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ELECTROPHILIC SUBSTITUTION OF INDOLES : PART 7[1] - APPLICATION OF HOMCOR (COSY) - 2D NMR SPECTROSCOPY IN STRUCTURE ELUCIDATION

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Abstract - The electrophilic substitution of 2-methylindole with acetone in the presence of $BF_3.Et_2O$ has been discussed and the application of the HOMCOR (COSY) 2D NMR spectroscopy in settling the structure of the product.

The electrophilic substitution reactions of indoles with various carbonyl compounds in the presence of the Lewis acid, $BF_3.Et_2O$, have been investigated in our laboratory[2-8]. Of special interest has been the reaction of indole[3,4] and 3-methylindole[7] with the very simple ketone, acetone. In this paper we discuss the structure of dimer 1, which was formed by the electrophilic substitution of 2-methylindole with acetone in the presence of the same Lewis acid.

Dimer 1, $C_{24}H_{26}N_2$ (M^+ 342), mp 175°C (ethanol), was obtained in 20% yield by the dimeric association of the indole moiety around two acetone units. The 400 MHz ^1H-NMR spectrum revealed the presence of four methyl singlets at δ 2.44, 1.35, 1.15 and 0.8 (3H, each). The appearance of only one downfield methyl signal was extremely important as it clearly pointed to the fact that of the two indole nuclei participating in the reaction only one had retained its indolic character while the other had been reduced to an indoline system. In conformity with this view only one indole $\geq N\underline{H}$ signal was discernible at δ7.80. The ill-defined signal at δ 3.35 integrating for one proton was due to the indoline $\geq N\underline{H}$. The resonances at δ 2.45 (d, with finer splitting, J = 12.0 and 2.0 Hz) and δ 2.22 (d, J = 12.0 Hz) showed the presence of a non-equivalent methylene pair. The one proton signal at δ 5.78 (J = 2.0 Hz) was assigned to an olefinic proton. This small coupling of 2.0 Hz clearly pointed to the absence of any proton bearing carbon as its immediate neighbour. A careful analysis of the ^1H-NMR spectrum indicated that the long-range coupling of 2.0 Hz was due to coupling of the olefinic proton with the methylene proton at δ 2.45. Eight protons were present in the aromatic region δ 7.59-6.65, [the $C_{5'}$-H appeared at δ 7.59 (1H, d, with finer splitting, J = 8.0 and 1.3 Hz); the $C_{7'}$-H at δ 6.75 (t, with finer splitting; J = 8.0 and 1.3 Hz); and the C_5-H at δ 6.65 (d, with finer splitting, J = 8.0 and 1.3 Hz); the remaining five aromatic protons resonated as a multiplet in the region δ 7.27-7.23]. The ^{13}C-NMR data have been given in Table 1.

Table 1 75 MHz ^{13}C-NMR signals of dimer 1 in $CDCl_3$, ppm

C	CH	CH_2	CH_3
149.9	129.0	44.5	30.9
135.3	127.9		29.4
131.1	126.8		20.8
130.3	126.7		12.9
130.2	121.3		
127.8	119.7		
118.5	119.3		
62.9	110.4		
34.9	110.2		
	57.8		

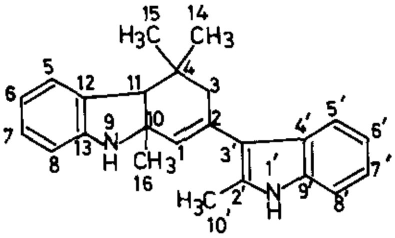
Two structures (1) or (2) could be proposed for dimer 1. A similar compound had been reported by Noland et al[9] from the reaction of 2-methylindole with acetone using ethanolic hydrochloric acid. On the basis of the ^{1}H NMR signals in $CDCl_3$ for the four methyl peaks at 9.19, 8.83, 8.66 and 7.57 τ, he proposed the two alternative structures (1) and (2) for his compound. The identity of Noland's product (≡ Scholtz's compound[10]) with dimer 1 was established by direct comparison of an authentic sample received from Professor Noland. The authors were able to unambiguously settle the structure of dimer 1 as (1) from a homonuclear correlation two dimensional experiment (HOMCOR COSY) (Fig.1). Important correlations could be made of which (b) and (c) were not perceptible in the 400 MHz ^{1}H-NMR spectrum.

(a) The proton at δ 2.45 coupled to the olefinic proton at δ 5.78. This would be expected from both structures (1) and (2).

