

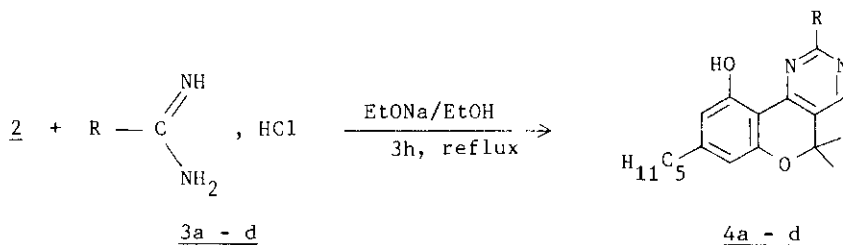
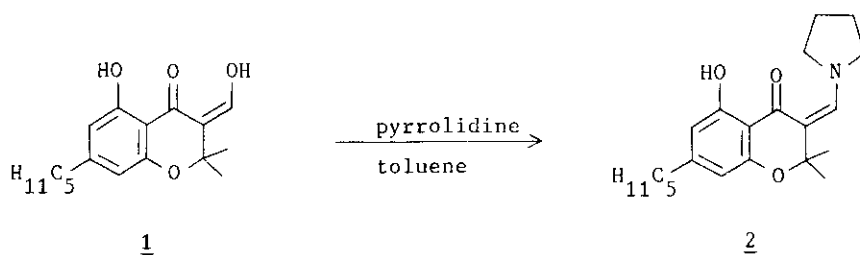
## SYNTHESIS OF NOVEL N-HETEROATOMIC CANNABINOL ANALOGUES

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Abstract- Cyclization of 2,2-dimethyl-3-pyrrolidinomethylene-5-hydroxy-7-pentyl-4-chromanone 2 with guanidine, formamidine, acetamidine and benzamidine hydrochlorides in the presence of 2 eq. of sodium ethoxide afforded novel 5H-[1]benzopyrano-[4,3-d]pyrimidines 4a-d in good yields.

The search for structural analogues of cannabinoids with potential biological activities continues to be an active area of interest<sup>1,2,3</sup>. It is known that the introduction of a heteroatom such as nitrogen into the terpenoid moiety does not result in a loss in activity<sup>4</sup>. In the present paper we report the synthesis of novel N-heteroatomic analogues with a pyrimidine ring fused onto a benzopyran ring. Only one synthesis for these compounds has been reported from 2,2-dimethyl-3-formyl-5-hydroxy-7-pentyl-4-chromanone 1<sup>5</sup> and benzamidine 3d, however yield was modest and the physical characteristics were not given<sup>6</sup>. Recent attempts<sup>1,7</sup> to prepare benzopyrano[4,3-d]pyrimidines from 3-formyl-4-chromanones and amidines were unsuccessful. These failures may be due to the instability of 3-formyl-4-chromanones under the required reaction conditions. In contrast, when the formyl group is replaced by pyrrolidinomethylene group, reaction with guanidine or amidines occurred. Thus, we have previously described<sup>7</sup> the synthesis of benzopyrano[4,3-d]pyrimidines by the reaction of 3-pyrrolidinomethylene-4-chromanone with guanidine and amidines hydrochlorides in the presence of sodium ethoxide. Application of this method to 2,2-dimethyl-3-pyrrolidinomethylene-5-hydroxy-7-pentyl-4-chromanone 2 provides a convenient route to the expected 5H-[1]benzopyrano[4,3-d]pyrimidines 4a-d in good yields.



Compound	R	Yield (%)
<u>4a</u>	NH <sub>2</sub>	91
<u>4b</u>	H	70
<u>4c</u>	CH <sub>3</sub>	93
<u>4d</u>	Ph	95

The pyrrolidine derivative 2 was prepared from the known aldehyde 1<sup>5</sup> with pyrrolidine in toluene at room temperature. Contrary to the unsubstituted 3-pyrrolidinomethylene-4-chromanone, Z configuration was assigned to the ethylenic bond of the enaminone 2 on the basis of <sup>1</sup>H nmr data<sup>8</sup>. When 3-pyrrolidinomethylene-4-chromanone 2 was heated with guanidine hydrochloride 3a in ethanol in the presence of sodium ethoxide under reflux for 3 h, 2-amino-5,5-dimethyl-8-pentyl-10-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine 4a was obtained in 91 % isolated yield. Likewise, treatment of the enaminone 2 with formamidine, acetamidine and benzamidine hydrochlorides 3b, 3c, and 3d gave 5,5-dimethyl-8-pentyl-10-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine 4b and the corresponding 2-methylpyrimidine 4c and 2-phenylpyrimidine 4d in 70, 93, and 95 % yields, respectively. These pyri-

midine derivatives 4a, 4b, 4c, and 4d were identified from ir and nmr spectra. The biological activities of the newly prepared benzopyranopyrimidines are presently under investigation.

## EXPERIMENTAL

Melting points were determined on a Büchi-Tottoli apparatus and are not corrected; ir and mass spectra were recorded on a Beckman IR 20 spectrometer and a MS 30 Kratos spectrometer, respectively.  $^1\text{H}$  Nmr spectra were recorded in  $\text{CCl}_4$  using TMS as an internal standard on a Varian A-60 spectrometer. Elemental analyses of all compounds were within accepted levels.

