Studies on Antianaphylactic Agents. 4.[1] Synthesis and Structure–Activity Relationships of 3-(4-Oxo-4*H*-1-benzopyran-3)acrylic Acids, a New Series of Antiallergic Substances, and Some Related Compounds

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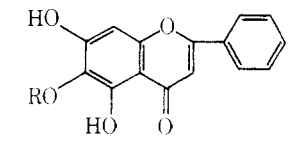
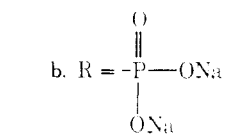
The syntheses of *trans*-3-(4-oxo-4*H*-1-benzopyran-3)acrylic acid and a number of analogs shown to be highly active in antiallergic bioassays are described. These compounds are of possible value in the treatment of asthma. The structural requirements for biological activity are discussed with reference to the type of the substituents on the chromone ring or positions of linkage of the acrylic acid on the pyrone ring.

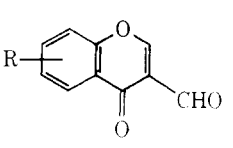
The dried radix of *Scutellaria baicalensis* Georg has been used from ancient times in Chinese medicine as a diuretic or antiallergic drug. Recently, Koda, *et al.*, showed that biacalein (**1a**), one of the flavonoids present in this radix, and its water-soluble derivative, sodium baicalein-6-phosphate **1b**, possess antianaphylactic activity in experimental animals.[2,3] The preliminary structure–activity studies on baicalein and related synthetic compounds revealed that the introduction of a carbonyl group at the 3 position of the chromone ring enhanced the antiallergic activity.[4] Starting from this observation, 4-oxo-4*H*-1-benzopyran-3-carboxaldehydes **2**[5,6] and 4-oxo-4*H*-1-benzopyran-3-carboxylic acids **3**[5] were synthesized but were found to be inactive in inhibiting the passive cutaneous anaphylaxis (PCA)[7] in the rat.



1a, R = H



b, R = $-P(=O)(ONa)_2$



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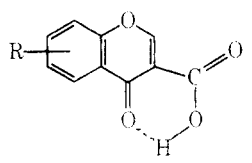

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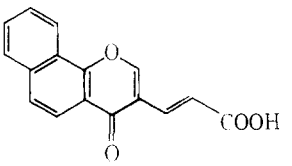

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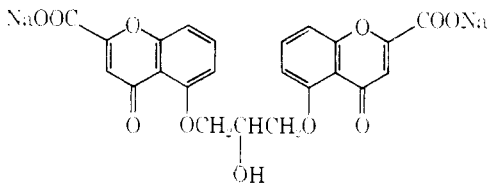
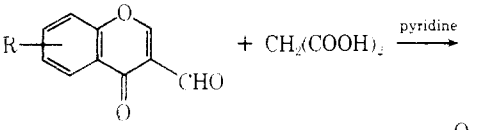


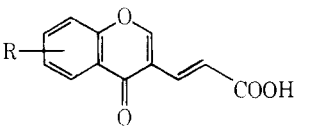
4

Since the 4-oxo-4*H*-1-benzopyran-2-carboxylic acids related to disodium cromoglycate (**4**) which exhibit high acid strength[8] are active in this test, we reasoned that an intramolecular hydrogen bond (as in structure **3**) might be responsible for the lack of activity in the 4-oxo-4*H*-1-benzopyran-3-carboxylic acids. To test this idea, a new series of chromonecarboxylic acids was synthesized based on 3-(4-oxo-4*H*-1-benzopyran-3)acrylic acid (**5a**) in which the hydrogen bond between the carboxylic acid group and the carbonyl group is sterically impossible. Both the parent compound and analog **5a**–h are active when administered

Scheme I

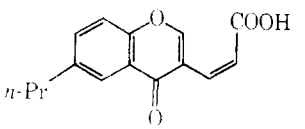


2a–p



5a–m

a, R = H
b, R = 6-Me
c, R = 6-Et
d, R = 6-*n*-Pr
e, R = 6-*i*-Pr
f, R = 6-*n*-Bu
g, R = 6-Cl
h, R = 6-OMe
i, R = 6-COOH
j, R = 6-NO_2
k, R = 6-NMe_2
l, R = 6,8-Me_2
m, R = 6,8-Br_2
n, R = 5-OAc
o, R = 7-OAc
p, R = 6,7-$(OAc)_2$



