Structure–Activity Relations in the Vitamin E Series.[1] I. Effects of 5-Methyl Substitution on 6-Hydroxy-2,2,5,7,8-pentamethylchroman

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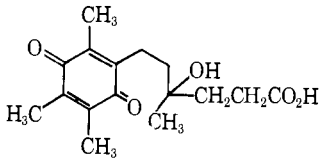
5-Methyl-substituted 6-hydroxy-2,2,5,7,8-pentamethylchromans and oxidation products of 6-hydroxy-2,2,5,7,8-pentamethylchroman were prepared and evaluated for vitamin E like activity. Significant activity was found in preventing the *in vitro* respiratory decline of liver slices from vitamin E deficient animals and in prevention of vitamin E deficiency induced liver necrosis in rats. However, none of the analogs of vitamin E showed significant activity in the vitamin E deficiency induced muscular dystrophy in rabbits, chick encephalomalacia, or resorption of embryo in rats.

Oxidation of *dl*-α-tocopherol with various mild oxidizing agents affects only the aromatic moiety and in some cases opening of the chroman ring. The phytyl side chain is left intact unless extremely drastic oxidizing conditions are utilized. Of the various proposed metabolites[5] of vitamin E only two involve changes of the phytyl side chain (**1** and **2**). The model compound



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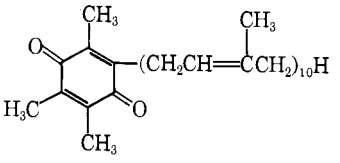

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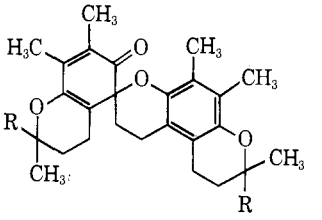
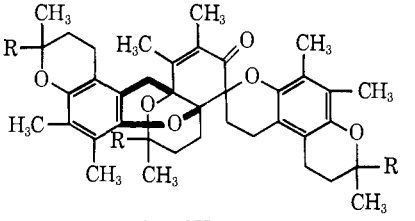
(6-hydroxy-2,2,5,7,8-pentamethylchroman) has been studied in place of *dl*-α-tocopherol for determination of changes induced by oxidation and has proven to be valuable for structural studies of the oxidation products analogous to those formed from *dl*-α-tocopherol, the products from the model series having the advantage of being crystalline. However, studies of the biological activities of this model compound and its oxidation products in various vitamin E deficiency induced states have been neglected.

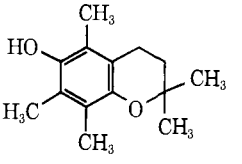
Among the several oxidation reactions of *dl*-α-tocopherol and its model that have been studied, one is the formation of products, dimers and trimers (**3** and **4**), explainable as being formed *via* the unstable intermediate, *o*-quinone methide. Furthermore, the formation of a metabolite resembling **4** has been reported,[5-7]



3, R = CH_3 or $C_{16}H_{33}$



4, R = CH_3 or $C_{16}H_{33}$



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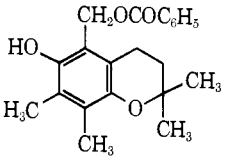

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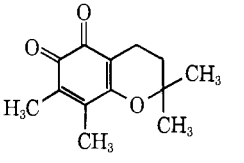

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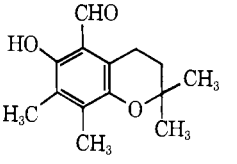

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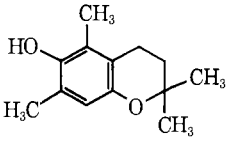

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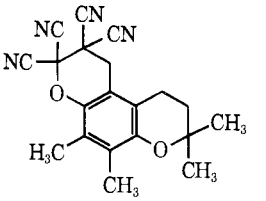

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(1) Paper IX. For the preceding paper see W. A. Skinner and R. M. Parkhurst, *J. Org. Chem.*, **31**, 1248 (1966).

(2) Vitamin E deficiency induced muscular dystrophy studies.

