The benzene layer was removed, dried (Na_2SO_4), and evaporated to an oily mixture. Chromatography on silica (20 g) gave 0.40 g (44%) of pure (+)-2-dipropylamino-5-methoxy-1,2,3,4-tetrahydronaphthalene [(+)-**7**] as an oil by eluting with 10% ethyl acetate–90% benzene. The HCl salt had mp 171–172° dec, $[\alpha]^{20}D$ +65° (methanol, *c* 2).

To (+)-**7** (0.30 g, 1.2 mmol) was added 0.8 g of 47% HI solution at 0 °C with stirring. Acetic anhydride (1.8 g) was then added dropwise. The solution was refluxed gently under N_2 for 1 h, cooled to room temperature, and triturated with 100 ml of ether. The yellow crystalline solid thus obtained was treated with HCl–methanol to exchange the halides.[7] After three recrystallizations from methanol–ethyl acetate, 0.20 g (61%) of (+)-**4**·HCl was obtained as a colorless crystalline solid: mp 228–229° dec; $[\alpha]^{20}D$ +70° (methanol, *c* 2). Anal. ($C_{16}H_{26}ClNO$) C, H, N.

By the same procedure (–)-**6** was converted to (–)-**4**·HCl: mp 228–229.5° dec; $[\alpha]^{20}D$ –71° (methanol, *c* 2). Anal. ($C_{16}H_{26}ClNO$) C, H, N.

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Drugs Derived from Cannabinoids. 3.[1a] Sulfur Analogs,[1b] Thiopyranobenzopyrans and Thienobenzopyrans

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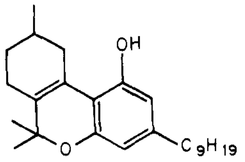
Received July 14, 1975

Sulfur analogs of cannabinoids corresponding to DMHP (**1**) were prepared utilizing the Pechmann condensation between the appropriate keto ester and 5-(1,2-dimethylheptyl)resorcinol, followed by Grignard reaction. Compounds of various structural types (**2**–**6**), which had different ring size and position of the sulfur atom substituted in the alicyclic ring, were found to be active CNS agents in pharmacological tests in mice, rats, and dogs. They showed profiles qualitatively similar to those of the nitrogen and carbocyclic analogs. Basic esters of the most interesting parent phenols **2** and **4** were also prepared and tested.

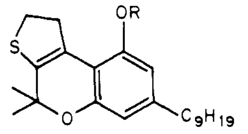
Extending our work on nitrogen and carbocyclic analogs of cannabinoids,[2] we report in this paper the synthesis of sulfur analogs[3] and their biological activity in selected pharmacological tests. In order to define a functional group–activity relationship in this series, we have varied the ring size and the position of the sulfur atom substituted in the alicyclic ring of compound **1**[4] and have prepared the structural types **2**–**6**. These compounds were made with the 1,2-dimethylheptyl substituent on the aromatic ring, because earlier work had shown that this side chain gave the most potent compounds.[2]

As with the nitrogen and carbocyclic analogs[2b] of cannabinoids, the sulfur analogs were water insoluble but very lipid soluble. Hence the water-soluble derivatives (**2b**,**c** and **4b**,**c**) of the most potent compounds of the series (**2a** and **4a**) were studied also. These derivatives were prepared by techniques utilized in solubilizing the nitrogen and carbocyclic analogs.[2b]

Chemistry. The general synthetic scheme developed in the synthesis of carbocyclic analogs[4,5] was suitable for the preparation of these sulfur analogs (Scheme I). Thus, the appropriate keto esters, which are known in the literature, were prepared and allowed to condense with 5-(1,2-dimethylheptyl)resorcinol under Pechmann conditions[2a,4,5] to give the corresponding pyrones. In the sulfur series, the pyrones were obtained as crystalline compounds and in good yields only when the Pechmann condensation was carried out with anhydrous HCl in methanol or ethanol. The ring-opened triols, which were obtained by a Grignard reaction with the pyrones, ring closed to the corresponding pyrans during an acid work-up.



