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STRUCTURE OF CANNABICYCLOL, A DETAILED NMR STUDY OF A SYNTHETIC ANALOG

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A recent paper on the X-ray structure of dibromocannabicyclol[1] prompts us to record the results of detailed nmr investigations of the compound 1, a synthetic analog of cannabicyclol 2. A minor constituent cannabicyclol(cannabipinol) was first isolated by Korte and Sieper[2a] and later again by Mechoulam and coworkers[2b] from Cannabis sativa L. Structure 3 (R_1=OH, R_2=C_5H_{11}) was suggested as a working hypothesis for this compound,[2b] while Korte and coworkers put forward 3 as a definite structure, including its relative stereochemistry as shown in 3 (R_1=OH, R_2=C_5H_{11}).[2c] The pyridine catalyzed condensation of citral with olivetol was shown to give cannabicyclol and 4 (R_1=OH, R_2=C_5H_{11}).[3,4] A revision of the structure from 3 (R_1=OH, R_2=C_5H_{11}) to 2 was suggested by Crombie and coworkers.[4] Cannabichromene 4 (R_1=OH, R_2=C_5H_{11}) can be converted on reaction with pyridine[4], under acidic conditions,[5a,b] and photochemically[6] into cannabicycol. However, we were unable to convert cannabichromene to cannabicyclol with pyridine in contrast to Crombie and Ponsford's results[4] and had suggested the necessity of further work.[7] The photochemical[6] and acid catalyzed[5a,b] rearrangements supported structure 2 but did not prove it unequivocally. In our subsequent paper[7] we indicated 2 and 3 (R_1=OH, R_2=C_5H_{11}) for cannabicyclol as either of the structures was acceptable to us in the absence of more definitive evidence. We had also pointed out that the structure of cannabicyclol could be settled by a detailed nmr study of a suitable synthetic analog.[8]

Condensation of citral with phloroglucinol dimethylether in the presence of pyridine gave a liquid as the only isolated product in 40% yield to which we attribute the structure 4 (R_1=R_2=OCH_3) based on nmr, mass spectrum, ir and uv. Subjecting pure chromene 4 (R_1=R_2=OCH_3) to thermal rearrangement conditons (170°/35mm., 18 hr.) afforded only unchanged starting material by nmr analysis. However, when the crude reaction product was directly distilled after the removal of pyridine (but not the phloroglucinol dimethylether), no chromene was obtained, but instead it gave a crystalline compound (after chromatography on florisil) mp. 107°-108°, homogenous on tlc and vpc, whose structure is elucidated as 1. The uv spectrum of this compound [λ_{max}^{EtOH}, 218(ε35980), 232sh (ε9000), 275nm (ε800)] was quite similar to cannabicylol. The mass spectrum indicates a molecular ion peak m/e 288 corresponding to $C_{18}H_{24}O_3$, indicating 1:1 adduct of citral and phloroglucinol dimethylether; nmr (100 MHz, $CDCl_3$) δ 0.69(3H, s, C-$\underline{CH_3}$), 1.35 (3H, s, O-$\underline{CH_3}$), 1.38 (3H, s, C-$\underline{CH_3}$), 1.62 (3H, m, -$\underline{CH_2}$-$\underline{CH}$), 1.95 (1H, m), 2.35 (1H, m), 3.05 (1H, d of d, J 9Hz and J 1Hz, benzylic proton), 3.72 (3H, s, O-$\underline{CH_3}$), 3.76 (3H, s, O-$\underline{CH_3}$), 6.08 (1H, d, J 2Hz, Aromatic $\underline{H}$), 6.12 (1H, d, J 2Hz, Aromatic $\underline{H}$). The multiplets of protons in the region δ 1.62-3.05 do not change their shape on irradiation of the signals of the remaining protons; from this it can be concluded that either no hydrogen atoms are present in their neighborhood or only one with a small (or approximately zero) vicinal interaction, and hence the presence of the following groups is evident: three tertiary methyls, two methoxy groups, two aromatic hydrogens and one benzylic proton. Further information on the benzylic proton and its relation to other protons at δ 2.35 and 2.54 was indicated by double resonance (NMDR) experiments. Irradiation at δ 2.35 collapsed the d of d at δ 3.05 into doublet (J 9Hz), indicating the presence of long-range coupling between the proton at δ 2.35 and the benzylic proton. Similar irradiation at δ 2.54 collapsed the d of d at δ 3.05 into a doublet (1Hz). Irradiation of the benzylic proton at δ 3.05 collapsed the multiplet at δ 2.54 into doublet (J 7Hz) and the multiplet at δ 2.35 into two doublets (J 7Hz). These experiments show that the benzylic proton is coupled to two protons at δ 2.35 and 2.54 respectively to form an ABX spectrum. This ABX spectrum formation was confirmed by a triple irradiation experiment. Simultaneous irradiation at δ 3.05 and broad band irradiation at δ 1.6 collapsed the multiplets at δ 2.35 and 2.54 into an AB quartet (J 7Hz). That these three protons have formed an ABX pattern was further confirmed by 300 MHz nmr in $CDCl_3$ where they form an AMX pattern, δ 2.54 (1H, d of d, J 9Hz and J 7Hz), 2.35 (1H, two overlapping doublets, J 7Hz), and 3.05 (1H, d, J9Hz).[9] Hence, the nmr spectrum substantiates the partial formulation of the partial structure 5. The remaining problem to be settled is the one regarding one hydrogen and a methylene group. Among ten carbons of the monoterpene component, the partial structure 5 accounts for nine carbon atoms, the remaining one is a methylene carbon which is evidently bonded to carbons C_3 and C_5 considering the original monoterpene structure (1). To locate positively two hydrogens at C_4(1) the nmr spectrum is decisive. Although the region from δ 1.62 (3H) to 1.95 (1H) is complicated by the presence of multiplets, the region is rather simple to analyse. In particular C_4H_A (1) is very strongly deshielded by ether oxygen (attached at C_3). C_4H_A appears at δ 1.96 as a multiplet. The multiplets of C_4H_A proton do not change their shape on irradiation of protons on C_1, C_2, C_6 indicating the correct assignment. Moreover, C_4H_B proton and C_5 methylene protons can be located at δ 1.45 (1H) and 1.62 (2H), respectively (300 MHz, C_6D_6 spectrum).[9] Structure 1 is thus in accord with all of the spectroscopic evidence, alternate structure 3 (R_1=R_2=OCH_3) being ruled out.

