

**4-Phenylsulfonyltrifluoromethanesulfonanilide (34-p).** A solution of 8.2 g (0.025 mol) of **33-p**, 8.9 ml (0.025 mol) of 10% NaOH, and 5.3 g (0.025 mol) of NaIO<sub>4</sub> in 150 ml of H<sub>2</sub>O was stirred 2 hr, filtered, and acidified. The product was extracted and recrystallized to 4.3 g (50%) of **34-p**: off-white powder; mp 164–166° (i-PrOH-i-Pr<sub>2</sub>O). *Anal.* (C<sub>13</sub>H<sub>10</sub>F<sub>3</sub>NO<sub>3</sub>S<sub>2</sub>) C, H, N.

Similarly, **33-o** yielded **34-o** in 47% yield: a white solid; mp 128–130° (PhH-PE). *Anal.* C, H, N.

**3-Phenylsulfonyltrifluoromethanesulfonanilide (35-m).** 3-Nitrodiphenylsulfone was prepared from 3-nitrobenzenesulfonyl chloride (0.2 mol) and AlCl<sub>3</sub> (0.22 mol) in PhH in 55% yield: mp 77–79° (EtOH).<sup>19</sup> Catalytic reduction of 23.4 g (0.089 mol) over Raney nickel in EtOH and recrystallization yielded 12.4 g of tan aniline: mp 94.5–95° (PhH-cyclohexane). Sulfonylation and recrystallization gave 14.9 g (60%) of **35-m**: white solid; mp 106–108° (TCE). *Anal.* (C<sub>13</sub>H<sub>10</sub>F<sub>3</sub>NO<sub>4</sub>S<sub>2</sub>) C, H, N.

**4-Phenylsulfonyltrifluoromethanesulfonanilide (35-p).** A solution of 11.0 g (0.033 mol) of **33-p** and 10 ml (0.10 mol) of 30% H<sub>2</sub>O<sub>2</sub> in HOAc was heated on steam for 5 hr, quenched, and extracted. Recrystallization gave **35-p**: 7.0 g (58%) as a tan solid; mp 121–123° (TCE-cyclohexane). *Anal.* (C<sub>13</sub>H<sub>10</sub>F<sub>3</sub>NO<sub>4</sub>S<sub>2</sub>) C, H, N. Likewise, **33-o** gave **35-o**: off-white solid (56%); mp 87–89°. *Anal.* C, H, N.

**Phenyltrifluoromethanesulfonanilide (36-o,m,p).** The *o*- and *p*-aminobiphenyls and the *m*-nitrobiphenyl were obtained commercially and converted to **36-o** [white solid; mp 49–51° (C<sub>6</sub>H<sub>12</sub>)]. *Anal.* (C<sub>13</sub>H<sub>10</sub>F<sub>3</sub>NO<sub>2</sub>S) C, H, N], **36-m** [tan oil; bp 105–110° (0.1 mm). *Anal.* H; C: calcd, 51.8; found, 51.0], and **36-p** [white solid; mp 136–138° (C<sub>6</sub>H<sub>12</sub>)]. *Anal.* C, H].

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## Antiallergic Activity of 4-Hydroxy-3-nitrocoumarins

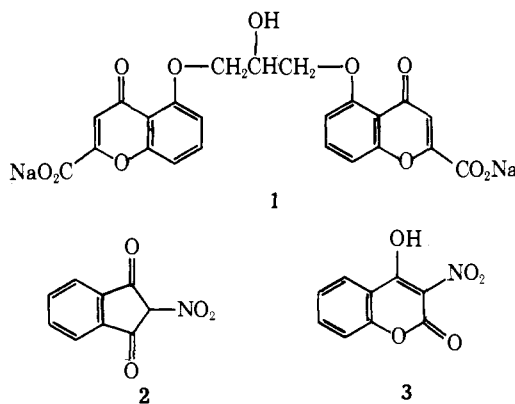
Derek R. Buckle, Barrie C. C. Cantello,\* Harry Smith, and Barbara A. Spicer

Beecham Pharmaceuticals Research Division, Brockham Park, Betchworth, Surrey, England. Received October 8, 1974

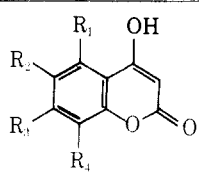
Twenty-four substituted 4-hydroxy-3-nitrocoumarins have been prepared by nitration of the corresponding 4-hydroxycoumarins. All were found to possess antiallergic activity as measured by the homocytotropic antibody-antigen induced passive cutaneous anaphylaxis reaction in the rat.