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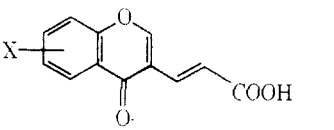


7a, X = 5-OH
b, X = 7-OH
c, X = 6,7-$(OAc)_2$
d, X = 6,7-$(OH)_2$
e, X = 7-OMe
f, X = 6-NH_2

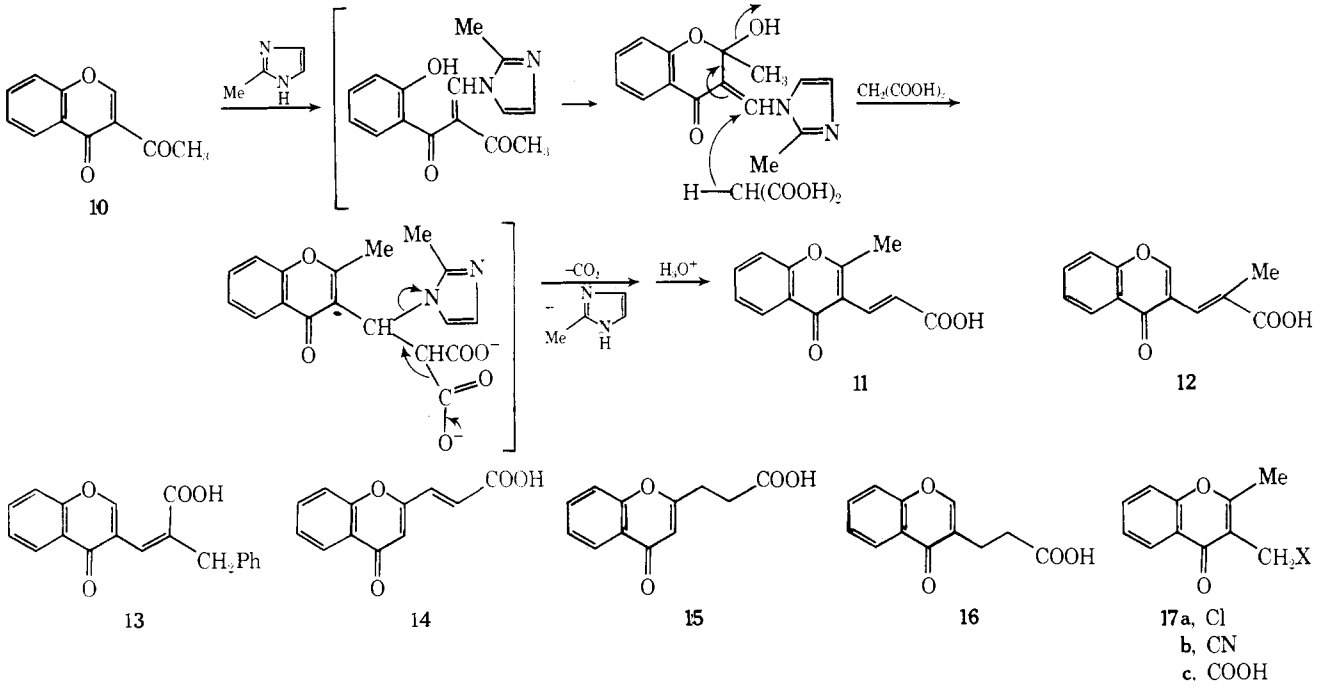
intravenously or orally. This is particularly significant because disodium cromoglycate (**4**) is inactive orally and is usually administered by inhalation. This paper describes the synthesis and some of the biological properties of these new antiallergic drugs.

Chemistry. Synthesis of 3-(4-oxo-4*H*-1-benzopyran-3)-acrylic acids was carried out by the synthetic routes shown in Schemes I and II. The major products were the trans isomers **5a**–m but in certain cases some cis isomer (*e.g.*, **6**) was also isolated. The hydroxy derivatives **7a,b** were prepared from the appropriate acetoxy starting materials **2n,o**[5,6] in one operation because water formed in the dehydration reaction produced hydrolysis of the initially formed acetate. In the synthesis of **7c** from **2p**, reacetylation of the crude product (**7d**) was necessary, because of this hydrolysis. Compound **7c** was hydrolyzed by acid to give the dihydroxy derivative **7d**.

