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SYNTHESIS OF THREE NEW DIHYDROPYRANOCHALCONES: STRUCTURAL REVISION OF CROTMADINE, AN ANTIFUNGAL CONSTITUENT OF *CROTALARIA MADURENSIS*

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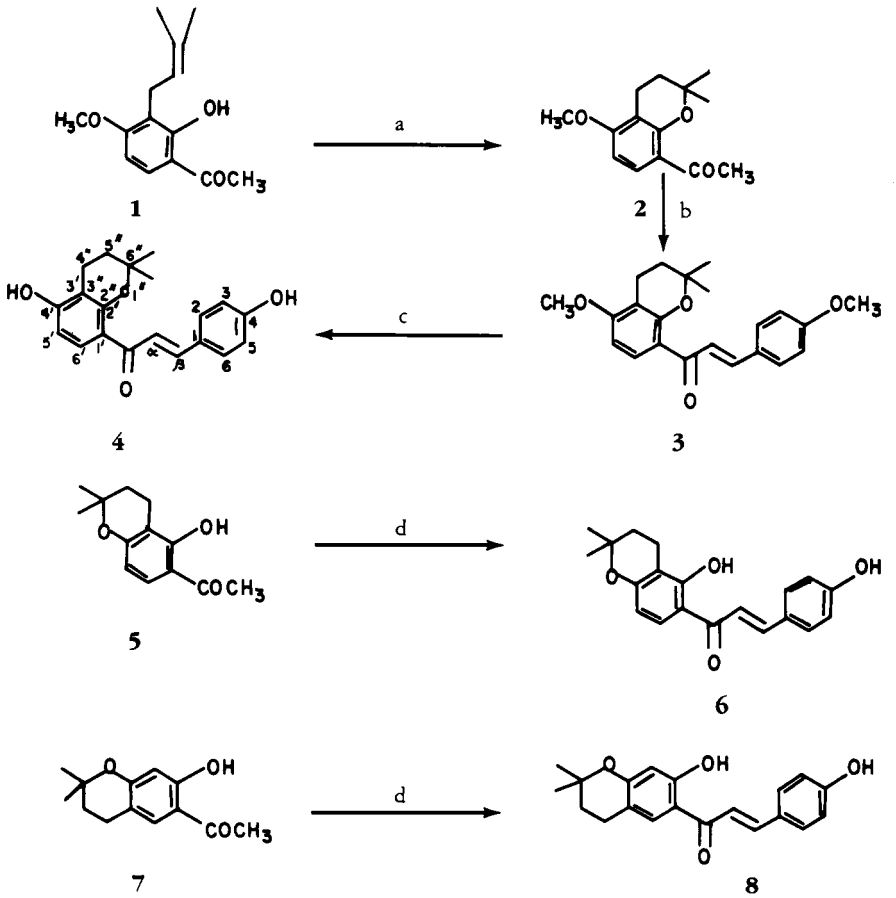
Several isopentenylated chalcones are known to be antibacterial (1), anti-ulcer (2–4), antimicrobial (5), and antifungal (6). Among naturally occurring cyclic isopentenylated chalcones there are very few examples (6–9) of those having the C-2′ hydroxyl group involved in the formation of a dihydropyran ring. One such chalcone, crotmadine, isolated (6) from *Crotalaria madurensis*, was found to exhibit activity against the fungus *Trichophyton mentagrophytes* (6); its structure was elucidated on the basis of its spectral characteristics alone. In order to confirm the proposed structure, we herein report the synthesis of the chalcone **4** and that of two of its isomers, **6** and **8** (Scheme 1).



a. HCO_2H
b. anisaldehyde/KOH-EtOH-H_2O
c. pyridinium HBr
d. *p*-hydroxybenzaldehyde/KOH-EtOH-H_2O

SCHEME 1.

