Studies on the Cannabinoid Field: Synthesis of New Cannabinoids from 4-Hydroxycoumarin and 4-Hydroxythiocoumarin by Pyridine-catalysed Condensation of Citral and Citronellal

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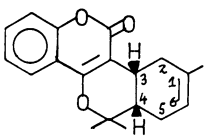
The reaction of 4-hydroxycoumarin and 4-hydroxythiocoumarin with citral in basic as well as acidic conditions led to the formation of tetrahydrocannabiol derivatives. With citronellal, the above hydroxycoumarins afforded the corresponding hexahydrocannabiol derivatives in moderate yields. The structures and the stereochemistry of the compounds obtained are established on the basis of spectral-analytical evidence.

In connection with studies[1] on the synthesis of cannabinoid analogs, we have investigated the reaction of 4-hydroxycoumarin (**1**) and 4-hydroxythiocoumarin (4-hydroxy-2*H*-1-benzothiopyran-2-one) (**2**) with citral and citronellal under different conditions. This work was prompted by the fact that both **1** and **2** can exist in tautomeric forms and that the hydroxyl group in them is highly acidic as indicated by their easy solubility in aqueous hydrogen carbonate solution. Another point of interest is the fact that the 4-hydroxycoumarin structure exists in a number of naturally occurring as well as physiological active compounds, such as the antibiotics novobiocin,[2] coumarmycin[3] and the well-known anticoagulants like dicoumarol[4] and warfarin.[5]

The reaction of **1** with citral in the presence of pyridine at 140 °C for 8 h or at 45—50 °C for 15 h gave a mixture of products, from which two compounds **3** and **4** could be isolated by careful chromatographic procedure. Their structural assignment is based on spectroscopic data, especially on NMR analysis.



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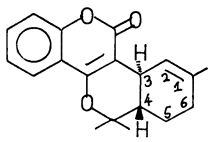

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These compounds exhibit similar spectral features. The mass spectrum of both shows the molecular ion peak at *m/e* 296. It also shows an M—43 peak which suggests that they are not the normal chromene derivatives in which this peak is invariably absent. The elemental analysis indicates their molecular formula as $C_{19}H_{20}O_3$. The UV spectra of **3** and **4** are also similar and show λ_{max} at 215, 280, and 300 nm, indicating that the reaction occurred with the retention of the coumarin ring and thus ruling out the alternate chromone structure. This assumption is supported by their IR spectra which show a carbonyl band at 1720 cm^{-1} corresponding to the coumarin ring.

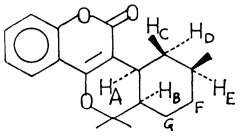
The analysis of NMR spectra of **3** and **4** is fully consistent with their assigned structures. The presence of a broad doublet for one olefinic proton at 5.19 and of a signal at 3.7 for one proton rules out other isomeric structures with a double bond in different positions in the cyclohexane ring. The four aromatic protons appeared as complex multiplet at 7.35—7.85. The assignment of *cis* configuration to **3** follows from the signal in the NMR at 3.7 due to the C_3 proton and the olefinic proton observed at 5.19 confirms that it is the Δ^6 isomer. A signal for the olefinic proton in **4** at 6.35 indicates that the compounds **3** and **4** should differ in the relative position of the double bond and the position of the C_3 proton at 3.25 supports a trans ring fusion. Hence **4** is a Δ^1-*trans* isomer. The NMR values we obtained are in perfect agreement with those obtained for Δ^1- and Δ^6-3,4-*cis*- and *trans*-tetrahydrocannabiol (abbreviated to THC) by Taylor[6] as well as by Archer and co-workers.[7]

It has been reported that the reaction of citral with *m*-benzenediols in the presence of pyridine generally leads to the synthesis of either chromene or cannabicyclol derivatives whereas, under acidic conditions, the formation of THC is observed.[8] The formation of THC in the presence of pyridine does not seem to have been reported so far.

In view of the above observations, the reaction of **1** which citral under mild acid conditions was studied. Compounds **3** and **4** were obtained after chromatography over silica gel (superimposable IR and NMR spectral).

