Synthesis of 2,2-Dimethyl-2*H*-thiochromenes, the Sulfur Analogs of Precocenes[1]

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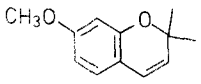
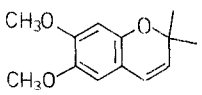
A new general synthesis of 2,2-dimethyl-2*H*-thiochromenes in good yield consists of the Michael addition of thiophenols to 3-methyl-2-butenoic acid, intramolecular cyclocondensation of the resultant 3-methyl-3-phenylthiobutanoic acids, reduction of the 2,2-dimethyl-4-oxothiochromenes thus obtained with sodium borohydride, and acid-catalyzed dehydration of the resultant 4-hydroxy-2,2-dimethylthiochromans.

Precocene I and II **(1a, b)** are antijuvenile hormones which have been isolated from the plant *Ageratum houstonianum*.[2] They represent the first insect endocrine antagonist to be discovered and appear to hold promise in the future development of insect-control agents.



1a



1b

We are particularly interested in the chemistry of insects which are plantation pests or vectors of tropical diseases. One of the most serious endemic diseases in Brazil is Chaga's disease for which the bug *Panstrongylus megistus* is the vector. It has been found[3] that when *P. megistus* was treated with precocene I, small anti-JH activity was observed. However, when precocene II was applied to the third and fourth instars of *P. megistus*, a high percentage of precocious adultoids resulted.

Several analogs of the precocenes have been synthesized[4,5,6], the most active being 7-ethoxy-6-methoxy-2,2-dimethyl-2*H*-chromene,[7] occasionally named Precocene III. However, almost all of these compounds are derived from the 2,2-dimethyl-2*H*-chromene system.

Bioisostery plays an important role in the search for new compounds of increased biological activity.[8] We report here the synthesis of various sulfur analogs of precocenes, in particular,

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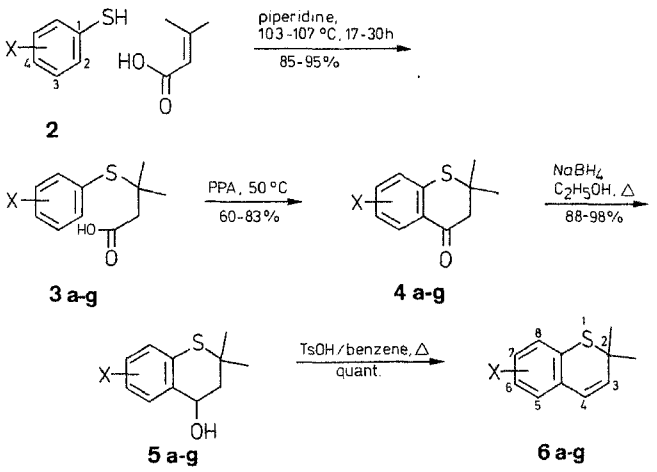
of the active compounds Precocene I, II, and III. The sulfur analogs of Precocenes I and II have already been described.[9] The synthetic route reported here appears to be general for these sulfur analogs and it represents a significant improvement in yield and ease of operation over the previous method.

The Michael addition of thiols to 2-alkenoic acids is generally performed at elevated temperatures in the presence of catalytic amounts of piperidine.[10] When we tried to prepare 3-arylthio-3-methylbutanoic acids (**3**) from benzenethiols (**2**) and 3-methyl-2-butenoic acid under the same conditions we obtained products **3** only in low yield and the reaction was reversible. We found, however, that compounds **3** can be prepared in high yields using an increased amount of piperidine at 103–107 °C. Friedel-Crafts cyclization of compounds **3** to give thiochromanones **4** is accomplished in polyphosphoric acid at 50 °C. Reduction of thiochromanones **4** with sodium borohydride affords the 4-hydroxythiochromans **5** which can be dehydrated to the 2,2-dimethyl-2*H*-thiochromenes **6** by heating with *p*-toluenesulfonic acid in benzene.