Disodium cromoglycate (1) is established as being of use in the treatment of some types of bronchial asthma.<sup>1</sup> It has been shown to inhibit the liberation of the mediators of immediate type allergic reactions initiated by reaginic antibody-antigen interactions.<sup>2</sup> It inhibits homologous passive cutaneous anaphylaxis (PCA) reactions in the rat induced by reaginic antibody and this reaction has been used as a routine screen for compounds with similar biological activity.<sup>3,4</sup> Some 2-nitroindan-1,3-diones (2) have shown greater activity than disodium cromoglycate as inhibitors of the rat PCA reaction<sup>5</sup> and as part of a continuing program on the investigation of compounds containing the 1,3-dicarbonyl-2-nitro moiety, we have prepared a series of 4-hydroxy-3-nitrocoumarins (3). We wish to report the synthesis and activities in the rat PCA test of some of these compounds.

**Chemistry.** The synthesis of 4-hydroxycoumarins (4) has been extensively documented in the literature. In this study, two general routes have been employed, as shown in Scheme I, using readily available phenols (route A) or 2-hydroxyacetophenones (route B) as starting materials.



**Route A.** Reaction of a phenol with malonic acid using phosphorus oxychloride-zinc chloride as condensing agent, as described by Bose and Shah,<sup>6</sup> gave the 4-hydroxycoumarin (4) which is readily separated from the diphenyl malonate side product (5) by alkaline extraction. Other Lewis

