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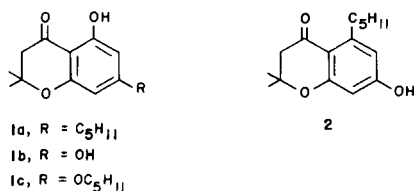
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A series of A-ring heterocyclic analogues of tetrahydrocannabinol were investigated. Chromanones **1a** and **1b** were functionalized by formylation with base and ethyl formate to give **6a** and **6b**. These formylketones were reacted with hydrazine, and phenylhydrazine to give pyrazoles **7a,b,e**, and **f**, respectively. When **6a** and **6b** were reacted with methylhydrazine, mixtures of methyl isomers **7c** and **8a** and **7d** and **8b** formed in a ratio of 1:2.5. Isoxazoles **10a** and **10b** formed similarly when hydroxylamine was used as the condensing agent. Attempts to prepare the pyrimidine derivatives **11** were thwarted by the rearrangements of **6a** and **6b** to chromenones **12a** and **12b**.

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The chemistry and pharmacology of Δ^9 -tetrahydrocannabinol (Δ^9 -THC) and other cannabinoids has been intensively investigated in the recent past [2]. Extensive modifications of the A ring of the carbocyclic nucleus have been reported in a definitive series of papers by Razdan, *et al.* [3] which led to the development of the clinical agent Nabutan. Other heterocyclic A ring analogues have been synthesized by numerous laboratories [4,5,6]. The latter paper prompts us to report some related work done in our laboratories as part of a THC analogue program investigating selective CNS agents.

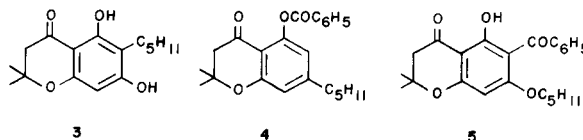
Chromanones **1a** [7] and **1b** were convenient starting materials for our studies. While **1a** had been prepared previously using boron trifluoride etherate catalyzed condensation of olivetol with 3-methylcrotonic acid [7], we found



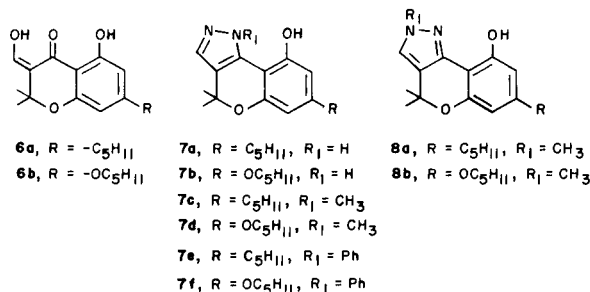
that reaction of 3,3-dimethylacryloyl chloride with olivetol using 1 equivalent of iron(III) chloride as catalyst gave higher and more easily reproducible yields of **1a**. Similar to what had been found earlier, the ratio of **1a**:**2** was dependent upon the amount of catalyst; greater amounts of **2** formed with less catalyst while overall yields (**1a** + **2**) decreased with excess catalyst. Separation of **1a** and **2** was accomplished by simple evaporative vacuum distillation. Catalysts such as aluminum chloride, stannic chloride or zinc chloride were ineffective for this condensation.

Condensation of anhydrous phloroglucinol using these conditions gave the dihydroxy derivative **1b**. Alkylation of **1b** occurred smoothly using pentyl bromide with potassium carbonate in acetone to give **1c** in high yield. Attempted alkylation using stronger bases caused the formation of the C-alkyl derivative **3** admixed with **1c**. This reac-

tivity of the dioxygenated aromatic ring toward substitution was also noted during the preparation of the benzoate derivatives of **1a** and **1c**. While **1a** reacted smoothly with benzoyl chloride in pyridine to give **4** in 77% yield, **1c** reacted to give the C-acyl derivative **5** in 81% yield. It is not clear whether the C-acylation occurred directly from aromatic substitution or by a Fries rearrangement of an intermediate O-acyl compound.