The methoxy derivative **7e** was prepared by simultaneous esterification and methylation of *trans*-3-(7-hydroxy-4-oxo-4*H*-1-benzopyran-3)acrylic acid (**7b**) with dimethyl sulfate followed by hydrolysis of the ester. The amino derivative **7f** was prepared by catalytic hydrogenation of the 6-nitro derivative **5j**. Benzo[*h*]chromone-3-acrylic acid (**9**) was prepared by hydrolysis and decarboxylation of the diester derivative **8** which was obtained by condensing benzo[*h*]chromone-3-carboxaldehyde[9] with diethyl malonate in acetic anhydride.

As an example of substitution on the pyrone ring, 3-(2-

Scheme II



methyl-4-oxo-4*H*-1-benzopyran-3)acrylic acid (**11**) was prepared by fusing 3-acetylchromone (**10**)[10] with malonic acid in the presence of 2-methylimidazole as shown in Scheme II. α-Substituted acrylic acid derivatives **12** and **13** were prepared by condensing **2a**[5,6,10] with substituted malonic acids. Compound **14** was prepared from chromone-2-carboxaldehyde[11] by the general method shown in Scheme I. Compounds **15** and **16** were prepared by the reduction of the corresponding acrylic acids **14** and **5a**. Compound **17c** was prepared by cyanation of the chloromethyl derivative **17a**[12] followed by hydrolysis.

Structure-Activity Relationships. The biological activities were measured by the standard rat PCA tests as described in the Experimental Section and compared with disodium cromoglycate (**4**). The results are shown in Tables I and II. Compounds marked B in Table I had approximately the same activity as the standard **4**. Compounds marked A were more active, while compounds marked C and D were less active. Compounds marked E were essentially inactive.

The effects of varying substituents on the carbocyclic ring of the chromone nucleus are shown Tables I and II. Only the trans isomers were active (compare Tables I and II). Almost all the compounds shown in Table I were active. Introduction of an alkyl or an alkoxy group at C-6 or C-8 led to the greatest enhancement of activity (see compounds **5b–f** and **5l**). It is interesting that compound **5i** containing a 6-carboxylic acid group has no activity, while **5k** containing a 6-dimethylamino group has high activity. The other analogs of compound **5** in Table II had either low activity or were inactive. Attachment of an acrylic acid side chain at the 2 position of the chromone nucleus destroys the biological activity. Substitution of the α-carbon of the acrylic acid side chain or saturation of the double bond in this side chain also destroys the activity.

Experimental Section

Melting points were determined with a Micro melting point apparatus (Yanagimoto) and are uncorrected. Where analyses are indicated only by symbols of the elements, the analytical results obtained for these elements were within ±0.4% of the theoretical value. Nmr spectra were recorded on a Varian Associates T-60 instrument in either DMSO-d_6 or $CDCl_3$ with TMS as an internal standard. Ir spectra were measured as KBr disks on a Hitachi infrared spectrophotometer EPI-S2. Mass spectra were recorded on Hitachi RMU-6D or Hitachi RMS-4 instruments. All spectra were consistent with the assigned structures.

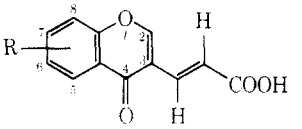
Method I. ***trans*-3-(4-Oxo-4*H*-1-benzopyran-3)acrylic Acid (5a).** A mixture of 4-oxo-4*H*-1-benzopyran-3-carboxaldehyde (**2a**,[5,6,10] 3.48 g, 20 mmol), malonic acid (2.08 g, 20 mmol), and pyridine (20 ml) was heated at 110°. After 1 hr, additional malonic acid (500 mg, 5 mmol) was added to the reaction mixture. After a further 30 min, the solvent was evaporated *in vacuo* and the resulting precipitate was recrystallized from Me_2CO to afford 3.20 g (74%) of light yellow needles, mp 253–254° dec.

