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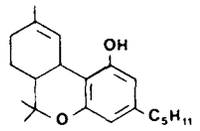
The synthesis of some [1]benzopyrano[3,4-*b*]pyrazine, -[3,4-*d*]imidazole, -[4,3-*c*]imidazole, -[4,3-*c*]pyrazole and -[3,4-*d*]isoxazole analogues of cannabinoids is reported.

J. Heterocyclic Chem., **18**, 23 (1981).

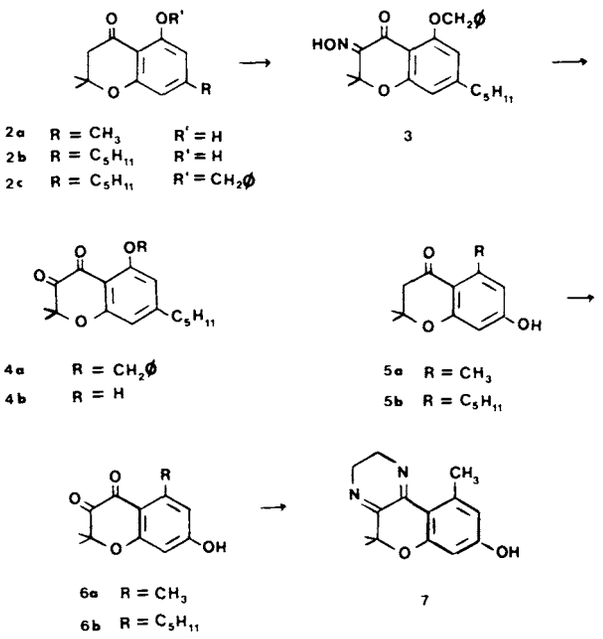
The search for structural analogues of cannabinoids with specific activity and therefore with potential therapeutical applications has continued in recent years (2). Most of the modifications of the parent Δ^1-tetrahydrocannabinol molecule (**1**) have concerned the "terpenoid" moiety, and also the introduction of heteroatoms, such as nitrogen and sulfur. However, only a few examples of *N*-heteroaromatic derivatives are known. Korte prepared some phenyl substituted pyrimidine and benzodiazepine derivatives in 1972 (3), without commenting on their activity. Recently, a series of benzopyrano[4,3-*c*]pyridine analogues with central nervous system (CNS) potency have been reported (4,5).



1

Block 1

This paper reports the synthesis of some new *N*-heteroaromatic analogues, with pyrazine, pyrazole, isoxazole and imidazole rings fused onto the benzopyran ring. The key intermediate for the synthesis of such compounds was the hitherto unknown 2,2-dimethyl-5-hydroxy-7-pentyl-3,4-chromandione (**4b**). Attempts to prepare **4b** or its methyl analogue by oxidation of the easily accessible (6) chromanones (**2b** and **2a**) with various oxidating agents failed, although such reactions have been reported for simple chromanones (7). On the contrary, the oxidation with isoamyl nitrite was successful with the isomeric chromanones (**5**), which, however, could only give analogues of the so called "abnormal" cannabinoids (*e.g.* **7**); these are not an attractive goal since the presence of a hydroxy group in position 5 seems to be an important requisite for biological activity (8). On the assumption that the free 5-hydroxyl was responsible for sensitivity to oxidating conditions, the difficulty was overcome by protection of the hydroxyl with a benzyl group. The oxidation of the benzyl ether (**2c**) with amyl nitrite now affording the



2a R = CH_3 R' = H
2b R = C_5H_{11} R' = H
2c R = C_5H_{11} R' = $CH_2\phi$

3

4a R = $CH_2\phi$
4b R = H

5a R = CH_3
5b R = C_5H_{11}

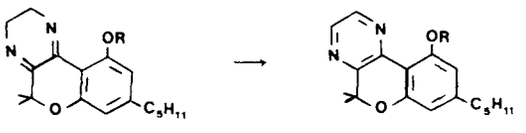
6a R = CH_3
6b R = C_5H_{11}

7

Block 2

oxime (**3**) in good yield. With prolonged reaction times the desired diketone (**4a**) was obtained directly. Although it was always contaminated with some oxime, it was enough pure for subsequent transformations. The removal of the benzyl group to give **4b** could be effected with boron trifluoride, but this step was postponed until the end of the synthesis of the heterocyclic derivatives.