Cyclol 1 is formed most probably by acid catalyzed thermal rearrangement of the intermediate chromene 4 ($R_1=R_2=OCH_3$). Similarities in the formation as well as properties such as uv, nmr and mass spectrum of this cyclol 1 and cannabicyclol suggest that cannabicyclol be assigned structure 2.[10] Thus, results of our nmr analysis concur with X-ray analysis.[1]

The effect of the protonic acid upon the transformation of 4 ($R_1=R_2=OCH_3$) to 1 was not completely understandable and thus one can only speculate on the role of this catalyst. One interpretation of the data would require the acid catalyst to assist the cleavage of the carbon-oxygen bond. The allylic carbonium ion (or one of its resonance forms) would be the resultant intermediate, which could be transformed to the cyclol 1.[11] This reaction pathway is shown in Scheme I. We feel this mechanism may be operative in the recently-reported[1] thermal transformation of cannabichromene to cannabicyclol. Similar nmr studies for the recently-described carbazole alkaloids, bicyclomahanimbine and bicyclomahanimbicine[12] (which has a cyclol as partial structure) are in progress.

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9. We would like to thank Mr. Leroy Johnson of Varian Associates for these measurements.

10. Further confirmation of the structure 1 is being carried out by ^{13}C nmr.

11. Inspection of Dreiding models indicates that there is clear overlap between the orbitals of the double bond and the newly created carbonium ion in the seven membered ring.

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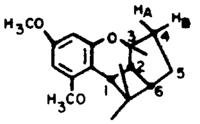
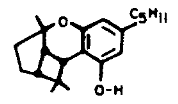


1



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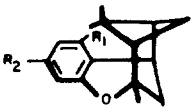
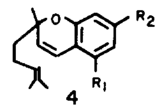
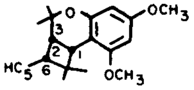


3 $R_1 = OH$, $R_2 = C_5H_{11}$
$R_1 = R_2 = OCH_3$



4
$R_1 = OH$, $R_2 = C_5H_{11}$
$R_1 = R_2 = OCH_3$



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SCHEME I