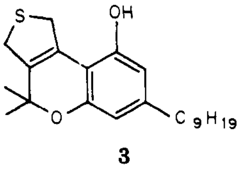
1 (Roger Adams' DMHP)



2a, R = H

b, R = $CO(CH_2)_3$-c-NC_5H_{10}·HCl

c, $CO(CH_2)_3$-c-$N(CH_2CH_2)_2O$·HCl



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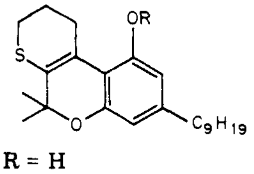
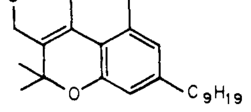


4a, R = H

b, R = $CO(CH_2)_3$-c-NC_5H_{10}·HCl

c, R = $COCH(CH_3)CH_2CH_2$-c-NC_5H_{10}·HCl



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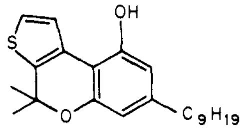


6

$C_9H_{19} = CH(CH_3)CH(CH_3)C_5H_{11}$

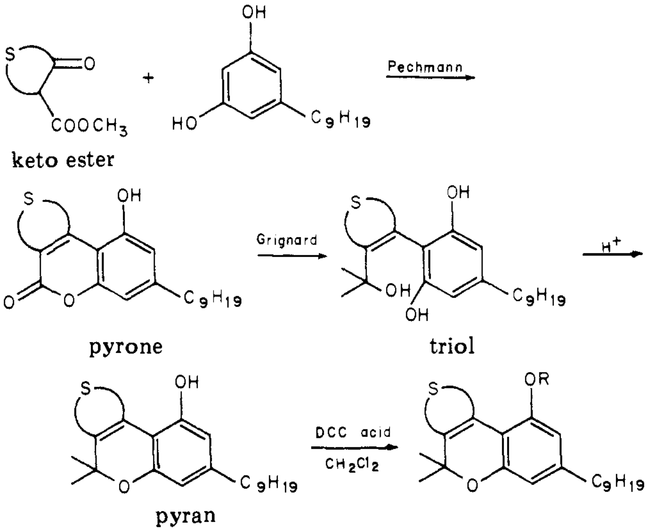
The water-soluble derivatives were prepared from the pyrans by treatment with the appropriate acid in the presence of dicyclohexylcarbodiimide (DCC) in methylene

Table I. Biological Activity of Sulfur Analogs of Cannabinoids[a]

Compd	Dopa, 5 mg/kg	Mouse fighting, mg/kg	Motor act., 5 mg/kg	Analgesia, ED$_{50}$, mg/kg	Dog ataxia, mg/kg
2a	+++	5 (+), 10 (++)	+	W (71.8), HP (12.1)	0.1 (+)
2b	+	10 (++)	+	W (24)	1 (IA)
2c	++	5 (+), 10 (++)	+	HP (>50)	1 (IA)
3	+++	10 (++)	+	W (51.7), HP (>120)	10 (++)
4a	+	10 (+)	+	W (8.6), HP (5.7), RTF (2.7)	1 (++)
4b	+	5 (+)	+++[b]	W (14.7)	
4c	+	10 (+++)	+	W (22.6)	
5	++	5 (+)	10 (+)	W (>40), HP (>40)	10 (++)
6	+	10 (+)	+	W (>10)	

[a] All doses are in mg/kg po; in the Dopa potentiation test, results have been graded as + (slight), ++ (moderate), and +++ (marked) increases. In the mouse fighting and motor activity tests, + corresponds to 1-33%, ++ (33-36%), and +++ (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; and IA = inactive. [b] Inconsistent data.

Scheme I



chloride at 25°.[2b,6] The thiophene derivative **6** was obtained from **2** by dehydrogenation with 10% Pd/C in boiling xylene for 90 h.

Pharmacology. The compounds were studied in selected pharmacological tests (Table I) in mice, rats, and dogs as described in our earlier work.[2b] Each of the compounds showed a very high therapeutic index in mice, because the approximate LD$_{50}$ (po) was >0.3 g/kg. The sulfur analogs showed a behavioral profile qualitatively similar to that of the nitrogen and carbocyclic analogs, i.e., decreased locomotor activity, increased sensitivity to stimuli ("popcorn effect"), CNS depression, and, at high doses, static and dynamic ataxia.[2]

