latter occurred since the two protons were at different distances from the irradiating frequency and consequently their reduced coupling constants had different values. Resolution enhancement and plot expansion to 1.0Hz/mm revealed that the peak at 37.61 ppm was a triplet with a residual coupling constant of ~ 1.75 Hz. This was due to the methylene protons on the adjacent carbon. In the absence of this irradiation the $^2J_{CCH}$ for the $-CH_2-$ protons and the quaternary carbon bearing the gem-dimethyls would be ~ 3.5 Hz. This would not be normally observed because of its coupling to the six methyl protons but irradiation at 79.542220 MHz completely eliminated the latter coupling leaving the partially collapsed triplet. The quaternary carbon at 61.60 ppm displayed a multiplet due to couplings to the adjacent methyl and methylene protons. These changes in the spectral characteristics, as explained earlier, confirmed structure (2) for dimer 1. This was further corroborated from the changes observed due to irradiation at 79.542333 MHz, mid-way between the methylene protons. Resolution enhancement and plot expansion to 1.0 Hz/mm showed the peak at 61.60 ppm is coupled only to the attached methyl. Since this methyl is at 79.5422275 MHz its $^2J_{CCH}$ to the quaternary carbon collapsed to an unresolvably small value. This would be expected from structure (2). On the other hand the gem-dimethyls at 79.542232 and 79.542207 MHz are over 100 Hz away from the irradiating frequency and their residual coupling to the carbon at 37.61 ppm clearly split it into a multiplet. In case of structure (1) the situation would have been reversed.

The difference in the carbon chemical shifts of the C-3 and C-3" methyls could also be explained on the basis of structure (2). Construction of the molecular model revealed that the C-3 methyl undergoes steric compression with one of the gem-methyls and this accounts for its shift to 7.79 ppm while the C-3" methyl showed the normal value of 9.40 ppm (skatole methyl appears at 9.55 ppm)[4].

The electrophilic substitution of skatole (3) with acetone in the presence of $BF_3.Et_2O$ led to the formation of two interesting structural isomers in 4:1 ratio. The compounds could not be separated by column or thin layer chromatography. Attempts to separate them by gas liquid chromatography resulted in extensive decomposition. Both the ^{1}H- and ^{13}C-NMR spectra clearly showed two sets of signals with integration ratio of 4:1 for two very similar compounds. In case of the 80% isomer (dimer 2) the two non-equivalent methylene protons appeared at δ3.02 and 2.78 (1H, d each; J=14.0Hz) and the two methyls at δ1.84 and 1.69 (3H, s each). In case of the 20% isomer (dimer 3) the non-equivalent methylene protons appeared at δ3.05 and 2.67 (1H, d each; J=14.0Hz) and two methyls at δ1.55 and 1.28 (3H, s each). The third methyl appeared at δ2.30 (3H, s). In case of both the isomers the aromatic protons merged in the region δ7.55-7.05. The fact that the ^{1}H-NMR data could explain half of the total number of protons in the molecule in each case pointed to their symmetrical nature. This could be further corroborated from their ^{13}C-NMR data (Tables 2 and 3).

Table 2 20 MHz ^{13}C-NMR Spectrum of Dimer 2, ppm

C	CH	CH_2	CH_3
137.21	120.00	60.05	28.80
131.49	118.75		27.86
130.12	118.21		7.35
99.90	109.53		
60.50			
36.00			

Table 3 20 MHz ^{13}C-NMR Spectrum of Dimer 3, ppm

C	CH	CH_2	CH_3
137.52	119.91	59.92	28.69
131.40	118.70		28.82
130.00	118.15		7.53
99.87	109.40		
60.48			
36.04			

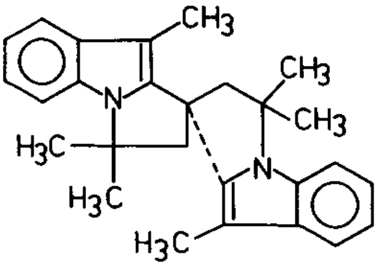
Two sets of fourteen resolved lines were obtained for both the dimers. The off-resonance decoupled spectrum showed the presence of three methyls, one methylene, four methines and six non-protonated carbons in each case. The spiro carbon appeared at 36.00 and 36.04 in case of dimers 2 and 3 respectively. The shifts in the C-3 methyls compared to skatole (3) in both these compounds was due to the steric compression imposed by one of the gem-methyls which is in close proximity.

The structures of the 80% (dimer 2) and the 20% species (dimer 3) could be distinguished as (4) and (5) respectively from comparison of the ^{1}H-NMR data of the gem-dimethyl protons of these compounds with those of dimer 1 (2) and compounds (6)[5] and (7)[5] (Table 4). The latter two compounds had been earlier obtained[5] during the electrophilic substitution of indole with acetone in the presence of $BF_3.Et_2O$.

