Drugs Derived from Cannabinoids. 4.[1a] Effect of Alkyl Substitution in Sulfur and Carbocyclic Analogs[1b]

R. K. Razdan,* G. R. Handrick, H. C. Dalzell, J. F. Howes,

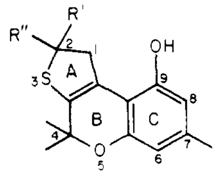
SISA Incorporated, Cambridge, Massachusetts 02138

M. Winn, N. P. Plotnikoff, P. W. Dodge, and A. T. Dren

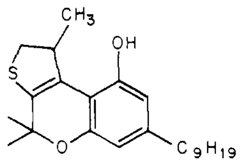
Abbott Laboratories, Abbott Park, North Chicago, Illinois 60064. *Received July 14, 1975*

Various CNS-active cannabinoids in which the alicyclic ring was thiopheno, cyclopenteno, or cyclohexeno with the alkyl substituent in various positions (structural types 1–6) were synthesized by procedures described previously. These compounds were compared in selected pharmacological tests in mice, rats, dogs, and cats. The results suggested that methyl substitution in the close proximity of the phenolic hydroxyl group strongly influenced the activity of some cannabinoids, particularly of those which had a planar five-membered alicyclic ring rather than a six-membered ring.

We have recently reported the synthesis and pharmacology of nitrogen,[2,3] carbocyclic,[3] and sulfur analogs[4] of cannabinoids with CNS activity. In this paper we report the effect of alkyl substitution in the alicyclic ring of sulfur and carbocyclic analogs. We prepared structural types **1–6** and varied the position of the alkyl substituent in the ring A. The methyl substitution in position C-1 in compounds **2** and **4** and C-10 in compound **6a** was of particular interest to us, since the close proximity of this position to the phenolic hydroxyl group was expected to put some conformational constraint on the molecule. An examination of molecular models (Dreiding) confirmed this view. In addition, it was considered that, since the phenolic hydroxyl group in tetrahydrocannabinols (THC's) is extremely important for eliciting activity,[5] substitution in a position close to this important group should exert a modifying influence on the pharmacological activity of these compounds. It should be pointed out that Adams[6] and Todd,[7] during their classical study of THC's, synthesized a number of alkyl-substituted analogs including **6b**.



1a, R' = R'' = H
b, R' = H; R'' = CH_3
c, R' = R'' = CH_3



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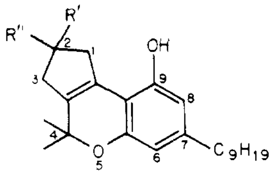
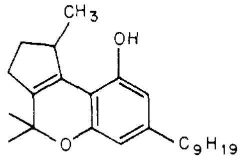


3a, R' = R'' = H
b, R' = H; R'' = CH_3
c, R' = R'' = CH_3



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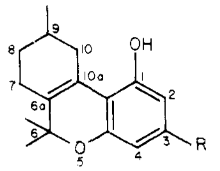
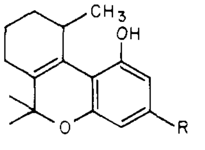
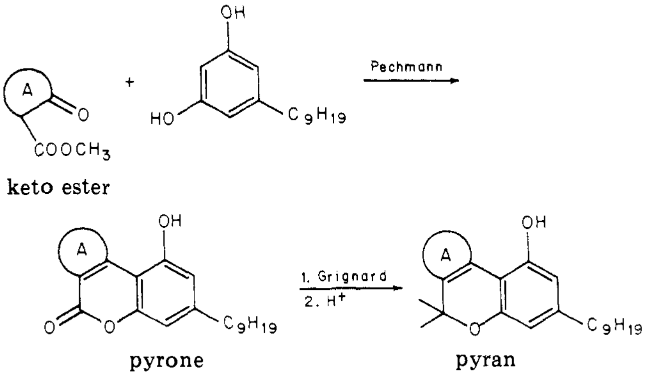