Condensation of **4a** with ethylenediamine gave the dihydropyrazine (**8a**). Reductive debenzylation with palladium as a catalyst gave a product of further reduction, which, however, was too unstable to be isolated. By



8a R = $CH_2\phi$
8b R = H

9a R = $CH_2\phi$
9b R = H
9c R = Ac

Block 3

preparative thin-layer chromatography it was oxidized

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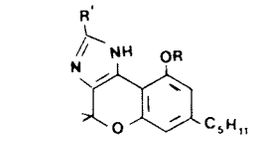
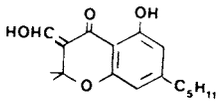
back to the desired **8b**. Dehydrogenation of **8a** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) proceeded smoothly to the fully aromatic compound (**9a**), which was then debenzylated to the benzopyranopyrazine (**9b**). Similar condensation with the free 7-hydroxy-3,4-chromandione (**6a**) afforded the corresponding "abnormal" product (**7**). When formaldehyde or paraldehyde were reacted with **4a** and formamide (9), the imidazole derivatives (**10**) (or their tautomers) were easily obtained.

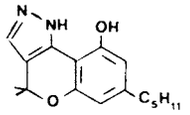
The pyrazole and isoxazole analogues (**12** and **13**) were prepared by condensation of hydrazine and hydroxylamine, respectively with the known aldehyde (**11**) (3).

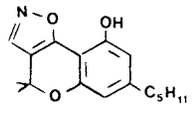




10a R = $CH_2Ø$ R' = H
10b R = H R' = H
10c R = $CH_2Ø$ R' = CH_3

11





12 13

Block 4

Compounds **3**, **7**, **9a**, **12** and **13** were evaluated in CNS pharmacological tests and were inactive.

EXPERIMENTAL

All melting points are uncorrected. Pmr spectra were taken on a Varian EM-390 or XL-100 instrument, in deuterochloroform solution, unless stated otherwise. Column chromatography was performed with Merck silica gel 60 and tlc with Merck 60 F-254 silica gel.

2,2-Dimethyl-5-benzyloxy-7-pentyl-4-chromanone (**2c**).

Benzyl chloride (7 g.) was added to a solution of 7.3 g. of 2,2-dimethyl-5-hydroxy-7-pentyl-4-chromanone (**2b**) and 7.7 g. of potassium carbonate in 130 ml. of methanol, and the mixture was refluxed 24 hours with stirring. Filtration, evaporation, taking up with water and chloroform, washing the organic phase and drying, and chromatography of the extract on silica gel with hexane:ethyl acetate (8:2) gave 4.3 g. of **2c**, m.p. 75° (hexane); ms: m/e (%) 352 (5), 337 (4), 262 (30), 247 (51), 220 (16), 207 (41), 206 (100); nmr: δ 1.43 (2 Me-2), 2.50 (t, Aryl-CH_2, J = 8), 2.64 (CH_2-3), 5.17 ($C_6H_5CH_2O$), 6.37 (H-6 and H-8), 7.1-7.7 (5 aromatic H).

Anal. Calcd. for $C_{23}H_{28}O_2$: C, 78.37; H, 8.01. Found: C, 78.10; H, 8.15.

2,2-Dimethyl-3-hydroximino-5-benzyloxy-7-pentyl-4-chromanone (**3**).

