SYNTHESIS OF NOVEL N-HETEROATOMIC CANNABINOL ANALOGUES

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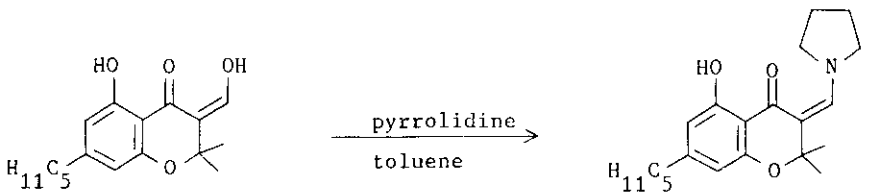
Abstract- Cyclization of 2,2-dimethyl-3-pyrrolidinomethylene-5-hydroxy-7-pentyl-4-chromanone 2 with guanidine, formamidine, acetamidine and benzamidine hydrochlorides in the presence of 2 eq. of sodium ethoxide afforded novel 5H-[1]benzopyrano-[4,3-d]pyrimidines 4a-d in good yields.

The search for structural analogues of cannabinoids with potential biological activities continues to be an active area of interest[1,2,3]. It is known that the introduction of a heteroatom such as nitrogen into the terpenoid moiety does not result in a loss in activity[4]. 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[5] and benzamidine 3d, however yield was modest and the physical characteristics were not given[6]. Recent attempts[1,7] 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[7] 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.



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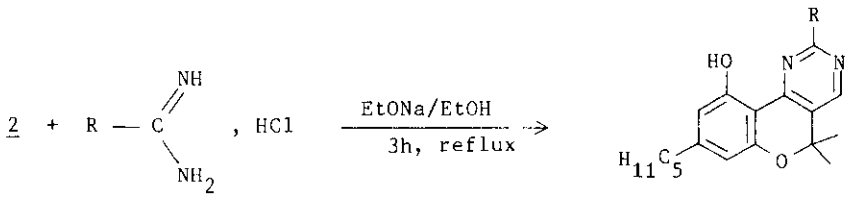

3a - d 4a - d

Compound	R	Yield (%)
4a	NH_2	91
4b	H	70
4c	CH_3	93
4d	Ph	95

The pyrrolidine derivative 2 was prepared from the known aldehyde 1[5] 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 ^{1}H nmr data[8]. 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, treatement 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}H Nmr spectra were recorded in 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}H nmr δ: 0.68-1.08 (3H, m, CH_3), 1.09-1.75 (6H, m, CH_2), 1.52 (6H, s, CH_3), 1.92 (4H, m, $\underline{CH_2}$–CH_2–N), 2.45 (2H, t, CH_2), 3.37 (4H, m, CH_2–$\underline{CH_2}$–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) ν: 1625 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 etheral 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}H nmr δ: 0.68-1.06 (3H, m, CH_3), 1.08-1.91 (6H, m, CH_2), 1.64 (6H, s, CH_3), 2.55 (2H, t, CH_2), 5.24 (2H, s, 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 ($CHBr_3$) ν: 3400, 3300,3160 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; ^{1}H nmr δ: 0.75-1.11 (3H, m, CH_3), 1.11-1.83 (6H, m, CH_2), 1.68 (6H, s, CH_3), 2.53 (2H, t, CH_2), 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 acetamidine 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; ^{1}H nmr δ: 0.75-1.08 (3H, m, CH_3), 1.12-1.93 (6H, m, CH_2), 1.63 (6H, s, CH_3), 2.50 (2H, t, CH_2), 2.67 (3H, s, CH_3-2), 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 benzamidine 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; ^{1}H nmr δ: 0.70-1.10 (3H, m, CH_3), 1.10-1.90 (6H, m, CH_2), 1.70 (6H, s, CH_3), 2.52 (2H, t, CH_2), 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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