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THE NONREGIOSPECIFIC CONDENSATION OF CITRAL AND 2-HYDROXY CARBAZOLE.

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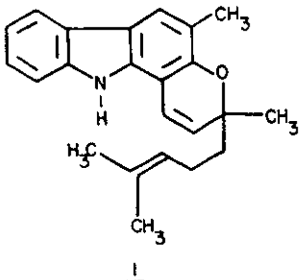
Condensation of citral and 2-hydroxycarbazole in the presence of pyridine has been shown to be regioselective and not regiospecific as has been reported previously. The isolation, characterization and spectral properties of the major (non linear) and the minor (linear) isomers are described.

Monoterpenoid attachments are common structural features which appear in phenolic as well as alkaloidal natural products. Such fused monoterpenoid units have been found in the form chromene, cyclol and tetracyclic ether moieties present in the various carbazole alkaloids isolated from the Indian plant Murraya koenigi Spreng[1]. The simplest of the monoterpenoid carbazole alkaloids is mahanimbine 1[2] which can easily be prepared from 2-hydroxy-3-methyl carbazole and citral. As part of our continuing interest in the ^{13}C nmr spectral properties of natural products we have begun an examination of some of these simple carbazole alkaloids[3]. Although a monograph reviewing ^{13}C nmr chemical shifts of alkaloids has appeared[4], no mention has been made regarding carbazole alkaloids. In the course of this work we have found that previously reported[5] regiospecificity of the reaction of citral 2 with 2-hydroxycarbazole 3 in the presence of pyridine is in error, and report our findings regarding this at this time.



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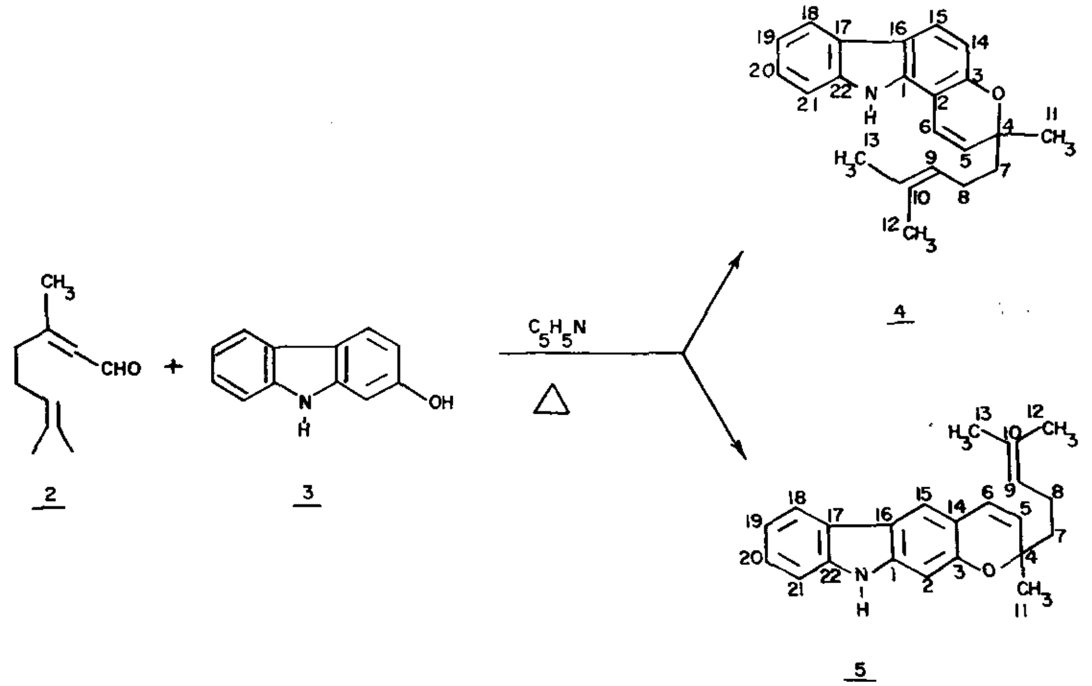
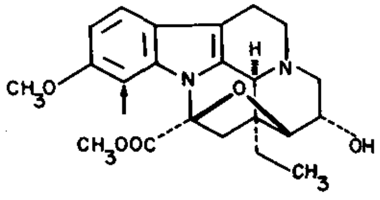