A solution of 5.2 g. of **2c** in 100 ml. of ether:toluene 1:1 was treated with 2.08 g. of amyl nitrite and 3 ml. of concentrated hydrochloric acid, and left overnight at −8°. The mixture was diluted with water. The organic phase was washed with water, then repeatedly with sodium bicarbonate and again with water. The product was dried and evaporated to give 6.3 g.of a crude product which was pure enough for the next step. A sample was purified by chromatography on silica gel with hexane:ethyl acetate (9:1) giving a yellow solid, m.p. 63-65°; ms: m/e (%) 381 (100), 365 (27), 350 (81), 207 (55), 91 (100); nmr: δ 1.61 (2 Me-2), 2.55 (t, Aryl-CH_2, J = 8), 5.21 ($C_6H_5CH_2O$), 6.44 (H-6 and H-8), 7.1-7.7 (5 aromatic H).

Anal. Calcd. for $C_{23}H_{27}NO_4$: C, 72.42; H, 3.32. Found: C, 72.78; H, 7.15; N, 3.32.

2,2-Dimethyl-5-benzyloxy-7-pentyl-chroman-3,4-dione (**4a**).

A mixture of 6.2 g. of **3**, 90 ml. of ether and 10 ml. of 5*N* hydrochloric acid was refluxed 16 hours. The organic phase was separated, washed with water and aqueous sodium bicarbonate, dried, evaporated, and the residue was chromatographed on silica gel with hexane:ethyl acetate (4:1). The product was obtained as a yellow viscous oil, still contaminated with some oxime (tlc), and was used as such; ms: m/e 366, 351, 338, 296.

2,2,5-Trimethyl-7-hydroxy-3,4-chromandione (**6a**).

A solution of 3.9 g. of **5a** in 300 ml. of ether:toluene 1:1 was added with 3.5 ml. of concentrated hydrochloric acid and 3.9 g. of isoamyl nitrite, and was left for two weeks at room temperature. Evaporation and chromatography with benzene:ethyl acetate (9:1) gave **6a**, m.p. 195-196°, yield 72%; ms: m/e (%) 220 (11), 193 (14), 192 (100), 191 (14), 186 (141), 177 (35); nmr (acetone-d_6): δ 1.53 (2 Me-2), 2.55 (Me-5), 6.34 and 6.46 (H-6 and H-8).

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.44; H, 5.19. Found: C, 65.49; H, 5.64.

2,2-Dimethyl-5-pentyl-7-hydroxy-3,4-chromandione (**6b**).

The chromanone (**5b**) (700 mg.) in 15 ml. of ether:toluene (1:1) was treated with 1 ml. of 12*N* hydrochloric acid and 750 mg. of isoamyl nitrite, and the mixture was stirred 2 days. Evaporation and preparative tlc with hexane:ethyl acetate 4:1 gve 250 mg. of **6b**, m.p. 135-136° (hexane:benzene, 3:1); ms: m/e (%) 276 (33), 261 (16), 248 (19), 219 (30), 205 (75), 192 (100); nmr: δ 1.70 (2 Me-2), 3.0 (Aryl-CH_2), 6.40 and 6.51 (H-6 and H-8, each J = 2).

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.80; H, 7.37.

5,5,10-Trimethyl-8-hydroxy-2,3-dihydro-5*H*-[1]benzopyrano[3,4-*b*]pyrazine (**7**).

A solution of 220 mg. of **6a** in 30 ml. of benzene were treated with 60 mg. of ethylenediamine and 1 ml. of acetic acid in 10 ml. of benzene, and the solvent slowly distilled for two hours. Filtration gave 80 mg. of **7**, m.p. 163-165° (benzene-hexane); ms: m/e 244, 243, 229, 227, 216, 214, 202, 201; nmr (acetone-d_6): δ 1.45 (2 Me-5), 2.56 (Me-10), 3.52 (4H), 6.30 and 6.42 (H-7 and H-9).

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.59; H, 6.64; N, 11.05.

5,5-Dimethyl-8-pentyl-10-benzyloxy-2,3-dihydro-5*H*-[1]benzopyrano[3,4-*b*]-pyrazine (**8a**).

