Synthesis of 6-Methoxy-2,2-dimethyl-2*H*-1-benzothiopyran and 6,7-Dimethoxy-2,2-dimethyl-2*H*-1-benzothiopyran, Sulfur Analogues of Precocene I and Precocene II

F. Camps*, O. Colomina, J. Coll and A. Messeguer

Instituto de Química Bio-orgánica (C.S.I.C.), J. Girona Salgado, s/n, Barcelona-34, Spain

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Preparation of title compounds **5**, sulfur analogues of the natural insect antijuvenile hormones precocene I and II, is described. The synthetic pathway involves conversion of the appropriate thiophenol **2** into the corresponding thiochroman-4-one **4** followed by reduction and dehydration. The ^{13}C nmr data for all the above products are also reported.

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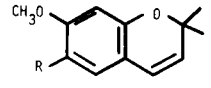
Since the isolation of precocenes I and II (**1a,b**) from the bedding plant *Ageratum houstonianum* [1], several analogues have been synthesized in different laboratories [2] to establish insect antijuvenile hormone (AJH) activity-structure relationships for potential application of these compounds in insect control.

Figure 1



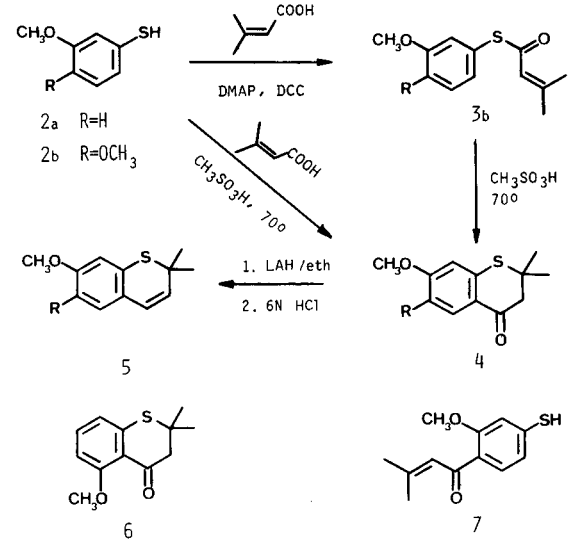
1

a: R = H Precocene I
b: R = OCH_3 Precocene II

In this context, we report herein the synthesis of thiochromenes **5**, precocene analogues with a sulfur atom substituting for the pyranyl oxygen atom in **1**. It should be pointed out that although compounds **5** had been reported by Ohta [3], this author gave no details about the preparation or physical data of these compounds.

The synthetic route chosen for preparation of **5** is depicted in Figure 2. Cyclo-condensation of 3-methoxythiophenol (**2a**) with 3-methylbut-2-enoic acid in the presence of methanesulphonic acid afforded a 6:1 mixture of thiochroman-4-ones **4** and **6** in 76% overall yield, which was separated by flash column chromatography. Both

Figure 2



compounds could be easily identified by differences in the aromatic proton absorptions in the corresponding nmr spectra: while in **4a** the H-5 and H-6 absorptions appeared as an AB system, in **6** the aromatic protons exhibited the characteristic pattern of 2,6-disubstituted acetophenones. Finally, lithium aluminum hydride reduction of **4a** followed by dehydration in acid media, afforded the thiochromene **5a** in 77% overall yield.

Table

Carbon Chemical Shifts for Thiochroman-4-ones and Thiochromenes

Compound	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	C-9, C-10	OCH_3
4a	44.70	53.62	193.17	123.42	130.68	112.06	163.48	110.70	143.41	28.58	55.35
6	43.71	55.58	194.17	133.57	183.78	108.02	143.51	119.82	161.08	28.78	55.95
4b	44.88	53.40	193.21	122.87	110.07	146.94	153.88	108.90	134.92	28.39	55.86
5a	41.49	131.49	125.82	124.40	128.93	111.40	159.11	112.12	133.19	29.87	55.24
5b	41.26	132.03	125.90	124.18 (a)	110.43	146.96	148.85	111.57	123.04 (a)	29.36	56.01

(a) These assignments can be reversed.

It is worthy of note that the regioselectivity of the cyclization step in the present case was lower than that observed starting from 3-methoxyphenol, where we could not detect the formation of the oxygenated analogue of **6** under the same reaction conditions [4]. Conversely, this phenol afforded a significant amount of the corresponding *p*-acylated derivative (9%), whereas in the present case we could not find any traces of ketone **7**.

On the other hand, direct reaction of 3,4-dimethoxythiophenol (**2b**) with 3-methylbut-2-enoic acid under the above conditions gave a poor yield (*ca.* 20%) of the desired thiochroman-4-one **4b**, plausibly due to the instability of the starting thiophenol **2b**, which led to the formation of side products and also to extensive resinification. We have overcome these drawbacks by carrying out the reaction with the thioester **3b** in which the thiophenol moiety becomes protected by the acylating reagent of the ensuing Fries rearrangement. Thus, treatment of **3b** in methanesulphonic acid for 30 minutes at 70° afforded the thiochroman-4-one **4b** in 60% yield. Attempts to improve the yield modifying the temperature or the reaction time were unsuccessful. Further reduction and dehydration of **4b** under the same reaction conditions described above afforded **5b** in 75% yield.