### 2,2-Dimethyl-3-pyrrolidinomethylene-5-hydroxy-7-pentyl-4-chromanone (2)

2,2-Dimethyl-3-formyl-5-hydroxy-7-pentyl-4-chromanone 1 (4.64 g, 16 mmol) and pyrrolidine (1.5 ml, 18 mmol) were dissolved in anhydrous toluene. After standing for 3 h at room temperature, the mixture was dried over sodium sulfate, filtered and concentrated. The oily residue was chromatographed on a silica gel column. Elution with diethyl ether-pentane (40:60) afforded the pure enaminone 2 as a yellow oil in 60 % yield; ms:  $m/z$  343;  $^1\text{H}$  nmr  $\delta$ : 0.68-1.08 (3H, m,  $\text{CH}_3$ ), 1.09-1.75 (6H, m,  $\text{CH}_2$ ), 1.52 (6H, s,  $\text{CH}_3$ ), 1.92 (4H, m,  $\text{CH}_2\text{-CH}_2\text{-N}$ ), 2.45 (2H, t,  $\text{CH}_2$ ), 3.37 (4H, m,  $\text{CH}_2\text{-CH}_2\text{-N}$ ), 5.98 and 6.10 (2H, H-6 and H-8), 6.70 (1H, s, olefinic proton), 12.85 (1H, s, OH); ir (neat)  $\nu$ : 1625  $\text{cm}^{-1}$ .

### 2-Amino-5,5-dimethyl-8-pentyl-10-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine (4a)

A mixture of enaminone 2 (1.71 g, 5 mmol), guanidine hydrochloride 3a (0.95 g, 10 mmol) and sodium ethoxide (0.68 g, 10 mmol) in absolute ethanol (50 ml) was refluxed for 3 h. After removal of the solvent, the residue was diluted with water and extracted with diethyl ether. The ethereal extracts were dried over sodium sulfate and evaporated to give 4a (91 %) which was recrystallized from ethanol (white needles), mp 153°C; ms:  $m/z$  313;  $^1\text{H}$  nmr  $\delta$ : 0.68-1.06 (3H, m,  $\text{CH}_3$ ), 1.08-1.91 (6H, m,  $\text{CH}_2$ ), 1.64 (6H, s,  $\text{CH}_3$ ), 2.55 (2H, t,  $\text{CH}_2$ ), 5.24 (2H, s,  $\text{NH}_2$ ), 6.31 and 6.43 (2H, H-7 and H-9), 8.13 (1H, s, H-4), 12.40 (1H, s, OH); ir ( $\text{CHBr}_3$ )  $\nu$ : 3400, 3300, 3160  $\text{cm}^{-1}$ .

### 5,5-Dimethyl-8-pentyl-10-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine (4b)

Enaminone 2 (1.71 g, 5 mmol) was treated with formamidine hydrochloride 3b

(0.80 g, 10 mmol) and sodium ethoxide (0.68 g, 10 mmol) in absolute ethanol and worked up as above to give 4b (70 %) which was purified on a silica gel column with diethyl ether-pentane (50:50), mp 57°C; ms: m/z 298; <sup>1</sup>H nmr δ: 0.75-1.11 (3H, m, CH<sub>3</sub>), 1.11-1.83 (6H, m, CH<sub>2</sub>), 1.68 (6H, s, CH<sub>3</sub>), 2.53 (2H, t, CH<sub>2</sub>), 6.20 and 6.35 (2H, H-7 and H-9), 8.41 (1H, s, H-4), 8.91 (1H, s, H-2), 11.96 (1H, s, OH).

2-Methyl-5,5-dimethyl-8-pentyl-10-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine (4c)

Enaminone 2 (1.71 g, 5 mmol) was treated with acetamide hydrochloride 3c (0.94 g, 10 mmol) and sodium ethoxide (0.68 g, 10 mmol) in absolute ethanol as above to provide 4c (93 %) as a yellow solid which was purified by chromatography as 4b, mp 65°C; ms: m/z 312; <sup>1</sup>H nmr δ: 0.75-1.08 (3H, m, CH<sub>3</sub>), 1.12-1.93 (6H, m, CH<sub>2</sub>), 1.63 (6H, s, CH<sub>3</sub>), 2.50 (2H, t, CH<sub>2</sub>), 2.67 (3H, s, CH<sub>3</sub>-2), 6.16 and 6.31 (2H, H-7 and H-9), 8.28 (1H, s, H-4), 12.23 (1H, s, OH).

2-Phenyl-5,5-dimethyl-8-pentyl-10-hydroxy-5H-[1]benzopyrano[4,3-d]pyrimidine (4d)

Enaminone 2 (1.71 g, 5 mmol) was treated with benzamide hydrochloride 3d (1.56 g, 10 mmol) and sodium ethoxide (0.68 g, 10 mmol) in absolute ethanol as above to afford 4d (95 %) as a white solid which was recrystallized from ethanol, mp 110°C; ms: m/z 374; <sup>1</sup>H nmr δ: 0.70-1.10 (3H, m, CH<sub>3</sub>), 1.10-1.90 (6H, m, CH<sub>2</sub>), 1.70 (6H, s, CH<sub>3</sub>), 2.52 (2H, t, CH<sub>2</sub>), 6.20 and 6.38 (2H, H-7 and H-9), 7.38-7.65 (3H, m, H-3', H-4' and H-5'), 8.23-8.45 (2H, m, H-2' and H-6'), 8.52 (1H, s, H-4), 12.13 (1H, s, OH).

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