5a, R = C_9H_{19} (DMHP)
b, R = C_5H_{11}



6a, R = C_9H_{19}
b, R = C_5H_{11}

Scheme I



Chemistry. The pyrans 1–6 were prepared following the sequence of reactions as shown in Scheme I and described by us previously.[4] In the sulfur series it was found that besides using HCl–ethanol for carrying out the Pechmann reaction, it could be replaced, in some cases with advantage, by benzene–$POCl_3$ at 30–35°C for 13 days. This procedure was used for Pechmann reaction for the synthesis of the pyrone of **2**. These experimental conditions are comparable to Adams' procedure[8] ($POCl_3$–benzene under reflux for ca. 5 h), used extensively with keto esters in the carbocyclic series.

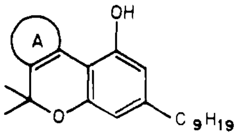
The Pechmann conditions in the synthesis of **6a** were the same as used in the preparation of the pyrone of **5a**[8b] but the rate of reaction was considerably slower (72 h of reflux compared to 3 h). This is rationalized on the basis of steric interaction between the methyl and the hydroxyl groups during the ring-closure step in the formation of the pyrone. The syntheses of **1a**,[4] **3a**,[3,9] and **5a**[8b] have been reported earlier.

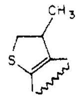
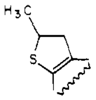
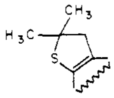
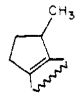
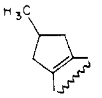
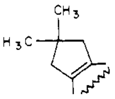
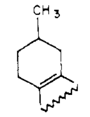
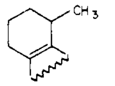
Pharmacology and SAR Results. Compounds 1–6 were subjected to selected pharmacological tests (Table I) in mice, rats, dogs, and cats (sedative–hypnotic) as described previously.[3] All the compounds showed a very high therapeutic index, the approximate LD_{50} (po) in mice being >0.5 g/kg.

As we expected, substitution at the C-1 position in the five-membered sulfur and carbocyclic series (compounds **2** and **4**) produced the most pronounced changes in the pharmacological activity. Thus a 9- to 15-fold increase in the analgesic and a 10-fold increase in the sedative–hypnotic potency were noted in the sulfur series (compare **2** with **1a**). On the other hand, in the five-membered carbocyclic analogs, the potency in the audiogenic seizure test (anticonvulsant activity) increased the most, but the change in analgesic activity was moderate and there was no change in the sedative–hypnotic activity (compare **4** with **3a**). In both series, however, the potency was increased in the dog ataxia test, as compounds **2** and **4** were more active than **1a** and **3a**.

In contrast to the marked pharmacological changes

Table I. Biological Activity of Various Cannabinoid Analogs[a]



Compd	Ring A	Dopa, 5 mg/kg	Audiogenic seizure, 10 mg/kg	Mouse fighting, 10 mg/kg	Analgesia, ED_{50}, mg/kg	Sedative-hypnotic		Dog ataxia, mg/kg
						mg/kg	TST	
1a		+++	++	++	W (71.8), HP (12.1)	1 2	+30, +31	0.1 (+), 10 (++)
2		++	++	++	W (4.7), HP (1.4)	0.1, 0.25	+21, +50	0.1 (++), 1 (++)
1b		+	+	++	W (34)			10 (++)
1c		+	+	+	W (>40)			10 (++)
3a		++	+	++	W (25.3), HP (45.1)	0.5 1.0	+59, +65	1 (+), 10 (++)
4		+	+++	+++	W (13.3)	0.5	+58	1 (++), 10 (++)
3b		+	IA	+	W (22.6)			1 (++), 10 (++)
3c		++	IA	++	W (>40), RTF (>40)			10 (++)
5a		+	+++	+++	W (19.6), HP (12.4)	0.5	+62	1 (++), 10 (++)
6a		+	++ at 30 mg/kg	++	W (10.5), HP (25.0)	0.5	+54	1 (++), 10 (++)