Using the above method we were able to synthesize a series of compounds **3**–**6** and to record their spectral data (spectral data of 2,2-dimethyl-2*H*-thiochromenes were not given in Lit.[9]). In particular, the present method can be used for the clean preparation of the positional isomers **6b**, **6d**, and **6e**.

The thiophenols **2** were prepared from arylmagnesium bromides and sulfur. 3-Ethoxy-4-methoxybenzenethiol (**2g**) was prepared by the following sequence: Baeyer-Villiger oxidation of 5-bromo-2-methoxybenzaldehyde (**7**) to give the phenol **8**, etherification of **8** with diethyl sulfate, and conversion of the bromocatechol diether **9** into the thiophenol **2g** via reaction of the corresponding arylmagnesium bromide with sulfur.



2

3 a-g

4 a-g

5 a-g

6 a-g

PPA = polyphosphoric acid
Ts = *p*-toluenesulphonyl

2–6	X (position in 4, 5, 6)	Position of X in 2, 3
a	H	
b	6-OCH_3	4
c	6-CH_3	4
d	8-OCH_3	2
e	7-OCH_3	3
f	6,7-di-OCH_3	3,4
g	6-OCH_3, 7-OC_2H_5	4,3

Table 1. 3-Arylthio-3-methylbutanoic Acids **3** Prepared

3	Reaction Time (h)	Yield[a] (%)	m.p. (°C)	Molecular Formula[b] or m.p. (°C) reported	IR (KBr) ν (cm^{-1})	^{1}H-NMR (CCl_4) δ (ppm)
a	19	87	71	69–71[11]	3333–2500, 2985, 1705, 1440, 1413, 1320, 1125, 950, 755, 690	1.33 (s, 6H, $2CH_3$); 2.40 (s, 2H, CH_2); 6.93–7.52 (m, $5H_{arom}$); 11.77 (s, 1H, OH)
b	17	85	67–68	$C_{12}H_{16}O_3S$ (240.25)	3436–2688, 2975, 1720, 1640, 1595, 1498, 1385, 1220, 838	1.30 (s, 6H, $2CH_3$); 2.37 (s, 2H, CH_2); 3.67 (s, 3H, OCH_3); 6.60 (d, 2H, J = 10 Hz, *m*-H, *m'*-H); 7.22 (d, 2H, J = 9 Hz, *o*-H, *o'*-H); 12.17 (s, 1H, OH)
c	18	90	78–80	$C_{12}H_{16}O_2S$ (224.25)	3413–2500, 2985, 1705, 1600, 1495, 1465, 1410, 1315, 1255, 818	1.33 (s, 6H, $2CH_3$); 2.28 (s, 3H, Ar–CH_3); 2.42 (s, 2H, CH_2); 6.88 (d, 2H, J = 8 Hz, *m*-H, *m'*-H); 7.23 (d, 2H, J = 8 Hz, *o*-H, *o'*-H); 11.68 (s, 1H, OH)
d	30	90	86–87	$C_{12}H_{16}O_3S$ (224.25)	3401–2400, 2980, 1710, 1593, 1485, 1440, 1259, 1032, 775	1.30 (s, 6H, $2CH_3$); 2.42 (s, 2H, CH_2); 3.67 (s, 3H, OCH_3); 6.43–6.80 (m, $2H_{arom}$); 6.87–7.40 (m, $2H_{arom}$); 11.03 (s, 1H, OH)
e	20	89	66–67	$C_{12}H_{16}O_3S$ (224.25)	3448–2381, 2967, 1700, 1600, 1570, 1310, 1285, 1235, 1149, 780, 695	1.35 (s, 6H, $2CH_3$); 2.45 (s, 2H, CH_2); 3.67 (s, 3H, OCH_3); 6.53–7.27 (m, $4H_{arom}$); 11.58 (s, 1H, OH)
f	18	92	79	$C_{13}H_{18}O_4S$ (270.3)	3401–2381, 2985, 1700, 1590, 1510, 1260, 1240, 1050, 1030, 880, 820	1.32 (s, 6H, $2CH_3$); 2.38 (s, 2H, CH_2); 3.70 (s, 6H, $2OCH_3$); 6.43–7.08 (m, $3H_{arom}$); 11.03 (s, 1H, OH)
g	18	95	–	$C_{14}H_{20}O_4S$ (284.3)	3500–2300, 2959, 1696, 1581, 1492, 1417, 1311, 1240, 1110, 1020, 917, 825[c]	1.07–1.57 (m, 9H, $OCH_2\underline{CH_3}$, $2CH_3$); 2.33 (s, 2H, CH_2); 3.63 (s, 3H, OCH_3); 3.82 (q, 2H, J = 7 Hz, OCH_2CH_3); 6.30–7.00 (m, $3H_{arom}$); 10.12 (br, 1H, OH)