***trans*-3-(6,7-Diacetoxy-4-oxo-4*H*-1-benzopyran-3)acrylic Acid (7c).** A mixture of 6,7-diacetoxy-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde (**2p**,[5,6] 2.90 g, 10 mmol), malonic acid (1.56 g, 15 mmol), and pyridine (20 ml) was heated to 100°. After 20 min, additional malonic acid (520 mg, 5 mmol) was added to the reaction mixture and heating was continued for a further 10 min. After solvent was removed from the mixture, EtOH was added to the residue to give a precipitate, which was removed by filtration. The filtrate was evaporated *in vacuo* to dryness. To the residue were added Ac_2O (5 ml) and pyridine (5 ml), and the resulting solution was allowed to stand at room temperature for 1 day. The solvent was evaporated *in vacuo* and trituration of the residue with Me_2CO gave a solid. Recrystallization of the crude solid from DMF–H_2O afforded 450 mg (13%) of yellow solid, mp 246–247° dec.

***trans*-3-(6,7-Dihydroxy-4-oxo-4*H*-1-benzopyran-3)acrylic Acid (7d).** A mixture of **7c** (100 mg), AcOH (2 ml), and concentrated HCl (0.4 ml) was heated to reflux for 2 min and diluted with H_2O (20 ml). After collecting the resulting precipitate by filtration, it was dissolved in a small amount of DMF and absorbed on silica gel. The solvent was evaporated and the treated silica gel was placed on the top of dry silica gel column which was eluted with $CHCl_3$–Me_2CO–HCO_2H (4:1:0:3). A fraction from this chromatography gave 10 mg of yellow crystals: mp >300°; mass spectrum *m/e* 248 (M^+).

***trans*-Methyl 3-(7-Methoxy-4-oxo-4*H*-1-benzopyran-3)acrylate.** To a solution of *trans*-3-(7-hydroxy-4-oxo-4*H*-1-benzopyran-3)acrylic acid (**7b**, 1.00 g, 4.31 mmol) in DMSO (30 ml) were added Me_2SO_4 (1.00 ml, 10.6 mmol) and anhydrous K_2CO_3 (2.07 g, 15 mmol). The mixture was stirred at room temperature for 2 hr. Additional Me_2SO_4 (0.5 ml, 5.3 mmol) and anhydrous K_2CO_3 (1.03 g, 7 mmol) were then added. After an additional 1-hr period, the reaction mixture was poured into ice-water (200 g). The resulting precipitate was collected and recrystallized from Me_2CO to afford 425 mg (38.1%) of light yellow scales, mp 164–168°. *Anal.* ($C_{14}H_{12}O_5$) C, H.

Table I. *trans*-3-(4-Oxo-4*H*-1-benzopyran-3)acrylic Acids



Compd	R and position	Mp, °C	Yield, %	Formula[a]	Method of prep	PCA assay[b]
4						B
5a	H	253–254 dec	74	$C_{12}H_8O_4$	I[c]	C
5b	6-Me	260–261 dec	63	$C_{13}H_{10}O_4$	I	B
5c	6-Et	230.5–232.5 dec	46	$C_{14}H_{12}O_4$	I	B
5d	6-*n*-Pr	205–207	42.9	$C_{15}H_{14}O_4$	I	B
5e	6-*i*-Pr	220–222 dec	74.8	$C_{15}H_{14}O_4$	I	A
5f	6-*n*-Bu	211–212	43	$C_{16}H_{16}O_4$	I	B
5g	6-Cl	281–282 dec	67	$C_{12}H_7ClO_4$	I	B
5h	6-OMe	261–262 dec	77	$C_{13}H_{10}O_5$	I	B
5i	6-COOH	316–317.5 dec	38	$C_{13}H_8O_6$	I	E
5j	6-NO_2	274–278 dec	67.7	$C_{12}H_7NO_6$	I	C
5k	6-NMe_2	240.5–242.5 dec	47.7	$C_{14}H_{13}NO_4$	I	B
5l	6,8-Me_2	286–288 dec	43.6	$C_{12}H_{12}O_4$	I	B
5m	6,8-Br_2	275–277 dec	33.9	$C_{12}H_6Br_2O_4$	I	C
7a	5-OH	284–285 dec	52	$C_{12}H_8O_5$	I	C
7b	7-OH	288–290 dec	48	$C_{12}H_8O_5$	I	C
7c	6,7-$(OAc)_2$	246–247 dec	13	$C_{16}H_{12}O_8$	*c*	C
7d	6,7-$(OH)_2$	>300			*c*	C
7e	7-OMe	264.5–265.5		$C_{13}H_{10}O_5$	*c*	C
7f	6-NH_2	225–227	73.9	$C_{12}H_9NO_4$	*c*	D

[a] All compounds were analyzed for C, H, and N. [b] ID_{50} mg/kg value: A, less than 1 mg/kg; B, 1–3 mg/kg; C, 4–10 mg/kg; D, 10–20 mg/kg; E, more than 20 mg/kg. [c] See Experimental Section.