(3) Resorption of embryo and chick encephalomalacia studies.

(4) Respiratory decline and liver necrosis studies.

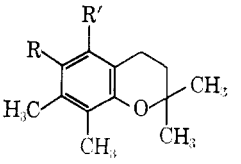
(5) A. Mellors and M. M. Barnes, *Brit. J. Nutr.*, **20**, 69 (1966).

(6) W. A. Skinner and P. Alaupovic, *J. Org. Chem.*, **28**, 2854 (1963).

(7) H. H. Draper, A. S. Csallany, and M. Chiu, *Federation Proc.*, **25**, (I), 242 (1966).

TABLE I

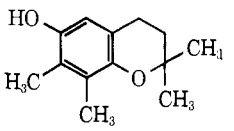
5-METHYL-SUBSTITUTED CHROMANS



Compd	R	R′	Mp, °C	Yield, %	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	Cl, S, or N, % Calcd	Cl, S, or N, % Found
12	CH_3CO_2	CH_2Cl	136–138	27	$C_{16}H_{22}ClO_3$	64.7	64.6	7.13	7.11	11.9	11.8
13	CH_3CO_2	$CH_2SC_{12}H_{25}$	38–40	20	$C_{28}H_{46}O_3S$	72.8	72.9	10.0	10.0	6.94	6.70
14	CH_3CO_2	$CH_2SC(=NH)NH_2 \cdot HCl$	232–235	68	$C_{17}H_{25}ClN_2O_3S$	54.6	54.4	6.74	6.75		
15	CH_3CO_2		120–122	51	$C_{26}H_{29}NO_4$	69.2	69.0	8.43	8.41	4.04	4.05
16	CH_3CO_2	CH_2I	129–131	94	$C_{16}H_{22}IO_3$	49.4	49.5	5.70	5.61		
17	CH_3CO_2	$CH_2SCH_2CH_3$	70–73	74	$C_{18}H_{28}O_3S$	67.1	67.1	8.13	8.20	9.95	9.70
18	HO		154–157	60	$C_{25}H_{29}NO_2$	75.2	75.3	9.64	9.78	4.63	4.59
19	HO	$CH_2N(CH_3)_2$	126–128	90	$C_{16}H_{25}NO_2$	72.9	72.8	9.57	9.63	5.33	5.06
20	HO	$CH_2OCH_2CH_3$	97–98	68	$C_{16}H_{24}O_3$	72.6	72.9	9.14	9.06	264	250[a]
21	HO	CH_2OCH_3	70–72	18	$C_{15}H_{22}O_3$	72.0	71.8	8.85	8.91		
22	HO	$CH_2OCH_2C_6H_5$	100–103	23	$C_{21}H_{26}O_3$	77.2	77.3	8.03	8.20		

[a] Molecular weight.

indicating that the *o*-quinone methide might be an *in vivo* intermediate of some importance. Since the 5-methyl group of *dl*-α-tocopherol is involved in many of its oxidation reactions including *o*-quinone methide formation, it was felt desirable to synthesize 5-methyl-substituted analogs of vitamin E and its model for biological evaluation. This paper reports these synthetic studies and the results of biological evaluation of several 5-methyl-substituted derivatives and oxidation



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products of the model chroman **5** in a number of vitamin E deficiency induced disorders.

The 5-methyl-substituted derivatives were synthesized *via* the common intermediate **12** which was prepared by a modification of the method previously reported[8] (Table I).

Biological Activities

Resorption Gestation in Rats.—Weanling female rats of the Sprague–Dawley strain were placed on a vitamin E free diet and handled as previously described by Crider, *et al.*[9] After the first resorption gestation, the the molecular distilled lard was removed from the diet and the essential fatty acids were supplied by adding a 60% methyl linoleate concentrate to the diet at a level of 3% twice weekly. The female rats were then mated to normal males, divided into groups, and received various supplements listed in Table II.