[a] Yield of recrystallized compound, except for **3g**.
[b] The microanalyses were in satisfactory agreement with the calculated values: C ±0.37, H ±0.05.
[c] In CCl_4.

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Table 2. 2,2-Dimethyl-4-oxothiochromans **4** Prepared

4	Reaction Time and Temperature	Yield[a] (%)	m.p. (°C)	Molecular Formula[b] or m.p. (°C) reported	IR (KBr) ν (cm^{-1})	^{1}H-NMR (CCl_4) δ (ppm)
a	70°C, 40 min	70	66–68	63–65[11]	3058, 1683, 1592, 1458, 1439, 1313, 765, 759, 724	1.38 (s, 6H, $2CH_3$); 2.65 (s, 2H, CH_2); 6.68–7.35 (m, $3H_{arom}$); 7.80 (dd, 1H, J = 8 Hz, 2 Hz, 5-H)
b	70°C, 30 min	[c]	–	$C_{12}H_{14}O_2S$ (222.25)	3073, 2990, 1668, 1600, 1546, 1435, 1400, 1042, 863, 802[d]	1.37 (s, 6H, $2CH_3$); 2.67 (s, 2H, CH_2); 3.70 (s, 3H, OCH_3); 6.83–7.00 (m, 2H, 7-H, 8-H); 7.33 (d, 1H, J = 2 Hz, 5-H)
c	70°C, 40 min	80	78	$C_{12}H_{14}OS$ (206.25)	3040, 2885, 1685, 1602, 1475, 1400, 1310, 904, 820	1.38 (s, 6H, $2CH_3$); 2.28 (s, 3H, $ArCH_3$); 2.67 (s, 2H, CH_2); 6.67–7.06 (m, 2H, 7-H, 8-H); 7.67 (br. s, 1H, 5-H)
d	70°C, 30 min	60	130	$C_{12}H_{14}O_2S$ (222.25)	3065, 2980, 693, 1594, 1560, 1430, 1330, 1260, 1045, 790, 722	1.37 (s, 6H, $2CH_3$); 2.58 (s, 2H, CH_2); 3.70 (s, 3H, OCH_3); 6.83–7.17 (m, 2H, 6-H, 7-H); 7.45 (dd, 1H, J = 8 Hz, 2 Hz, 5-H)
e	50°C, 40 min	72[e]	64–65	67–68[9]	3024, 2980, 1692, 1578, 1492, 1440, 1400, 1315, 1243, 1045, 885, 842, 820	1.40 (s, 6H, $2CH_3$); 2.65 (s, 2H, CH_2); 3.75 (s, 3H, OCH_3); 6.38–6.68 (m, 2H, 6-H, 8-H); 7.85 (d, 1H, J = 10 Hz, 5-H)
f	50°C, 30 min	83	132–133	123–124[9]	3038, 2980, 1678, 1603, 1510, 1452, 1400, 1265, 1050, 885, 850, 805	1.35 (s, 6H, $2CH_3$); 2.57 (s, 2H, CH_2); 3.70 (s, 6H, OCH_3); 6.27 (s, 1H, 8-H); 7.22 (s, 1H, 5-H)
g	50°C, 30 min	81	119–120	$C_{14}H_{18}O_3S$ (266.3)	3058, 2899, 1657, 1584, 1495, 1385, 1289, 1030, 870, 781	1.43 (s, 6H, $2CH_3$); 1.46 (t, 3H, J = 7 Hz, OCH_2CH_3); 2.68 (s, 2H, CH_2); 3.86 (s, 3H, OCH_3); 4.06 (q, 2H, J = 7 Hz, OCH_2CH_3); 6.46 (s, 1H, 8-H); 7.43 (s, 1H, 5-H)