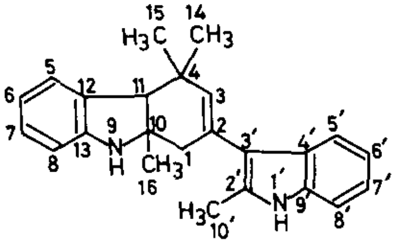
(b) The two methyls at the highest field (δ 0.80 and 1.15) in the COSY spectrum showed a weak cross-correlation and therefore have been correctly assigned to the *gem-methyls at C-4.*

(c) The methyl at δ 0.80 showed a long range coupling to one of the -CH$_2$-protons, viz, the one at δ 2.45, which falls close to the indole methyl. The gem-methyl therefore must be adjacent to the -CH$_2$- group in order to exhibit this 4-bond coupling, typical of an axial methyl and an axial proton. This type of coupling would not be observed if (2) had been the structure of the compound. Hence, the structure of the dimer 1 could be unequivocally settled as (1).

Construction of the Dreiding model revealed that the axial proton at δ 2.45 coupled to the olefinic proton at δ 5.78. It was further evident that the methyl at C-16 and the hydrogen at C-11 were cis to each other.

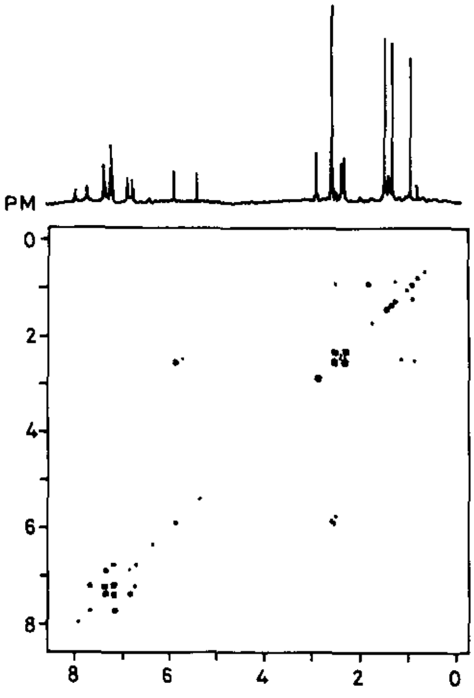


(1)



(2)

FIG.1 HOMONUCLEAR CORRELATION PLOT (COSY)



EXPERIMENTAL

Melting points were recorded in Kofler block apparatus and are uncorrected. The UV spectra (in 95% aldehyde free ethanol) were recorded in a Varian 634 spectrophotometer, the IR spectra (KBr) in a Perkin-Elmer 782 spectrophotometer, the 400 MHz ^{1}H-NMR (tetramethylsilane being used as the internal standard), the ^{13}C-NMR spectra (in $CDCl_3$) in a Varian XL-400 spectrometer and the mass spectra in a 70 e.v.-Hitachi RMU 6L mass spectrograph.

Isolation of dimer 1

To a solution of 2-methylindole (1 g) in dry methylene chloride (20 ml) at 0°C acetone (5 ml) was added and then boron trifluoride etherate (1.2 ml) was dropwise added with stirring (10 h). The reaction mixture was decomposed over ice chips, followed by extraction with methylene chloride. The extract was washed with 2% $NaHCO_3$, water and dried. The concentrate was chromatographed over Brockmann alumina (grade-basic) with solvents of increasing polarity. The dimer 1 was obtained in the benzene: ethyl acetate (1:1) eluate on careful chromatographic resolution. Dimer 1, mp 175°C (ethanol), was obtained in 20% yield, λ_{max}(EtOH) : 212, 228, 256, 282.5 and 291 nm (logε = 4.47, 4.44, 4.07, 3.96 and 3.91 respectively), λ_{max}(EtOH+50% $HClO_4$) : 211, 266 and 318 nm (logε = 4.11, 4.10 and 3.68 respectively); ν_{max}(KBr) : 3380, 3340, 1605, 1480, 1460, 740 cm^{-1}; m/z : 342(M^+), 327, 287, 223, 149 (100%), 104.

An authentic sample of 2-(2-methyl-3-indolyl)-3,4,4a,9a-tetrahydro-4,4,9a-trimethyl carbazole was obtained from Professor W.E. Noland. The identity of this compound with dimer 1 was established from the superimposable IR spectrum and co-TLC experiment, R_f = 0.54 [solvent system, benzene: ethyl acetate (1:1) and adsorbing material, silica gel (BDH, product No.27335, Batch No. L5864411)].

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