TABLE II

THE EFFECT OF MODEL CHROMAN AND ITS OXIDATION PRODUCTS ON THE REPRODUCTION OF FEMALE RATS

Treatment[a]	No. of females	No. of positive matings	No. of litters
dl-α-Tocopherol, 25 mg	4	3	3
None	3	1	0
5, 25 mg	4	4	0
6, 25 mg	4	2	0
3, 25 mg	4	4	0

[a] One oral dose 6 days following onset of mating.

Encephalomalacia in Chickens.—Day-old chicks were placed on the encephalomalacia-producing diet described by Smith, *et al.*[10] The corn oil was added every other day immediately prior to feeding to retard oxidation. The experiments were terminated when all the chicks in the negative control group either had died or exhibited positive symptoms of encephalomalacia as described by Pappenheimer, *et al.*[11] The oxidation products in both the rat and chick experiments were administered in an ethanol–16% aqueous Tween 80 emulsion (1:9, v/v). The results are reported in Table III.

Vitamin E Deficiency Induced Muscular Dystrophy in Rabbits.—Nutritional muscular dystrophy was produced in New Zealand white rabbits as previously described.[12,13] Rabbits of mixed sex, ranging in weight from 0.7 to 1.1 kg, were maintained for the first 48 hr on commercial rabbit pellets containing 0.5% sulfaquinoxaline. The animals were then placed on a vitamin E deficient diet which had been diluted with

(8) A. F. Wagner, A. Lusi, C. H. Shunk, B. O. Linn, D. E. Wolf, C. H. Hoffman, R. E. Erickson, B. Arison, N. R. Trenner, and K. Folkers, *J. Am. Chem. Soc.*, **85**, 1534 (1963).

(9) Q. E. Crider, P. Alaupovic, and B. C. Johnson, *J. Nutr.*, **73**, 64 (1961).

(10) J. L. Smith, H. N. Bhagavan, R. B. Hill, S. Gaetani, P. B. R. Rao, Q. E. Crider, B. C. Johnson, C. H. Shunk, A. F. Wagner, and K. Folkers, *Arch. Biochem. Biophys.*, **101**, 388 (1963).

(11) A. M. Pappenheimer, M. Goettsch, and A. Alexieff, *J. Exptl. Med.*, **57**, 365 (1933).

(12) J. L. Smith, H. W. Moore, and K. Folkers, *Proc. Soc. Exptl. Biol. Med.*, **118**, 782 (1965).

(13) J. L. Smith, J. Scholler, H. W. Moore, T. M. Farley, and K. Folkers, *Arch. Biochem. Biophys.*, **116**, 129 (1966).

TABLE III
THE EFFECT OF MODEL CHROMAN AND ITS OXIDATION PRODUCTS ON THE INCIDENCE OF ENCEPHALOMALACIA IN THE CHICK

Compd	Dose,[a] mg	No. of chicks	Incidence of encephalomalacia	Mortality[b]
Experiment C5 (20 days)				
dl-α-Tocopherol	10	10	0	0
Control		10	6	4
5	40	10	7	3
6	40	10	4	4
Experiment C6 (18 days)				
dl-α-Tocopherol	10	10	0	0
Control		10	8	0
3	20	7	4	0
4	16	5	3	0
5	20	6	2	1
5	40	5	2	2
5	50	5	4	0

[a] One oral dose on 7th day. [b] Deaths after the 7th day; no symptoms noted.

one-third its weight of cellulose. Sulfaquinoxaline in a concentration of 0.04% was added to the drinking water for 3 out of every 5 days. Under this regime of treatment, coccidiosis was controlled.

For the first 21 days, the animals were weighed twice weekly and then daily thereafter. Starting with day 21, urine samples were collected periodically and creatine:creatinine ratios were determined.[14]

An animal was scored as dystropic if the creatine:creatinine ratio (c:c) exceeded 0.7 and/or if the rabbit could not recover its natural position after being placed on its right side 20 times. Treatment was initiated when the animal was first scored as dystrophic by one or both criteria.

To determine vitamin E like activity in these rabbits, the compounds under study were suspended in water with Tween 80, 2 drops/10 ml, by sonification and injected intravenously every 3 to 4 days until death or recovery. In most instances, the doses indicated in Table IV were the maximum tolerated dose. To determine if the compounds were antagonistic to vitamin E, the compounds were given at the same time as a "curative dose," 25 mg/rabbit, of vitamin E.