[a] Yield of isolated pure product.
[b] The microanalyses were in satisfactory agreement with the calculated values: C ±0.38, H ±0.07.
[c] Yield not determined. The product was used directly in the next reaction step.
[d] In CCl_4.
[e] The 5-methoxy isomer (*o*-acylation product) was also isolated in 21% yield. It was separated from **4e** by column chromatography.

Table 3. 2,2-Dimethyl-4-hydroxythiochromans **5** Prepared

5	Yield[a] (%)	m.p. (°C)	Molecular Formula[b]	IR (KBr) ν (cm^{-1})	^{1}H-NMR (60 MHz, CCl_4) δ (ppm)
a	[c]	–		3600–3200, 2970, 1585, 1460, 1430, 1065, 1024[d]	1.30 (s, 6H, $2CH_3$); 1.57–2.22 (m, 2H, CH_2); 3.13 (br., 1H, OH); 4.48 (dd, 1H, J = 9 Hz, 6 Hz, CH); 6.65–6.97 (m, $3H_{arom}$); 7.33–7.38 (m, $1H_{arom}$)
b	[c]	–		3600–3200, 2985, 1600, 1575, 1450, 1094, 870, 800[d]	1.30 (s, 6H, $2CH_3$); 1.55–2.23 (m, 2H, CH_2); 2.32 (br., 1H, OH); 3.62 (s, 3H, OCH_3); 4.47 (dd, 1H, J = 9 Hz, 6 Hz, CH); 6.42 (dd, 1H, J = 8 Hz, 3-Hz, 7-H); 6.67 (br, 1H, 5-H); 6.9 (m, 1H, 8-H)
c	95	55–56	$C_{12}H_{16}OS$ (208.3)	3400–3100, 2970, 1485, 1368, 1175, 1080, 1025, 812	1.30 (s, 6H, $2CH_3$); 1.60–2.08 (m, 2H, CH_2); 2.18 (br. 4H, $ArCH_3$, OH); 4.48 (dd, 1H, J = 9 Hz, 6 Hz, CH); 6.68 (br., $2H_{arom}$); 7.10 (br. 1H, 5-H)
d	98	152–154	$C_{12}H_{16}O_2S$ (224.3)	3340, 2980, 1575, 1478, 1440, 1262, 1090, 795, 742	1.33 (s, 6H, $2CH_3$); 1.62–2.52 (m, 3H, CH_2, OH); 3.67 (s, 3H, OCH_3); 4.40–4.93 (m, 1H, CH); 6.33–7.27 (m, $3H_{arom}$)
e	94	60–61	$C_{12}H_{16}O_2S$ (224.3)	3400–3100, 2970, 1605, 1500, 1455, 1250, 880, 835	1.25 (s, 6H, $2CH_3$); 1.53–2.23 (m, 2H, CH_2); 2.78 (br, 1H, OH); 3.57 (s, 3H, OCH_3); 4.40 (dd, 1H, J = 9 Hz, 6 Hz, CH); 6.17–6.50 (m, $2H_{arom}$); 7.12 (d, 1H, J = 9 Hz, 5-H)
f	90	93–94	$C_{13}H_{18}O_3S$ (254.3)	3510, 2980, 1610, 1505, 1455, 2258, 2179, 1070, 890, 804	1.30 (s, 6H, $2CH_3$); 1.57–2.28 (m, 2H, CH_2); 2.65 (br, 1H, OH); 3.67 (s, 6H, OCH_3); 4.45 (dd, 1H, J = 9 Hz, 6 Hz, CH); 6.32 (s, 1H, 8-H); 6.88 (s, 1H, 5-H)[e]
g	88	98–100	$C_{14}H_{20}O_3S$ (268.3)	3506, 2965, 1598, 1496, 1376, 1059, 875, 805	1.10–1.35 (m, 9H, $2CH_3$, OCH_2CH_3); 1.67–2.37 (m, 3H, CH_2, OH); 3.70 (s, 3H, OCH_3); 3.90 (q, 2H, J = 7 Hz, OCH_2CH_3); 4.33–4.90 (m, 1H, CH); 6.37 (s, 1H, 8-H); 6.93 (s, 1H, 5-H)[e]