Treatment of 2-hydroxy-4-methoxy-3-(3-methyl-2-butenyl)-acetophenone [**1**] (10) with HCO_2H furnished the hitherto unknown chroman **2**. The condensation of **2** with anisaldehyde gave the new chalcone **3**, which on demethylation with pyridinium HBr (11,12) yielded the chalcone **4**. The mp and spectral characteristics (Tables 1–3) of dihydroxy-6″,6″-dimethyldihydropyrano-(3′,4′:3″,2″)-chalcone [**6**] and 2′,4-dihydroxy-6″,6″-dimethyldihydropyrano-(4′,5′:2″,3″)-chalcone [**8**] by the condensation of *p*-hydroxybenzaldehyde with 6-acetyl-5-hydroxy-2,2-dimethylchroman [**5**] (14) and 6-acetyl-7-hydroxy-2,2-dimethylchroman [**7**] (15), respectively; the mp's and the spectral

TABLE 1. ^{1}H nmr of Compounds **4**, **6**, **8**, and Crotmadine.

Proton	Compound			
	4 ($CDCl_3$)	**6** (CD_3COCD_3)	**8** (CD_3COCD_3)	Crotmadine (6) ($CDCl_3$/DMSO-d_6)
gem-dimethyl . .	1.34, 1.43	1.36	1.34	1.36
H-5″	1.80	1.70	1.70	1.82
H-4″	2.70	2.40	2.30	2.71
H-α	7.45	7.20	7.50	7.43
H-β	7.85	8.00	7.90	7.82
H-5′	6.35	6.95	7.12 (H-3′)	6.37
H-6′	7.70	7.65	7.70	7.61
H-3, H-5	6.85	7.05	6.90	6.89
H-2, H-6	7.50	7.85	7.60	7.52

synthetic **4** were not consistent with those reported (6) for crotmadine. While synthetic **4** melted at 239–240°, the mp reported (6) for crotmadine is 191°. The extent of bathochromic shift in the presence of NaOMe (13) in the uv spectrum of **4** was markedly different from that exhibited by crotmadine (6). Synthetic **4** also showed ir absorptions different from those of crotmadine (6). In view of the marked discrepancies in the mp's and the spectral characteristics of synthetic **4** and natural crotmadine, the structure of the chalcone occurring in *C. madurensis* needs revision. In an attempt to revise the constitution of crotmadine, we have synthesized the hitherto unknown 2′,4-

characteristics of either **6** or **8** (Tables 1–3) were also not consistent with those of crotmadine (6), showing thereby that crotmadine has a structure different from these. On the basis of the data reported (6) for the natural sample of crotmadine, its most probable structure could be 4′,4-dihydroxy-6″,6″-dimethyldihydropyrano-(2′,3′:3″,2″)-chalcone [**9**], which to our knowledge is not known earlier.

The ^{1}H-nmr spectrum of the diacetate of natural crotmadine was reported (6) to exhibit a downfield shift of 0.27 ppm for the H-3 and H-5 as compared to the ^{1}H-nmr spectrum of the parent compound, thereby confirming the presence

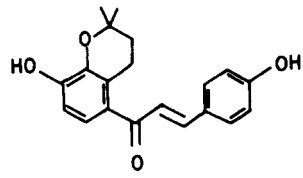
TABLE 2. Uv (λ max) Spectral Data of **4**, **6**, **8**, and Crotmadine.

	Compound			
	4	**6**	**8**	crotmadine (6)
λ max (MeOH) (nm) . . .	368, 282, 226	358, 282	364, 328	372
+ NaOMe (nm)	456, 326, 264	452, 328, 274	450, 338, 262	435

TABLE 3. Mp's and ir ν max (Nujol) Spectral Data of Compounds **4**, **6**, **8**, and Crotmadine.

Compound	Data
4	mp 239–240° 3350, 2900, 1650, 1575, 1500, 1430, 1365, 1150, 1090, 1010 cm^{-1}
6	mp 150–151° 3200, 2900, 1670, 1580, 1505, 1435, 1350, 1200, 1150, 1080, 960, 820 cm^{-1}
8	mp 170–171° 3200, 1640, 1500, 1480, 1450, 1370, 1270, 1150, 1080, 970, 815 cm^{-1}
Crotmadine (6)	mp 191° 3200, 1630, 1580, 1570, 1480, 1370, 1280, 1220, 1165, 1110, 1040, 830 cm^{-1}

of a hydroxyl group at C-4. A similar downfield shift of 0.35 ppm was also shown for the H-5′, which established the presence of a second hydroxyl group at C-4′. These observations support our proposed structure **9** for the chalcone occurring in *C. madurensis*.