Mechanistically, the formation of **3** and **4** in acid medium could be explained in the same way as that described by Crombie and Ponsford[8] for the acid-catalyzed reaction of citral and olivetol. In pyridine medium the formation of **3** and **4** is somewhat surprising. Our findings can be explained by the earlier observations of Berkoff and Crombie[9] who, in their work on citrylidenemalonic acid involving the reaction of citral with malonic acid in pyridine, reported that whenever "weak proton sources are available, the reaction seems to be so catalyzed." In our case strongly acidic 4-hydroxycoumarin is a good proton source and the reaction follows the acid-catalyzed pathway described above giving **3** and **4**.

Due to the ready reaction of citral with **1** leading to the formation of **3** and **4**, we investigated the reaction of **1** with citronellal in the presence of pyridine (molar proportions) at 140 °C. The reaction has not been studied so far and this is the first report of its use in the work connected with synthesis of cannabinoids. After purification by chromatography over silica gel only one compound **5** was isolated as a crystalline solid.



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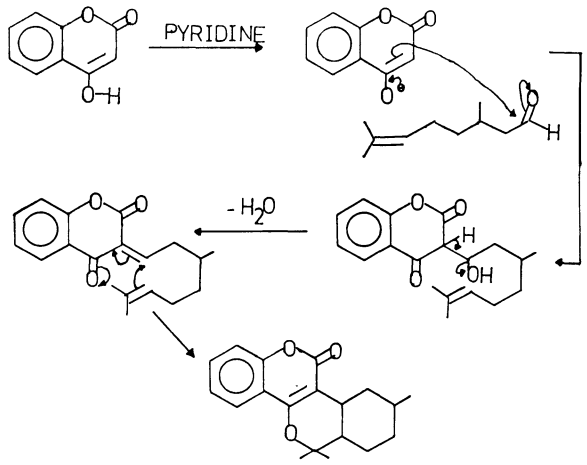
The mass spectrum of **5** showed a molecular ion peak at *m/e* 298. Comparison of the mass spectra of **3** and **5** revealed that the fragmentation pattern in both is very similar. The above observation and the analytical data show that **5** has the molecular composition $C_{19}H_{22}O_3$. Its UV showed λ_{max} at 215 and 300 nm whereas in the IR spectrum the carbonyl frequency was observed at 1725 cm^{-1}. The NMR spectrum of **5** revealed four aromatic protons at 7.1—7.7 in addition to other signals. The 100 MHz NMR ($CDCl_3$) spectrum provided additional proof for the structure as well as its stereochemistry.

The proton H_D unusually appears upfield at 0.66 as a quartet and is coupled to protons H_C (geminal), H_A, and H_E. The analysis of the system (three J_s of 11 Hz) requires the proton to be axial in order to have two ax-ax and one geminal couplings. This makes protons H_A, H_E, and H_D axial as H_D is diaxially coupled to H_A and H_E. Hence CH_3 at C_8 is equatorial. Arnone *et al.*[10] have also observed that the most stable conformation is the one where the Me group is disposed equatorially. The fact permits the assignment 1,3-*trans* configuration (Me-eq, H_B–A_X) to compound **5**. The chemical shifts of the methyl group on C_1 of **5** in the ^{13}C NMR spectrum (22.0 ppm, $CDCl_3$) confirms its equatorial orientation[11]. Similarly, the proton H_C appears unusually low field at 3.14 as a doublet of tripletes (J=11,3,3Hz). The samll values of coupling constants require the H_C proton to be equatorial. The abnormal downfield shift exhibited by the proton H_C as well as the upfield shift of the proton H_D are presumably due to the effect of a carbonyl functionality on the γ-methylene hydrogen and is well documented in the work of Williams *et al.*[12] on 11-keto steroids. Further, such methylene units are characterized by a marked upfieild shift of H axial and a very marked downfield shift of H equatorial. A triplet of doublet signals at 2.39 is attributed to the tertiary H_A proton as the protons oriented 1,3-diaxial to the methyl groups are deshielded. The H_A proton is coupled to H_B and H_D (J=11 Hz) diaxially. This defines the realtive stereochemistry of all the chiral centres in **5**.