Table 4 Comparison of the Chemical Shift Values for the Gem-dimethyl Protons

Compound 6	Compound 7	Dimer 2 (80%)	Dimer 3 (20%)	Dimer 1
1.61	1.67	1.69	1.28	1.31
1.70	1.78	1.84	1.55	1.63

The great similarity of the gem-dimethyl shifts of the 80% species with those of compounds (6) and (7) confirmed the structure of the former as (4) with similar environments for the gem-dimethyls, while the similarity of the 20% species with dimer 1 confirmed its structure as (5). The C-3 and C-3" methyl carbons in dimer 1 appeared at 7.79 and 9.40 ppm while in the 80% species (4) both the methyls moved upto 7.35 ppm. Comparing the ^{1}H-NMR spectra we found that in dimer 1 the C-3 and C-3" methyls are at δ2.38 and 2.45 while both appeared at δ1.90 in the 80% species (4). The methyl carbon a in (2) appeared at 7.79 ppm. This has shifted upfield to 7.35 ppm in the 80% species while the protons have also shifted upfield by about the same amounts, 0.48 to 0.55 ppm. Both of those shifts are consistent with the methyl being held over the face of the indole aromatic system which is the case in (4) and not in (5).



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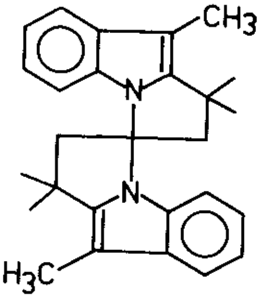

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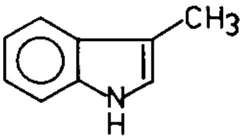

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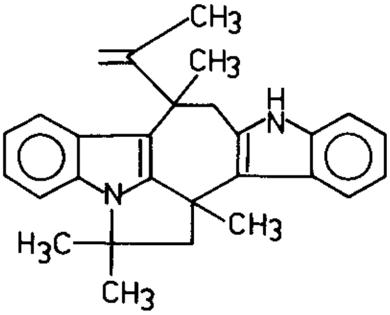

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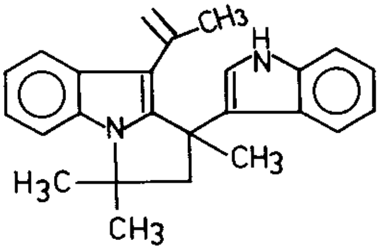

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EXPERIMENTAL

The melting points were recorded in a Kofler block apparatus and are uncorrected. The UV spectra (95% aldehyde free ethanol) were recorded in a Varian-634 spectrophotometer, the IR spectra (KBr) in a Beckman IR 20 spectrophotometer, the 80 MHz ^{1}H-NMR and the 20 MHz ^{13}C-NMR spectra (in $CDCl_3$, tetramethyl silane being used as internal standard) in a Varian FT-80A spectrometer.

Isolation of dimer 1

To a solution of skatole (1 g) in dry methylene chloride (40 ml) at 25°C mesityl oxide (5 ml) was added followed by dropwise addition of boron trifluoride etherate (1.2 ml) with stirring (10 h). The reaction mixture was decomposed over ice chips followed by extraction with methylene chloride, washed with 2% $NaHCO_3$, water and dried. The concentrated extract was chromatographed over Brockmann alumina (grade - basic) with solvents of increasing polarity. The dimer was obtained in the petrol : benzene (1:1) eluate on careful chromatographic resolution. Dimer 1, mp 206°C (petrol : benzene = 1:1) was obtained in 20% yield, λ_{max} (EtOH) : 227, 285 and 293 nm (log ε 4.32, 3.69 and 3.68 respectively), λ_{max} (EtOH + 50% $HClO_4$) : 204, 224, 269 and 290 nm (log ε 3.97, 3.96, 3.55 and 3.54 respectively); ν_{max}(KBr): 3460, 2980, 1620, 1455, 1350 and 745 cm^{-1}; m/z 342.2068 (M^+, calculated for $C_{24}H_{26}N_2$: 342.2095), 327, 212, 172 (100%) and 130.

Isolation of dimers 2 and 3

To a solution of skatole (1 g) in dry methylene chloride (40 ml) at 25°C acetone (10 ml) was added followed by dropwise addition of $BF_3.Et_2O$ (1.2 ml) with stirring (11 h). The reaction mixture was decomposed over ice chips followed by extraction with methylene chloride, washed with 2% $NaHCO_3$ solution, water and dried. The concentrated extract was chromatographed over Brockmann alumina (grade - basic). The two structural isomers (4) and (5) were obtained in the petrol eluate. Dimers 2 and 3 were obtained in 20% yield; λ_{max}(EtOH) : 234, 288 and 295 nm (log ε 4.83, 4.23 and 4.21 respectively); λ_{max}(EtOH + 50% $HClO_4$); 207, 288 and 299.5 nm (log ε 4.39, 4.36 and 3.93

respectively); ν_{max}(KBr); 2980, 1600, 1460, 1350 and 740 cm^{-1}; m/z 382.2412 (M^+, calculated for $C_{27}H_{30}N_2$: 382.2409), 367, 342, 327, 311, 211, 196, 172 (100%), 156 and 130.

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REFERENCES

1. J. Banerji, R. Saha, A. Patra, S. Manna, J.N. Shoolery, T. Prangé and C. Pascard, Ind. J. Chem., 1982, 83.

2. The ^{1}H-NMR values have been revised on the basis of the present study done using the Varian 80A spectrometer.

3. The ^{13}C-NMR data have been given to two decimal places.

4. R.G. Parker and J.D. Roberts, J. Org. Chem., 1970, **35**, 996.

5. A. Chatterjee, S. Manna, J. Banerji, C. Pascard, T. Prangé and J.N. Shoolery, J. Chem. Soc. Perkin Trans. I, 1980, 553.

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