[a] Yield of isolated pure product.
[b] The microanalyses were in satisfactory agreement with the calculated values: C ±0.37, H ±0.04.
[c] Yield not determined. The product was used directly in the next reaction step.
[d] In CCl_4.
[e] In $CDCl_3$.

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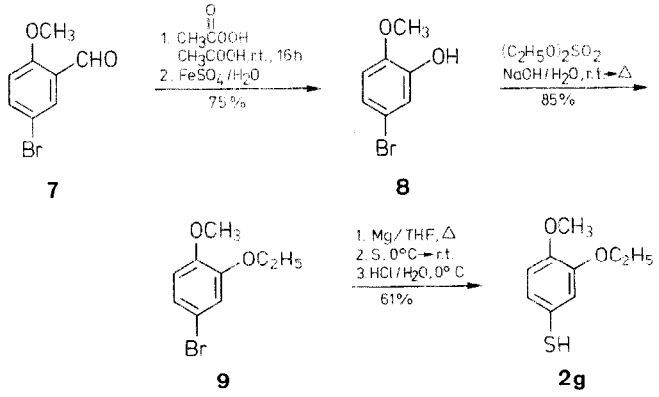
Table 4. 2,2-Dimethyl-2*H*-thiochromenes **6** Prepared

6	Overall Yield (%)[a]	m.p. (°C) or b.p. (°C)/torr	Molecular Formula[b] or Lit. Data	IR (KBr) ν(cm^{-1})	^{1}H-NMR (CCl_4) δ(ppm)
a	50	b.p. 50/0.3	$C_{11}H_{12}S$ (176.2)	3058, 3030, 2778, 1575, 1490, 1440, 1365, 1385, 770[c]	1.32 (s, 6H, $2CH_3$); 5.45 (d, 1H, J = 10 Hz, 3-H); 6.13 (d, 1H, J = 10 Hz, 4-H); 6.70–7.05 (m, $4H_{arom}$)
b	50	m.p. 39 b.p. 70/0.002	$C_{12}H_{14}OS$ (206.2)	3021, 2959, 2857, 1598, 1480, 1460, 1362, 820, 872	1.28 (s, 6H, $2CH_3$); 3.58 (s, 3H, OCH_3); 5.48 (d, 1H, J = 10 Hz, 3-H); 6.08 (d, 1H, J = 10 Hz, 4-H); 6.30–6.55 (m, 2H, 5-H, 7-H); 6.82 (d, 1H, J = 9 Hz, 8-H)
c	65	b.p. 50/0.016	$C_{12}H_{14}S$ (190.2)	3021, 2703, 1460, 1360, 1380, 1115, 804, 880	1.32 (s, 6H, $2CH_3$); 2.20 (s, 3H, $ArCH_3$); 5.50 (d, 1H, J = 10 Hz, 3-H); 6.13 (d, 1H, J = 10 Hz, 4H); 6.57–7.07 (m, $3H_{arom}$)
d	50	m.p. 50 b.p. 70/0.3	$C_{12}H_{14}OS$ (206.2)	3021, 2967, 1552, 1459, 1422, 1252, 780, 700	1.32 (s, 6H, $2CH_3$); 3.68 (s, 3H, OCH_3); 5.43 (d, 1H, J = 10 Hz, 3-H); 6.13 (d, 1H, J = 10 Hz, 4-H); 6.30–6.95 (m, $3H_{arom}$)
e	56	b.p. 42/0.02	b.p. 125–130/0.4[9]	3023, 2950, 1600, 1550, 1490, 1465, 1440, 1385, 1365, 905, 810[c]	1.32 (s, 6H, $2CH_3$); 3.67 (s, 3H, OCH_3); 5.37 (d, 1H, J = 10 Hz, 3-H); 6.13 (d, 1H, J = 10 Hz, 4-H); 6.27–6.63 (m, $2H_{arom}$); 6.80 (d, 1H, J = 8 Hz, 5-H)
f	64	m.p. 60–62 b.p. 125/0.3	b.p. 140–145/0.4[9]	3021, 2985, 1605, 1560, 1505, 1410, 1395, 1270, 870	1.30 (s, 6H, $2CH_3$); 3.60 (s, 3H, OCH_3); 3.63 (s, 3H, OCH_3); 5.33 (d, 1H, J = 10 Hz, 3-H); 6.06 (d, 1H, J = 10 Hz, 4-H); 6.37 (s, 1H, 8-H); 6.42 (s, 1H, 5-H)