TABLE IV
VITAMIN E DEFICIENCY INDUCED MUSCULAR DYSTROPHY IN THE RABBIT

Compd	Max tolerated dose, mg/rabbit	Therapeutic[a] effect	Vitamin E[b] antagonism
5	250	0/2	0/2
6	100	0/2	0/2
7	50	0/2	0/2
8	50	0/2	0/2
12	12.5	0/2	0/2
13	25	0/2	0/2
14	6.25	0/2	0/2
15	50	0/2	0/2
16	25	0/2	0/2
18	50	0/2	0/2
19	50	0/2	0/2
20	50	0/2	0/2

[a] Compound given intravenously at the maximum tolerated dose every third or fourth day until death or recovery; 25 mg/rabbit of *dl*-α-tocopherol acetate is curative. [b] Maximum tolerated dose of each compound given intravenously with 25 mg/rabbit of *dl*-α-tocopherol acetate.

Control Rabbits.—Over the past several years, information has been collected for both negative and positive control rabbits. One out of every ten rabbits on the synthetic diet was not treated and served as a negative control.[12] These control animals, numbering as many as 20 in our over-all program, survived approximately 7 to 9 days after failure of the righting criterion. The creatine:creatinine ratio was usually above 1.0_1 and there was an accompanying loss of weight. In no instance was an untreated animal observed to respond even partially, though occasionally a moribund animal would linger for several days before dying; *i.e.*, there was never a false positive response without treatment.

At least one out of every 20 rabbits served as a positive control and was treated with 25 mg of *dl*-α-tocopherol intravenously after the animal became dystrophic by the criteria. In most instances, the creatine:creatinine ratio was normalized, the righting reflex was regained, and weight improved by the fifth day and in all rabbits by the eighth day.

Protection of Rats against Dietary Necrotic Liver Degeneration.—Assays for protective activity against dietary necrotic liver degeneration were carried out as described previously, using the Torula yeast diet of Schwarz.[15] Weanling male Sprague–Dawley rats were maintained for 13 days on the liver necrosis inducing basal Torula diet in groups of five/cage. They were then transferred into individual cages and distributed into experimental groups of five or ten animals each. The unsupplemented basal diet was used as negative control. Groups of animals on diets supplemented with various levels of *dl*-α-tocopheryl acetate served as positive controls. The experiment was discontinued on the 40th day.

The average survival time of unsupplemented controls was approximately 26 days, while 0.3 mg of tocopherol afforded a significant degree of protection and 1 mg protected completely over the duration of the experiment. "Per cent protection" was calculated by using a formula which averages the reciprocals of the individual survival times for each group (velocity, V_{ST}) and compares the velocity of the experimental group to that of the unsupplemented, simultaneous control group.

All assays were performed with 10 mg of substance per 100 g of diet. The results of these preliminary tests showed clearly that a considerable degree of protection against liver necrosis is afforded by certain of the vitamin E analogs. However, none of these substances came close to the potency of α-tocopherol. Variations of the substituent in the 5 position of the molecule from CH_3 (**5**) to CHO (**8**) reduced activity from 82 to 21% protection. The CH_2Cl- (**12**) and CH_2I-substituted (**16**) analogs afforded 82 and 24% protections, respectively. The $CH_2OCH_2CH_3$- (**20**) and $CH_2OCH_2C_6H_5$-substituted (**22**) compound were both active, affording 67 and 61% protection. All other compounds investigated in the course of these studies were inactive at the 10 mg % level (Table V). These results are of preliminary nature. For a more accurate comparison each of the analogs would have to be tested repeatedly

(14) R. S. Hare, *Proc. Soc. Exptl. Biol. Med.*, **74**, 148 (1950).

(15) K. Schwarz, *ibid.*, **77**, 818 (1951).