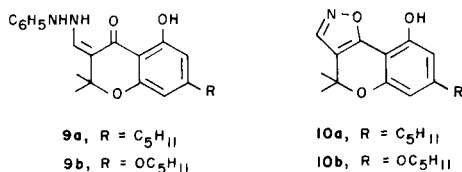


Under carefully controlled conditions, both **1a** and **1c** could be α -formylated in 80% or greater yields to give **6a** and **6b**, respectively. As expected, reaction of these formylketones with hydrazine in ethanol gave pyrazoles **7a** and **7b** in good yield. Spectral analysis indicated these products to exist only in this tautomeric form which probably results

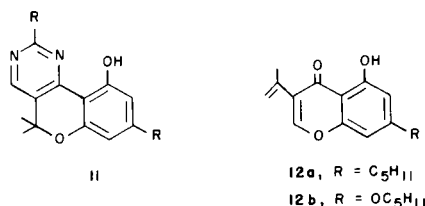


from internal hydrogen bonding with the phenolic oxygen. Condensation of **6a** or **6b** with methyl hydrazine in ethanol also gave the expected pyrazoles, however, both possible isomers **7c** and **8a** and **7d** and **8b** were formed with the less sterically crowded isomer **8** predominating (ratio of 2.5:1). When phenylhydrazine was condensed with **6a** or **6b** in ethanol, only enehydrazinones **9a** and **9b** formed. The desired phenylpyrazoles **7e** and **7f** could be prepared

by treating **9a** and **9b** with acetic acid or by reacting the formylketones with phenylhydrazine in acetic acid solvent.



Isoxazoles **10a** [6] and **10b** formed as expected when hydroxylamine hydrochloride was used as the condensation agent, but attempts to prepare pyrimidine derivatives **11** failed. When **6a** or **6b** were reacted with amidines under basic conditions, retro-aldol reactions occurred regenerating ketones **1a** and **1c** in high yield. Using buffered acidic reaction conditions, **6a** and **6b** rearranged to isopropenyl chromenones **12a** and **12b** with no evidence of pyrimidine formation.



Compounds **7a-f**, **8a-b** and **10a-b** were evaluated for CNS activities [9] but had no interesting levels of activity.

EXPERIMENTAL

Melting points were determined in a Mel-Temp capillary block apparatus and are uncorrected. We wish to thank Dr. G. Jordan and Mr. G. Morton and staff for spectral measurements and helpful discussions and Dr. R. Hargreaves and staff for combustion analytical measurements. The ¹H nmr spectra were determined on a Varian Associates HA100A spectrometer in deuteriochloroform solution unless otherwise noted. All compounds were homogenous by thin layer chromatographic analysis on Whatman K5F or K6F analytical plates.

2,2-Dimethyl-5-hydroxy-7-pentyl-4-chromanone (**1a**) and 2,2-Dimethyl-7-hydroxy-5-pentyl-4-chromanone (**2**).

Olivetol (18.0 g, 0.1 mole) and iron(III) chloride (16.2 g, 0.1 mole) were dissolved in absolute chloroform (100 ml) and treated with a solution of 3,3-dimethylacryloyl chloride (11.8 g, 0.1 mole) in absolute chloroform (100 ml) and the mixture was stirred overnight. The reaction mixture was filtered through magnesium silicate and concentrated which afforded a black liquid which was distilled in a Kugelrohr apparatus. Compound **1a** was the lower boiling component (oven 115°, 0.1 mm Hg), 12.54 g (48%) and remained a yellow liquid; ms: m/z 262 (M⁺); ir (neat): 1645 cm⁻¹; uv (ethanol): 225 sh, 277, 245 nm; ¹H nmr: δ 12.75 (s, 1H, OH), 6.30 (dd, 2H, aryl-H), 2.75 (s, 2H, CH₂), 2.50 (t, 2H, CH₂), 1.46 (s, 6H, CH₃), 1.30 (m, 6H, CH₂), 0.90 (t, 3H, CH₃).

Anal. Calcd. for C₁₆H₂₂O₃: C, 73.25; H, 8.45. Found: C, 72.90; H, 8.66.

Compound **2** distilled as a viscous liquid (oven 160°, 0.075 mm Hg) which crystallized from petroleum ether, 3.65 g (14%), mp 91-93°; ms: m/z 262 (M⁺); ir (potassium bromide): 1640, 1600, 1560 cm⁻¹; uv (ethanol): 221, 231, 277, 310 nm; ¹H nmr: δ 8.30 (br s, 1H, OH), 6.25 (d, 2H, aryl-H), 3.00 (t, 2H, CH₂), 2.75 (s, 2H, CH₂), 1.50 (br s, 12H, CH₂ and CH₃), 0.90 (br t, 3H, CH₃).