g	67	m.p. 36–37 b.p. 103/0.025	$C_{14}H_{18}O_2S$ (250.3)	3023, 2941, 1596, 1501, 1462, 1353, 1346, 1261, 862	1.12–1.57 (m, 9H, $2CH_3$, OCH_2CH_3); 3.55 (s, 3H, OCH_3); 3.80 (q, 2H, J = 7 Hz, OCH_2CH_3); 5.27 (d, 1H, J = 10 Hz, 3-H); 5.98 (d, 1H, J = 10 Hz, 4-H); 6.33 (s, 1H, 8-H); 6.37 (s, 1H, 5-H)

[a] Yield of isolated pure product, based on benzenethiol **2**.
[b] The microanalyses were in good agreement with the calculated values: C ±0.28, H ±0.06.
[c] Film.

Table 5. ^{13}C-NMR-Spectral Data of Compounds **6** (in CCl_4)

6	δ(ppm)													
	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	C-9, C-10	OCH_3	$ArCH_3$	OCH_2CH_3	OCH_2CH_3
a	41.14	134.06	126.27	130.92	127.66	125.06	127.77	127.05	131.64	29.54	–	–	–	–
b	41.10	135.15	126.38	132.03	113.21	157.59	113.82	128.01	122.41	29.32	55.23	–	–	–
c	41.08	134.17	126.35	130.84	128.46	134.57	128.56	126.95	128.08	29.58	–	20.83	–	–
d	40.48	133.80	126.36	131.83	120.82	124.78	109.76	155.41	123.26	30.13	55.87	–	–	–
e	41.33	131.31	125.69	124.21	128.81	111.21	158.94	111.96	133.04	29.73	55.03	–	–	–
f	41.24	131.96	125.91	124.13	110.43	146.87	148.76	111.57	122.98	29.34	55.87	–	–	–
g	41.33	132.04	126.01	124.17	111.70	147.25	148.21	111.79	122.98	29.42	56.17	–	14.77	64.46



The biological activity of the precocene thia analogs **6** is currently under investigation for *P. megistus* (vector of Chaga's desease) and *D. saccharallis* (sugar-cane borer).

Melting points were determined with a Kofler apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrophotometer. ^{1}H-NMR spectra were recorded on Varian T-60 and Perkin-Elmer Hitachi R-24 A spectrometers at 60 MHz and on a Varian FT-80 A spectrometer at 80 MHz. ^{13}C-NMR spectra were recorded on a Varian FT-80 A spectrometer.