[a] All doses are in mg/kg po; in the Dopa potentiation test, results have been graded as + (slight), ++ (moderate), +++ (marked) increases; in the audiogenic seizure test, + corresponds to 1–33%, ++ (33–66%), and +++ (66–100%) protection after 1 h; in the mouse fighting test, + corresponds to 1–33%, ++ (33–66%), +++ (66–100%) reduction; in the dog ataxia test, + corresponds to decreased activity only and ++ to decreased activity and ataxia; W = writhing; RTF = rat tail flick; HP = hot plate; TST = total sleep time; IA = inactive.

caused in the five-membered series, moving the methyl group to the C-10 position in the six-membered carbocyclic series, compound **6a**, affected the activity only slightly, similar to the findings of Adams[6] and Todd[7] with **6b** vs. **5b**. Our results for compound **6a** compared to **5a** (DMHP) show that the anticonvulsant activity was decreased only slightly, the analgesic activity was increased (slightly), and the dog ataxia test results were unchanged.

From a study of these compounds it appears that methyl substitution in the close proximity of the phenolic hydroxyl group is very important in influencing the activity of some cannabinoids, particularly of those which have a planar five-membered alicyclic ring rather than a six-membered ring.

Experimental Section

Melting points are uncorrected and were determined on a Thomas-Hoover capillary melting point apparatus. Elemental analyses were carried out by Spang Microanalytical Laboratories, Ann Arbor, Mich. NMR spectra were determined on a Varian T-60 instrument. Ir and NMR spectra of all compounds were consistent with the assigned structures. TLC used silica gel (Adsorbosil-2) on microscope slides and visualized in iodine. The petroleum ether used was bp 30–60° grade. All compounds prepared and tested were racemates or mixtures of racemates.

1,2-Dihydro-7-(1,2-dimethylheptyl)-2,4,4-trimethyl-9-hydroxy-4*H*-thieno[2,3-*c*][1]benzopyran (1b). The general procedure described previously for the preparation of **1a** was followed.[4] The solid from 8.8 g (0.0468 mol) of the keto ester, ethyl 5-methyl-3-oxo-tetrahydrothiophene-2-carboxylate,[10] and 5-(1,2-dimethylheptyl)resorcinol was recrystallized from CH_3CN to give 4.65 g (28%) of the pyrone, 1,2-dihydro-7-(1,2-dimethylheptyl)-9-hydroxy-2-methyl-4-oxo-4*H*-thieno[2,3-*c*][1]benzopyran, mp 146–149°. Anal. ($C_{21}H_{28}O_3S$) C, H.

After the Grignard reaction between the pyrone and methylmagnesium bromide, **1b** was obtained as a yellow gum in 81% yield. Anal. ($C_{23}H_{34}O_2S$) C, H, S.

1,2-Dihydro-7-(1,2-dimethylheptyl)-9-hydroxy-2,2,4,4-tetramethyl-4*H*-thieno[2,3-*c*][1]benzopyran (1c). Michael addition of ethyl mercaptoacetate to ethyl dimethylacrylate (C_2H_5ONa in ethanol) gave diethyl 4,4-dimethyl-3-thiahexanedioate, bp 90–95° (0.5 mm). This ester, under Dieckmann cyclization conditions (potassium *tert*-butoxide–ether), formed the keto ester, ethyl 5,5-dimethyl-3-oxotetrahydrothiophene-2-carboxylate, bp 70–75° (0.5 mm).

Similar to the preparation of **1b**, the solid from 6.2 g (0.307 mol) of the keto ester and the dimethylheptylresorcinol was recrystallized from CH_3CN to give 5 g (44%) of the pyrone, 1,2-dihydro-2,2-dimethyl-7-(1,2-dimethylheptyl)-9-hydroxy-4-oxo-4*H*-thieno[2,3-*c*][1]benzopyran, mp 155–163°. Anal. ($C_{22}H_{30}O_3S$) H, S; C: calcd, 70.56; found, 70.06.