A solution of 1 g. of **4a** in 10 ml. of ether was dropped into a cooled (0°) solution of 0.16 g. of ethylenediamine in 7 ml. of ether, and the mixture slowly brought at room temperature, and then refluxed 15 minutes. Dilution with ether, drying and evaporation gave 980 mg. of **8a**, as an unstable, quickly reddening oil; ir (neat): cm^{-1} 2960, 1615, 1580; nmr: δ 1.52 (2 Me-5), 2.51 (t, Aryl-CH_2, J = 7) 3.35-3.82 (4H, 5.21 (Aryl OCH_2), 6.41 and 6.45 (H-7 and H-9), 7.1-7.7 (5 aromatic H).

5,5-Dimethyl-8-pentyl-10-hydroxy-2,3-dihydro-5*H*-[1]benzopyrano[3,4-*b*]-pyrazine (**8b**).

A solution of 536 mg. of **8a** in 25 ml. of ethyl acetate was hydrogenated with 200 mg. of 10% palladium on carbon as a catalyst. Filtration and evaporation gave 336 mg. of an unstable product, which, by preparative tlc with hexane:ethyl acetate (3:2) afforded **8b** as a viscous oil; ir (neat): cm^{-1} 2930, 2960, 1640, 1590; nmr: δ 1.53 (2 Me-5), 2.51 (t, Aryl-CH_2, J = 7), 3.62 (m, 4H), 6.23 and 6.41 (H-7 and H-9).

Anal. Calcd. for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 71.59; H, 7.83; N, 9.35.

5,5-Dimethyl-8-pentyl-10-benzyloxy-5*H*[1]benzopyrano[3,4-*b*]pyrazine (**9a**).

A mixture of 187 mg. of **8a** and 108 mg. of DDQ in 10 ml. of benzene were refluxed 2 hours. Filtration, washing with 10% sodium hydroxide

and water, drying, evaporation gave 140 mg. of **9a**, m.p. 75-80° (diluted ethanol); nmr (acetone-d_6): δ 1.61 (2 Me-5), 2.58 (t, Aryl-CH_2, J = 7), 5.25 (Aryl OCH_3), 6.50 and 7.72 (H-7 and H-9), 8.35 and 8.61 (H-2 and H-3, each J = 3).

Anal. Calcd. for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.27; N, 7.21. Found: C, 76.83; H, 7.23; N, 6.87.

5,5-Dimethyl-8-pentyl-10-hydroxy-5*H*-[1]benzopyrano[3,4-*b*]pyrazine (**9b**).

Hydrogenation of a solution of 470 mg. of **9a** in 20 ml. of ethyl acetate with 150 mg. of 10% palladium on carbon as a catalyst, filtration, evaporation and preparative tlc with hexane:ethyl acetate (4:1) afforded 311 mg. of **9b**, m.p. 44-45°; ms: m/e (%) 298 (41), 284 (56), 256 (13), 242 (100), 226 (18); nmr: δ 1.67 (2 Me-5), 2.52 (t, Aryl-CH_2), 6.33 and 6.44 (H-7 and H-9), 8.21 and 8.34 (H-2 and H-3, each J = 2), 11.80 (OH).

Anal. Calcd. for $C_{18}H_{22}N_2O_2$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.71; H, 7.50; N, 9.03.

Acetylation of **9b** with acetic acid and sodium acetate at 80° for 1 hour gave the monoacetate (**9c**); nmr: δ 1.68 (2 Me-5), 2.33 (MeCO), 2.60 (Aryl-CH_2), 6.62 and 6.78 (H-7 and H-9), 8.33 and 8.43 (H-2 and H-3, J = 3).

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

A mixture of 200 mg. of the diketone (**4a**), 100 mg. of paraformaldehyde and 15 ml. of formamide was heated at 180-185° for 15 minutes, cooled, poured in water, extracted with ether and dried. Preparative tlc (ethyl acetate) gave 76 mg. of **10a**, m.p. 95-98°; ms: m/e (%) 376 (20), 361 (91), 244 (18), 214 (34), 185 (11), 91 (100); nmr: δ 1.65 (2 Me-4), 2.52 (t, Aryl-CH_2), 5.11 (Aryl OCH_2), 6.40 and 6.48 (H-6 and H-8), 7.42 (s, 6H).