Anal. Calcd. for C₁₆H₂₂O₃: C, 73.25; H, 8.45. Found: C, 73.52; H, 8.59.

5,7-Dihydroxy-2,2-dimethyl-4-chromanone (**1b**).

Phloroglucinol dihydrate was dehydrated in an oven at 120° over phosphorus pentoxide for 12 hours. Phloroglucinol (12.6 g, 0.1 mole), dimethylacryloyl chloride (11.8 g, 0.1 mole) and iron(III) chloride (16.2 g, 0.1 mole) were reacted in absolute chloroform (200 ml) as above. The chloroform was removed *in vacuo* and the brown black residue was triturated with 1N hydrochloric acid (100 ml). The solid was collected by filtration, washed with water and air dried to provide a red-brown solid, 15.70 g (75%) which was suitable for further transformations. The analytical sample of **1b** was prepared from chloroform-petroleum ether, mp 187-189°; ms: m/z 208 (M⁺); uv (ethanol): 222 sh, 287, 326 nm; ¹H nmr: δ 12.04 (s, 1H, OH), 5.93 (dd, 2H, aryl-H), 5.73 (brs, 1H, non-bonded OH), 2.70 (s, 2H, CH₂), 1.47 (s, 6H, CH₃).

Anal. Calcd. for C₁₁H₁₂O₄: C, 63.45; H, 5.81. Found: C, 63.24; H, 6.09.

2,2-Dimethyl-5-hydroxy-7-pentoxy-4-chromanone (**1c**).

A solution of **1b** (8.32 g, 0.04 mole), *n*-pentyl bromide (7.55 g, 6.2 ml, 0.05 mole) in dry acetone (300 ml) containing anhydrous potassium carbonate (15 g) was heated under reflux for 3 days. The mixture was filtered, concentrated and distilled to give pure **1c**, 8.62 g (78%), bp 145° (0.075 mm Hg) which crystallized upon standing, mp 44-47°; ms: m/z 278 (M⁺); ir (neat): 1640 cm⁻¹; uv (ethanol): 227 sh, 288, 320 sh; ¹H nmr: δ 12.00 (s, 1H, OH), 6.00 (dd, 2H, aryl-H), 3.97 (t, 2H, OCH₂), 2.69 (s, 2H, CH₂), 1.80 (m, 6H, CH₂), 1.46 (s, 6H, CH₃), 0.94 (br t, 3H, CH₃).

Anal. Calcd. for C₁₆H₂₂O₄: C, 69.04; H, 7.97. Found: C, 69.23; H, 8.10.

5,7-Dihydroxy-2,2-dimethyl-6-pentyl-4-chromanone (**3**).

Phenol **1b** (0.52 g, 0.0025 mole) was dissolved in ethanol (25 ml) containing sodium ethoxide (0.33 g, 0.006 mole) and treated with *n*-pentyl bromide (0.91 g, 0.006 mole). The mixture was heated under reflux for 3 hours and concentrated to dryness. The residue was partitioned between methylene chloride and water and the organic layer was decolorized with charcoal, dried over sodium sulfate and concentrated to give a yellow oil (0.55 g) which was a mixture of **1c** and **3** by thin layer chromatographic analysis. Trituration of the oil with petroleum ether and subsequent cooling to -20° provided pure **3**, 0.15 g (22%); mp 147-149°; ms: m/z 378 (M⁺); ir: (potassium bromide): 1640, 1590 cm⁻¹; uv (ethanol): 228 sh, 292, 334 sh nm; ¹H nmr: δ 12.24 (s, 1H, OH), 5.89 (s, 1H, aryl-H), 5.80 (br s, 1H, OH), 2.80 (s, 2H, CH₂), 2.70 (t, 2H, CH₂), 1.50 (s, 2H, CH₂ and CH₃), 0.97 (br t, 3H, CH₃).

Anal. Calcd. for C₁₆H₂₂O₄: C, 69.04; H, 7.97. Found: C, 69.09; H, 8.23.

6-Benzoyl-2,2-dimethyl-5-hydroxy-7-pentoxy-4-chromanone (**5**).