TABLE V

PREVENTIVE EFFECTS OF TOCOPHEROL ANALOGS ON DIETARY NECROTIC LIVER DEGENERATION

Compd	No. of animals	No. of survivors	% protection[a]
5	5	4	82
6	5	0	0
7	5	0	0
8	5	1	21
10	5	0	0
11	5	1	24
	5	0	0
12	5	4	82
14	5	0	2
15	5	0	19
16	5	1	24
18	5	0	3
19	5	0	2
20	5	3	67
21	5	1	15
22	5	3	61

[a] Per cent protection = $100 - 100V_{ST,\ expl}/V_{ST,\ control}$, where V_{st} is the reciprocal of the survival time.

in a variety of dose levels and with larger numbers of animals.

In Vitro **Prevention of Respiratory Decline of Liver Homogenates from Rats on Liver Necrosis Inducing Diets.**—In animals during the prenecrotic phase of dietary necrotic liver degeneration, a peculiar inability to maintain normal oxidative behavior *in vitro* is seen. The defect, designated respiratory decline, can be demonstrated in the Warburg apparatus with liver slices and liver homogenates, but not with mitochondria.[16-18] Respiratory decline consists of a loss of O_2 consumption to approximately 10–20% of the initial level over 60–90 min of incubation. The initial level of oxidation, maintained for the first 15–30 min, is normal. Respiratory decline is prevented not only by the dietary supplementation of vitamin E and other effective substances, but also by the *in vivo* addition of active compounds to the Warburg medium. Certain tocopherol derivatives have been found to be effective in the prevention of this metabolic lesion.[19-21] Some of the current analogs of *dl*-α-tocopherol and its oxidation products were screened for protective effects on respiratory decline *in vitro*, as shown on Table VI.

TABLE VI

PREVENTION OF RESPIRATORY DECLINE BY TOCOPHEROL MODEL COMPOUNDS

	% prevention of respiratory decline[a]							
	Dose level, μg							
Compd	0.5	1	1.5	2.5	5	7.5	10	ED_{50}[b]
dl-α-Tocopherol	4	13	13	25	50	63	100	5.4
5				37	100			3.4
7	18	71	100	100	100			0.8
9				12	72	100		4.5

[a] Per cent prevention of respiratory decline (RD) during the 60–90-min interval = $100 - RD_{expl}100/RD_{control}$. [b] ED_{50} is the 50% effective dose, calculated from the results at various dose levels. Supplements are in micrograms per 3 ml of medium with 100 mg of tissue homogenate.

It is evident from these figures that the *in vitro* potency of the 5-methyl model compound without side chain (**5**) is not much different from α-tocopherol itself. The 5-oxo model derivative (**7**), which is an analog of tocopherol red, was compared to *dl*-α-tocopherol in eight successive Warburg experiments, each carried out with six different dose levels of the two substances. Values presented in Table VI for α-tocopherol and **7** constitute the averages of these eight experiments; they are statistically highly valid. The other compounds were tested less thoroughly. It is seen that the tocopherol red analog is approximately seven times as active as α-tocopherol. The model compound **9**, which is an analog of ζ_2-tocopherol, is approximately as active as α-tocopherol in this *in vitro* system.

If compared to the results of the dietary assay against liver necrosis (see above) it is evident that potency *in vivo* does not run parallel with that found *in vitro*. It is likely that the activity of some of these compounds in the *in vivo* prevention of liver necrosis is greatly diminished by barriers in resorption, permeability, and transfer through cell membranes. Similar differences have been observed in the *in vivo* and *in vitro* effects of other tocopherol derivatives.[19,20]

Discussion

Although the model chromans and oxidation products evaluated did not show vitamin E like activity in vitamin E deficiency induced muscular dystrophy in rabbits, chick encephalomalacia, or resorption of embryo in rats, significant activity was shown by several of these compounds in preventing the *in vitro* respiratory decline and liver necrosis induced by a vitamin E deficient diet in rats.