3-Ethoxy-4-methoxybenzenethiol (2g):

4-Bromo-2-methoxyphenol (**8**): To a stirred suspension of 5-bromo-2-methoxybenzaldehyde (**7**; 85.6 g, 0.398 mol) in acetic acid (480 ml) at 0°C under nitrogen, 30% peracetic acid (111.0 g, 0.439 mol) is added

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dropwise over 30 min at a temperature below 40°C, and stirring is continued for 16 h at room temperature. A solution of iron(II) sulfate (5.0 g) in water (100 ml) is then added, the mixture stirred for 20 min, and concentrated under reduced pressure. To the residue, water (150 ml), is added and the mixture is extracted with ethyl acetate (3 × 80 ml). The extract is dried with magnesium sulfate, the solvent evaporated, and the product purified by short-path distillation; yield: 60.6 g (75%); b.p. 55–60°C/0.25 torr; m.p. 60–64°C.

$C_7H_7BrO_2$	calc.	C 41.41	H 3.48
(203.0)	found	41.48	3.47

IR (KBr): ν = 3493, 3399, 1596, 1495, 1329, 1119, 800, 784 cm^{-1}.

^{1}H-NMR (CCl_4): δ = 3.66 (s, 3H, CH_3); 5.27 (br. s, 1H, OH); 6.25–6.90 (m, 3 H_{arom}).

1-Bromo-3-ethoxy-4-methoxybenzene (**9**): To a stirred solution of sodium hydroxide (8.0 g, 0.2 mol) in water (100 ml) is slowly added 5-bromo-2-methoxyphenol (**8**; 40.0 g, 0.197 mol). The resultant solution is cooled to 0°C and diethyl sulfate (30.8 g, 0.2 mol) is added dropwise over 20 min. Stirring is continued at room temperature for 1 h and the mixture then refluxed for 40 min. After cooling, product **9** is isolated by suction and purified by short-path distillation; yield: 38.68 g (85%); m.p. 54–56°C.

IR (KBr): ν = 3064, 2965, 1586, 1500, 1445, 1127, 927, 840, 786 cm^{-1}.

^{1}H-NMR (CCl_4): δ = 1.28 (t, 3H, J = 6 Hz, CH_3); 3.55 (s, 3H, OCH_3); 3.77 (q, 2H, J = 6 Hz, CH_2); 6.33 (d, 1H, J = 10 Hz, 5-H); 6.50–6.80 ppm (m, 2H, 2-H), 6-H).

3-Ethoxy-4-methoxybenzenethiol (**2g**): A three-necked flask equipped with reflux condenser, stirrer, and addition funnel is charged with magnesium turnings (3.31 g, 0.136 g-atom) and tetrahydrofuran (70 ml). To this is added, dropwise with stirring, a solution of 1-bromo-3-ethoxy-4-methoxybenzene (**9**; 28.67 g, 0.124 mol) in tetrahydrofuran (70 ml). The mixture is heated to boiling for 30 min, then cooled to 0°C, sulfur (3.99 g, 0.124 mol) is added over 15 min, and stirring is continued at room temperature for 2 h. The mixture is poured into crushed ice (100 g)/conc. hydrochloric acid (20 ml) and the product is extracted with ether (3 × 60 ml). The organic extract is dried with magnesium sulfate, the solvent is evaporated, and the residue is purified by short-path distillation; yield: 13.9 g (61%); b.p. 94°C/0.5 torr.

IR (film): ν = 2978, 2555, 1590, 1500, 1253, 1126, 880, 820 cm^{-1}.

^{1}H-NMR (CCl_4): δ = 1.30 (t, 3H, J = 7 Hz, CH_3); 3.08 (s, 1H, SH); 3.61 (s, 3H, OCH_3); 3.80 (q, 2H, J = 7 Hz, CH_2); 6.27–6.80 ppm (m, 3 H_{arom}).

