reflux for 2 h and then allowed to stand overnight at room temperature. The mixture was poured into cold water (150 mL) and extracted with methylene chloride (3 × 50 mL). The methylene chloride extract was washed with 5% $NaHCO_3$ solution and finally with water and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. Purification on a silica column using hexane–ethyl acetate (3:1) as eluent gave 0.067 g of the desired product **6**. The compound **6** was further purified by crystallization from ether–hexane–ethyl acetate, affording 0.036 g of the pure compound: mp 78–80 °C; IR (KBr) 1805, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (s, 3 H), 3.52–3.57 (m, 2 H), 4.59–4.65 (m, 1 H), 4.64 (s, 1 H), 5.09 (s, 2 H), 5.39 (m, 2 H), 7.01 (s, 1 H), 7.26–7.50 (m, 16 H), 8.23 (s, 1 H). Anal. ($C_{31}H_{29}N_5O_7S$) C, H, N.

A solution of 0.070 g of the ester **6** in 20 mL of ethyl acetate was added to a suspension of 0.014 g of 10% Pd/C in 20 mL of H_2O. The mixture was hydrogenated at a low pressure (1–5 kg/cm^2) at room temperature. After the absorption of hydrogen ceased, the catalyst was removed by filtration and the aqueous layer was separated, washed twice with ethyl acetate, and then lyophilized to afford a white powder, which weighed 0.030 g.

Acknowledgment. We thank Taiho Pharm. Co., Tokyo, Japan, for their generous support of this work.

Heteroarotinoids. Synthesis, Characterization, and Biological Activity in Terms of an Assessment of These Systems To Inhibit the Induction of Ornithine Decarboxylase Activity and To Induce Terminal Differentiation of HL-60 Cells

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The synthesis of certain heteroarotinoids has been achieved, namely the systems (2*E*,4*E*,6*E*)-3,7-dimethyl-7-(1,2,3,4-tetrahydro-4,4-dimethyl-6-thiochromanyl)-2,4,6-heptatrienoic acid (**1a**), ethyl (2*E*,4*E*,6*E*)-3,7-dimethyl-7-(1,2,3,4-teterahydro-4,4-dimethyl-6-thiochromanyl)-2,4,6-heptatrienoate (**1b**), (2*E*,4*E*,6*E*)-3,7-dimethyl-7-(1,2,3,4-tetrahydro-4,4-dimethyl-6-chromanyl)-2,4,6-heptatrienoic acid (**1c**), 2-phthalimidoethyl 3,7-dimethyl-7-(1,2,3,4-tetrahydro-4,4-dimethyl-6-thiochromanyl)-2,4,6-heptatrienoate (**1d**), methyl (*E*)-*p*-[2-(4,4-dimethyl-6-chromanyl)-1-propenyl]benzoate (**2a**), (*E*)-*p*-[2-(4,4-dimethyl-6-chromanyl)-1-propenyl]benzyl alcohol (**2b**), (*E*)-*p*-[2-(4,4-dimethyl-6-chromanyl)-1-propenyl]benzonitrile (**2c**), (*E*)-*p*-[2-(4,4-dimethyl-6-chromanyl)-1-propenyl]benzaldehyde (**2d**), methyl 4-[2-(2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-1-propenyl]benzoate (**3a**), and (*E*)-*p*-[2-(2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-1-propenyl]benzoic acid (**3b**). Characterization via elemental, IR, ^1H NMR, and ^{13}C NMR analyses was completed for these heterocycles. The biological activity of these heteroarotinoids was assayed by either the suppression of the 12-*O*-tetradecanoylphorbol 13-acetate (TPA) induced synthesis of ornithine decarboxylase (ODC) in mouse skin or the induction of differentiation of human (HL-60) promyelocytic cells. In the ODC assay, systems **1a–c** exhibited strong activity (within 10% of or less than the control) whereas alcohols **2b** and **3a** showed good activity (within 50% of the control) as compared to either 13-*cis*-retinoic acid or *trans*-retinoic acid. Moderate activity was observed with **2a** and **2b** while **1d** and **2c** were essentially inactive. With the HL-60 assay, **1a** and **1c** were approximately 2- and 5-fold less active, respectively, than *trans*-retinoic acid. In contrast, **2a**, **3a**, and **3b** induced differentiation of only a very small percentage of the cells. Acids **1a** and **1c** were the most active heteroarotinoids in the two biological assays. Consequently, the presence of the heteroatom does not eradicate the activity of the heteroarotinoids and thus they may have potential as chemotherapeutic agents.

Retinoids have recently received considerable attention as agents that may have utility for both cancer prevention and treatment.[1] A particularly interesting series of synthetic retinoids contain aromatic rings within the system[2-5] and have been called "arotinoids" and/or "retinoidal benzoic acid derivatives". Since neither of these terms can be used without some ambiguity, in this paper we prefer to use "heteroarotinoids" for **1–3** since the systems possess both an aryl ring fused to a partially saturated ring and a heteroatom. [The use of the term "heteroarotinoids" was introduced previously[3] and its meaning in our work refers to the presence of an aryl ring and a heteroatom within the skeletal framework. The term "arotinoid" has previously[2] been reserved for systems containing an aryl ring within the side chain or fused to the cyclohexyl ring.] In system **3**, there is an aryl ring fused to a five-membered ring. Three groups[3-5] have studied a few examples of such rare heterocycles that one might expect would inhibit a

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[∥] National Cancer Institute.

(1) For general reviews, see: (a) Sporn, M. B.; Roberts, A. B.; Goodman, D. S. *The Retinoids*; Academic: New York, 1984; Vol. 1 and 2. (b) Orfanoes, C. E., Ed., *Retinoids*–Advances *in Basic Research and Therapy*; Springer-Verlag: Berlin, 1981. (c) Pawson, B. A.; Ehmann, C. W.; Itri, L. M.; Sherman, M. I. *J. Med. Chem.* **1982**, *25*, 1269. (d) Sporn, M. B.; Newton, D. L.; Roberts, A. B.; DeLarco, J. E.: Todaro, G. J. In *Molecular Actions and Targets for Cancer Chemotherapeutic Agents*; Sartorelli, A. C., Bertino, J. R., Lazo, J. S., Eds., Academic: New York, 1980. (e) Saurat, J. H., Ed. *Retinoids: New Trends in Research and Therapy*; Karger: Basel, 1985.
(2) Loeliger, P.; Bollag, W.; Mayer, E. *Eur. J. Med. Chem.* **1980**, *15*, 9.
(3) Waugh, K. M.; Berlin, K. D.; Ford, W. T.; Holt, E. M.; Carrol, J. P.; Schomber, P. R.; Thompson, M. D.; Schiff, L. J. *J. Med. Chem.* **1985**, *28*, 116.
(4) (a) Dawson, M. I.; Hobb, P. D.; Derdzinski, K.; Chen, R. L.-S.; Gruber, J.; Chao, W.; Smith, S.; Thies, R. W.; Schiff, L. J. *J. Med. Chem.* **1984**, *27*, 1516. (b) Metra, R. G.; Schiff, L. J.; Moore, S. J.; Buckley, A. M.; Dawson, M. I. *In Vitro Cellular Dev. Biol.* **1986**, *22*, 164.

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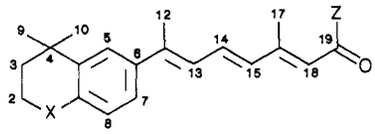
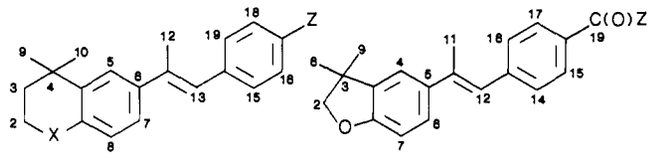
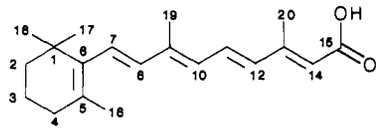


1a: X = S, Z = OH
b: X = S, Z = OC_2H_5
c: X = O, Z = OH
d: X = S, Z = OCH_2CH_2—N



2a: Z = CO_2CH_3, X = O
b: Z = CH_2OH, X = O
c: Z = CN, X = O
d: Z = CHO, X = O
e: Z = CO_2H, X = O
f: Z = CO_2H, X = S

3a: Z = OCH_3
b: Z = OH



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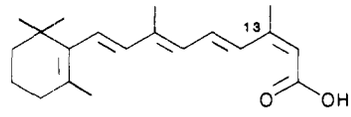
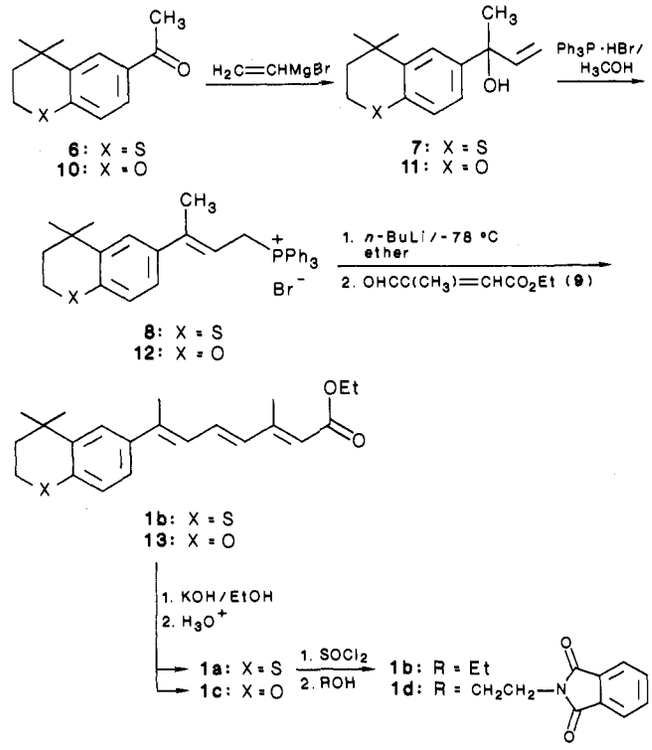


5

different catabolism than *trans*-retinoic acid (**4**), which undergoes oxidation in test animals at C(4) and at the C(5)–C(6) bonds.[6] The presence of the heteroatom and the aromatic ring might be capable of blocking these latter positions in terms of the normal mechanism of oxidative degradation. Thus, systems such as **1–3** have potential for clinical utility. 13-*cis*-Retinoic acid (**5**) is in wide clnical use for the treatment of acne[1,7] and there have been recent encouraging reports of its utility in various human myeloproliferative diseases.[8] Thus it was our intention to

Scheme I



6: X = S
10: X = O

7: X = S
11: X = O

8: X = S
12: X = O

1b: X = S
13: X = O

1a: X = S
1c: X = O

1b: R = Et
1d: R = CH_2CH_2—N

incorporate the aryl ring into modified retinoids to alter catabolism[6] and to include a cis arrangement at C(13) for possible improved biological activity.[8] Two recognized screens for measuring such activity of retinoids are the suppression of the 12-*O*-tetradecanoylphorbol 13-acetate (TPA) induced synthesis of ornithine decarboxylase (ODC) in mouse skin[9,10] and the induction of differentiation of the human promyelocytic cell line HL-60.[11–13] These screens were used in the present study to assess biological activity of members of **1–3**.