It would appear that the requirements proposed by Boyer[22] for vitamin E activity hold for some of the vitamin E deficiency induced disorders but not all of them. The high *in vitro* activity of the *o*-quinone **7** was not found *in vivo*; however, the α-tocopherol model **5** was active both *in vitro* and *in vivo*. Substitution on the 5-methyl group of the model chroman (**5**) did not always destroy the activity in the assay against dietary necrotic liver degeneration of the rat.

Current efforts are directed toward the synthesis and evaluation of α-tocopherol derivatives corresponding to those model compounds reported here.

Experimental Section[23]

6-Acetoxy-5-chloromethyl-2,2,7,8-tetramethylchroman (12).—6-Hydroxy-2,2,5,7,8-pentamethylchroman (4 g) in 200 ml of warm (50°) ethanol was mixed with 10 g of $AgNO_3$ in 200 ml of warm ethanol and the mixture was stirred for 15 min. The precipitated silver was removed from the yellow solution by filtration. The solution was concentrated to a small volume *in vacuo*, water was added, and the water solution was extracted with petroleum ether (bp 30–60°). The petroleum ether solution was washed with water and dried (Na_2SO_4). To the petroleum ether solution was added excess acetyl chloride which was removed *in vacuo* after standing overnight. The yellow crystalline product was recrystallized from benzene–petroleum ether mixtures to give 1.47 g of colorless needles (27%): mp 136–138°;

(16) S. S. Chernick, J. G. Moe, G. P. Rodnan, and K. Schwarz, *J. Biol. Chem.*, **217**, 829 (1955).

(17) L. M. Corwin and K. Schwarz, *ibid.*, **234**, 191 (1959).

(18) L. M. Corwin and K. Schwarz, *ibid.*, **235**, 3387 (1960).

(19) K. Schwarz, W. Mertz, and E. J. Simon, *Biochem. Biophys. Acta*, **32**, 484 (1959).

(20) K. Schwarz, *Vitamins Hormones*, **20**, 463 (1962).

(21) K. Schwarz, *Federation Proc.*, **24**, 58 (1965).

(22) P. Boyer, M. Rabinovitz, and E. Liebe, *J. Biol. Chem.*, **192**, 95 (1951).

(23) Melting points were determined on a Fisher-Johns block and are uncorrected. Nmr spectra were run in $CDCl_3$ at 60 Mc using Me_4Si as a reference standard

λ_{max}^{Nujol} (μ) 5.75 (C=O, acetate), 6.39 (aryl), 9.10 (COC, chroman); nmr spectrum, CH_2 (singlet, τ 5.60), CH_2 (triplet, τ 7.23), CH_3 (singlet, τ 7.70), CH_3 (singlet, τ 7.92), CH_3 (singlet, τ 8.03), CH_2 (triplet, τ 8.23), $2CH_3$ (singlet, τ 8.73).

6-Acetoxy-5-dodecylthiomethyl-2,2,7,8-tetramethylchroman (**13**).—A mixture of 6-acetoxy-5-chloromethyl-2,2,7,8-tetramethylchroman (2.0 g), 1.35 g of *n*-dodecylthiol, 1 g of KOH, 20 ml of dioxane, and 20 ml water was heated on the steam bath for 1 hr. Water was added and the mixture was extracted with ether. The ether extract was washed (H_2O), dried (Na_2SO_4), and evaporated *in vacuo*. The oily product was taken up in petroleum ether; cooling and scratching finally gave a solid (0.62 g, 20%): mp 38–40°; λ_{max}^{Nujol} (μ) 5.61 (C=O, acetate), 6.38 (aryl), 9.10 (COC, chroman); nmr spectrum, CH_2 (singlet, τ 6.51), CH_2 (triplet, τ 7.23), CH_3 (singlet, τ 7.72), CH_3 (singlet, 8.03), CH_2 (triplet, τ 8.25); 3ICH (singlet, τ 8.74).