3-(3,4-Dimethoxyphenylthio)-3-methylbutanoic Acid (3f); Typical Procedure:

A mixture of 3-methyl-2-butenoic acid (5.0 g, 50 mmol), piperidine (1.28 g, 15 mmol), and 3,4-dimethoxybenzenethiol (**2f**; 8.51 g, 50 mmol) is heated in a sealed ampoule at 103–107°C for 18 h. The ampoule is then opened and the mixture diluted with ether (80 ml), washed with 1 normal hydrochloric acid (60 ml), dried with sodium sulfate, filtered, and evaporated. Compound **3f** is thus obtained sufficiently pure for use in the following reaction step; yield: 12.5 g (93%). It can be further purified by recrystallization from benzene/petroleum ether; m.p. 79–80°C.

6,7-Dimethoxy-2,2-dimethyl-4-oxothiochroman (4f); Typical Procedure:

Polyphosphoric acid is prepared immediately before use by mixing phosphoric acid (7.7 ml, 135 mmol) and phosphorus pentoxide (19.16 g, 135 mmol) with vigorous stirring at 110°C under nitrogen. The mixture is maintained at 110°C for 40 min, then cooled to 50°C, 3-(3,4-dimethoxyphenylthio)-3-methylbutanoic acid (**3f**; 4.5 g, 16.65 mmol) is added, and stirring is continued for 30 min. The mixture is then cooled to 0°C and water (40 ml) and ether (30 ml) are added. This mixture is transferred to a separatory funnel and the layers are separated. The aqueous layer is extracted with ether (1 × 50 ml) and the combined organic phases are washed with aqueous 1 normal sodium hydroxide (50 ml). The solution is dried with magnesium sulfate, the solvent is evaporated, and the crude product is recrystallized from petroleum ether/ethyl acetate; yield: 3.5 g (83%); m.p. 123–124°C.

4-Hydroxy-6,7-dimethoxy-2,2-dimethyl-thiochroman (5f); Typical Procedure:

6,7-Dimethoxy-2,2-dimethyl-4-oxothiochroman (**4f**; 2.24 g, 8.9 mmol) is added to a stirred suspension of sodium borohydride (0.17 g, 4.45 mmol) in dry ethanol (80 ml) and this mixture is refluxed for 15 min. The solvent is removed under reduced pressure and water (60 ml) is added to the residue. This mixture is extracted with ether (2 × 60 ml), the extract is dried with magnesium sulfate, and the solvent is evaporated. The product thus obtained is pure according to GLC analysis; yield: 2.22 g (98%). It can be further purified by recrystallization from hexane; yield: 2.03 g (90%); m.p. 93–94°C.

6,7-Dimethoxy-2,2-dimethyl-2*H*-thiochromene (6f); Typical Procedure:

A solution of 4-hydroxy-6,7-dimethoxy-2,2-dimethyl-thiochroman (**5f**; 1.5 g, 5.9 mmol) and *p*-toluenesulfonic acid (60 mg) in benzene (60 ml) is refluxed for 15 min. After cooling, the mixture is washed with saturated sodium hydrogen carbonate solution (30 ml) and with water (50 ml), and dried with magnesium sulfate. The solvent is removed in vacuum and the residue is purified by bulb-to-bulb distillation; yield: 1.36 g (92%); b.p. 125°C/0.3 torr; m.p. 60–62°C.

The authors thank FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo) for the financial support of this work (grant 82/1816-4). V.C. also thanks FAPESP for a graduate fellowship.

Received: 6 November 1985
(Revised form: 16 March 1986)

(1) Preliminary results of this work were presented at the 6th Annual Congress of the Brazilian Chemistry Society (SBQ), July 1983, and in complete form at the 10th International Congress of Heterocyclic Chemistry, Waterloo, Canada, 1985.
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