Chemistry

The strategy for the work involved, in addition to the

(5) (a) Klaus, M.; Loeliger, P. Hoffmann-LaRoche, F. and Co., A.-G., Ger. Offen. DE 3316932 (Cl. CO7D311/58), Nov 17, 1983, CH Appl. 82/2, 956, May 12, 1982; *Chem. Abstr.* **1984**, *100*, 51468z. No properties of any compounds were reported in the abstract. Previous papers in this general area (no heteroarotinoids are included) by this group: (b) Rosenberger, M.; Neukom, C. *J. Org. Chem.* **1982**, *47*, 1782. (c) Olson, G. L.; Cheung, H.-C.; Morgan, K. D.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3287.

(6) Metabolic oxidation at C(4) and at the C(5)–C(6) bonds in 4 is well known in studies with animals; see: Deluca, H. F. *Fed. Proc., Fed, Am. Soc. Exp. Biol.* **1979**, *38*, 2519. Roberts, A. B.; Frolik, C. A. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1979**, *38*, 2524. Mayer, H.; Bollag, W.; Hanni, R.; Ruegg, R. *Experientia* **1978**, *34*, 1105.

(7) For a general review of the benefits and disadvantages of 13-*cis*-retinoic acid, see: (a) Reference 1. (b) Pawson, B. A.; Ehmann, C. W.; Itri, L. M.; Sherman, M. I. *J. Med. Chem.* **1982**, *2*, 111. (d) Hill, D. L.; Struck, R. F. *Anticancer Res.* **1983**, *3*, 1971. (e) Lammer, E. J.; Chen, D. T.; Hoar, R. M.; Agnish, N. D.; Benke, P. J.; Braun, J. T.; Curry, C. J.; Fernoff, P. M.; Grix, A. W.; Lott, I. T.; Richard, J. M.; Sun, S. C. *N. Engl. J. Med.* **1985**, *313*, 837. (f) Robertson, R.; MacLeod, P. M. *Can. Med. Assoc. J.* **1985**, *133*, 1147.

(8) Systems with a 12-s-cis topology have been reported to have high activity in the chemopropylaxis of epithelial cancer; see: (a) Reference 2. (b) Dawson, M. I; Hobbs, P. D.; Chen, W.; Fund, V. A. *J. Med. Chem.* **1981**, *24*, 583. This same topology is present in **2** and **3**. For work on myeloproliferative diseases, see: (c) Daenen, S.; Vellenga, E.; van Dobbenburgh, O. A.; Halie, M. R. *Blood* **1986**, *67*, 559. (d) Nilsson, B. *Br. J. Haematol.* **1984**, *57*, 365. (e) Gold, E. J.; Mertelsmann, R. H.; Itri, L. M.; Gee, T.; Arlin, Z.; Kempin, S.; Clarkson, B.; Moore, M. A. *S. Cancer Treat. Rep.* **1983**, *67*, 981.

(9) Verma, A. K.; Shapas, B. G.; Rice, H. M.; Boutwell, R. K. *Cancer Res.* **1979**, *39*, 419. Boutwell, R. K.; Verma, A. K. *Pure Appl. Chem.* **1979**, *51*, 857.

(10) (a) Verma, A. K.; Rice, H. M.; Shapas, B. G.; Boutwell, R. K. *Cancer Res.* **1977**, *38*, 2196. (b) The use of 13-*cis*-retinoic acid or *trans*-retinoic acid as standards for this ODC assay appears to be of about equivalent value; see: Verma, A. K.; Boutwell, R. K. *Cancer Res.* **1978**, *38*, 793.

(11) Breitman, T. R.; Collins, S. J.; Keene, B. R. *Exp. Cell Res.* **1980**, *126*, 494.

(12) (a) Breitman, T. R.; Collins, S. J.; Keene, B. R. *Blood* **1981**, *57*, 1000. (b) Breitman, T. R.; Keene, B. R.; Hemmi, H. In *Methods for Serum-Free Culture of Neuronal and Lymphoid Cells*; Barnes, D. W., Sirbasku, D. A., Sato, G. H., Eds.; Liss: New York, 1984; p 215.

(13) Strickland, S.; Breitman, T. R.; Frickel, F.; Nurrenbach, A.; Hadicke, E.; Sporn, M. B. *Cancer Res.* **1983**, *43*, 5268. Evidence for a possible low concentration of esterases in HL-60 cells has been reported; see: Hemmi, H.; Breitman, T. R. in ref le (pp 48–54). See also: Shudo, K.; Kagechika, H.; Kawachi, E.; Hashimoto, Y. *Chem. Pharm. Bull.* **1985**, *33*, 404.

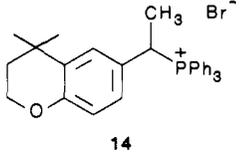
incorporation of the heteroatom and aromatic ring, the selection of various esters that had a range of polarities and sizes and could alter the activity in the assays to be investigated. It has been established[14] that no single assay can unequivocally eliminate a retinoid from having potentially useful activity but such a variety of groups at the terminus was reasoned to provide some scope for the assessment of biological action. Since we had previously examined certain ethyl esters,[3] a methyl ester was scheduled for evaluation to determine if such a small change caused a significant activity change. It is noted that ethyl esters and the corresponding acids in selected carbocyclic retinoids have had very little difference in ODC activity.[4] No study could be found in the literature with heteroarotinoids where any methyl esters were examined.

Initiation of the synthesis of **1a** involved the known ketone **6**[3] in a reaction with vinylmagnesium bromide in THF to give the vinyl alcohol **7** as an oil (Scheme I). The latter gave satisfactory spectral data, but an immediate conversion to salt **8** was effected with triphenylphosphine hydrobromide in methanol.[15] Recrystallization of **8** from methanol/ether gave a crystalline substance melting at 268.5–269.5 °C with a ^{31}P NMR signal at 21.6 ppm (from 85% H_3PO_4) as compared to that of 22.2 ppm for $PhCH{=}CHCH_2P^+Ph_3$, Br^- as a model system.[16] Suitable crystals could be hand-picked from a mass and, when subjected to X-ray diffraction analysis,[17] proved to have the structure shown. This confirmed the trans arrangement of the CH_3 and proton attached to the double bond in the side chain. The X-ray data for **8** will be published elsewhere and is not presented herein. The X-ray data does confirm the *E* arrangement of groups in **8**.

Formation of the Wittig reagent from **8** in ether was accomplished with *n*-butyllithium in hexane at room temperature (orange-red color produced). Treatment of the Wittig reagent with aldehyde **9**[18] in ether at −78 °C led, after workup, to crude ester **1b**. The ester was saponified and, following acidification, the acid **1a** (Z = OH) could be isolated.

The acid was converted to the acid chloride, which was then treated with ethanol or *N*-(2-hydroxyethyl)phthalimide in the presence of dry pyridine to give the pure ester **1b** or **1d**, respectively (Scheme I). A similar reaction sequence starting from ketone **10**[3] gave the ester **13**, which led to acid **1c**. Intermediates **11** and **12** were characterized and had properties similar to those of **7** and **8**, respectively.