**Table I.** Physical Constants of 4-Hydroxycoumarins


Compd no.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	Method of prepn <sup>a</sup>		Mp, °C	Lit. mp, °C (ref) <sup>f</sup>	Formula	Analyses	Recrystn solvent
					(ref)	yield %					
8	H	H	H	CH <sub>3</sub>	A	8	231–235	223 (22)	C <sub>10</sub> H <sub>8</sub> O <sub>3</sub>	C, H	MeOH–H <sub>2</sub> O
9	H	CH <sub>3</sub>	H	H	A	29	261–264	240 (22)	C <sub>10</sub> H <sub>8</sub> O <sub>3</sub>	C, H	MeOH–EtOAc
10	H	C <sub>2</sub> H <sub>5</sub>	H	H	B (10)	63	216–218		C <sub>11</sub> H <sub>10</sub> O <sub>3</sub>	C, H	MeOH
11	H	H	CH <sub>3</sub>	CH <sub>3</sub>	A	38	237–239		C <sub>11</sub> H <sub>10</sub> O <sub>3</sub>	Crude	MeOH–H <sub>2</sub> O
12	H	CH <sub>3</sub>	H	CH <sub>3</sub>	A	33	254–260	246–247 (23)	C <sub>11</sub> H <sub>10</sub> O <sub>3</sub>	H; C <sup>b</sup>	MeOH–H <sub>2</sub> O
13	H	CH <sub>3</sub>	CH <sub>3</sub>	H	B, C	91, 86	252–253	243 (23)	C <sub>11</sub> H <sub>10</sub> O <sub>3</sub>	C, H	EtOH
14	H	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	H	B <sup>c</sup>	89	234–237		C <sub>12</sub> H <sub>12</sub> O <sub>3</sub>	C, H	MeOH
15	H	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	H	B (11)	90	213–216		C <sub>13</sub> H <sub>14</sub> O <sub>3</sub>	C, H	EtOAc
16	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	H	A	89	262–264		C <sub>12</sub> H <sub>12</sub> O <sub>3</sub>	Crude	MeOH–H <sub>2</sub> O
17	H	H	OH	H	A	22	268–276	282 <sup>d</sup> (7)	C <sub>9</sub> H <sub>6</sub> O <sub>4</sub> H <sub>2</sub> O	Crude	EtOH–H <sub>2</sub> O
18	H	H	OCH <sub>3</sub>	H	B	47	258–260	256 (8)	C <sub>10</sub> H <sub>8</sub> O <sub>4</sub>	C, H	MeOH
19	H	OCH <sub>3</sub>	H	H	B (15)	93	271–272	270 (24)	C <sub>10</sub> H <sub>8</sub> O <sub>4</sub>		MeOH
20	OCH <sub>3</sub>	H	H	H	B (16)	17	154.5–156	155 (25)	C <sub>10</sub> H <sub>8</sub> O <sub>4</sub>	C, H	EtOH
21	H	H	OC <sub>2</sub> H <sub>5</sub>	H	B <sup>c</sup>	91	267–268		C <sub>11</sub> H <sub>10</sub> O <sub>4</sub>	Crude	
22	H	H	O- <i>n</i> -C <sub>3</sub> H <sub>7</sub>	H	B <sup>c</sup>	87	216–218		C <sub>12</sub> H <sub>12</sub> O <sub>4</sub>	C, H	EtOH
23	H	PhCH <sub>2</sub> O	H	H	B (7)	67	226–228	230–231 (7)	C <sub>13</sub> H <sub>12</sub> O <sub>4</sub>	C, H	MeOH
24	H	H	OCH <sub>3</sub>	CH <sub>3</sub>	B (17)	89	261–264	260–261 (26)	C <sub>11</sub> H <sub>10</sub> O <sub>4</sub>	C, H	MeOH
25	H	C <sub>2</sub> H <sub>5</sub>	OCH <sub>3</sub>	H	B <sup>c</sup>	72	262–265		C <sub>12</sub> H <sub>12</sub> O <sub>4</sub>	C, H	MeOH
26	H	Cl	H	H	C (12)	62	266–268	264 (22)	C <sub>9</sub> H <sub>5</sub> O <sub>3</sub> Cl		MeOH
27	H	H	Cl	H	B (12)	98	251–252	248–249 (27)	C <sub>9</sub> H <sub>5</sub> O <sub>3</sub> Cl	C, H, Cl	EtOH
28	H	Br	H	H	B (14)	85	275–277	276 (22)	C <sub>9</sub> H <sub>5</sub> O <sub>3</sub> Br	H, Br; C <sup>e</sup>	
29	H	H	Br	H	B (13)	97	248–249	243 (27)	C <sub>9</sub> H <sub>5</sub> O <sub>3</sub> Br	C, H, Br	EtOH

<sup>a</sup>See Experimental Section. Numbers in parentheses are references which refer to preparation of starting material. <sup>b</sup>C: calcd, 69.46; found, 68.96. <sup>c</sup>See Experimental Section under 2-hydroxyacetophenones. <sup>d</sup>Literature melting point is for anhydrous material. <sup>e</sup>C: calcd, 44.84; found, 45.40. <sup>f</sup>Numbers in parentheses are literature references for the melting points.

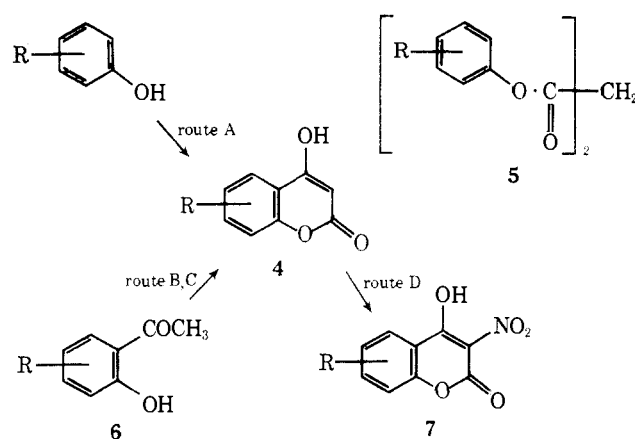
acids such as stannic chloride, aluminum chloride, and ferric chloride have been reported to be less effective in this reaction.<sup>6</sup> The coumarin 4 may also be prepared from 5 and malonic acid in the presence of phosphorus oxychloride–zinc chloride.<sup>6</sup> In general, route A has been used where the phenolic substitution allows the formation of only one isomer. Where a mixture of 4-hydroxycoumarins (4) may result, the regiospecific route B, described below, was utilized.