Alcohol **1c** (1.39 g, 0.005 mole) and benzoyl chloride (1.41 g, 0.01 mole) were combined in dry pyridine (5 ml) and the mixture was stored at room temperature overnight. The reaction was quenched with 3N hydrochloric acid (25 ml) and the aqueous layer was extracted with methylene chloride (3 × 25 ml). The combined organic layers were dried over sodium sulfate and concentrated and the residue was distilled in a Kugelrohr apparatus to give an oil (bp 175°, 0.075 mm Hg) which crystallized upon standing, mp 54-56°; 1.55 g, (81%); ms: m/z 382 (M⁺); ir (neat): 1785, 1750, 1690, 1620 cm⁻¹; uv (ethanol): 219, 231, 274, 310 nm; ¹H nmr: δ 8.17 (m, 2H), 7.54 (m, 3H, phenyl-H), 6.33 (s, 1H, aryl-H), 3.98 (t, 2H, CH₂), 2.58 (s, 2H, CH₂), 1.45 (m, 12H, CH₂ and CH₃), 0.91 (br t, 3H, CH₃).

Anal. Calcd. for C₂₃H₂₆O₅: C, 72.23; H, 6.85. Found: C, 72.01; H, 6.93.

5-Benzoyloxy-2,2-dimethyl-7-pentyl-4-chromanone (**4**).

Alcohol **1a** (0.52 g, 0.002 mole) and benzoyl chloride were reacted as above and distillative work-up provided **4** as a yellow oil, bp 150° (0.075 mm Hg), 0.56 g (77%); ms: m/z 366 (M⁺); ir (potassium bromide): 1790, 1750, 1695, 1630 cm⁻¹; uv (ethanol): 228, 238 sh, 261 sh, 333 nm; ¹H nmr: δ 8.17 (m, 2H), 7.54 (m, 3H, phenyl-H), 6.62 (dd, 2H, aryl-H), 2.61 (m, 4H, CH₂), 1.44 (s, 6H, CH₃), 1.40 (m, 6H, CH₂), 0.88 (t, 3H, CH₃).

Anal. Calcd. for C₂₃H₂₆O₄: C, 75.38; H, 7.15. Found: C, 74.98; H, 6.82.

2,2-Dimethyl-3-formyl-5-hydroxy-7-pentyl-4-chromanone (**6a**).

Ketone **1a** (5.24 g, 0.02 mole) in ether (250 ml) was poured onto freshly

pentane-washed sodium hydride (4.6 g of 50% suspension in mineral oil, 0.10 mole) and methanol (0.1 ml) was added. Ethyl formate (20 ml) was added and the mixture was heated to reflux overnight. The reaction was quenched with 5*N* hydrochloric acid (50 ml), and the layers were separated. The organic layer was dried over sodium sulfate and concentrated and the residue distilled to give the product as a yellow oil, bp 150° (0.1 mm Hg), 5.09 g (88%); ms: *m/z* 290 (*M*⁺); ir (neat): 1640 cm⁻¹; uv (ethanol): 225 sh, 275, 334 nm; ¹H nmr: δ 13.46 (d, 1H, enolic OH), 11.34 (s, 1H, OH), 7.34 (d, 1H, =CH), 6.30 (d, 2H, aryl-*H*), 2.52 (t, 2H, CH₂), 1.59 (s, 6H, CH₃), 1.25 (m, 6H, CH₂), 0.90 (t, 3H, CH₃).

Anal. Calcd. for C₁₇H₂₂O₄: C, 70.32; H, 7.64. Found: C, 70.57; H, 8.00.

2,2-Dimethyl-3-formyl-5-hydroxy-7-pentoxy-4-chromanone (**6b**).

Ketone **1c** (5.56 g, 0.02 mole) was treated with sodium hydride and ethyl formate in a manner similar to the above to provide **6b** as a yellow oil by distillation (bp 145° (0.1 mm Hg)) which crystallized upon standing, mp 47-50°; 4.77 g (73%); ms: *m/z* 306 (*M*⁺); ir (neat): 1645, 1626 cm⁻¹; uv (ethanol): 228 sh, 288, 336 nm; ¹H nmr: δ 13.40 (d, 1H, enolic OH), 11.65 (s, 1H, OH), 7.30 (d, 1H, =CH), 6.00 (d, 2H, aryl-*H*), 3.90 (t, 2H, OCH₂), 1.58 (s, 6H, CH₃), 1.40 (m, 6H, CH₂), 0.93 (t, 3H, CH₃).

Anal. Calcd. for C₁₇H₂₂O₅: C, 66.65; H, 7.24. Found: C, 66.58; H, 7.54.