SAR Results. Only the five-membered ring compounds (**2a** and **3**) gave marked activity in the Dopa test, which was reduced when the five-membered ring was aromatized (compound **6**). Basic esters (**2b,c**) of the parent phenol (**2a**) showed reduced activity in this test. A similar SAR was found in the nitrogen analogs.[2b] In the mouse fighting and rat motor-activity tests, no SAR was obvious. Potent analgetic activity was found only in the parent phenol **4a**, and this activity was reduced in the ester derivatives **4b** and **4c**. This change is in contrast to the nitrogen and carbocyclic analogs, in which esterification with the piperidino and morpholino acids retained analgetic activity.[2b]

Among the sulfur analogs, compounds **2a** and **4a** were of most pharmacological interest (Table I). The former showed good activity in the Dopa and the dog ataxia tests, and the latter showed good analgesic properties and caused ataxia in dogs at low doses. Both compounds lowered blood pressure in spontaneous hypertensive rats at 10 mg/kg po. Compound **2a** showed 17-31% hypotension (as percent of control blood pressure) at 4 h and 2-18% at 24 h, whereas compound **4a** produced hypotension lasting 48 h, 15-21% (4 h), 28-30% (24 h), and 19-23% (48 h). Furthermore in sedative-hypnotic activity tests in cats (data not given in the table), compound **2a** showed marginal activity and compounds **4a** and **4c** were inactive. These results differ from those found with the nitrogen and carbocyclic analogs, some of which showed potent sedative-hypnotic activity.[2b]

From our study (Table I), it appears that the sulfur atom should be adjacent to the double bond in order to elicit interesting activity in sulfur analogs and the ring size has no influence. However, a planar ring (as in compound **6**) eliminates activity.

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 and the ethanol was 200 proof. All compounds prepared and tested were racemates or mixtures of racemates.

1,2-Dihydro-4,4-dimethyl-7-(1,2-dimethylheptyl)-9-hydroxy-4*H*-thieno[2,3-*c*][1]benzopyran (2a). The procedure of Woodward and Eastman[7] was followed for the cyclization of 100 g (0.55 mol) of methyl 3-(methoxycarbonylmethylthio)propionate to give 56 g (65%) of the keto ester, methyl 3-oxo-2,3,4,5-tetrahydrothiophene-2-carboxylate, after fractionation through a 4-in. Vigreux column: bp 112-115° (6 mm). By NMR analysis the product was shown to be a mixture of isomers having the composition of 80% desired product and 20% methyl 4-oxo-2,3,4,5-tetrahydrothiophene-3-carboxylate.[7] The mixture was used in the subsequent condensation without further purification.

A solution of 48.8 g (0.206 mol) of 5-(3-methyl-2-octyl)resorcinol and 39 g (0.253 mol) of methyl 3-oxo-2,3,4,5-tetrahydrothiophene-2-carboxylate in 500 ml of C_2H_5OH in a three-necked flask equipped with drying tube was cooled in an ice-water bath and saturated with dry HCl gas. The reaction mixture was allowed to stand for 3 days at room temperature during which time a copious amount of yellow solid formed. The solid was collected by filtration and washed with C_2H_5OH. The mother liquors were concentrated in a rotary evaporator and left in the refrigerator to yield more solid. The combined solid was recrystallized three times from C_2H_5OH (12-15 ml for 1 g of solid) to yield 16 g (19%) of the pyrone, 1,2-dihydro-7-(1,2-dimethylheptyl)-9-hydroxy-4-oxo-4*H*-thieno[2,3-*c*][1]benzopyran, as crystals: mp 208-211°; pure by TLC (1:4 ethyl acetate-hexane). Anal. ($C_{20}H_{26}O_3S$) C, H, S.

The Grignard reagent was prepared by bubbling CH_3Br into a mixture of 7.2 g (0.3 mol) of magnesium turnings in ether. After all the magnesium had reacted, the solution was refluxed for a short time to remove excess CH_3Br. A solution of 9.0 g (0.026 mol) of the above pyrone in 250 ml of benzene was added to the methylmagnesium bromide and the reaction mixture was kept at 45° for 24 h. After the addition of saturated NH_4Cl, the benzene–ether layer was separated, and the aqueous layer was extracted with ether. The combined organic layer was washed with water, dried over sodium sulfate, and evaporated to give a greenish, gummy residue. The material was pure by TLC (10% $MeOH-CHCl_3$) and the ir and NMR showed the compound to be the triol 2-[4,5-dihydro-2-(1-hydroxy-1-methylethyl)thien-3-yl]-5-(1,2-dimethylheptyl)resorcinol.