6-Acetoxy-5-isothiocarbamidomethyl-2,2,7,8-tetramethylchroman Hydrochloride (**14**).—6-Acetoxy-5-chloromethyl-2,2,7,8-tetramethylchroman (1 g, 3.37 mmoles) and 0.28 g (3.68 mmoles) of thiourea were refluxed in alcohol for 2 hr under N_2. Most of the solvent was allowed to boil off under a stream of nitrogen and the concentrated solution was cooled in Dry Ice. Colorless crystals were deposited, washed with ether, and dried; yield 850 mg (68%); mp 232–235°; λ_{max}^{Nujol} (μ) 2.95, 2.10, 3.23 (NH), 5.64 (C=O, acetate), 6.02 (C=N), 9.20 (COC, chroman).

6-Acetoxy-5-morpholinomethyl-2,2,7,8-tetramethylchroman (**15**).—The 5-chloromethyl compound (1 g) was dissolved in an ether–alcohol–water mixture and excess morpholine was added. The mixture was allowed to stand for several days, and water was added and then extracted with ether. The ether solution was washed with water and the product was taken into dilute HCl. Addition of NaOH solution to the acidic, aqueous phase allowed the product to be extracted back into ether. The ether was evaporated and the yellow solid was recrystallized from alcohol as small colorless needles: mp 120–122°; yield 0.6 g (51%); λ_{max}^{Nujol} (μ) 5.65 (C=O, acetate), 6.30 (aryl), 9.28 (COC, chroman); nmr spectrum, $2CH_2$ (multiplet, τ 6.47), CH_2 (singlet, τ 6.74), CH_2 (triplet, τ 7.24), $2CH_2$ (multiplet, τ 7.67), CH_3 (singlet, τ 7.77), CH_3 (singlet, τ 7.94), CH_2 (triplet, τ 8.28), $2CH_3$ (singlet, τ 8.74).

6-Acetoxy-5-iodomethyl-2,2,7,8-tetramethylchroman (**16**).—The 5-chloromethyl compound (1.5 g) was refluxed overnight in acetone with excess NaI. The NaCl was removed by filtration and the solvent was evaporated to give a tan solid product. Recrystallization from acetone–water mixtures gave 1.85 g (94%) of product; mp 129–131°; λ_{max}^{Nujol} (μ) 5.75 (C=O, acetate), 6.40 (aryl), 9.18 (COC, chroman).

6-Acetoxy-5-ethylthiomethyl-2,2,7,8-tetramethylchroman (**17**).—5-Chloromethyl compound (1 g) was treated with excess ethyl mercaptan in a dioxane–water–KOH mixture. The mixture was allowed to stand for 7 hr and then excess solvent was boiled off on the steam bath. The product precipitated as an orange gum upon addition of ice water. The gum was taken up in ether, washed with water, dried, and evaporated *in vacuo*. The oily product was chromatographed on a silica gel column with petroleum ether–benzene mixtures. A middle cut from the column, 0.8 g (74%), melted at 70–73°; λ_{max}^{Nujol} (μ) 5.63 (C=O, acetate), 6.30 (aryl), 9.15 (COC, chroman); nmr spectrum, CH_2 (singlet, 6.49), CH_2 (triplet, τ 7.24), CH_2 (quartet, τ 7.53), CH_3 (singlet, τ 7.74), CH_3 (singlet, τ 7.93), CH_3 (singlet, τ 8.04), CH_2 (triplet, τ 8.28), $2CH_3$ (singlet, τ 8.75), CH_2 (triplet, τ 8.79).

6-Hydroxy-5-piperidinomethyl-2,2,7,8-tetramethylchroman (**18**).—Chloromethyl compound (1 g), dissolved in an ether–alcohol–water mixture, was treated with excess piperidine and allowed to stand for several days. The mixture was diluted with cold water, extracted with ether, and washed and removed from the ether with dilute HCl. The HCl was neutralized with NaOH and the product was extracted back into ether. The ether was removed by evaporation *in vacuo* and the yellow semisolid, 0.6 g (60%), was recrystallized from a water–alcohol mixture to give a product: mp 154–157°; λ_{max}^{Nujol} (μ) 6.16 (aryl), 9.15 (COC, chroman); nmr spectrum, CH_2 (singlet, τ 6.47), CH_2 (multiplet, τ 7.50), CH_3 (singlet, τ 7.90), CH_3 (singlet, τ 7.94), $4CH_2$ (multiplet, τ 8.35 τ), $2CH_3$ (singlet, τ 8.75).