1,4-Dihydro-4,4-dimethyl-9-hydroxy-7-pentyl[1]benzopyrano[4,3-*c*]pyrazole (**7a**).

Formylketone **6a** (0.87 g, 0.003 mole) and anhydrous hydrazine (0.16 g, 0.005 mole) were combined in ethanol (20 ml) and the solution was stirred overnight. The solvent was removed and the residue was eluted through a silica gel column with chloroform to give product **7a** as a yellow foam after drying under high vacuum, 0.76 g (88%); ms: *m/z* 286 (*M*⁺); ir (neat): 3330 cm⁻¹; uv (ethanol): 220, 272, 281, 296 sh nm; ¹H nmr: δ 9.0 (v br s, 2H, OH, NH), 7.30 (s, 1H, pyrazolyl-*H*), 6.44 (d, 2H, aryl-*H*), 2.54 (t, 2H, CH₂), 1.64 (s, 6H, CH₃), 1.34 (m, 6H, CH₂), 0.92 (t, 3H, CH₃).

Anal. Calcd. for C₁₇H₂₂N₂O₂: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.08; H, 7.94; N, 9.72.

This product was dissolved in ether (50 ml) and treated dropwise with 2*N* ethanolic hydrogen chloride until the amount of precipitate stopped increasing. The product **7a** hydrochloride was collected by filtration and dried, 0.72 g (92%), mp 167-171°.

Anal. Calcd. for C₁₇H₂₃ClN₂O₂: C, 63.25; H, 7.18; N, 8.68; Cl, 10.98. Found: C, 62.86; H, 7.22; N, 8.66; Cl, 10.87.

1,4-Dihydro-4,4-dimethyl-9-hydroxy-7-pentoxy[1]benzopyrano[4,3-*c*]pyrazole (**7b**).

Formyl ketone **6b** (1.23 g, 0.004 mole) was treated with hydrazine (0.004 mole) in ethanol as above to provide **7b** as a cream solid after chromatography, 0.68 g (56%); mp 137-138°; ms: *m/z* 302 (*M*⁺).

Anal. Calcd. for C₁₇H₂₂N₂O₃: C, 67.53; H, 7.33; N, 9.26. Found: C, 67.93; H, 7.59; N, 9.34.

1-Methyl- and 2-Methyl-1,4-dihydro-4,4-dimethyl-9-hydroxy-7-pentyl[1]benzopyrano[4,3-*c*]pyrazoles (**7c** and **8a**).

Formylketone **6a** (0.87 g, 0.003 mole) was treated with methylhydrazine (0.14 g, 0.003 mole) in ethanol (20 ml) overnight. Chromatographic workup as above provided **8a** as the more mobile band as a yellow oil, 0.58 g (64%); ms: *m/z* 300 (*M*⁺); uv (ethanol): 217, 266 sh, 276 nm; ¹H nmr: δ 8.30 (s, 1H, OH), 7.08 (s, 1H, pyrazolyl-*H*), 6.40 (d, 2H, aryl-*H*), 3.91 (s, 3H, NCH₃), 2.54 (t, 2H, CH₂), 1.61 (s, 6H, CH₃), 1.32 (m, 6H, CH₂), 0.89 (t, 3H, CH₃).

Anal. Calcd. for C₁₈H₂₄N₂O₂: C, 71.97; H, 8.05; N, 9.33. Found: C, 72.31; H, 8.31; N, 8.92.

Conversion of **8a** to its hydrochloride salt as above gave 0.54 g of salt as a white solid, mp 148-152°.

Anal. Calcd. for C₁₈H₂₅ClN₂O₂: C, 64.18; H, 7.48; N, 8.32; Cl, 10.52. Found: C, 64.46; H, 7.53; N, 8.35; Cl, 10.54.

The more polar band was **7c**, 0.18 g (20%), mp 109-112°; ms: *m/z* 300 (*M*⁺); uv (ethanol): 223, 282, 298 sh nm; ¹H nmr: δ 7.35 (s, 1H, pyrazolyl-*H*), 6.46 (d, 2H, aryl-*H*), 4.22 (s, 3H, NCH₃), 2.54 (t, 2H, CH₂), 1.60 (s, 6H, CH₃), 1.36 (m, 6H, CH₂), 0.90 (t, 3H, CH₃).

Anal. Calcd. for C₁₈H₂₄N₂O₂: C, 71.97; H, 8.05; N, 9.33. Found: C, 71.78; H, 8.14; N, 8.99.