The syntheses of **2a** and **2b** paralleled to some degree that from our laboratory for acid **2e**,[3] namely that the Wittig reagent from salt **14**[3] was allowed to react with the aldehyde **15**[19] to give ester **2a**. Reduction of ester **2a** with



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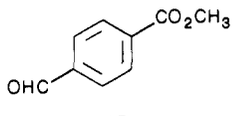

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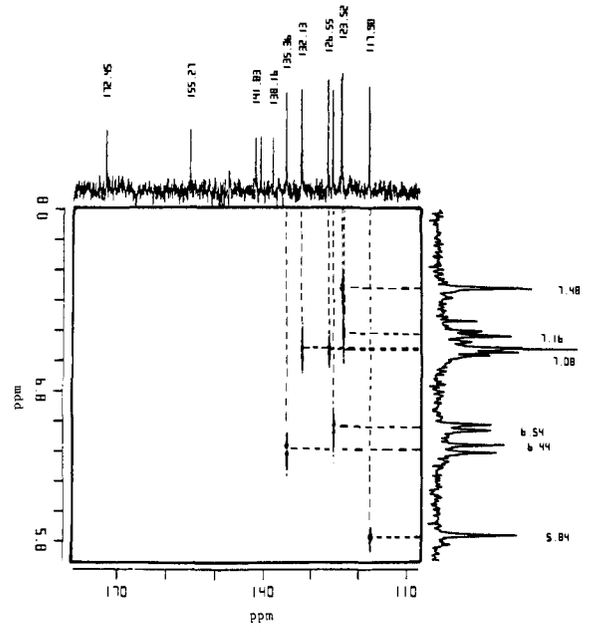
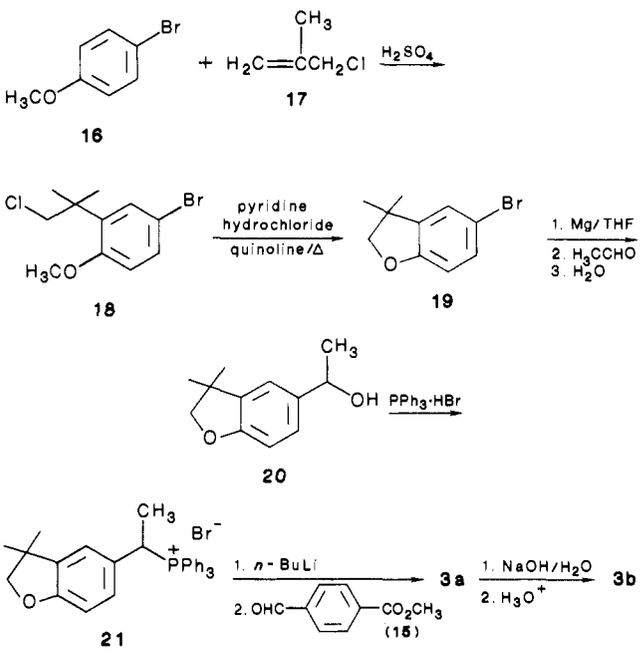


Figure 1. HETCOR 2-D spectrum for 1a.

Scheme II



$LiAlH_4$ in THF yielded alcohol **2b**. Treatment of the same Wittig reagent from salt **14** with *p*-formylbenzonitrile gave the nitrile **2c**. Reduction of the latter with DIBAL-H (diisobutylaluminum hydride) in ether/hexane led to aldehyde **2d**.

One other related system was prepared to assess the impact of size of the heterocyclic ring on ornithine decarboxylase activity. The methyl ester **3a** was obtained by the sequence of reactions shown, namely starting with **16** + **17** → **18** → **19** → **20** → **21** → **3a**. Saponification of **3a**, followed by neutralization, gave the acid **3b**. Acid **3b** was made for screening in the HL-60 line since ester **3a** showed low activity, which may be the result of an inadequate concentration of esterases.[13] In Scheme II, the final step involved the condensation of the Wittig reagent from

(14) See Chapter 5 in ref 1a for a discussion on this point.
(15) For a peripherally related analogy, see ref 3 and 5b.
(16) Grim, S. O.; McFarlane, W.; Davidoff, E. F.; Marks, T. *J. Phys. Chem.* **1966**, *70*, 581.
(17) To the best of our knowledge, no X-ray diffraction analysis of a phosphonium salt of this type has heretofore been recorded.
(18) We thank Dr. Rosenberger of the Hoffmann-LaRoche Co. for a generous supply of compound **9**. An important method to obtain **9** has recently appeared; see: Curley, R. W.; Ticovas, C. J. *J. Org. Chem.* **1986**, *51*, 256; *Synth. Commun.* **1986**, *16*, 627.
(19) Landesberg, J. M.; Slam, M. A.; Mandel, M. *J. Org. Chem.* **1981**, *46*, 5025.

Table I. ^{13}C NMR Resonances for the Heteroarotinoids

carbon	1a	1b	1c	1d	2a	2b	2c	2d	3a	3b
2	23.0	23.1	63.2	23.1	63.1	63.1	63.2	63.1	84.9	84.9
3	37.5	37.6	37.6	37.6	37.6	37.6	35.6	37.6	41.9	41.9
4	33.0	33.1	30.7	33.1	30.7	30.7	30.7	30.7	120.0	120.0
4a	141.7*[a]	141.7*	131.4*	141.8*						
5	123.6	123.6	124.3	123.6	124.6	124.0	124.6	124.5		
6	138.1*	138.2*	134.6*	138.2*					126.0	126.1
7	123.3	123.4	124.7†	123.4	124.9	124.9	124.3	124.9	109.3	109.4
7a									159.0	159.1
8	126.4	126.4	116.9	126.5	116.9	116.9	116.9	116.8	27.6	27.6
8a	131.5*	131.7*	153.7*	131.8*	153.4	153.0	156.6	153.6		
9	30.1	30.1	31.0	30.2	31.3	31.7	31.6	31.1	27.6	27.6
10	30.1	30.1	31.0	30.2	31.3	31.7	31.6	31.1		
11	140.2	139.9	140.8	140.1					17.9	18.0
12	16.1	16.2	16.4	16.2	17.9	17.9	17.8	17.8	125.1	129.1
13	125.4	125.5	124.9†	125.5	124.9	124.9	124.9	125.9		
14	131.7	131.1	132.3	132.0					129.0	129.1
15	135.4	135.5	134.9	135.4	129.6	129.0	129.7	129.0	129.4	130.1
16	154.0	152.3	155.3	153.5	131.4	131.4	131.9	129.5		
17	13.8	13.8	14.1	13.9					129.4	130.1
18	118.3	118.7	117.6	117.7	131.4	131.4	131.9	129.5	129.0	129.1
19	170.8	167.1	172.4	166.6	129.6	129.6	129.7	129.0	167.0	171.7
20					191.8	191.8	119.2	167.0	52.0	

[a] In the vertical column, these signals could be interchanged (*, †).

salt **21** with the known aldehyde **15**.[19]

The ^1H NMR spectral analyses for members of **1** and **2** as well as for **3** were somewhat helpful in total structural elucidation, particularly for the vinyl methyl signals. However, the ^{13}C NMR signals were more revealing, and with the help of HETCOR 2-D[3,20] analysis (Figure 1) on **1a**, it was possible to unravel, at least partially, the ^1H–^{13}C resonances for **1a** and the other members of the heteroarotinoids in this work. The parallel signals between related members in the two families are obvious from Table I although care must be taken to correlate positions correctly since the numbering varies between members of **1**, **2**, and **3**. Assignments were made on the basis of analysis of previous work[3] as well as the HETCOR 2-D plot.[21] Table I contains the ^{13}C signals for the identified carbons. Several signals could not be unequivocally assigned, but all signals are included in the Experimental Section. The signals in the HETCOR 2-D plot vary slightly from those in Table I since the spectrometer lock used to obtain the HETCOR data was less precise over the long run.

Analysis of the NMR spectral data and the HETCOR 2-D plot for **1a** revealed the following stereochemistry, which is applicable to other members of **1**. The HETCOR 2-D experiment established unequivocally that the ^{13}C signal at 125.4 ppm was for C(13), which in turn was bonded to H(13) at δ 6.59. Signals at 131.7 ppm [C(14)] and 135.4 [C(15)] were associated with protons H(14) (δ 7.10) and H(15) (δ 6.44). The $^3J_{HH}$ for H(13) and H(14) was 12 Hz, and for H(14) and H(15) it was 15 Hz. This confirms a trans relationship at this juncture of the side chain. It has been observed that the corresponding J values in *all-trans*-retinal were approximately 11.3 and 14.7 Hz, respectively, as determined from 2-D work.[22] Since the ethyl ester of **2e** was previously[3] subjected to X-ray diffraction analysis and since the ^{13}C signal appeared at 125.7 ppm, we conclude that C(12) (CH_3) and H(13) are in a trans arrangement. The same stereochemistry persists in members of **2** as assessed from the data in Table I. It is noteworthy that there is a consistency in the chemical shifts for many carbons, except those, of course, that are α or β to the oxygen atoms in **1c**, **2**, and **3**. This strongly supports our contention that the stereochemistry at C-(11)–C(13) is identical in all of the examples.

Biological Activity of 1a–d, 2a–e, and 3. Inhibition of ODC Induction. A good correlation has been demonstrated between the ability of retinoids to inhibit the induction of epidermal ornithine decarboxylase (ODC) and skin tumor promotion by 12-*O*-tetradecanoylphorbol 13-acetate (TPA).[9,10] Thus, inhibition of TPA induction of ODC by a retinoid is a rapid screen for the evaluation of its antitumor-promoting activity. In this experiment (Table II), a test was made of the ability of the synthesized retinoids to inhibit ODC induction by TPA. The retinoids were applied 1 h before the application of 10 nmol of TPA to the shaved backs of mice; mice were killed for ODC assays 5 h after TPA treatment. The retinoids were evaluated in three independent experiments and the results from the experiments were normalized (percent inhibition) for comparison. It is clear from the data in Table II that the ethyl ester **1b** has excellent activity and is more active than the acid **1a**. The related ester **1d** with the large polar group was less active than either **1a** or **1b**.

With members of **2**, the alcohol **2b** had the strongest activity while the ester **2a** and aldehyde **2d** were less active in inhibiting ODC induction by TPA. Under the same conditions as used for alcohol **2b** and aldehyde **2d**, acid **1c** and ester **3a** were as active as **2b**.

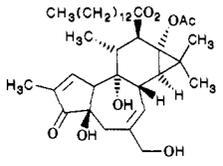
In the experiments with 13-*cis*-retinoic acid as the standard (Table II), the relative activities of the retinoids in suppressing TPA induction of ODC are **1** > 13-*cis*-retinoic acid = **1a** > **2a** = **1d** > **2c**. In the experiments with *trans*-retinoic acid as the standard, the relative activities are *trans*-retinoic acid > **1c** = **3a** ≅ **2b** > **2d**. Which standard is used appears to be relatively unimportant[9,10] for determining activity in the assay, but we have elected to keep the data separate in Table II for the sake of clarity and accuracy of presentation. *Thus, the presence of a heteroatom in these arotinoids has not eliminated biological activity.* It is also clear that the acids and simple esters are the most active regardless of whether sulfur or oxygen is the heteroatom. Moreover, the nature of the

(20) Gray, G. A. *VIA, Varian Instrum. Appl.* 1982, 16, 11. Gray, G. A. *Org. Magn. Reson.* **1983**, *21*, 111 (and pertinent references therein).
(21) Englert, G. *Helv. Chim. Acta* **1975**, *58*, 2367. For a general review of ^{13}C NMR data in the area, see: Liu, R. S. J.; Asoto, A. E. *Tetrahedron* **1984**, *30*, 126.
(22) Wernly, J.; Lauterwin, J. *Helv. Chim. Acta* **1983**, *66*, 1576. McNicol, D. D.; Hardy, A. D. U.; McKendrick, J. J. *Nature (London)* **1975**, *56*, 343.