Table II. Miscellaneous Compounds

Compd	Mp, °C	Yield, %	Formula[a]	Method of prep	PCA assay[b]
6	144–146	16.7	$C_{15}H_{14}O_4$	I	E
9	261–262 dec		$C_{16}H_{10}O_4$	*c*	C
11	232–234	38.4	$C_{13}H_{10}O_4$	II[c]	E
12	216–217 dec	16	$C_{13}H_{10}O_5$	II	E
13	149–150	11	$C_{15}H_{14}O_4$	II[c]	E
14	238–240	23.7	$C_{12}H_8O_4$	I	D
15	206–208		$C_{12}H_{10}O_4$	*c*	E
16	168–169		$C_{12}H_{10}O_4$	*c*	D
17c	169–173		$C_{12}H_{10}O_4$	*c*	E

[a–c] See Table I, footnotes a–c.

trans-3-(7-**Methoxy-4-oxo-4*H*-1-benzopyran-3)acrylic Acid (7e).** A suspension of *trans*-methyl 3-(7-methoxy-4-oxo-4*H*-1-benzopyran-3)acrylate (300 mg, 1.15 mmol) in concentrated HCl (20 ml) was heated at 90° for 1 hr and the reaction mixture was then diluted with H_2O (30 ml). The resulting precipitate was collected and recrystallized from DMF–Me_2CO (1:2) to afford 160 mg (56.5%) of colorless needles, mp 264.5–265.5° dec.

trans-3-(**6-Amino-4-oxo-4*H*-1-benzopyran-3)acrylic Acid (7f).** A suspension of 3-(6-nitro-4-oxo-4*H*-1-benzopyran-3)acrylic acid (**5j**) (502 mg, 1.85 mmol) and PtO_2 (15 mg) in MeOH (80 ml) was hydrogenated under atmospheric pressure at room temperature for 2 hr. After the catalyst was removed from the mixture by filtration, the solvent was evaporated *in vacuo* and the resulting residue was recrystallized from MeOH–EtOAc to afford 315 mg (73.9%) of light yellow crystals, mp 225–227°.

Ethyl 2-Ethoxycarbonyl-3-(benzo[*h*]chromon-3-yl)acrylate (8). A mixture of benzo[*h*]chromone-3-carboxaldehyde[9] (1.120 g, 5 mmol), diethyl malonate (2.5 ml), and Ac_2O (5 ml) was heated at 120° for 12 hr. The solvent was evaporated from the mixture *in vacuo* and trituration of the resulting residue with EtOH gave a solid which was recrystallized from EtOH to afford 820 mg (45%) of light yellow microcrystals, mp 140.5–142°. *Anal.* ($C_{21}H_{18}O_6$) C, H.

trans-3-(**Benzo[*h*]chromon-3-yl)acrylic Acid (9).** A mixture of 8 (810 mg, 2.2 mmol), AcOH (10 ml), and 6 *N* H_2SO_4 (10 ml) was heated at 120° for 4 hr. After cooling the mixture, a precipitate was collected by filtration. Recrystallization of the crude solid from Me_2CO afforded 150 mg (25%) of yellow prisms, mp 261–262° dec.

Method II. *trans*-3-(**2-Methyl-4-oxo-4*H*-1-benzopyran-3)acrylic Acid (11).** A mixture of 3-acetylchromone (**10**,[10] 1.13 g, 6 mmol), malonic acid (936 mg, 9 mmol), and 2-methylimidazole (1.20 g, 14.6 mmol) was fused at 120° for 4 min. The reaction mixture was cooled and was extracted with H_2O and then 5% $NaHCO_3$ aqueous solution. The combined extract was made acidic with concentrated HCl to precipitate crude **11**. Recrystallization of the crude material from Me_2CO afforded 503 mg (38.4%) of pale yellow crystals: mp 232–234° dec; ir (KBr) 3000–2500 (CO_2H), 1695 (CO_2H), 1650 cm^{-1} (CO); nmr (DMSO-d_6) δ *ca.* 8.12 (1 H, m, chromone H_5), 7.48 (1 H, d, J = 16.5 Hz, H_β of acrylic acid), 7.18 (1 H, d, J = 16.5 Hz, H_α of acrylic acid), 7.3–7.8 (3 H, m, chromone $H_{6,7,8}$), 2.63 (3 H, s, CH_3).