1-Methyl- and 2-Methyl-1,4-dihydro-4,4-dimethyl-9-hydroxy-7-pentoxy[1]benzopyrano[4,3-*c*]pyrazoles (**7d** and **8b**).

Formylketone **6b** (0.92 g, 0.003 mole) was treated with methylhydrazine as above to give after chromatography **8b** as a yellow oil, 0.50 g (53%); ms: *m/z* 316 (*M*⁺); uv (ethanol): 232 sh, 266 sh, 277, 290 nm.

Anal. Calcd. for C₁₈H₂₄N₂O₃: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.19; H, 8.09; N, 6.96.

The hydrochloride salt of **8b** was prepared as a yellow solid, mp 191-195°.

Anal. Calcd. for C₁₈H₂₅ClN₂O₃: C, 61.27; H, 7.14; N, 7.94; Cl, 10.05. Found: C, 61.10; H, 7.22; N, 7.99; Cl, 9.78.

Compound **7d** was the more polar product, 0.23 g (24%), mp 149-152°; ms: *m/z* 316 (*M*⁺); uv (ethanol): 221, 231 sh, 282, 296 sh nm.

Anal. Calcd. for C₁₈H₂₄N₂O₃·½H₂O: C, 66.54; H, 7.60; N, 8.62. Found: C, 66.57; H, 7.64; N, 8.61.

2-Phenyl-1,4-dihydro-4,4-dimethyl-9-hydroxy-7-pentyl[1]benzopyrano[4,3-*c*]pyrazole (**7e**).

Formylketone **6a** (0.87 g, 0.003 mole) was treated with phenylhydrazine (0.32 g, 0.003 mole) in acetic acid (20 ml) at 80° for 2 hours. The solvents were removed *in vacuo*, the residue was dissolved in chloroform and purified through a silica gel column to provide **7e** as a white solid, 0.9 g (82%), mp 204-206°; ms: *m/z* 362 (*M*⁺); uv (ethanol): 230 sh, 286, 306 sh nm; ¹H nmr: δ 8.90 (s, 1H, OH), 7.48 (s, 1H, pyrazolyl-*H*), 7.38 (m, 5H, phenyl-*H*), 6.40, 6.24 (s, 2H, aryl-*H*), 2.48 (t, 2H, CH₂), 1.60 (s, 6H, CH₃), 1.36 (m, 6H, CH₂), 0.88 (t, 3H, CH₃).

Anal. Calcd. for C₂₃H₂₆N₂O₂: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.17; H, 7.21; N, 7.70.

2-Phenyl-1,4-dihydro-4,4-dimethyl-9-hydroxy-7-pentoxy[1]benzopyrano[4,3-*c*]pyrazole (**7f**).

Formylketone **6b** (0.92 g, 0.003 mole) was treated with phenylhydrazine (0.32 g, 0.003 mole) in acetic acid and worked up as above to give **7f** (0.79 g, 57%) which was crystallized from chloroform, mp 185-187°; ms: *m/z* 378 (*M*⁺); uv (ethanol): 225 sh, 290, 308 sh nm.

Anal. Calcd. for C₂₃H₂₆N₂O₃: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.92; H, 7.07; N, 7.27.

2,2-Dimethyl-3-(phenylhydrazomethylidene)-5-hydroxy-7-pentyl-4-chromanone (**9a**).

Formylketone **6a** (0.87 g, 0.003 mole) was treated with phenylhydrazine (0.32 g, 0.003 mole) in ethanol (20 ml) at room temperature overnight. The solvent was removed *in vacuo* and the residue recrystallized from methylene chloride-petroleum ether to provide **9a** as a yellow crystalline solid, 0.75 g (69%), mp 139-141°; ms: *m/z* 380 (*M*⁺); ir (potassium bromide): 1640 cm⁻¹; uv (ethanol): 230 sh, 281, 364 nm; ¹H nmr: δ 11.36 (br s, 1H, OH), 7.02 (m, 6H, phenyl-*H*, NH), 6.28 (m, 3H, aryl-*H*, NH), 2.60 (t, 2H, CH₂), 1.60 (s, 6H, CH₃), 1.3 (m, 6H, CH₂), 0.90 (t, 3H, CH₃).

Anal. Calcd. for C₂₃H₂₈N₂O₃: C, 72.61; H, 7.42; N, 7.36. Found: C, 72.32; H, 7.46; N, 7.42.