Table II. Suppression of ODC Activity by Heteroarotinoids

heteroarotinoid	test system	retinoid dose, nmol	ODC activity[a]	% of inhibn as compared to control
			nmol CO_2/30 min/mg protein	
	acetone	0	0.00 ± 0.0	
1a	acetone + TPA	0	0.90 ± 0.31	control[a]
	13-*cis*-retinoic acid + TPA	17	0.1 ± 0.01	89
	1a + TPA	17	0.1 ± 0.01	89
1b	**1b** + TPA	17	0.0 ± 0.0	100
			nmol CO_2/60 min/mg protein	
	acetone	0	0.00 ± 0.0	
2a	acetone + TPA	0	1.67 ± 0.14	control
	13-*cis*-retinoic acid + TPA	17	0.14 ± 0.04	92
	2a + TPA	34	0.95 ± 0.06	43
2c	**2c** + TPA	34	1.77 ± 0.32	0
1d	1d + TPA	34	0.97 ± 0.13	42
			nmol CO_2/60 min/mg protein	
	acetone	0	0 ± 0	
2b	acetone + TPA	0	5.3 ± 0.7	control
	trans-retinoic acid + TPA	34	1.0 ± 0.1	81
	2b + TPA	34	1.7 ± 0.1	68
2d	2d + TPA	34	3.5 ± 0.2	34
1c	1c + TPA	34	1.4 ± 0.2	74
3a	3a + TPA	34	1.5 ± 0.4	72

[a] The percentage of inhibition as compared to control was calculated as [(ODC with acetone + TPA) − (ODC with retinoid)/(ODC with acetone + TPA)] × 100. [b] TPA =



terminus group is also important.

Induction of Differentiation. Retinoids, including arotinoids containing a benzene ring, induce HL-60 cells to differentiate along the granulocytic maturation pathway.[11-13] These mature cells, unlike the uninduced HL-60, produce superoxide anion when stimulated with an appropriate agent, such as TPA. The ability of individual cells to produce superoxide can be measured by incubating cells with the water-soluble yellow dye nitroblue tetrazolium (NBT). NBT is reduced to a water-insoluble blue-black formazan by superoxide. This formazan precipitate is associated with those cells that produce superoxide. Thus, the percentage of cells in a population that produces superoxide (NBT-positive cells) can be enumerated under a light microscope. The dose–response of HL-60 to *trans*-retinoic acid, **1a**, and **1c** is shown in Figure 2. The concentration of retinoid effective in achieving a half-maximal response (ED_{50}) is 41 nM for *trans*-retinoic acid, 72 nM for **1a**, and 200 nM for **1c**. The ED_{50} values for esters **2a**, **3a**, **3b**, and the free acid **2e** were all greater than 3 μM, the highest concentration tested (data not shown). At a concentration of 3 μM, both **2a** and **2e** induced approximately 15% of the cells to differentiate while **3a** and **3b** gave values of 3–5%, the same as the control. It has been reported previously that (*E*)-4-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)1-propenyl]-benzoic acid (TTNPB) has an ED_{50} of approximately 200 nM in the HL-60 differentiation assay.[13] The finding in this study that acid **2e** has an ED_{50} of >3000 nM indicates that substitution of an oxygen atom in the cyclohexyl ring of TTNPB is responsible for this decrease in activity. In a related finding, **2f** (sulfur in place of oxygen) results in decreases in biological activity measured as the effectiveness either in reversing keratinization in tracheas from vitamin A deficient hamsters or in competing with retinoic acid for sites on the cellular retinoic acid binding protein from the same tissue.[4,23] Because **2e** and the sulfur-substituted TTNPB derivative **2f** have not been tested for biological activity in the same assay, the relative activities of these two retinoids is not known. However, on the basis

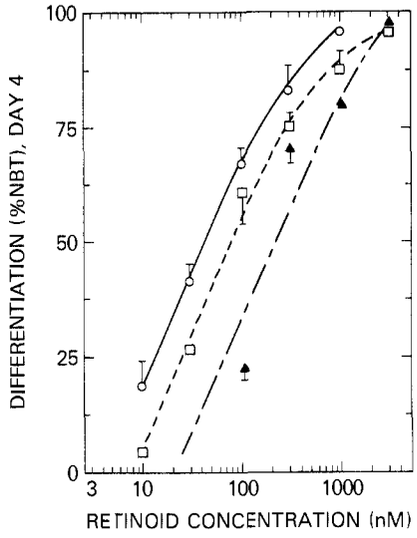


Figure 2. Dose–response curves for retinoids in the HL-60 differentiation assay: (○) *trans*-retinoic acid; (□) 1a, (▲) 1c. Differentation is measured as the percentage of cells that reduce NBT after a 4-day incubation in the presence of the retinoid. This value for control cells was 4%. The values presented are from at least three independent experiments with duplicate measurements. Bars, SD. The two blocks gave reproducible values so close so as to preclude any bar representations.

(23) Binding properties of retinoic acid to proteins has been reviewed; see: (a) Chytil, F.; Ong, D. E. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1979**, *38*, 2510. (b) Ross, A. C.; Goodman, D. S. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1979**, *38*, 2515. Goodman, D. S. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1980**, *39*, 2716. For an account of the purification of a cellular binding protein for retinoic acid, see: (d) Ong, D.; Chytil, F. *Methods Enzymol.* **1980**, *67*, 288.

of the relative activities of **1a** and **1c** in this present study (Figure 2), it is likely that the oxygen-substituted derivative **2e** would have a lower biological activity than the sulfur-substituted derivative. Or course TTNPB contains a benzene ring in place of the side chain present in **1c**, a difference that also is likely to influence any activity variation between the two systems. Other examples are needed to assess this type of structural change on activity.

In summary, the heteroarotinoids examined display a range of activities in the ODC and HL-60 screens. The highest activity was found in systems in which sulfur replaced the C(1) position in the cyclohexyl ring system although the replacement by oxygen gave examples with only slightly less activity.

Experimental Section

All reactions were carried out under nitrogen or argon. All melting points are uncorrected as are all boiling points. NMR spectra were recorded for ^1H on a Varian XL-300 NMR spectrometer and all ^{13}C spectra (fully decoupled and off-resonance spectra) were recorded on a Varian XL-100(15) or XL-300 NMR unit. All ^1H signals are reported in δ values downfield from Me_4Si and all ^{13}C signals are in ppm downfield from Me_4Si. All IR spectra were recorded on a Perkin-Elmer 681 either in KBr pellets or as films. Analytical samples were analyzed by Galbraith Laboratories, Knoxville, TN. The following compounds were prepared by reported procedures: **2e**,[3] **6**,[3] **10**,[3] **14**,[3] **15**.[19] The Chromatotron (Model 7924T) is available from Harrison Research, 340 Moana Court, Palo Alto, CA 94306.

2-(4,4-Dimethyl-6-thiochromanyl)-2-hydroxy-3-butene (7). To a freshly prepared solution of vinylmagnesium bromide [7.65 g (0.0715 mol) of vinyl bromide and 1.75 g (0.0720 g-atom) of magnesium, in 40 mL of dry THF] was added dropwise 10.5 g (0.0477 mol) of 6-acetyl-4,4-dimethylthiochroman[3] (**6**) in 25 mL of THF under N_2. The solution was then boiled for 1 h and allowed to stir for 10 h at room temperature. Saturated NH_4Cl was added in 1-mL portions until the solution was slightly acidic (pH ca. 6.8), and the layers were separated. The aqueous layer was extracted with ether (4 × 100 mL), and the ether extracts were combined with the THF layer. The organic layer was washed with 50 ml of H_2O and 50 mL of brine and was then dried (Na_2SO_4, 4 h). Evaporation gave crude alcohol **7** as an oil, which was used without further purification: IR (neat) 2300–3600 cm^{-1} (OH); ^1H NMR ($DCCl_3$) δ 1.32 [s, 6 H, $(CH_3)_2C$], 1.95 [m, 2 H, $PhSCH_2CH_2$], 2.11 [br s, 1 H, O*H*], 3.00 [m, 2 H, $PhSCH_2CH_2$], 5.14 [dd, 1 H, J = 2.0 Hz, J = 10.5 Hz, CH=CH_2 (cis)], 5.30 [dd, 1 H, J = 2.0 Hz, J = 15.0 Hz, CH=CH_2 (trans)], 6.16 [dd, 1 H, J = 10.5 Hz, J = 15.0 Hz, C*H*=CH_2], 7.05 [d, 1 H, J = 8 Hz, H(8)], 7.12 [dd, 1 H, J = 2 Hz, J = 8 Hz, H(7)], 7.52 [d, 1 H, J = 2 Hz, H(8)]; ^{13}C NMR ($DCCl_3$) ppm 22.9 29.1, 30.2, 33.1, 37.7 (Ar SCH_2), 74.5 (CH_3COH), 112.1, 123.1, 123.2, 126.2, 130.2, 141.6, 142.1, 144.7.