**Route B.** Reaction of 2-hydroxyacetophenones (6) with diethyl carbonate and sodium hydride in benzene, as described by Barker, Hermodson, and Link,<sup>7</sup> afforded 4-hydroxycoumarins (4). In general, products of both higher purity and yield were obtained by this method and it is recommended where the 2-hydroxyacetophenone (6) is readily available. The synthesis of 6,7-dimethyl-4-hydroxycoumarin (13) has occasionally failed by this route, probably due to the insolubility of the initially formed sodium salt of the 2-hydroxyacetophenone in the reaction medium. An alternative procedure, described by Boyd and Robertson,<sup>8</sup> using pulverized sodium in diethyl carbonate (see route C in the Experimental Section) obviates this problem, though the reaction may become violent.

The physical data of the 4-hydroxycoumarins (4) prepared are given in Table I.

Nitration of 4-hydroxycoumarins was effected in very high yield with fuming nitric acid in chloroform at room temperature, as described by Klosa.<sup>9</sup> 4-Hydroxy-3-nitrocoumarins (7) are highly acidic and readily form stable salts. The physical data and biological activities of these nitro derivatives (7) are summarized in Table II.

### Scheme I<sup>a</sup>

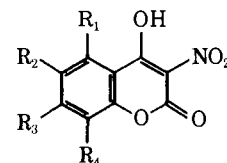


<sup>a</sup>Reagents: route A, POCl<sub>3</sub>–ZnCl<sub>2</sub>–CH<sub>2</sub>(CO<sub>2</sub>H)<sub>2</sub>, 60–75°; route B, NaH–(EtO)<sub>2</sub>CO–PhH, reflux; route C, Na–(EtO)<sub>2</sub>CO, reflux; route D, fuming HNO<sub>3</sub>–CHCl<sub>3</sub>, room temperature.

### Results and Discussion

The rat PCA test has been used to evaluate a series of 4-hydroxy-3-nitrocoumarins as potential antiallergic compounds and, in this screen, the parent compound 3 showed similar activity to that of disodium cromoglycate (1) and 2-nitroindan-1,3-dione (2). In the previously reported 2-nitroindan-1,3-dione series, substitution at positions C-5 and C-6 with carbon residues produced compounds showing highest PCA activity.<sup>5</sup> Analogous substitution in the 4-hydroxy-3-nitrocoumarins leads to derivatives of high ac-