When **9a** was dissolved in acetic acid and allowed to stand overnight, **7e** was formed quantitatively.

2,2-Dimethyl-3-(phenylhydrazomethylidene)-5-hydroxy-7-pentoxy-4-chromanone (**9b**).

Formylketone **6b** (0.92 g, 0.003 mole) was treated as above to give **9b** as a yellow solid, 0.67 g (59%); mp 134-136°; ms: *m/z* 396 (*M*⁺); uv (ethanol): 330 sh, 290, 360 nm.

Anal. Calcd. for C₂₃H₂₈N₂O₄: C, 69.68; H, 7.12; N, 7.07. Found: C, 69.22; H, 7.15; N, 6.93.

4,4-Dimethyl-9-hydroxy-7-pentyl-4*H*[1]benzopyrano[3,4-*d*]isoxazole (**10a**).

Formylketone **6a** (0.87 g, 0.003 mole) and hydroxylamine hydrochloride (0.31 g, 0.0045 mole) were combined in acetic acid (15 ml) and heated

to reflux for 15 minutes. Water was added dropwise to turbidity and the mixture was cooled. The oily precipitate was extracted with methylene chloride and the organic layer was eluted through silica gel with chloroform. The resultant cream solid was triturated with petroleum ether to provide the analytical sample, 0.60 g (69%); mp 98-100°; ms: m/z 287 (M^+); ir (potassium bromide): 3225 cm^{-1} ; uv (ethanol): 229, 295, 315 sh nm; ^1H nmr: δ 8.10 (s, 1H, isoxazolyl-*H*), 6.42 (s, 2H, aryl-*H*), 6.26 (brs, 1H, OH), 2.54 (t, 2H, CH_2), 1.64 (s, 6H, CH_3), 1.36 (m, 6H, CH_2), 0.88 (t, 3H, CH_3).

Anal. Calcd. for $\text{C}_{17}\text{H}_{21}\text{NO}_3$: C, 71.28; H, 7.37; N, 4.62. Found: C, 71.27; H, 7.55; N, 4.76.

4,4-Dimethyl-9-hydroxy-7-pentoxo-4*H*-[1]benzopyrano[3,4-*d*]isoxazole (10b).

Formylketone **6b** (0.92 g, 0.003 mole) was treated with hydroxylamine hydrochloride as above to provide **10b**, 0.49 g, (53%), mp 112-114°; ms: m/z 303 (M^+); uv (ethanol): 236, 299, 322 sh nm.

Anal. Calcd. for $\text{C}_{17}\text{H}_{21}\text{NO}_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.18; H, 6.94; N, 4.45.

5-Hydroxy-3-isopropenyl-7-pentyl-4-chromenone (12a).

Formylketone **6a** (0.87 g, 0.003 mole) was treated with 1 equivalent of either benzamidine hydrochloride (0.52 g) or acetamidine hydrochloride (0.28 g) in acetic acid (10 ml) containing sodium acetate (0.25 g, 0.003 mole) at 100° overnight. The solvent was removed and the residue purified on thick layer chromatography to give **12a** as a pale yellow solid, 0.60 g (73%), mp 38.5-39.5°; ms: m/z 272 (M^+); ir (mull): 1660 cm^{-1} ; uv (ethanol): 226, 250, 330 nm; ^1H nmr: δ 12.59 (s, 1H, OH), 7.79 (s, 1H, =CHO-), 6.63 (d, 2H, aryl-*H*), 5.42, 5.20 (s, 2H, = CH_2), 2.62 (t, 2H, CH_2), 2.10 (s, 3H, CH_3), 1.5 (m, 6H, CH_2), 0.86 (t, 3H, CH_3).

Anal. Calcd. for $\text{C}_{17}\text{H}_{20}\text{O}_3$: C, 74.97; H, 7.40. Found: C, 75.22; H, 7.38.

5-Hydroxy-3-isopropenyl-7-pentoxo-4-chromenone (12b).

Formylketone **6b** (0.92 g, 0.003 mole) was treated in a manner similar to the above to give **12b** as yellow needles, 0.41 g (47%), mp 64-65.5°;

ms: m/z 388 (M^+); uv (ethanol): 256, 295, 325 nm.

Anal. Calcd. for $\text{C}_{17}\text{H}_{20}\text{O}_4$: C, 70.81; H, 6.99. Found: C, 71.19; H, 6.96.

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