[3-(1,2,3,4-Tetrahydro-4,4-dimethyl-6-thiochromanyl)-2-butenyl]triphenylphosphonium Bromide (8). To a suspension of 15.6 g (45.4 mmol) of triphenylphosphine hydrobromide in methanol (100 mL) was added the prepared crude alcohol **7** (11.3 g, 45.4 mmol; in CH_3OH, 50 mL) and this was stirred at room temperature for 3 h. Methanol was removed (vacuum) from the resulting clear solution and ether (ca. 400 mL) was added; crystallization occurred within a short time. After the mixture was allowed to stand overnight, 26.0 g of white crystals of salt **8** was collected, recrystallized (methanol/ether), and dried (vacuum) (25.7 g, 98.8%): mp 268.5–269.5 °C dec; ^1H NMR ($DCCl_3$) δ 1.26 [s, 6 H, $(CH_3)_2C$], 1.63 (d, 3 H, J = 4.0 Hz, CH_3C=CH), 1.93 (m, 2 H, $PhSCH_2CH_2$), 3.02 (m, 2 H, $PhSCH_2CH_2$), 4.89 [dd, 2 H, J = 8.0 Hz, J = 15.1 Hz (J_{PH}), C=CHCH_2P], 5.60 (tq, 1 H, J = 4.0 Hz, J = 8.0 Hz, CH_3C=C*H*CH_2P), 6.85 [dd, 1 H, J = 2.0 Hz, J = 8.1 Hz, H(7)], 7.00 [d, 1 H, J = 8.1 Hz, H(8)], 7.17 [d, 1 H, J = 1.7 Hz, H(5)], 7.66–8.00 [m, 15 H, P(Ph-*H*)$_3$]; ^{13}C NMR ($DCCl_3$) ppm 17.0 (CH_3C=CH), 23.0 ($PhSCH_2CH_2$), 25.4 (d, J_{CP} = 49 Hz, C=CH*C*H_2), 30.1 [(CH_3)$_2$C], 33.0 [$(CH_3)_2C$], 37.4 (Ar SCH_2CH_2), 110.2, 110.3, 117.6, 118.8, 123.4, 123.9, 126.4, 130.2, 130.4, 132.1, 133.9, 134.1, 135.0, 138.0, 138.1, 141.9, 145.4, 145.6; ^{31}P NMR ($DCCl_3$) ppm 21.6. Anal. ($C_{33}H_{34}SPBr$) C, H, P.

(2*E*,4*E*,6*E*)-3,7-Dimethyl-7-(1,2,3,4-tetrahydro-4,4-dimethyl-6-thiochromanyl)-2,4,6-heptatrienoic Acid (1a). To a suspension of 5.82 g (0.010 mol) of phosphonium salt **8** in 80 mL of ether was added dropwise *n*-butyllithium (6.76 mL, 1.50 M, 0.0101 mol) at room temperature under N_2. The resulting, dark red solution was cooled to −78 °C, and 1.44 g (0.010 mol) of ethyl (*E*)-β-formylcrotonate (**9**) in 10 mL of ether was added dropwise in the dark. The solution was allowed to warm to room temperature and stir for 24 h. The resulting orangish-yellow suspension was diluted with 25 mL of hexane and filtered. The clear solution was washed with water (2 × 50 mL), passed through anhydrous Na_2SO_4, and evaporated (vacuum) to give a yellow oil. The oil was dissolved in 50 mL of absolute ethanol and added to a mixture of 2.3 g of KOH in 10 mL of H_2O under N_2. The new solution was boiled for 1 h and the reddish mixture was allowed to cool to room temperature. The solution was acidified with 50% acetic acid which formed a yellow suspension and, after extraction with ether (3 × 100 mL) and evaporation (vacuum), gave a yellow solid. After fractional recrystallization (absolute ethanol) and drying under high vacuum at room temperature for 36 h in the dark, there was obtained 1.50 g [45.0% from the phosphonium salt **8**] of acid **1a** as yellow needles: mp 204–204.5 °C dec; ^1H NMR ($DCCl_3$) δ 1.37 [s, 6 H, $(CH_3)_2C$], 1.98 (m, 2 H, $PhSCH_2CH_2$), 2.25 (s, 3 H, CH_3), 2.42 (s, 3 H, CH_3), 3.06 (m, 2 H, $PhSCH_2CH_2$), 5.86 (br s, 1 H, C*H*=CO_2H), 6.44 [d, 1 H, J = 15 Hz, C*H*C(CH_3)CHCO_2H], 6.59 [d, 1 H, J = 12 Hz, PhC(CH_3)C*H*], 7.09 [d, 1 H, J = 7 Hz, H(8)], 7.10 (dd, 1 H, J = 12 Hz, J = 15 Hz, CHCH=CH), 7.21 [dd, 1 H, J = 2 Hz, J = 7 Hz, H(7)], 7.52 [d, 1 H, J = 2 Hz, H(5)], 11.2 (br s, H, CO_2H); ^{13}C NMR ($DCCl_3$), the ^{13}C NMR signals are given in the Table I. Anal. ($C_{30}H_{24}O_2S$) C, H, S.

Ethyl (2*E*,4*E*,6*E*)-3,7-Dimethyl-7-(1,2,3,4-tetrahydro-4,4-dimethyl-6-thiochromanyl)-2,4,6-heptatrienoate (1b). To a suspension of 0.503 g (1.53 mmol) of *trans*-heteroarotinoic acid **1a** in 8 mL of dry ether was added 0.142 g (1.80 mmol) of freshly distilled pyridine, and the mixture was cooled to −10 °C under N_2. A solution of 0.2005 g (1.67 mmol) of $SOCl_2$ in ether (1 mL) was added and stirring was continued at room temperature for 1 h. The resulting dark red solution was filtered and cooled to −20 °C. Then 0.142 g (1.80 mmol) of pyridine was added and 0.21 g (4.59 mmol) of dry ethanol was introduced all at once, and stirring was maintained at room temperature for 3 h. The yellow solution was diluted with 25 mL of ether, and the new solution was washed with water (4 × 30 mL); the ether layer was dried (Na_2SO_4, 1 h). The solvent was removed (vacuum), and the resulting yellow oil was chromatographed on silica gel with hexane/ether (15:1) with the silica gel retaining the *trans*-acid **1a**. The ethyl ester **1b** (0.4923 g, 33.1%) was obtained as a viscous yellow oil: ^1H NMR ($DCCl_3$) δ 1.30 (t, 3 H, $CO_2CH_2CH_3$), 1.36 [s, 6 H, $(CH_3)_2C$], 1.96 (m, 2 H, Ar SCH_2CH_2), 2.22 (s, 3 H, CH_3), 2.38 (s, 3 H, CH_3), 3.14 (m, 2 H, Ar SCH_2), 4.19 (q, 2 H, $CO_2CH_2CH_3$), 5.82 (s, 1 H, C*H*CO_2Et), 6.39 (d, 1 H, J = 15 Hz, C*H*C(CH_3)CHCO_2Et], 6.55 [d, 1 H, J = 12 Hz, Ar C(CH_3)C*H*], 7.03 (dd, 1 H, J = 12 Hz, J = 15 Hz, CHC*H*=CH), 7.07 [d, 1 H, J = 9 Hz, H(8)], 7.18 [dd, 1 H, J = 2 Hz, J = 8 Hz, H(7)], 7.48 [d, 1 H, J = 2 Hz, H(5)]; ^{13}C NMR ($DCCl_3$), the ^{13}C NMR signals are given in Table I. Anal. ($C_{22}H_{28}O_2S$) C, H.

[3-(1,2,3,4-Tetrahydro-4,4-dimethyl-6-chromanyl)-2-butenyl]triphenylphosphonium Bromide (12). A solution of **10**[3] (15.0 g, 73.4 mmol) in dry THF (50 mL) was added dropwise under N_2 to a stirred solution of H_2C=CHMgBr in THF (150 mL of 1 M solution; 220 mmol). The mixture was allowed to react for 1 h and was then quenched with dilute H_2SO_4. The supernatant liquid was decanted and the residue was washed with dry ether (3 × 100 mL). The combined organic extracts and original layer were dried (Na_2SO_4), and the solvent was removed in vacuo to give crude **11** as an oil. Treatment with CH_3OH (150 mL) gave a solution which, after the addition of triphenylphosphine hydrobromide (25.5 g, 73.4 mmol), was allowed to react (stir) at room temperature for 2 h. Evaporation of the solvent gave an oil which, when trituated with ether, gave salt **12**, which was filtered off. Recrystallization (CH_3OH/ether, 1:6) gave white, crystalline **12**. After **12** was dried under vacuum overnight, the weight of salt **12** was 33.8 g (82.6%): mp 261–262 °C dec; ^1H NMR ($DCCl_3$) δ 1.29 [s, 6 H, $(CH_3)_2$], 1.76–1.84 [t, 2 H, H(3)], 4.14–4.20 [m, 2 H, H(2)], 4.75–4.83 [dd, 2 H, H(12)], 5.54 [m, 1 H, H(11)], 6.88–6.91

[d, 1 H, H(7)], 7.07 [s, 1 H, H(5)], 7.60–8.00 [m, 15 H, $(C_6H_5)_3$]. Crude **12** was used without further purification.