Table II. 4-Hydroxy-3-nitrocoumarins



Compd no.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	% yield <sup>a</sup>	Mp, °C	Lit. mp, °C (ref)	Formula	Analyses	Recrystn solvent	Act. in rat PCA, ED <sub>50</sub> , <sup>b</sup> mg/kg sc at T <sub>max</sub> <sup>c</sup>	T <sub>max</sub> , <sup>c</sup> min
1	Disodium cromoglycate										6.7 (4.9–9.3, 147, 56)	10
3	H	H	H	H	95	174–175	177 (28)	C <sub>9</sub> H <sub>5</sub> NO <sub>5</sub>	C, H, N	EtOH	9.1 ( <i>h</i> , –, 35)	10
30	H	H	H	CH <sub>3</sub>	92	177–179		C <sub>10</sub> H <sub>7</sub> NO <sub>5</sub>	C, H, N	EtOH	7.3 (2.4–21.9, 83.4, 47)	10
31	H	CH <sub>3</sub>	H	H	98	171–171.5	171 (29)	C <sub>10</sub> H <sub>7</sub> NO <sub>5</sub>	C, H, N	EtOH	11.3 (7.3–17.5, 136.5, 18)	10
32	H	C <sub>2</sub> H <sub>5</sub>	H	H	96	117–119		C <sub>11</sub> H <sub>9</sub> NO <sub>5</sub>	C, H, N	PhH–ligroine	5.8 (3.6–9.1, 153.3, 18)	10
33	H	H	CH <sub>3</sub>	CH <sub>3</sub>	96	186–190		C <sub>11</sub> H <sub>9</sub> NO <sub>5</sub>	C, H, N	EtOH	3.3 (1.0–10.8, 83.1, 23)	10
34	H	CH <sub>3</sub>	H	CH <sub>3</sub>	72	169.5–170	169–171 (23)	C <sub>11</sub> H <sub>9</sub> NO <sub>5</sub>	C, H, N	EtOH	Id <sup>i</sup>	
35	H	CH <sub>3</sub>	CH <sub>3</sub>	H	97	203–204		C <sub>11</sub> H <sub>9</sub> NO <sub>5</sub>	C, H, N	EtOH	1.0 (0.3–2.7, 75.8, 42)	10
36	H	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	H	94	170–172		C <sub>12</sub> H <sub>11</sub> NO <sub>5</sub>	C, H, N	EtOH	1.3 ( <i>h</i> , –, 24)	0
37	H	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	H	97	119–120		C <sub>13</sub> H <sub>13</sub> NO <sub>5</sub>	C, H, N	EtOH	0.4 ( <i>h</i> , –, 28)	10
38	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	H	96	134–137		C <sub>12</sub> H <sub>11</sub> NO <sub>5</sub>	C, H, N		2.8 (0.8–10.9, 96.1, 18)	10
39	H	H	OH	H	70	253–256	245 (30)	C <sub>9</sub> H <sub>5</sub> NO <sub>6</sub>	H, N; C <sup>d</sup>	EtOH	5.7 (3.2–10.4, 113.5, 18)	10
40	H	H	OCH <sub>3</sub>	H	94	167–168	167 (31)	C <sub>10</sub> H <sub>7</sub> NO <sub>6</sub>	C, H, N	EtOH	1.6 (0.3–7.1, 51, 30)	10
41	H	OCH <sub>3</sub>	H	H	88	176–177	186 (32)	C <sub>10</sub> H <sub>7</sub> NO <sub>6</sub>	C, H; N <sup>e</sup>	EtOH	19.1 ( <i>h</i> , –, 17)	20
42	OCH <sub>3</sub>	H	H	H	89	175–177.5	167 (31)	C <sub>10</sub> H <sub>7</sub> NO <sub>6</sub>	C, H, N		8.3 (3.5–18.7, 119.6, 18)	10
43	H	H	OC <sub>2</sub> H <sub>5</sub>	H	95	153–154		C <sub>11</sub> H <sub>9</sub> NO <sub>6</sub>	C, H, N	EtOH	2.3 ( <i>h</i> , –, 18)	20
44	H	H	O- <i>n</i> -C <sub>3</sub> H <sub>7</sub>	H	95	151–152		C <sub>12</sub> H <sub>11</sub> NO <sub>6</sub>	C, H, N	EtOH	2.5 (0.6–11.8, 63.5, 23)	10
45	H	PhCH <sub>2</sub> O	H	H	46	262–264 <sup>f</sup>		C <sub>16</sub> H <sub>10</sub> NO <sub>6</sub> Na <sup>f</sup>	C, H, N, Na <sup>f</sup>		Id <sup>i</sup>	
46	H	H	OCH <sub>3</sub>	CH <sub>3</sub>	96	195–197	197–198.5 (32)	C <sub>11</sub> H <sub>9</sub> NO <sub>6</sub>	C, H, N	PhH	2.7 (0.8–11.4, 77.8, 18)	10
47	H	C <sub>2</sub> H <sub>5</sub>	OCH <sub>3</sub>	H	93	193–195		C <sub>12</sub> H <sub>11</sub> NO <sub>6</sub>	C, H, N	MeOH	2.6 (0.9–7.8, 68.0, 30)	0
48	H	NO <sub>2</sub>	H	H	81 <sup>e</sup>	182–183	185 (28)	C <sub>9</sub> H <sub>4</sub> N <sub>2</sub> O <sub>7</sub>	C, H, N	EtOH–PhH	17.6 (1.5–24.2, 40.3, 24)	30
49	H	Cl	H	H	91	158–159	164 (33)	C <sub>9</sub> H <sub>4</sub> NO <sub>5</sub> Cl	C, H, N, Cl		>20 ( <i>h</i> , –, 24)	45
50	H	H	Cl	H	96	174–175	178 (31)	C <sub>9</sub> H <sub>4</sub> NO <sub>5</sub> Cl	C, H, N, Cl		13.8 (4.9–39.0, 69.4, 24)	30
51	H	Br	H	H	93	161–164		C <sub>9</sub> H <sub>4</sub> NO <sub>5</sub> Br	C, H, N, Br	EtOH	22.9 (7.2–72.1, 75.6, 22)	10
52	H	H	Br	H	90	155–157	184 (31)	C <sub>9</sub> H <sub>4</sub> NO <sub>5</sub> Br	C, H, N, Br		22.9 (7.2–72.1, 75.6, 28)	10