6-Hydroxy-5-dimethylaminomethyl-2,2,7,8-tetramethylchroman (**19**).—5-Chloromethyl compound (2 g), dissolved in an ether–methanol mixture, was treated with 25% aqueous dimethylamine and the reaction mixture was allowed to stand at room temperature for several days. Dilute NaOH was added, and the product was extracted into ether; the ether was washed with water and the product taken into dilute HCl. The product was extracted from the neutralized HCl with ether. Evaporation of the ether and crystallization from water–methanol mixtures gave a colorless crystalline product: 1.6 g (90%); mp 126–128°; λ_{max}^{Nujol} (μ) 6.25 (aryl), 9.25 (COC, chroman); nmr spectrum, CH_2 (singlet, τ 6.48), CH_2 (triplet, τ 7.45), $2CH_3$ (singlet, τ 7.75), CH_3 (singlet, τ 7.90), CH_3 (singlet, τ 7.92), CH_2 (triplet, τ 8.28); $2CH_3$ (singlet, τ 8.76).

5-Ethoxymethyl-6-hydroxy-2,2,7,8-tetramethylchroman (**20**).—To 2.5 g of the 5-chloromethyl compound dissolved in ethanol were added 5 g of NaOH and a small amount of water. The mixture was warmed on a steam bath for 0.5 hr and then diluted with excess cold water. The product was extracted with ether, the ether was evaporated, and the mushy material was twice recrystallized from ethanol–water mixtures as large shiny plates: 1.5 g (68%); mp 97–98°; λ_{max}^{Nujol} (μ) 2.99 (OH), 6.17 (aryl), 9.10 COC, chroman); nmr spectrum, OH (singlet, τ 2.40), CH_2 (singlet, τ 5.35), CH_2 (quartet, τ 6.45), CH_2 (triplet, τ 7.42); CH_3 (singlet, τ 7.89), CH_3 (singlet, τ 7.91), CH_2 (triplet, τ 8.27), CH_3 (triplet, τ 8.74), $2CH_3$ (singlet, τ 8.74).

6-Hydroxy-5-methoxymethyl-2,2,7,8-tetramethylchroman (**21**).—To 1 g of the 5-chloromethyl compound dissolved in methanol were added 5 g of NaOH and a small amount of water. The mixture was warmed on the steam bath for 0.5 hr and then diluted with excess cold water. The product was extracted with ether, the ether was evaporated *in vacuo*, and the yellow gum was recrystallized from methanol–water several times to give colorless crystals: 150 mg (18%); mp 70–72°; λ_{max}^{Nujol} (μ) 3.00 (OH), 9.18 (COC, chroman); nmr spectrum, CH_2 (singlet, τ 5.47), CH_3 (singlet, τ 6.69), CH_2 (triplet, τ 7.45), CH_3 (singlet, τ 7.90), CH_3 (singlet, τ 7.93), CH_2 (triplet, τ 8.33), $2CH_3$ (singlet, τ 8.75).

5-Benzoxymethyl-6-hydroxy-2,2,7,8-tetramethylchroman (**22**).—The 5-chloromethyl compound (2 g) and 750 mg of benzyl alcohol, dissolved in a dioxane–water mixture, was treated with 5 g of KOH at steam-bath temperature for 1 hr. Cold water was added to the mixture, and the product was extracted with ether. Evaporation of the ether and recrystallization of the residue from alcohol–water gave 500 mg (23%) of colorless crystals: mp 100–103°; λ_{max}^{Nujol} (μ) 2.97 (OH), 6.23 (aryl), 9.25 (COC, chroman); nmr spectrum; 5 aryl H (singlet, τ 2.85), CH_2 (singlet, τ 5.42), CH_2 (singlet, τ 5.56), CH_2 (triplet, τ 7.56), CH_3 (singlet, τ 7.88), CH_3 (singlet, τ 7.95), CH_2 (triplet, τ 8.35), $2CH_3$ (singlet, τ 8.78).

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