We have found that heating equimolar quantities of citral 2, 2-hydroxycarbazole 3 and pyridine under reflux for 18 hr gave a mixture, containing the chromenes 4 and 5 which was chromatographed on silica gel. Elution with hexane, followed by elution with increasing proportions of ethyl acetate in hexane (2:98), gave in about 33% yield a pale yellow crystalline solid 4, m.p. 78-80° (reported m.p. 63-65°C)[5], homogenous on tlc, nmr: (250 MHz, $CDCl_3$) δ 1.46 (3H, s, O-C$\underline{H}_3$), 1.58, 1.67 (6H, 2s, olefinic C$\underline{H}_3$), 1.78 (2H, m, - C$\underline{H}_2$-CH_2-), 2.17 (2H, m,-CH_2-C$\underline{H}_2$ -CH=C-), 5.12 (1H, m, olefinic proton), 5.63 (1H, d, A part of AB quartet, J=10 Hz, -CH=C$\underline{H}$-C), 6.59 (1H, d, B part of AB quartet, J=10 Hz,-C$\underline{H}$=CH-), 6.76 (1H, d, A part of AB quartet, J=8.6 Hz $C_{14}\underline{H}$), 7.77 (1H, d, B part of AB quartet, J=8.6 Hz, $C_{15}\underline{H}$), 7.94 and 7.30 (5H, aromatic and NH). The uv spectrum of this compound $\lambda_{max}^{CH_3OH}$ 348, 333, 331, 286, 277(sh), 236, 221(sh), 198 (log ε 4.13, 4.15, 4.13, 4.93, 4.90, 4.95, 4.78, 4.70) was very similar to 1. The mass spectrum confirms the molecular composition $C_{22}H_{33}NO$ (m/e calcd for $C_{22}H_{23}NO$ 317.1779; found 317.1775) indicating 1:1 adduct of citral 2 and 2-hydroxycarbazole 3; it also exhibited peaks at m/e 302 (M-15), 248 (M-69), 234 (M-83), 191 (M-126). The data clearly supports structure 4. Further elution with ethyl acetate-hexane (2:98, 3:97) gave in about 3% yield a crystalline solid, m.p. 138-140°, homogenous on tlc, nmr: ($CDCl_3$) δ 1.46 (3H, s, 0-C$\underline{H}_3$),1.56, 1.66 (6H, 2s, olefinic C$\underline{H}_3$), 1.78 (2H, m, C$\underline{H}_2$-CH_2 -), 2.16 (2H, m, -CH_2-C$\underline{H}_2$-CH=C), 5.12 (1H, m, olefinic proton), 5.57 (1H, d, A part of AB quartet, J=10 Hz, CH=C$\underline{H}$), 6.55 (1H, d, B part of AB quartet, J=10 Hz, C$\underline{H}$=CH-), 6.81 (1H, s, $C_2\underline{H}$ aromatic) 7.1 to 7.4 (3H, m, aromatic protons and NH) 7.62 (1H, s, $C_{15}\underline{H}$, aromatic protons), 7.94 (2H, aromatic protons). The uv spectrum of this compound gave $\lambda_{max}^{CH_3OH}$ 352, 339(sh), 336, 319, 293, 274, 250, 243, 227(sh), 201 (log ε 4.09, 3.87, 3.94, 4.02, 4.41, 4.73, 4.65, 4.41, 4.37) respectively, which indicates a fused carbazole chromene skeleton. The mass spectrum confirms molecular composition $C_{22}H_{23}NO$ (m/e calcd for $C_{22}H_{23}NO$ 317.1779; found 317.1798) which again clearly indicates a (1:1) adduct of 2 and 3. In addition, like the mass spectrum of 4, it also showed peaks at m/e 302, 248, 234, 191, which are characteristic of the fragmentation of a chromene monoterpenoid unit fused to aromatic and phenolic rings. The combined nmr, uv and ms data support 5 as the structure for this compound.

Further confirmation for structure 5 came from the single frequency off resonance decoupled (SFORD) ^{13}C nmr spectrum, which gave a doublet at 97.8 ppm for the C_2 carbon, the most highly shielded of the aromatic carbons of the carbazole ring system. The assigned carbon chemical shift for C_2 compares well with that of the corresponding carbon in vincarodine 6[6], N_b-methyltetrahydroharmine 7[7] and also that in 6-methoxyindole 8[3]. This data confirmed the assigned structure beyond doubt as a linear isomer 5.



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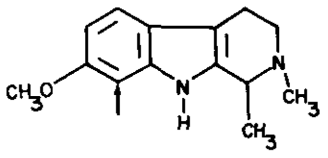

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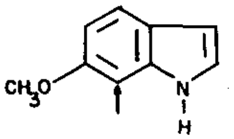

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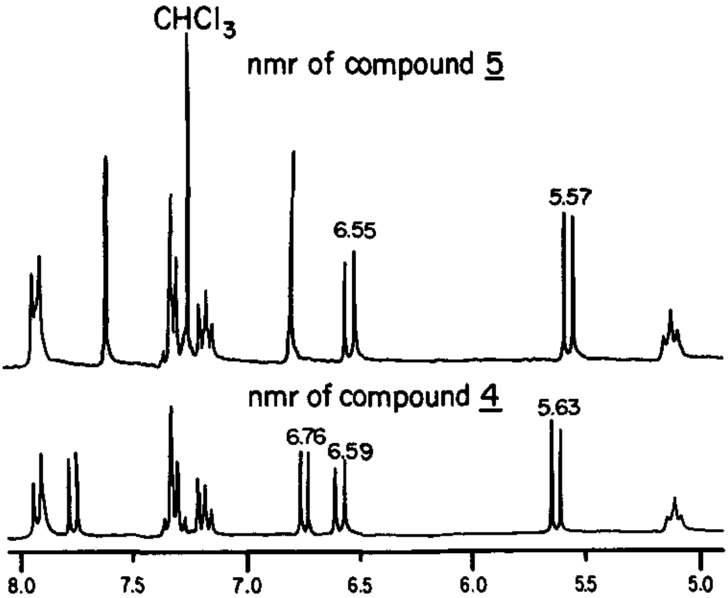

The nmr spectrum of compounds 4 and 5 on 250 MHz in $CDCl_3$ respectively between δ 5.00 to δ 8.00 ppm.

These results suggest that the pyridine catalysed reactions of resorcinols and similar substrates with citral in general are not regiospecific, but rather regioselective. It is quite possible that careful analysis of other chromene forming reactions which have been claimed[5] to be regiospecific may also be in fact be regioselective. The question of whether the mechanisms of these reactions involve C-alkylation followed by cyclization to the hetero atom (oxygen)[5,9], O-alkylation followed by cyclization[10] or both remains unresolved, especially in the case of resorcinols.

References and Notes

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