<sup>a</sup>Prepared by nitration of the 4-hydroxycoumarin with fuming HNO<sub>3</sub> in CHCl<sub>3</sub> unless stated otherwise. <sup>b</sup>Figures in parentheses are 95% confidence limits, slope of inhibition/log dose line, number of animals used. <sup>c</sup>T<sub>max</sub> is the time between sc administration of the drug and challenge to give maximum activity. <sup>d</sup>C: calcd, 48.44; found, 47.78. <sup>e</sup>N: calcd, 5.91; found, 5.47. <sup>f</sup>Isolated

as sodium salt. <sup>g</sup>Prepared by nitration of 4-hydroxycoumarin with fuming HNO<sub>3</sub> in concentrated sulfuric acid.<sup>28</sup> <sup>h</sup>Insufficient data for calculation of confidence limits. <sup>i</sup>Insufficient data for complete analysis, ED<sub>50</sub> > 20 mg/kg.

tivity. Thus, compounds **35**, **36**, **37**, and **38**, which all possess alkyl substituents at C-6 and C-7, show good activity, though statistically significant efficacy over disodium cromoglycate was shown only by compound **35**. As with the 2-nitroindan-1,3-dione series,<sup>5</sup> other reported substitutions in the 4-hydroxy-3-nitrocoumarins tended to have little effect on the activity compared to that of the parent compound **3**.

### Experimental Section

Melting points are recorded uncorrected. The structures of all compounds were confirmed by ir and nmr spectroscopy. Where analogs are represented by elemental symbols, the results of these elements fall within  $\pm 0.4\%$  of the calculated values.

**Precursors for Synthesis of 4-Hydroxycoumarins. (i) Phenols (for Route A).** All phenols used were commercially available.

**(ii) 2-Hydroxyacetophenones.** 4,5-Dimethyl-2-hydroxy- and 2-hydroxy-4-methoxyacetophenone were commercially available. All other 2-hydroxyacetophenones were prepared as described in the literature<sup>7,10-17</sup> unless stated otherwise below.

4-Ethoxy-2-hydroxyacetophenone, mp 45-46° (lit.<sup>18</sup> mp 49-50°), and 2-hydroxy-4-*n*-propyloxyacetophenone were prepared from 2,4-dihydroxyacetophenone by the procedure of Vyas and Shah.<sup>15</sup> In a similar manner, 5-ethyl-2-hydroxy-4-methoxyacetophenone, mp 49-50° (lit.<sup>19</sup> mp 48°), was prepared from 2,4-dihydroxy-5-ethylacetophenone.<sup>20</sup> 5-Ethyl-2-hydroxy-4-methylacetophenone, mp 92.5-94° (lit.<sup>21</sup> mp 96.5-97°), was prepared by an analogous procedure to the preparation of the 4,5-diethyl homolog.