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EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All mp's were measured on a Nalge micromelting point apparatus and are uncorrected. Si gel G-13% $CaSO_4$ was used for tlc and Si gel (Merck, 35–70 mesh) was used for cc. The uv spectra were recorded on a Beckman DU-2 spectrophotometer, and the ir spectra were recorded on a Perkin-Elmer infracord-137 instrument or on a Shimadzu infrared spectrophotometer ir-435. The ^{1}H-nmr spectra were recorded on a Perkin-Elmer R-32 (90 MHz) instrument or on a JEOL JNM FX-200 FT nmr instrument in δ scale using TMS as the internal standard.

8-ACETYL-5-METHOXY-2,2-DIMETHYLCHROMAN [**2**].—A solution of 2-hydroxy-4-methoxy-3-(3-methyl-2-butenyl)-acetophenone [**1**] (200 mg) (10) in HCO_2H (85%) (4 ml) was heated on an H_2O bath at 60° for 2 h. After the reaction mixture cooled H_2O (25 ml) was added and extracted with Et_2O (4 × 20 ml). Removal of the solvent gave the chroman **2** as a colorless oil (180 mg): yield 90%; R_f 0.43 (Si gel, C_6H_6-EtOAc, 9:1); ir ν max (Nujol) 1665, 1585, 1485, 1455, 1360, 1270, 1160, 1095, 880, 800 cm^{-1}; ^{1}H nmr ($CDCl_3$) 1.20 (6H, s, 2 × Me), 1.50 (2H, t, H-3), 2.40 (2H, t, H-4), 2.30 (3H, s, -COMe), 3.60 (3H, s, -OMe), 6.20 (1H, d, J = 9 Hz, H-6), and 7.50 (1H, d, J = 9 Hz, H-7); eims *m/z* (rel. int.) $[M+1]^+$ 235 (9.27), $[M]^+$ 234 (61.32), $[M-Me]^+$ 219 (38.67), $[M-COMe]^+$ 191 (19.53), $[M-C_4H_7]^+$ 179 (100), 163 (35.09), 149 (10.92), 133 (4.37), 105 (4.63), 77 (5.29), 57 (3.17), $[COMe]^+$ 43 (23.97); ^{13}C nmr ($CDCl_3$) 17.02 (C-4), 26.50, 26.71 (*gem*-dimethyl), 31.56 (-$COCH_3$), 32.14 (C-3), 55.49 (-OMe), 74.89 (C-2), 101.45 (C-6), 103.62 (C-8), 109.74 (C-4a), 129.60 (C-7), 155.11 (C-1a), 161.17 (C-5), 199.35 (-*C*OMe).

4′,4-DIMETHOXY-6″,6″-DIMETHYLDIHYDROPYRANO-(2′,3′:2″,3″)-CHALCONE [**3**].—To a solution of **2** (100 mg) in EtOH (1.5 ml) was added a solution of KOH (1.4 g in 7 ml EtOH and 1.4 ml H_2O), followed by dropwise addition of anisaldehyde (100 mg in 2 ml EtOH) during 30 min. The solution was continuously stirred during the course of addition, temperature being maintained between 0–5°. The reaction mixture was kept at room temperature for 72 h. Then it was acidified with dilute HOAc. The crude chalcone which separated, crystallized from C_6H_6/petroleum ether as orange crystals (120 mg), mp 179–180°. It gave an orange color with concentrated H_2SO_4: λ max (MeOH) 230 and 340 nm; ir ν max (KBr) 2900, 2500, 1670, 1595, 1510, 1420, 1290, 1255, 1160, 1020, 915, 840, 765, 610 cm^{-1}; ^{1}H nmr ($CDCl_3$) 1.38 (6H, s, 2 × -Me), 1.82 (2H, t, H-5″), 2.71 (2H, t, H-4″), 3.81 and 3.84 (6H, 2s, 2 × -OMe), 6.85–7.13 (3H, m, H-3, H-5, H-α), 7.53–7.90 (4H, m, H-2, H-6, H-6′, H-β); eims (*m/z*) (rel. int.) $[M+1]^+$ 353 (23.55), $[M]^+$ 352 (100), 325 (12.17), 324 (52.5), 309 (15.65), 296 (61.97), 163 (95.65), 161 (17.43), 134 (17.10), 121 (11.97), 105 (6.44), 77 (3.61), 28 (6.25).