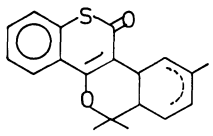
Mechanistically the formation of **5** can be explained as shown in the upper part of the next column.

The pyridine catalysed condensation of citral and citronellal was studied with 4-hydroxythiocoumarin **2**.

The chemistry of the latter is equally interesting in that it possesses the same physiological and chemical properties as **1**. Citral on condensation with **2** afforded a yellow oil which after chromatography over silica gel was found to contain a mixture of isomers in the ratio 1:1 as evident from the NMR spectrum. Its IR showed only a strong carbonyl band at 1610 cm^{-1} indicating that the coumarin ring was not present.



Further, in the NMR spectrum, the aromatic protons gave two different signals at 7.4 and 8.15 integrating for three and one proton, respectively, The latter downfield shift of the aromatic proton can be explained on the basis of structure **7** in which the C_5 proton is deshielded due to its proximity to the carbonyl group of the chromone ring whereas in **6** the aromatic protons would have shown signals at 7.3—7.8 as observed in **5**. The position of the olefinic protons at 6.2 and 5.4 of nearly equal intensity suggests that the compound is a mixture of stereoisomers, the difference being only in the position of double bond. The mass spectrum also favours the THC structure as, in addition to M^+ peak at 312, it shows M—43 peak due the loss of a C_3H_7 unit from the molecule.



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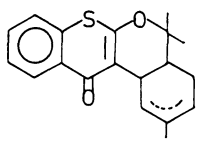

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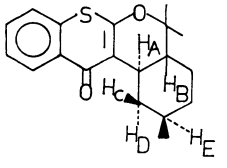
The reaction of **2** with citronellal in the presence of pyridine yielded after purification by chromatography only a single crystalline compound which was assigned the structure **8** on the basis of spectral-analytical evidence. Its UV spectrum showed only two bands at λ_{max} 225 and 305 nm and the IR gave a NMR spectrum was also in line with the structure **8** and the various proton positions indicated its stereochemistry as shown. In the mass spectrum prominent peaks were obtained at *m/e* 314, 299 (M—15), and 271 (M—43).



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Experimental

Melting points are uncorrected. UV spectra were measured in MeOH solutions. The IR spectra were measured

with a Perkin Elmer instrument, NMR (values in δ, J in Hz, TMS as internal standard, $CDCl_3$ as solvent unless otherwise stated) with a Varian A-60 spectrophotometer, and NMR 100 MHz with a Varian XL-15-100 spectrometer. Chromatography was performed with silica gel.

General procedure for the condensation of hydroxycoumarins with citral and citronellal.

4-Hydroxycoumarin or 4-hydroxythiocoumarin (0.01 mol) in dry pyridine (0.01 mol) was heated to 120 °C, and pure citral or citronellal (0.01 mol) was added slowly in 10 min. The resulting reaction mixture was refluxed at 140 °C for 7 h and then extracted with chloroform. The solvent layer was washed with dilute HCl and water to remove pyridine. Further washing of aqueous $NaHCO_3$ solution was carried out in order to remove unreacted 4-hydroxycoumarin or thiocoumarin. The organic phase was dried (Na_2SO_4) followed by removal of the solvent to yield a gummy mass which was subjected to chromatography over silica gel.

(a) Compound **3** (0.2 g), mp 113—114 °C. Found: C, 77.2; H, 7.1%. Calcd for $C_{19}H_{20}O_3$: C, 77.0; H, 6.8%. IR (Nujol) cm^{-1}: 1720(CO), 1600, 1560 (ar.). NMR ($CDCl_3$) δ: 1.2 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.65 (3H, s, CH_3), 0.9—2.2 (4H, m), 2.89 (1H, br, d, C_2H), 3.7 (1H, m, C_3H), 5.19 (1H, s, olefinic-H), 7.35—7.8 (4H, m, ar.), MS *m/e*: 296, 281, 253, 213.