After Grignard reaction and a work-up which included chromatography (magnesium silicate, 5:95 ether–petroleum ether), 10 g (0.0267 mol) of the pyrone gave 7.85 g (76%) of **1c** as a yellow gum. Anal. ($C_{24}H_{36}O_2S$) C, H.

1,2-Dihydro-1,4,4-trimethyl-7-(1,2-dimethylheptyl)-9-hydroxy-4*H*-thieno[2,3-*c*][1]benzopyran (2). A solution of 70.9 g (0.3 mol) of 5-(1,2-dimethylheptyl)resorcinol and 52.2 g (0.3 mol) of methyl 4-methyl-3-oxotetrahydrothiophene-2-carboxylate[11] [bp 76–77° (0.25 mm)] in 340 ml of dry benzene was heated in an oil bath at 35°. With gentle stirring 27.5 ml (46 g, 0.3 mol) of $POCl_3$ was added rapidly dropwise. The reaction was allowed to proceed at 35–37° for 13 days.

Most of the solvent and hydrogen chloride were removed at reduced pressure and the tarry residue was mixed with 250 ml of ether and 150 ml of ice water and stirred until solution was complete. The aqueous layer was separated and the ether layer was washed successively with water, saturated $NaHCO_3$, 2% NaOH, water, and saturated NaCl solutions. After being dried, the ether solution was concentrated to leave the crude pyrone, which was purified by column chromatography on Florisil eluted with $CHCl_3$ and 1:99 CH_3OH–$CHCl_3$ mixture. Fractions containing the desired pyrone as monitored by TLC (1:4 ethyl acetate–hexane) were combined and concentrated to leave a gum, which was crystallized from ether–petroleum ether to yield 44.5 g (41%) of the pyrone, 1,2-dihydro-7-(1,2-dimethylheptyl)-9-hydroxy-1-methyl-4-oxo-4*H*-thieno[2,3-*c*][1]benzopyran as crystals, mp 105–107°. Anal. ($C_{21}H_{28}O_3S$) C, H, S.

After Grignard reaction with methylmagnesium bromide and a work-up with chromatography (2:98 ether–petroleum ether) as described previously,[4] 4.6 g (0.0128 mol) of the pyrone gave 4.3 g (90%) of **2** as a yellow gum. Anal. ($C_{23}H_{34}O_2S$) C, H, S.

The remaining compounds (**3b,c**, **4**, and **6a**) were prepared according to Adams procedure[8] for compound **5a**, except that *p*-toluenesulfonic acid was used in the acid work-up after Grignard reaction and the pyrans were purified by column chromatography (see synthesis of **3a**[9]). In the synthesis of compound **6a**, the Pechmann reaction was very slow and the mixture was refluxed for 72 h.

7-(1,2-Dimethylheptyl)-9-hydroxy-1,2,3,4-tetrahydro-2,4,4-trimethylcyclopenta[*c*][1]benzopyran (3b). The solid from 14 g (0.0823 mol) of the keto ester, ethyl 4-methyl-2-oxocyclopentanecarboxylate,[12] was recrystallized from CH_3CN to give 7.5 g (27%) of the pyrone, 7-(1,2-dimethylheptyl)-9-hydroxy-2-methyl-4-oxo-1,2,3,4-tetrahydrocyclopenta[*c*][1]benzopyran, mp 176–178°. Anal. ($C_{22}H_{30}O_3$) C, H.

After Grignard reaction and work-up with chromatography (5:95 ether–petroleum ether), 12.6 g (0.0368 mol) of the pyrone gave 10.95 g (84%) of **3b** as a yellow gum. Anal. ($C_{24}H_{36}O_2$) C, H.