(2*E*,4*E*,6*E*)-3,7-Dimethyl-7-(1,2,3,4-tetrahydro-4,4-dimethyl-6-chromanyl)-2,4,6-heptatrienoic Acid (1c). A solution of *n*-butyllithium in hexane (1.31 M, 8.20 mL, 10.77 mmol) was added dropwise under argon to a stirred suspension of salt **12** (6.00 g, 10.77 mmol) in dry ether (100 mL). The resulting dark, reddish-brown mixture was stirred at room temperature for 10 min. A solution of ethyl (*E*)-β-formylcrotonate (**9**: 1.45 g, 10.77 mmol) in dry ether (30 mL) was then added. After being stirred for 2 h at room temperature, the mixture was filtered. The resulting solid obtained was washed with ether (240 mL). The combined filtrate and washings were concentrated in vacuo to give crude ester **13** (2.40 g, 68.41%). Ester **13** was then chromatographed on silica gel and eluted with ethyl acetate/petroleum ether (1:49). The middle fraction contained **13**. Saponification was effected with KOH (1.20 g) in water (2 mL) and ethanol (80 mL) with 70 mg of **13**. After being stirred at 50 °C for 4 h under N_2 (protected from light), the solution was cooled to 0 °C and then acidified with 6 N HCl. The resulting solution was extracted (2 × 30 mL) with $HCCl_3$ and the final solution was dried (Na_2SO_4). Evaporation to near dryness resulted in the formation of yellow crystals of acid **1c** which, after recrystallization (absolute ethanol), weighed 29 mg (45.3%) and had mp 218–218.5 °C: IR (KBr) 3250–2500 (O—H), 1680 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.35 [s, 6 H, $(H_3C)_2$], 1.79–1.83 [t, 1 H, H(3)], 2.20 [s, 3 H, CH_3], 4.15–41.8 [t, 1 H, H(2)], 5.76 [s, 1 H, $C(CH_3)$=$CHCO_2$], 6.4–6.45 [d, 1 H, H(13)], 6.53–6.57 [d, 1 H, H(11)], 6.97–7.05 [d, 1 H, H(8)], 6.53–6.57 [dd, 1 H, H(12)], 7.19–7.23 [dd, 1 H, H(7)], 7.41–7.42 [s, 1 H, H(5)]; ^{13}C NMR ($DCCl_3$), the ^{13}C NMR signals are given in Table I. Anal. ($C_{20}H_{24}O_3$) C, H.

2-Phthalimidoethyl 3,7-Dimethyl-7-(1,2,3,4-tetrahydro-4,4-dimethyl-6-thiochromanyl)-2,4,6-heptatrienoate (1d). To suspension of 0.503 g (1.53 mmol) of *trans*-acid **1a** in 8 mL of dry ether was added 0.142 g (1.8 mmol) of freshly distilled pyridine under N_2 and the suspension was cooled to −10 °C. A solution of 0.200 g (1.69 mmol) of $SOCl_2$ in ether (1 mL) was added, and the solution was stirred at room temperature for 1 h. The resulting dark red solution was filtered and cooled to −20 °C; 0.1420 g (1.80 mmol) of pyridine was added. Then 0.2963 g (1.55 mmol) of *N*-(2-hydroxyethyl)phthalimide in 8 mL of dry DMF was introduced at room temperature, and the solution was allowed to stir for 10 h. The resultant yellow solution was diluted with ether (25 mL) and washed with water (5 × 60 mL); and the ether layer was dried (Na_2SO_4). The solvent was removed and the resulting yellow solid was chromatographed on silica gel with $HCCl_3$. The phthalimide-substituted ester **1d** [0.2731 g (35.6%)] was a yellow solid (ethanol): mp 64–65 °C; IR (KBr) 1760–1710 cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.36 [s, 6 H, $(CH_3)_2C$], 1.98 (m, 2 H, SCH_2CH_2), 2.24 (s, 3 H, CH_3), 3.24 (s, 3 H, CH_3), 3.06 (m, 2 H, Ar SCH_2CH_2), 4.03 (t, 2 H, $CO_2CH_2CH_2$), 4.40 (t, 2 H, $CO_2CH_2CH_2$), 5.78 (s, 1 H, $CHCO_2CH_2CH_2$), 6.38 [d, 1 H, J = 15 Hz, $CHC(CH_3)CHCO_2CH_2$], 6.55 (d, 1 H, J = 12 Hz, Ar $C(CH_3)CH$), 7.03 (dd, 1 H, J = 12 Hz, J = 15 Hz, $CHCH$=CH), 7.08 [d, 1 H, J = 8 Hz, H(8)], 7.18 [dd, J = 2 Hz, J = 8 Hz, H(7)], 7.48 [d, 1 H, J = 2 Hz, H(5)], 7.75 (m, 2 H, Ar H), 7.80 (m, 2 H, Ar *H*); ^{13}C NMR ($DCCl_3$), the ^{13}C NMR signals are given in Table I. Anal. ($C_{30}H_{31}NO_4S$) C, H, N.

Methyl (*E*)-*p*-[2-(4,4-Dimethyl-6-chromanyl)-1-propenyl]benzoate (2a). A solution of *n*-butyllithium in hexane (1.44 M, 9.76 mL, 15.04 mmol) was added dropwise under N_2 to a stirred suspension of the phosphonium salt[3] (**14**; 8.0 g, 15.04 mmol) in dry ether (145 mL). The resulting dark, reddish-brown mixture was cooled to −78 °C, and a solution of methyl 4-formylbenzoate (**15**; 2.47 g, 15.04 mmol) was added over a period of 3 min. The solution was stirred for a few minutes at −78 °C and then at room temperature for 48 h. The mixture changed from reddish brown to an off-white color. After 48 h, the reaction mixture was filtered, and the resulting solid was washed with 350 mL of ether (dry); the filtrate was concentrated to give a yellow oil. This yellow oil was refrigerated (0–5 °C) overnight and gave a yellow solid. This yellow solid was chromatographed on 30 g of silica gel (column, 3 × 220 mm). The product was eluted with 400 mL of hexane/ethyl acetate (9:1). Concentration of the eluent gave a viscous oil, which spontaneously crystallized at room temperature. The white crystals were filtered and dissolved in a minimum amount of boiling absolute ethanol. Cooling the ethanol solution to room temperature gave 1.82 g (35%) of ester **2a** as white needles: mp 90–90.5 °C; IR(KBr) 1710–1715 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.4 [s, 6 H, H(9), H(10)], 1.9 [m, 2 H, H(3)], 2.3 [s, 3 H, H(12)], 3.9 [s, 3 H, H(21)], 4.2 [m, 2 H, H(2)], 6.8 [s, 1 H, H(13)], 6.84 [d, J = 9 Hz, 1 H, H(8)], 7.3 [dd, J = 9 Hz, J = 3 Hz, 1 H, H(7)], 7.4 [d, J = 3 Hz, 1 H, H(5)], 7.5 [d, 2 H, H(15), H(19)], 8.6 [d, 2 H, H(16), H(18)]; ^{13}C NMR ($DCCl_3$), the majority of ^{13}C NMR signals are given in Table I; nonprotonated and vinylic carbons (127.6, 131.3, 135.7, 139.5, 143.4); mass spectral data for $C_{22}H_{24}O_3$ m/e (M^+) 336.1725; found 336.1728. Anal. ($C_{22}H_{24}O_3$) C, H.

(*E*)-*p*-[2-(4,4-Dimethyl-6-chromanyl)-1-propenyl]benzyl Alcohol (2b). A solution of methyl (*E*)-4-[2-(4,4-dimethyl-6-chromanyl)-1-propenyl]benzoate (**2a**; 0.29 g, 0.86 mmol) in anhydrous THF (2 mL) was added dropwise under N_2 to a stirred suspension of $LiAlH_4$ (0.04 g, 1.10 mmol) in dry THF. The mixture was heated at reflux for 8 h, and after the mixture was cooled to room temperature, ethyl acetate (8 mL) was added to destroy residual $LiAlH_4$. The resulting mixture was stirred for 5 min. The two layers were separated, and the aqueous layer was washed (ether, 2 × 25 mL). The combined organic layers were washed with 5% Na_2CO_3 (50 mL), H_2O (25 mL), and brine (25 mL). After drying ($MgSO_4$, 2 H), the organic solution was evaporated, leaving a thick yellow oil. Chromatography using a Chromatotron with a silica gel plate (4 mm) and eluting with 80% hexane/ethyl acetate (200 mL total) gave, after concentration, a viscous oil, which solidified after refrigeration overnight. Dissolving this solid in a minimum of boiling hexane produced, after cooling, 65 mg (25%) of alcohol **2b** as a white amorphous powder: mp 79–80 °C (lit.[5a] mp 80–81 °C); IR (KBr) 3060–3510 (O–H) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.18 [s, 6 H, (H_3C)], 1.86 [m, 2 H, H(3)], 1.90 (s, 1 H, O*H*], 2.26 [s, 3 H, H(12)], 4.22 (m, 2 H, OCH_2CH_3), 4.70 [s, 2 H, H(20)], 6.76 [s, 1 H, CH=$C(CH_3)$], 6.82 [d, J = 9 Hz, 1 H, H(8)], 7.28 [dd, J = 9 Hz, J = 3 Hz, 1 H, H(7)], 7.38 [s, 4 H, H(15), H(16), H(18), H(19)], 7.44 [d, J = 3 Hz, 1 H, H(5)]; ^{13}C NMR ($DCCl_3$), the ^{13}C signals are given in Table I; there are other nonprotonated and vinyl carbons that could not be distinguished (131.2, 136.0, 137.4, 138.7); mass spectral data for $C_{21}H_{24}O_2$ m/e (M^+) 308.1776, found 308.1765. Anal. ($C_{12}H_{24}O_2$) C, H.

(*E*)-*p*-[2-(4,4-Dimethyl-6-chromanyl)-1-propenyl]benzonitrile (2c). A solution of *n*-butyllithium in hexane (1.39 M, 10.15 mL, 14.1 mmol) was added dropwise under N_2 to a stirred suspension of phosphonium salt **14** (5.00 g, 9.40 mmol) in dry ether (100 mL). The resulting dark, reddish-brown mixture was cooled to −78 °C, and to this was added a solution of 1.56 g (9.4 mmol) of *p*-cyanobenzaldehyde in 50 mL of anhydrous ether over a period of 1 min. The solution was stirred for 2 min at −78 °C and at room temperature for 2 h. The mixture changed from a reddish brown to a pale yellow color. After 2 h, the reaction mixture was filtered, and the solid material was washed with anhydrous ether (30 mL). The ethereal filtrate was evaporated to give a yellow oil, which was refrigerated overnight to yield a yellow solid. The yellow solid was dissolved in a minimum amount of boiling 95% ethanol from which fine white crystals of nitrile **2c** were deposited [1.43 g (48.6%)]: mp 134–134.5 °C; IR (KBr) 2220–2240 cm^{-1} (C≡N); ^1H NMR ($DCCl_3$) δ 1.80 [s, 6 H, $(CH_3)_2C$], 2.21 [s, 3 H, CH_3C], 2.30 [m, 2 H, CH_2C], 4.22 [m, 2 H, CH_2O], 6.33 [s, 1 H, *CH*=C], 6.80 [d, 1 H, J = 9 Hz H(8)], 7.21 [dd, 1 H, J = 9 Hz, J = 3 Hz, H(7)], 7.44 [d, J = 3 Hz, 1 H, H(5)], 7.50 [d, 2 H, H(15), H(19)], 7.90 [d, 2 H, H(16), H(18)]; ^{13}C NMR ($DCCl_3$), the majority of ^{13}C NMR signals are given in Table I; nonprotonated and vinylic carbons [109.4, 131.6, 135.3, 140.6] could not be assigned; mass spectral data for $C_{21}H_{21}NO$ m/e (M^+) 303.1623, found 303.1627. Anal. ($C_{21}H_{21}NO$), C, H, N.