A solution of the triol in benzene was refluxed for 3 h in the presence of a small amount of *p*-toluenesulfonic acid. The residue left after removal of the benzene was chromatographed on Florisil with graded mixtures of ether–petroleum ether as solvent. A total of 7.5 g (80%) of **2a** was obtained as a gum: pure by TLC (20% ether–petroleum ether); $\lambda_{\max}^{\mathrm{EtOH}}$ 320 nm (log ϵ 3.951). Anal. ($C_{22}H_{32}O_2S$) C, H, S.

1,2-Dihydro-4,4-dimethyl-7-(1,2-dimethylheptyl)-9-(1-piperidinebutyryloxy)-4*H*-thieno[2,3-*c*][1]benzopyran Hydrochloride (2b). **2a** (2.86 g, 7.95 mmol), 1.65 g (7.95 mmol) of 1-piperidinebutyric acid hydrochloride,[2b,8] and 1.72 g (3.35 mmol) of dicyclohexylcarbodiimide (DCC) were combined in 150 ml of CH_2Cl_2 and stirred at room temperature for 4 h. The insoluble by-product, dicyclohexylurea, was removed by filtration and the CH_2Cl_2 was removed on a rotary evaporator. The residue was dissolved in 30 ml of benzene, and ether was added until a colorless solid appeared. The material was filtered and recrystallized from benzene–ether to give 3.7 g (73%) of **2b** as colorless crystals: mp 165–167°; single spot on TLC (10% $CH_3OH-CHCl_3$). Anal. ($C_{31}H_{48}ClNO_3S$) C, H, N.

1,2-Dihydro-4,4-dimethyl-7-(1,2-dimethylheptyl)-9-(1-morpholinebutyryloxy)-4*H*-thieno[2,3-*c*][1]benzopyran Hydrochloride (2c). The procedure for the preparation of **2b** was followed, using γ-morpholinobutyric acid hydrochloride.[2b,8] The solid was recrystallized from benzene–ether to give **2c** (29% yield) as colorless crystals: mp 123–124°; pure by TLC (5% $CH_3OH-CHCl_3$). Anal. ($C_{30}H_{46}ClNO_4S$) H, N; C: calcd, 65.27; found, 64.46.

2,3-Dihydro-4,4-dimethyl-7-(1,2-dimethylheptyl)-9-hydroxy-4*H*-thieno[3,4-*c*][1]benzopyran (3). The general procedure described for the preparation of **2a** was followed. The solid from 20 g (0.125 mol) of the keto ester, methyl 4-oxo-2,3,4,5-tetrahydrothiophene-3-carboxylate,[7] was recrystallized from C_2H_5OH to give 16 g (37%) of the pyrone, 1,3-dihydro-7-(1,2-dimethylheptyl)-9-hydroxy-4-oxo-4*H*-thieno[3,4-*c*][1]benzopyran, mp 165–166°.

After Grignard reaction and work-up, 6 g (0.017 mol) of the pyrone gave 2.6 g (42%) of **3** as a colorless gum: pure by TLC (20% ether–petroleum ether); $\lambda_{\max}^{\mathrm{EtOH}}$ 284 nm (log ϵ 4.157). Anal. ($C_{22}H_{32}O_2S$) C, H.

5,5-Dimethyl-8-(1,2-dimethylheptyl)-10-hydroxy-1,2,3,5-tetrahydrothiopyrano[2,3-*c*][1]benzopyran (4a). The procedure for the preparation of **2a** was followed, beginning with 11.1 g (0.063 mol) of the keto ester, methyl 3-oxo-2,3,4,5-tetrahydro-6*H*-thiopyran-2-carboxylate.[9] Because a solid was not obtained in the Pechmann reaction, the reaction mixture was concentrated in a rotary evaporator to remove alcohol. The residue was dissolved in ether, washed with sodium bicarbonate solution, and dried over sodium sulfate. Evaporation of the solvent gave 28.0 g of a residue, which was chromatographed using Florisil and graded $CH_3OH-CHCl_3$ solvent mixtures. A total of 10 g of crude solid was obtained from the 1% $CH_3OH-CHCl_3$ fractions. The material was recrystallized twice from ethyl acetate–hexane to give 8.5 g (40%) of the pyrone, 8-(1,2-dimethylheptyl)-10-hydroxy-5-oxo-1,2,3,4-tetrahydrothiopyrano[2,3-*c*][1]benzopyran, as colorless crystals, mp 131–133°. Anal. ($C_{21}H_{28}O_3S$) C, H, S.