cis-2-**Benzyl-3-(4-oxo-4*H*-1-benzopyran-3)acrylic Acid (13).** A mixture of **2a**[5,6,10] (3.83 g, 22 mmol), benzylmalonic acid (5.24 g, 25 mmol), and 2-methylimidazole (5.5 g) was fused at 110° for 30 min. H_2O and EtOAc were then added to the cooled reaction mixture. The EtOAc layer was extracted with 5% $NaHCO_3$ aqueous solution. The combined water solution was acidified with concentrated HCl and then extracted with EtOAc. The EtOAc extract was dried with Na_2SO_4 and concentrated *in vacuo*. The residual oil was dissolved in MeOH, and after cooling this solution, crystals separated. These were collected by filtration, dissolved in $CHCl_3$, and chromatographed on silica gel (350 g) using $CHCl_3$–Me_2CO–HCO_2H (30:1:0.2) as the eluent. Two fractions containing cis and trans isomers were concentrated *in vacuo*, and the residues were recrystallized from MeOH–H_2O. Compound 13 was assigned the cis configuration on the basis of the higher field signal for the β-proton of acrylic acid in the nmr spectrum.[13] **13**: mp 149–150° dec; colorless prisms; 740 mg (11%); ir (KBr) 3000–2500 (CO_2H), 1690 (CO_2H), 1660 cm^{-1} (CO); nmr ($CDCl_3$) δ 10.53 (1 H, s, OH), 8.16 (1 H, chromone H_2), *ca.* 8.08 (1 H, dd, J = 8 and 2 Hz, chromone H_5), 7.2–7.6 (3 H, m, chromone $H_{6,7,8}$), 7.20 (5 H, s, Ph), 6.67 (1 H, m, H_β of acrylic acid), 3.75 (2 H, d, J

= 1.6 Hz, CH_2). Trans isomer: mp 206.5–207.5° dec; colorless crystals; 130 mg (1.9%); ir (KBr) 3000–2500 (CO_2H), 1670 (CO_2H), 1640 cm^{-1} (CO); nmr (DMSO-d_6) δ 8.20 (1 H, s, chromone H_2), 8.08 (1 H, dd, chromone H_5), 7.0–8.0 (4 H, m, OH and chromone $H_{6,7,8}$), 7.68 (1 H, H_β of acrylic acid), 7.20 (5 H, s, Ph), 3.87 (2 H, s, CH_2). *Anal.* ($C_{19}H_{14}O_4$) C, H.

3-(4-Oxo-4*H*-1-benzopyran-2)propionic Acid (15). A mixture of 3-(4-oxo-4*H*-1-benzopyran-2)acrylic acid (14, 500 mg), zinc powder (2.5 g), and AcOH (17 ml) was heated to mild reflux for 1 hr. After cooling the mixture, the separated salt was removed by filtration and washed with a small amount of AcOH. The combined filtrate and washings were concentrated *in vacuo* and trituration of the residue with Me_2CO gave a solid. Recrystallization of the crude solid from AcOH afforded 350 mg of colorless plates, mp 206–208°.

3-(4-Oxo-4*H*-1-benzopyran-3)propionic Acid (16). Compound **5a** (1 g, 4.63 mmol) was dissolved in AcOH (30 ml) at 90°. To this solution was added a small amount of Pd black and the mixture was hydrogenated under atmospheric pressure at 90°. After 1 equiv of hydrogen was absorbed by the mixture, the catalyst was removed by filtration. The filtrate was concentrated *in vacuo* and the residual solid was recrystallized from MeOH to afford 715 mg (71%) of colorless crystals, mp 168–169°.