Anal. Calcd. for $C_{24}H_{28}N_2O_2$: C, 76.56; H, 7.50; N, 7.44. Found: C, 76.32; H, 7.35; N, 7.60.

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

Hydrogenation of 133 mg. of **10a** in 20 ml. of ethyl acetate with 50 mg. of 10% palladium on carbon as a catalyst gave 100 mg. of a product, which, after grinding with ether, melted at 198-200°, ms: m/e (%) 286 (27), 271 (100), 230 (10), 227 (10), 214 (34); nmr (acetone-d_6): δ 1.62 (2 Me-4), 2.48 (t, Aryl-CH_2), 6.27 and 6.33 (H-6 and H-8), 7.68 (H-2), 9.1 (OH, NH).

Anal. Calcd. for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 70.97; H, 8.01; N, 10.09.

2,4,4-Trimethyl-7-pentyl-9-benzyloxy-1*H*,4*H*-[1]benzopyrano[3,4-*d*]imidazole (**10c**).

A few drops of paraldehyde were added to a solution of 100 mg. of **4a** in 10 ml. of formamide, and the mixture heated 30 minutes at 180°, cooled, poured in water and extracted with ether. Preparative tlc with hexane:ether (1:1) gave 28 mg. of **10c** as a viscous oil; nmr: δ 1.67 (2 Me-4), 2.33 (Me-2), 2.51 (Aryl-CH_2), 5.13 (Aryl OCH_2), 6.40 and 6.47 (H-6 and H-8), 7.45 (5 aromatic H).

4,4-Dimethyl-7-pentyl-9-hydroxy-1*H*,4*H*-[1]benzopyrano[4,3-*c*]pyrazole (**12**).

A mixture of 2.8 g. of 2,2-dimethyl-7-pentyl-5-hydroxy-4-chromanone-3-carbaldehyde (**11**) and 3.05 g. of hydrazine hydrochloride in 90 ml. of ethanol was heated, while hot water was added until the hydrazine salt was completely dissolved, then stirred 6 hours at room temperature. Dilution with water, adding aqueous sodium bicarbonate, extraction with ether and chromatography of the extract on silica gel with hexane:ethyl acetate (7:3) gave 1.55 g. of **12**, m.p. 59-62° (ether-petroleum ether). Further crystallization from petroleum ether gave m.p. 68-70°; ms: m/e (%) 286 (53), 271 (100), 230 (44), 214 (28); nmr: δ 1.57 (2 Me-4), 2.49 (t, Aryl-CH_2), 6.40 (s, H-6 and H-8), 7.29 (broad s, H-3), 9.25 (OH and NH).

Anal. Calcd. for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74. Found: C, 70.90; H, 8.00.

4,4-Dimethyl-7-pentyl-9-hydroxy-4*H*-[1]benzopyrano[3,4-*d*]isoxazole (**13**).

A mixture of 700 mg. of **11** and 154 mg. of hydroxylamine hydrochloride in 9 ml. of acetic acid was quickly heated at 170°, refluxed for 7 minutes, then treated with hot water until the solution became turbid, cooled, and extracted with benzene. The extract was washed with water, 10% aqueous sodium bicarbonate, water, dried and evaporated. Chromatography with hexane:ethyl acetate (4:1) gave 406 mg. of **13**, m.p. 95-97° (ether-petroleum ether); ms: m/e (%) 287 (98), 273 (99), 272 (100), 231 (97), 215 (78), 164 (40), 150 (97), 121 (30); nmr: δ 1.60 (2 Me-4), 2.50 (Aryl-CH_2), 6.40 and 6.45 (H-6 and H-8), 8.18 (H-3), 8.09 (OH).

Anal. Calcd. for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 70.93; H, 7.40; N, 4.76.

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