**4-Hydroxycoumarins.** 4-Hydroxycoumarin was commercially available. The physical data of the substituted 4-hydroxycoumarins prepared are shown in Table I. One example of each route to these is given below.

**Route A. 6,8-Dimethyl-4-hydroxycoumarin (12).** A mixture of 2,4-dimethylphenol (17.74 g, 0.145 mol), anhydrous ZnCl<sub>2</sub> (59.53 g, 0.437 mol), POCl<sub>3</sub> (40 ml, 0.43 mol), and malonic acid (15.05 g, 0.145 mol) was heated at 60-65° for 24 hr, cooled, decomposed with water, and filtered. The solid was extracted with 10% aqueous Na<sub>2</sub>CO<sub>3</sub> and filtered and the filtrate was acidified and filtered. Recrystallization of this solid gave the product (9.17 g, 0.0482 mol, 33% yield): mp (MeOH-H<sub>2</sub>O) 254-260° (lit.<sup>23</sup> mp 246-247°). *Anal.* C, H.

**Route B. 6-Ethyl-4-hydroxy-7-methylcoumarin (14).** 5-Ethyl-2-hydroxy-4-methylacetophenone (9.07 g, 0.0509 mol) in dry PhH (100 ml) was added to a stirred, refluxing suspension of 60% NaH in mineral oil (4.60 g, 0.115 mol) in dry PhH (100 ml) over 30 min. After a further 10 min, diethyl carbonate (12.02 g, 0.102 mol) in dry PhH (100 ml) was added over 30 min at reflux. After a further 19 hr at reflux, the mixture was cooled, poured into iced 2 N HCl (550 ml), and filtered. The solid was dissolved in 4 N NaOH, washed twice with ether, acidified, and filtered to give the product (9.20 g, 0.045 mol, 89% yield): mp 230-232°. Recrystallization from MeOH raised the melting point to 234-237°. *Anal.* C, H.

**Route C. 6,7-Dimethyl-4-hydroxycoumarin (13).** A stirred mixture of 4,5-dimethyl-2-hydroxyacetophenone (14.0 g, 0.0853 mol), pulverized Na (4.0 g, 0.174 mol), and diethyl carbonate (200 ml) was carefully heated until a vigorous reaction occurred. After the vigorous reaction had subsided, the mixture was heated under reflux for 1 hour and cooled, and excess Na was destroyed with MeOH (50 ml) and poured into water (ca. 1 l.) containing 4 N NaOH (50 ml). After washing twice with ether, the aqueous phase was carefully acidified and filtered. Recrystallization of the solid from ethanol gave the product (13.9 g, 0.0731 mol, 86% yield): mp 252-253° (lit.<sup>22</sup> mp 243°). *Anal.* C, H.

**4-Hydroxy-3-nitrocoumarins.** The physical data and biological activities of the 4-hydroxy-3-nitrocoumarins prepared are shown in Table II. All the nitrocoumarins were prepared by nitration with fuming nitric acid in chloroform<sup>9</sup> as described below, ex-

cept 3,6-dinitro-4-hydroxycoumarin (**48**) which was obtained by the procedure described by Huebner and Link.<sup>28</sup>

**6-Ethyl-4-hydroxy-7-methyl-3-nitrocoumarin (36).** Fuming nitric acid (16 ml, *d* 1.52) was added to a stirred suspension of 6-ethyl-4-hydroxy-7-methylcoumarin (3.17 g, 0.0155 mol) in CHCl<sub>3</sub> (250 ml) at room temperature over 1 hr. After a further hour, the solvent was removed *in vacuo* at room temperature and cold 5 N HCl (60 ml.) added to the residue. Filtration gave the product (3.64 g, 0.0146 mol, 94% yield): mp 170-172°. Recrystallization from EtOH failed to raise the melting point. *Anal.* C, H, N.

**Rat PCA Test.** The rat PCA test and its statistical evaluation were carried out as previously described.<sup>5</sup>

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