(b) Compound **4** (180 mg), a viscous oil. Found: C, 76.8; H, 6.9%. Calcd for $C_{19}H_{20}O_3$: C, 77.0; H, 6.8%. IR (CH_2Cl_2) cm^{-1}: 1720 (CO), 1600, 1500 (ar.). NMR ($CDCl_3$)δ: 1.2 (3H, s, CH_3), 1.55 (1H, s, CH_3), 1.66 (1H, s, CH_3), 0.9—2.5 (4H, m), 3.2 (1H, br, m, C_3H), 6.35 (1H, br, d, olefinic-H), 7.3—7.85 (4H, m, ar.). MS *m/e*: 296, 281, 253, 213. Compound **5** from citronellal (600 mg), mp 113—114 °C (light petroleum ether (40—60 °C)). Found: C, 76.7; H, 7.4%. Calcd for $C_{19}H_{22}O_3$: C, 76.5; H, 7.4%. IR (CH_2Cl_2) cm^{-1}: 1725 (CO), 1600, 1500 (ar.). NMR ($CDCl_3$: 60 MHz) δ: 0.66 (1H, q, J=11 Hz, 11 Hz, and 11 Hz, H_D), 1.0 (3H, d, CH_3), 1.2 (3H, s, CH_3), 1.55 (3H, s, CH_3), 1.8—2.0 (6H, m), 2.4 (1H, 3d, H_A), 3.1 (1H, m, H_C), 7.35—7.8 (4H, m, ar.). NMR ($CDCl_3$, 100 MHz) δ: 0.66 (1H, q, $J_{DC}=J_{DE}$=11.5 Hz), 0.96 (3H, d, CH_3), 1.2 (1H, s, CH_3), 1.54 (1H, s, CH_3), 0.90—2.00 (6H, br, m, CH_{2F}, CH_{2G}, H_E, H_B), 2.39 (1H, 3d, $J_{AD}=J_{CE}$=3 Hz), 7.35—7.78 (4H, m, ar.). ^{13}C NMR: 19.47 (q, C_{12} or C_{13}), 22.00 (q, C_8), 35.07 (T, C_5), 37.2 (T, C_9), 26.91 (T, C_6), 27.35 (q, C_{12}, C_{13}), 32.13 (d, C_7), 34.15 (d, C_{10}), 48.2 (d, C_{11}), 81.05 (s, C_4) ppm.

(c) Compound **7**, from 4-hydroxythiocoumarin and citral viscous oil, 1 : 1 mixture. Found: C, 73.1; H, 6.5%; Calcd for $C_{19}H_{28}O_2S$: C, 73.4; H, 6.7%. IR (CH_2Cl_2) cm^{-1}: 1610 (>C=O), 1600, 1500 (ar.). NMR (CCl_4) δ: 1.25 (3H, s, CH_3), 1.4 (1H, s, CH_3), 1.65 (1H, d, CH_3), 1.8—2.5 (5H, m), 3.2 (1H, m, CH), 5.4 (1H, br, m, olefinic H), 6.2 (1H, d, olefinic H), 7.42 (3H, s, ar.), 8.15 (1H, broad, ar.).

(d) Compound **8**, from 4-hydroxythiocoumarin and citronellal (400 mg), mp 172—175 °C (ethyl acetate). Found C, 72,6; H, 7.0%; Calcd for $C_{19}H_{22}O_2S$: C, 72.8; H, 7.1%. IR (KBr) cm^{-1}: 1610 (>C=O), 1600, 1500 (ar.). NMR ($CDCl_3$) δ: 0.56 (1H, q, J=11.5, 11.5, 11.5 Hz, H_D), 1.0 (3H, d, CH_3), 1.2 (3H, s, CH_3), 1.5 (3H, s, CH_3), 1.8—2.2 (5H, m), 2.51 (1H, 3d, J=11.5 Hz, 3.5 Hz, 3.5 Hz, H_A), 3.0 (1H, 2t, J=11.5, 11.5, 11.5 Hz, H_C), 7.35 (3H, m, ar.), 8.15 (1H, m, ar.), MS *m/e*: 314, 299, 271.

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