(*E*)-*p*-[2-(4,4-Dimethyl-6-chromanyl)-1-propenyl]benzaldehyde (2d). A solution of the nitrile **2c** (0.200 g, 0.66 mmol) in 25 mL of dry ether under N_2 was stirred at room temperature, and a solution of diisobutylaluminum hydride (DIBAL-H) in hexane (1.0 M, 1.34 mL, 1.34 mmol) was added dropwise. When the addition was complete (2 min), the mixture was allowed to boil with stirring for 38 h and then allowed to warm to room temperature. The resulting solution was diluted with CH_3OH (10 mL). The dilute H_2SO_4 (5%, 25 mL) was added cautiously until the aqueous phase was acidic. This aqueous layer was

extracted with ether (2 × 25 mL). The combined organic phases and extract were washed with 5% $NaHCO_3$ (2 × 50 mL), water (50 mL), and finally brine (25 mL). After drying ($MgSO_4$, 30 min) the solution was evaporated to a viscous yellow oil. Chromatography of the oil was performed with silica gel (ca. 12 g) through a vertical column (8 × 200 mm). Elution was effected with hexane/ethyl acetate (4:1, 200 mL). Concentration of the eluent gave a viscous oil, which solidified upon standing in an ice bath for 2 h. Solution of the solid in a minimum amount of hot hexane gave, upon cooling, 51 mg (26%) of aldehyde **2d** as a white crystalline material; mp 85–86 °C (lit.[5a] mp 102–104 °C). We have no explanation for the large discrepancy in our melting point and that reported [5a] in the patent. We present the following supporting data for our compound **2d**: IR (KBr) 2750 (CH=O), 1700 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.39 [s, 6 H, $(H_3C)_2$], 1.86 [m, 2 H, H(3)], 2.29 [s, 3 H, H(12)], 4.22 (m, 2 H, OCH_2CH_3), 6.77 (s, 1 H, CH=CCH_3), 6.81 [d, J = 9 Hz, 1 H, H(8)], 7.26 [dd, J = 9 Hz, J = 3 Hz, 1 H, H(7)], 7.43 [d, J = 3 Hz, 1 H, H(5)], 7.51 [d, J = 9 Hz, 2 H, H(15), H(17)], 7.87 [d, J = 9 Hz, 2 H, H(16), H(18)], 10.0 (s, 1 H, CHO); ^{13}C NMR ($DCCl_3$), the majority of ^{13}C NMR signals were given in Table I; nonprotonated and vinyl carbons could not be assigned (129.7, 131.4, 135.5, 140.4, 145.1); mass spectral data for $C_{21}H_{22}O_2$ m/e (M^+) 306.1619, found 306.1617. Anal. ($C_{21}H_{22}O_2$) C, H.

2-(2-Methoxy-5-bromophenyl)-2-methyl-1-chloropropane (18). Concentrated H_2SO_4 (4 mL, 7.6 g, 0.077 mol) was added dropwise under N_2 to stirred 4-bromoanisole (44.0 g, 0.235 mol). After the mixture was warmed to 36 °C (warm water bath), distilled β-methallyl chloride (**17**; 21.5 mL, 20.0 g, 0.221 mol) was added dropwise to the stirred mixture in 4 equal portions over a period of 1.6 h (4 × 0.4 h). During the addition of **17**, the temperature of the mixture was maintained at 35–44 °C (with a warm water bath). After the addition of **17** was complete, the reaction mixture became solid and was allowed to stand [1 h over water bath (29–32 °C), 2 h at room temperature]. The wet solid was partitioned between H_2CCl_2 (500 mL) and H_2O (175 mL). The organic layer was separated and then washed with 5% aqueous $NaHCO_3$ (175 mL) and H_2O (175 mL); 5 mL of brine followed to destroy an emulsion that formed. After the organic solution was dried ($MgSO_4$, 36 h), the solvent was removed, and the solid residue was vacuum distilled to remove a lower boiling liquid (bp 42 °C 0.04 mm–95 °C/0.015 mm, mostly 4-bromoanisole). A solution of the remaining solid residue in H_2CCl_2 was treated with decolorizing charcoal. Evaporation of the H_2CCl_2 gave a tan solid, which was recrystallized (heptane) and dried [traces of solvent were removed (high vacuum)] to give ether **18** as a white crystalline solid (37.7 g, 61.5%); mp 87.8–89.1 °C (lit.[24] mp 82–84 °C). Another 3.4 g (5.5%) could be obtained by the following procedure. Evaporation of the mother liquors gave a solid, which was dissolved in H_2CCl_2. Partial decolorization (charcoal) of the H_2CCl_2 solution followed by evaporation gave a solid residue, which was recrystallized (heptane); total yield of **18** was 41.1 g (67%): IR (KBr) 1246 cm^{-1} (C–O); ^1H NMR ($DCCl_3$) δ 1.43 [s, 6 H, $C(CH_3)$], 3.84 (s, 3 H, OCH_3), 3.96 (s, 2 H, OCH_2Cl), 6.78 (d, 1 H, Ar H), 7.32–7.41 (m, 2 H, Ar H); ^{13}C NMR ($DCCl_3$) ppm 25.8 [$C(CH_3)_2$], 40.4 [$C(CH_3)_2$], 53.3 (CH_2Cl), 55.3 (OCH_3), Ar C [113.1, 130.6, 131.2, 135.4, 157.2].

5-Bromo-2,3-dihydro-3,3-dimethylbenzofuran (19). A mixture of 2-(2-methoxy-5-bromophenyl)-2-methyl-1-chloropropane (ether **18** above; 12.60 g, 0.045 mol), pyridine hydrochloride 23.7 g, 0.205 mol), and quinoline (22.9, 0.177 mol) was heated to 164 °C (boiling isobutylbenzene bath) under N_2 with stirring over a period of 0.6 h. After stirring at reflux (164–167 °C) for 3 h, the mixture was partitioned between ice-cold 6 N HCl (225 mL) and ether (200 mL). The organic layer was separated and the aqueous layer was extracted (ether, 200 mL). After the combined organics were dried ($MgSO_4$), the solvent was evaporated, and the residual oil was vacuum distilled to give either **19** (8.5 g, 82%) as a colorless liquid: bp 58.9–60.0 °C/0.007–0.01 mm (lit.[24] bp 62–64 °C/0.01 mm); IR (neat) 1197 cm^{-1} (C–O); ^1H NMR ($DCCl_3$) δ 1.31 [2, 6 H, $C(CH_3)_2$], 4.24 (s, 2 H, OCH_2), 6.67 (d, 1 H, Ar H), 7.18–7.25 (m, 2 H, Ar H); ^{13}C NMR ($DCCl_3$) ppm 27.3 [$C(CH_3)_2$], 42.1 [$C(CH_3)_2$], 84.7 (OCH_2), Ar C (111.2, 112.2, 125.4, 130.6, 138.9, 158.2).

1-(2,3-Dihydro-3,3-dimethyl-5-benzofuranyl)ethanol (20). A mixture of ether **19** (0.21 g, 0.9 mmol), Mg turnings (1.0 g, 0.041 g-atom), and dry THF (3 mL) was heated under N_2 until the mixture turned cloudy (ca. 15 min). Dry THF (15 mL) was added to the mixture, which was then heated to reflux. A solution of ether **19** (2.92 g, 12.9 mmol) in dry THF (25 mL) was added dropwise to the vigorously stirred mixture over a period of 0.75 h. After vigorous stirring at reflux for 2.75 h, another 0.25 g (0.010 g at) of Mg turnings were added. The new mixture was stirred at reflux for 0.75 h and with no external heat for 0.5 h. Upon cooling of the mixture (−5 to −10 °C, ice–salt bath), a solution of freshly distilled acetaldehyde (2.0 g, 0.045 mol) in dry THF (20 mL) was added dropwise to the vigorously stirred mixture over a period of 0.7 h. This reaction mixture was stirred in an ice–salt bath (−5 to −10 °C) for 1.5 h, after which time a solution of acetaldehyde (0.9 g, 0.020 mol) in dry THF (5 mL) was added dropwise (over a period of about 0.2 h), and the new mixture was stirred 0.3 h. With continued cooling (−5 to −10 °C), saturated aqueous NH_4Cl (3 mL) was added, and the excess Mg turnings were removed from the mixture by filtration. Saturated aqueous NH_4Cl (10 mL) and ether rinses (from glassware and Mg turnings, 40 mL) were added to the filtrate. After separation of the organic layer, the aqueous phase (pH >8) was acidified (pH 6.5–7) with saturated aqueous NH_4Cl (15 mL) and 4% H_2SO_4 (4 mL). The aqueous solution was extracted with ether (5 × 40 mL) and ether (90 mL) was added to the combined organics. The organic solution was washed with saturated aqueous $NaHCO_3$ (75 mL) and brine (50 mL). After the solution was dried ($MgSO_4$), the solvent was removed, and the residual oil was chromatographed though a circular silica gel plate (4 mm) spun by a Chromatotron. Half of the product was eluted with petroleum ether (bp 50–110 °C)/ether [20:1, 8:1, then 4:1], and then the same solvent system was used to elute the other half. In both separations, the 4:1 ratio was required to elute the title compound. Concentration of the eluent in the desired fractions gave 1.18 g (44%) of alcohol **20** as a light yellow, viscous oil. TLC analysis (4:1 petroleum ether/ether] indicated the compound was essentially pure and was used without further purification: IR (neat) 3150–3650 cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.31 [s, 3 H, $C(CH_3)CH_3$], 1.32 [s, 3 H, $C(CH_3)CH_3$], 1.45 [d, 3 H, $CH(CH_3)$], 2.36 (br s, 1 H, OH), 4.81 [q, 1 H, $CH(CH_3)$], 6.71 [d, J = 8 Hz, 1 H, H(7)], 7.08 [dd, J = 8 Hz, J = 1.9 Hz, 1 h, H(6)], 7.13 [d, J = 1.9 Hz, 1 H, H(4)]; ^{13}C NMR ($DCCl_3$) ppm 25.1 [$CH(CH_3)$], 27.5 [$C(CH_3)_2$], 41.9 [$C(CH_3)_2$], 84.7 [OCH_2]; Ar C (109.3, 119.5, 125.4, 136.8, 138.3, 158.6).