After Grignard reaction and work-up 6.96 g (0.02 mol) of the pyrone gave 5.2 g (60%) of **4a** as a colorless gum: $\lambda_{\max}^{\mathrm{EtOH}}$ 305 nm (log ϵ 4.2625). Anal. ($C_{23}H_{34}O_2S$) C, H, S.

5,5-Dimethyl-8-(1,2-dimethylheptyl)-10-(1-piperidinebutyryloxy)-1,2,3,5-tetrahydrothiopyrano[2,3-*c*][1]benzopyran Hydrochloride (4b). The procedure used in the preparation of **2b** was followed. The material was crystallized from cyclohexane to give **4b** (80% yield) as colorless crystals, mp 136–138°. Anal. ($C_{32}H_{50}ClNO_3S$) C, H, N.

5,5-Dimethyl-8-(1,2-dimethylheptyl)-10-(α-methyl-1-piperidinebutyryloxy)-1,2,3,5-tetrahydrothiopyrano[2,3-*c*][1]benzopyran Hydrochloride Hydrate (4c). It was prepared as in **4b** using α-methyl-1-piperidinebutyric acid hydrochloride[2b] in the reaction. Compound **4c** failed to crystallize and was obtained as a beige solid after evaporation of the solvent (50% yield): pure by TLC (10% $CH_3OH-CH_2Cl_2$). Anal. ($C_{33}H_{52}ClNO_3S \cdot H_2O$) H, N; C: calcd, 66.4; found, 65.84.

5,5-Dimethyl-8-(1,2-dimethylheptyl)-10-hydroxy-1,2,4,5-tetrahydrothiopyrano[3,4-*c*][1]benzopyran (5). The general procedure developed for **2a** was followed. The keto ester, ethyl 4-oxo-3,4,5,6-tetrahydro-2*H*-thiopyran-3-carboxylate,[10] was converted to the pyrone, 8-(1,2-dimethylheptyl)-10-hydroxy-5-oxo-1,2,4,5-tetrahydrothiopyrano[3,4-*c*][1]benzopyran, in 68% yield and was crystallized from ethyl acetate–petroleum ether: mp 153–155°; $\lambda_{\max}^{\mathrm{EtOH}}$ 310 nm (log ϵ 3.996). Anal. ($C_{20}H_{28}O_3S$) C, H, S.

The above pyrone (10.8 g, 0.03 mol) after Grignard reaction and work-up and chromatography (2:98 ether–petroleum ether) gave 7.9 g (71%) of **5** as a dark green resin: $\lambda_{\max}^{\mathrm{EtOH}}$ 275 nm (log ϵ 3.6). Anal. ($C_{23}H_{34}O_2S$) C, H, S.

4,4-Dimethyl-7-(1,2-dimethylheptyl)-9-hydroxy-4*H*-thieno[2,3-*c*][1]benzopyran (6). A stirred mixture of 1.74 g (4.8 mmol) of **2a** and 1.3 g of 10% Pd/C in 40 ml of xylene was heated at reflux for 90 h under N_2 atmosphere. After removal of the solvent, chromatography (Florisil, 1:99 ether–petroleum ether) of the residue furnished 0.98 g (56%) of **6** as an amber-colored resin. Anal. ($C_{22}H_{30}O_2S$) C, H, S.

Pharmacology. All water-insoluble compounds were administered orally as a suspension in 0.5% methylcellulose. The basic esters **2b,c** and **4b,c** were dissolved in water prior to oral administration.

Mice were used for the Dopa potentiation, mouse fighting, writhing, and hot-plate tests, rats for the motor activity, tail-flick, and cardiovascular studies, dogs for ataxia, and cats for the sedative–hypnotic studies. All these tests have been described by us previously.[2b]

References and Notes

(1) (a) For paper 2, see ref 2b. (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.

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