2-Methyl-4-oxo-4*H*-1-benzopyran-3-acetonitrile (17b). To a solution of NaCN (2.0 g, 40.8 mmol) in dried DMSO (50 ml) maintained at 60–63° was added 2-methyl-3-chloromethylchromone (**17a**,[13] 8.00 g, 38.4 mmol) over a 50-min period. The mixture was stirred at 60–65° for 1 hr, cooled, and poured into 300 ml of ice-water. The resulting precipitate was collected by filtration and dried. Chromatography of the resulting solid on silica gel with benzene–Et_2O (2:1) as the eluent afforded 5.9 g (77%) of colorless crystals, mp 118–121°. An analytical sample was recrystallized from benzene to afford colorless needles, mp 122–124°. *Anal.* ($C_{12}H_9NO_2$) C, H, N.

2-Methyl-4-oxo-4*H*-1-benzopyran-3-acetic Acid (17c). A solution of **17b** (100 mg, 0.50 mmol) in AcOH (1 ml) and 6 *N* H_2SO_4 (1 ml) was heated to reflux for 36 hr. After cooling the mixture, the separated crystals were collected by filtration, washed with water, and dried to afford 65 mg (59%) of colorless needles, mp 169–173°.

Biological Assay. Male Sprague-Dawley rats, 7 weeks old and weighing 250 g, were used. Rat antiserum containing homocytotropic antibody was prepared according to the method of Mota.[7] In brief, the animals were sensitized by intramuscular injections of 1 mg of egg albumin in 1 ml of saline solution concomitantly with an intraperitoneal injection of 20 billion of *B. pertussis* vaccine. Serum collected from each animal 12 days after sensitization was pooled and frozen until use. The biological properties of the skin sensitizing antibody contained in these sera satisfy the requirements for a homocytotropic antibody, *i.e.*, it fixes homologous skin tissue for a long time and is heat labile. The antisera showed passive cutaneous anaphylaxis (PCA, 72-hr latent period) titers of 1:32–1:64. Homologous rat PCA response was elicited as follows. Four 0.05-ml aliquots of serum diluted fourfold with physiological saline solution were injected intradermally into the shaved dorsal skin of the rat. After 72 hr the rat was challenged with an intravenous injection of 1 ml of saline solution containing 5 mg of egg albumin and 10 mg of Evans Blue. Drugs to be tested or vehicles (saline or polyethylene glycol 400) were administered intravenously immediately before antigen challenge. Rats were sacrificed by bleeding 30 min later, and the area of the dye leakage was measured in square millimeters. The dose giving 50% inhibition (ID_{50}) for each drug was calculated graphically from the dose–inhibition relationship expressed in inhibition per cent of the bluing areas against doses on a logarithmic scale. At least three doses and three animals for each dose (*i.e.*, 12 spots) were used for obtaining the dose–inhibition relationship.

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Synthesis and Absolute Stereochemistry of 5-Alkyl-5-(3′-hydroxy-1′-methylbutyl)barbituric Acid and 5-Alkyl-5-(3′-hydroxy-1′-methylbutyl)-2-thiobarbituric Acids[1]

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5-Alkyl-5-(3′-hydroxy-1′-methylbutyl)barbituric acid (**2**) and 5-alkyl-5-(3′-hydroxy-1′-methylbutyl)-2-thiobarbituric acids (**3**) are metabolites of 5-alkyl-5-(2′-pentyl)barbituric acid and 5-alkyl-5-(2′-pentyl)-2-thiobarbituric acid, respectively. We have synthesized the four possible optical isomers of **2** and **3** by a procedure which established the absolute stereochemistry of each isomer. The two racemic pairs in each case were also prepared. The properties of these synthetic samples of **2** and **3** of known stereochemistry are compared to the properties of **2** and **3** which have been isolated from metabolism studies.

5-Ethyl-5-(2′-pentyl)barbituric acid (**1a**)† and 5-allyl-5-(2′-pentyl)barbituric acid (**1b**)† are metabolized *in vivo* to give 5-ethyl- and 5-allyl-5-(3′hydroxy-1′-methylbutyl)-barbituric acids (**2**)[1,2] as their major metabolites. In addition, 5-ethyl-5-(2′-pentyl)-2-thiobarbituric acid (**1c**)† and 5-allyl-5-(2′-pentyl)-2-thiobarbituric acid (**1d**)† give 5-ethyl- and 5-allyl-5-(3′-hydroxy-1′-methylbutyl)-2-thiobarbituric acids (**3**) as minor metabolites.[3,4] The metabo-

†The generic names of compounds **1a**, **1b**, **1c**, and **1d** are pentobarbital, secobarbital, thiopental, and thiamylal, respectively.