4′,4-DIHYDROXY-6″,6″-DIMETHYLDIHYDROPYRANO-(2′,3′:2″,3″)-CHALCONE [**4**].—The mixture of chalcone **3** (100 mg) and pyridinium HBr (500 mg) were heated in a dry test tube until it just melted. After cooling, H_2O (30 ml) was added and the crude chalcone extracted with Et_2O (4 × 25 ml). Evaporation of the

solvent yielded a gummy mass which was purified by chromatography using $CHCl_3$ as the eluent. It crystallized from EtOH as yellow crystals (50 mg), mp 239–240°. It gave an orange-red color with concentrated H_2SO_4. Eims (*m/z*) (rel. int.) $[M+1]^+$ 325 (23.38), $[M]^+$ 324 (100), $[M-1]^+$ 323 (18.22), $[M-43]^+$ 281 (19.67), $[M-55]^+$ 269 (20.32), $[M-56]^+$ 268 (12.56), 232 (10.96), 218 (9.03), [A ring fragment]$^+$ 205 (38.70), 178 (15.16), 162 (15.80), 149 (79.03), [B ring fragment]$^+$ 120 (48.06), 71 (14.54), $[C_4H_7]^+$ 57 (25.16), $[COMe]^+$ 43 (16.12), 28 (4.03).

2′,4-DIHYDROXY-6″,6″-DIMETHYLDIHYDROPYRANO-(3′,4′:3″,2″)-CHALCONE [**6**].—6-Acetyl-5-hydroxy-2,2-dimethylchroman [**5**] (250 mg) (14) was condensed with *p*-hydroxybenzaldehyde, as described for the synthesis of chalcone **3**. The crude chalcone crystallized from EtOH as yellow needles (200 mg), mp 150–151°, R_f 0.80 (Si gel, C_6H_6-EtOAc, 1:1). It gave an orange-red color with concentrated H_2SO_4. Eims (*m/z*) (rel. int.) $[M]^+$ 324 (0.52), $[M-43]^+$ 281 (2.18), $[M-55]^+$ 269 (3.22), 268 (8.06), 267 (21.29), 266 (100), 237 (10.96), 205 (3.98), 172 (8.06), 171 (25.48), 149 (8.06), [B ring fragment]$^+$ 147 (62.96), 121 (42.76), [B ring fragment -CO]$^+$ 120 (36.77), 107 (34.19), $[C_7H_7]^+$ 91 (32.57), 65 (26.12), 44 (28.22), 28 (14.15), 18 (35.16).

2′,4-DIHYDROXY-6″,6″-DIMETHYLDIHYDROPYRANO-(4′,5′:2″,3″)-CHALCONE [**8**].—6-Acetyl-7-hydroxy-2,2-dimethylchroman [**7**] (100 mg) (15) was condensed with *p*-hydroxybenzaldehyde as described for the synthesis of **3**. The crude chalcone was purified by cc using C_6H_6 as the eluent. It crystallized from EtOH as yellow-orange crystals (75 mg), mp 170–171°, R_f 0.37 (Si gel, C_6H_6-EtOAc, 9:1). It gave an orange-red color with concentrated H_2SO_4. Eims (*m/z*) (rel. int.) $[M+1]^+$ 325 (0.70), $[M]^+$ 324 (0.80), $[M-1]^+$ 323 (1.10), 281 (2.30), 269 (2.63), 268 (7.10), 267 (18.28), 266 (83.35), 265 (23.55), 249 (5.92), 237 (9.73), 225 (7.10), 205 (5.26), 176 (2.63), 172 (23.81), 149 (13.48), 121 (100), 120 (41.51), 107 (61.44), 91 (26.31), 69 (21.57), 65 (27.30), 57 (26.84), 55 (28.15), $[COMe]^+$ 43 (52.30), 28 (25.32), 18 (60.52).

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