7-(1,2-Dimethylheptyl)-9-hydroxy-1,2,3,4-tetrahydro-2,2,4,4-tetramethylcyclopenta[*c*][1]benzopyran (3c). The keto ester (10.5 g, 0.057 mol), ethyl 4,4-dimethyl-2-oxocyclopentanecarboxylate,[13] gave the pyrone, 2,2-dimethyl-7-(1,2-dimethylheptyl)-9-hydroxy-4-oxo-1,2,3,4-tetrahydrocyclopenta[*c*][1]benzopyran, as a gummy solid, which was used in the subsequent reaction without further purification. After Grignard reaction and work-up as in **3b**, the pyrone yielded 10.49 g (49% overall yield) of **3c** as a gum. Anal. ($C_{25}H_{38}O_2$) C, H.

7-(1,2-Dimethylheptyl)-9-hydroxy-1,2,3,4-tetrahydro-1,4,4-trimethylcyclopenta[*c*][1]benzopyran (4). The keto ester (11 g, 0.0647 mol), ethyl 5-methyl-2-oxocyclopentanecarboxylate,[14] gave the pyrone, 7-(1,2-dimethylheptyl)-9-hydroxy-1-methyl-4-oxo-1,2,3,4-tetrahydrocyclopenta[*c*][1]benzopyran, as a gummy solid, 10.4 g (47% yield). After Grignard reaction and work-up as in **3b**, 53 g (0.1549 mol) of the pyrone gave 25 g (45%) of **4** as a gum. Anal. ($C_{24}H_{36}O_2$) C, H.

7-(1,2-Dimethylheptyl)-1-hydroxy-7,8,9,10-tetrahydro-6,6,10-trimethyl-6*H*-dibenzo[*b*,*d*]pyran (6a). The keto ester (10.5 g, 0.06 mol), ethyl 6-methyl-2-oxocyclohexanecarboxylate,[15] gave a dark resin, which on column chromatography (15:85 ether–petroleum ether) afforded the pyrone, 7-(1,2-dimethylheptyl)-1-hydroxy-10-methyl-6-oxo-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran, as a sticky solid: 8.7 g (40%); mp 108–110°.

After Grignard reaction and work-up with chromatography (1:99 ether–petroleum ether), 8.3 g (0.0232 mol) of the pyrone yielded 8.6 g (82%) of **6** as a gum, which drying turned into a sticky solid, mp 65–70°. Anal. ($C_{25}H_{38}O_2$) H; C: calcd, 81.02; found, 80.18.

Pharmacology. All compounds were administered orally as a suspension of 0.5% methylcellulose. The compounds for the sedative–hypnotic study (cat) were mixed with food.

Mice were used for the Dopa potentiation, mouse fighting, audiogenic seizure, writhing, and hot-plate tests, rats for the motor activity and tail-flick tests, dogs for ataxia, and cats for the sedative–hypnotic studies. All of these tests have been described previously.[3]

References and Notes

(1) (a) For paper 3, see ref 4. (b) A part of this work was presented by R. K. Razdan at a symposium at the 168th National Meeting of the American Chemical Society, Atlantic City, N.J., Sept 1974.

(2) H. G. Pars, F. E. Granchelli, R. K. Razdan, J. K. Keller, D. Teiger, F. J. Rosenberg, and L. S. Harris, part 1, accompanying paper in this issue.

(3) R. K. Razdan, B. Z. Terris, H. G. Pars, N. P. Plotnikoff, P. W. Dodge, A. T. Dren, J. Kyncl, and P. Somani, part 2, accompanying paper in this issue.

(4) R. K. Razdan, B. Z. Terris, G. R. Handrick, H. C. Dalzell, H. G. Pars, J. F. Howes, N. Plotnikoff, P. Dodge, A. Dren, J. Kyncl, L. Shoer, and W. R. Thompson, part 3, accompanying paper in this issue.

(5) D. B. Uliss, H. C. Dalzell, G. R. Handrick, J. F. Howes, and R. K. Razdan, *J. Med. Chem.*, 18, 213 (1975), and references cited therein.

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