[1-(2,3-Dihydro-3,3-dimethyl-5-benzofuranyl)ethyl]triphenylphosphonium Bromide (21). A solution of alcohol **20** (0.28 g, 1.46 mmol) in methanol (5 mL) was added dropwise (about 3 min) under N_2 to a stirred mixture of triphenylphosphine hydrobromide (0.50 g, 1.46 mmol) in methanol (10 mL). After 7 min, the mixture became a solution, which was stirred at room temperature for 40 h. Evaporation of the solvent resulted in foaming (care) and gave a colorless solid. The solid was changed to a powder by stirring the suspension of crude **20** in ether for 4.5 h. After the solid was filtered, the fine powder was partially air-dried and finally dried by high vacuum (P_2O_5, 100 °C) to give 0.69 g 91%) of salt **21** as a creamy white powder: mp 207–212 °C; ^1H NMR ($DCCl_3$) δ 1.13 [s, 3 H, $(CH_3)CCH_3$], 1.18 [s, 3 H, $(CH_3)CCH_3$], 1.82 (dd, 3 H, $CHCH_3$), 4.22 (s, 2 H, OCH_2), 6.56 (m, 1 H, $CHCH_3$), 6.61 (d, 1 H, Ar H), 6.85–6.98 (m, 2 H, Ar H), 7.64–7.92 [m, 15 H, $P(C_6H_5)_3$]. The salt was used without further purification.

Methyl 4-[2-(2,3-Dihydro-3,3-dimethyl-5-benzofuranyl)-1-propenyl]benzoate (3a). A solution of n-butyllithium (1.38 M, 1.1 mL, 1.51 mmol) in hexane was added dropwise (about 2 min) under N_2 to a stirred mixture of the phosphonium salt **21** (0.753 g, 1.45 mmol) in dry THF (23 mL). The resulting dark red mixture was stirred at room temperature (0.5 h). After the mixture was cooled in a dry ice–acetone bath (−78 °C, 0.15 h), a solution of aldehyde **15** (0.230 g, 1.40 mmol) in dry THF (7 mL) was added dropwise over a period of 30 s. The mixture became creamy light yellow and was cloudy. After being stirred at room temperature for 47 h, the reaction mixture was eluted through a short column (silica gel, 7 cm × 9 mm) with THF (75 mL) and ether (100 mL). Evaporation of the solvent gave a thick oil, which

(24) Gates, D. S.; Baldwin, D.; Wilson, C. A.; Gillon, J. (Fison's Ltd) U.S. Patent 4 333 759; *Chem. Abstr.* **1982**, *97*, 215,978*p*.

was dissolved in ethyl acetate/hexanes (1:1, 2 mL). This solution was chromatographed via a circular silica gel plate (2 mm) spun by a Chromatotron. The product was eluted with hexanes/ethyl acetate [9:1 (130 mL), then 7:1 (100 mL)]. Fractions 3 and 4 were combined. After removal of the solvent, the resulting thick oil (0.27 g) solidified on standing. Recrystallization (hot 95% ethanol) gave, after washing (cold 95% ethanol) and drying under high vacuum [P_2O_5, room temperature (4 h) and 40 °C (1 h)], 143 mg (30.5%) of ester **3a** as colorless flakes: mp 100.3–100.8 °C; IR (KBr) 1717 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.38 [s, 6 H, $C(CH_3)_2$], 2.29 [d, J = 1.2 Hz, 3 H, $CH{=}C(CH_3)$], 3.93 (s, 3 H, OCH_3), 4.28 (s, 2 H, OCH_2), 6.77 [br s, 1 H, $CH{=}C(CH_3)$], 6.80 [d, J = 8.3 Hz, 1 H, H(7)], 7.28 [d, J = 2 Hz, 1 H, H(4)], 7.31 [dd, J = 8.3 Hz, J = 2 Hz, 1 H, H(6)], 7.41 (d, 2 H, Ar H), 8.03 (d, 2 H, Ar H); ^{13}C NMR ($DCCl_3$), majority of ^{13}C NMR signals are given Table I; nonprotonated and vinylic carbons (127.6, 136.4, 136.8, 139.6, 143.4). Anal. ($C_{21}H_{22}O_3$) C, H.

4-[2-(2,3-Dihydro-3,3-dimethyl-5-benzofuranyl)-1-propenyl]benzoic Acid (3b). Ester **3a** (85 mg, 0.26 mmol) was heated at reflux under N_2 for 5 h in a solution of NaOH (0.06 g, 1.5 mmol) in 95% C_2H_5OH (1.3 mL) and H_2O (2.8 mL). After cooling slowly to a few degrees above room temperature, the solution was acidified (litmus) with concentrated HCl. A white solid formed and was filtered, washed (H_2O, about 10 mL), and recrystallized (hot ethanol followed by a wash with dry hexane) to give after drying 41 mg (51%) of acid **3b** as white crystals: mp 197.0–198.6 °C; ^1H NMR ($DCCl_3$) δ 1.39 [s, 6 H, $(CH_3)_2C$], 2.30 [d, J = 1 Hz, 3 H, $CH{=}C(CH_3)$], 4.28 (s, 2 H, OCH_2), 6.78–6.83 [m, 2 H, $CH{=}C(CH_3)$ and H(7)], 7.29 [d, J = 2 Hz, 1 H, H(4)], 7.32 [dd, J = 8.2 Hz, J = 2 Hz, 1 H, H(6)], 7.46 (d, 2 H, Ar H], 8.12 (d, 2 H, Ar H); ^{13}C NMR ($DCCl_3$), the majority of ^{13}C NMR signals are given in Table I; nonprotonated and vinylic carbons (126.7, 136.4, 136.8, 140.0, 144.3). Anal. ($C_{20}H_{20}O_3$) C, H.

Biological Screening Procedures. The method for determining the effect of a retinoid upon the TPA-induced ODC activity in mouse epidermus has been fully described.[9,10] Briefly, the test sample in 0.2 mL of acetone is applied 1 h prior to application of 10 nmol of TPA to the mouse skin. The mice were sacrificed 5 h after treatment in preparation for the ODC assay. Epidermus was separated, homogenized, and centrifuged at 30000 g. Soluble epidermal ODC activity was assayed. Each value in Table II is the mean ± SE of determinations carried out on three groups of mice with three mice per group.

The experimental methodology for performing the assay with the HL-60 cell line have been detailed previously.[12,13] Briefly, HL-60 cells were grown in a serum-free defined medium consisting of RPMI 1640 supplemented with 10 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid, 5 μg of insulin/mL, and 5 μg of transferrin/mL. The retinoids were dissolved in Me_2SO or ethanol and diluted into the culture medium so that the final concentration of the solvent did not exceed 0.1%, a concentration that has no effect on differentiation. After incubation for 4 days at 37 °C in a humidified atmosphere of 5% CO_2 in air, the capacity of the cells to reduce NBT was determined. Viable cells (10^6) were harvested by centrifugation and suspended in 0.5 mL of RPMI 1640 containing 20% fetal bovine serum. This cell suspension was mixed with an equal volume of phosphate buffered saline containing 1 mg of NBT/mL and 200 ng of TPA/mL. The reaction mixture was incubated at 37 °C for 25 min, and the reaction was terminated by cooling in an ice–water bath. Cytospin slides were prepared from a portion of this reaction mixture and stained with Wright-Giemsa. A minimum of 200 cells were counted under light microscopy to determine the percentage of cells with cell-associated formazan.

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Synthesis and Antidepressant Properties of Novel 2-Substituted 4,5-Dihydro-1*H*-imidazole Derivatives[1]

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A unique combination of α_2-adrenoreceptor antagonist and serotonin-selective reuptake inhibitory activities has been identified in a series of 2-substituted 4,5-dihydro-1*H*-imidazole derivatives. This combination of blocking activities has provided one of these derivatives, napamezole hydrochloride (**2**), with potential as an antidepressant. A discussion of the syntheses of these compounds includes a convenient method for the conversion of nitriles to imidazolines with ethylenediamine and trimethylaluminum.

Inhibition of norepinephrine release in central nervous system adrenergic neurons via presynaptic stimulation of α_2-adrenoreceptors has been found to be blocked in vitro and in vivo by idazoxan,[2] mianserin,[3] yohimbine,[4] and other α_2-adrenoreceptor antagonists. The characterization and pharmacology of subtypes 1 and 2 of α-adrenoreceptors has been extensively reviewed.[5-8] The structure–activity relationships of α_2-adrenoreceptor antagonists has also been reviewed.[9]

Since depletion of biogenic amines in the brain is thought to contribute to the symptomology of depression, α_2-adrenoreceptor antagonists have emerged as potential antidepressants having a novel mechanism.[3] These agents

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