Finally, carbon chemical shifts for thiochroman-4-ones **4a**, **4b** and **6**, and for thiochromenes **5a** and **5b** are summarized in the table. Assignments are based on multiplicity in the single-frequency off-resonance decoupled spectrum, the use of established parameters and internal consistency.

Results on the biological activity of the precocene analogues **5** are in progress and will be published elsewhere.

EXPERIMENTAL

Melting points were determined with a Kofler apparatus and are uncorrected. Boiling points refer to bulb-to-bulb distillation. The ir spectra were obtained with a Perkin-Elmer 399B instrument. The ^1H and ^{13}C nmr spectra were recorded on a Bruker WP-80-SY spectrometer operating at 80.13 MHz for ^1H and 20.15 MHz for ^{13}C in the Fourier transform mode. All chemical shifts in the table are given in ppm downfield from internal tetramethylsilane for solutions in deuteriochloroform at normal probe temperature (32°). Gas chromatography-mass spectra were determined on a Hewlett-Packard 5995B apparatus, using a column packed with 3% OV-101 on Chromosorb Q. 3-Methoxythiophenol (**2a**) and 3,4-dimethoxythiophenol (**2b**) were prepared from the corresponding xanthates [5] according to a general procedure [6].

2,3-Dihydro-7-methoxy-2,2-dimethyl-4*H*-1-benzothiopyran-4-one (**4a**).

A mixture of 1.0 g (7.1 mmoles) of **2a** and 0.71 g (7.1 mmoles) of 3-methylbut-2-enoic acid in 20 ml of methanesulphonic acid was stirred for 30 minutes at 70°. The crude reaction mixture was poured into ice-water (100 g) and extracted with diethyl ether (3 × 50 ml). The combined ethereal fractions were washed with 1*N* sodium hydroxide, brine, dried (magnesium sulphate) and evaporated to yield 1.20 g of 1:6/**6:4a** isomeric mixture (76% yield) which was separated by flash column chromatography [7]. Compound **4a** had mp 67-68° (lit [8] 60-61°); ir (carbon tetrachloride): 2950, 1670, 1590, 1240, 1090 and 730 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.44 (s, 6H, CH_3) , 2.80 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3), 6.55-6.70 (2H, ArH), 8.07 (d, J = 9.5 Hz, 1H, H-5); ms: 222 (M^+, 26), 166 (M^+-56, 100).

Anal. Calcd. for $C_{12}H_{14}O_2S$: C, 64.85; H, 6.35; S, 14.44. Found: C, 64.75; H, 6.53; S, 14.60.

Compound **6** was isolated as an oil (lit [8] mp 40°) and showed ir (carbon tetrachloride): 2985, 1675, 1585, 1570, 1460, 1430, 1265, 1165 and 730 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.44 (s, 6H, CH_3), 2.85 (s, 2H, CH_2), 3.88 (s, 3H, OCH_3), 6.55-6.85 (2H, ArH), 7.15-7.30 (1H, ArH); ms: 222 (M^+, 34); 166 (M^+-56, 100).

Anal. Calcd. for $C_{12}H_{14}O_2S$: C, 64.85; H, 6.35; S, 14.44. Found: C, 64.68; H, 6.42; S, 14.52.

S-(3,4-Dimethoxy)phenyl 3-Methylbut-2-enthioate (**3b**).

According to a general procedure [9], a mixture of 0.80 g (4.7 mmoles) of 3,4-dimethoxythiophenol (**2b**), 0.47 g (4.7 mmoles) of 3-methylbut-2-enoic acid, 0.97 g (4.7 mmoles) of *N,N'*-dicyclohexylcarbodiimide and 0.12 g (0.47 mmoles) of 4-dimethylaminopyridine in 50 ml of dichloromethane was allowed to react for 6 hours at room temperature. The *N,N'*-dicyclohexylurea was filtered off and the residue obtained after solvent removal was purified by column chromatography (silica gel, hexane:diethyl ether/2:1), affording **3b** (1.06 g, 90% yield). Compound **3b** had bp 138-141°/0.7 torr; ir (carbon tetrachloride): 2920, 2820, 1685, 1630, 1500, 1435, 1250, 1140, 1090, 1000 and 725 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.91 (d, J = 1.3 Hz, 3H, CH_3), 2.14 (d, J = 1.2 Hz, 3H, CH_3), 3.87 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.06 (br, 1H, CH=), 6.80-7.15 (3H, ArH); ^{13}C nmr (deuteriochloroform): δ 21.08 (*Z*, *C*H_3-C=), 27.08 (*E* *C*H_3-C=), 55.81 (OCH_3), 111.63 (C-5), 117.69 (C-2), 119.43 (C-1), 122.00 (CH=), 127.78 (C-6), 149.13 (C-3), 150.11 (>C=), 155.02 (C-4) and 187.83 (C=O); ms: 252 (M^+, 14), 83 (M^+-169, 100).

Anal. Calcd. for $C_{13}H_{16}O_3S$: C, 61.90; H, 6.39; S, 12.72. Found: C, 62.25; H, 6.75; S, 12.44.

2,3-Dihydro-6,7-dimethoxy-2,2-dimethyl-4*H*-1-benzothiopyran-4-one (**4b**).

A solution of the thioester **3b** (0.42 g, 1.7 mmoles) in 10 ml of methanesulphonic acid was stirred for 30 minutes at 70° under nitrogen atmosphere. After cooling, the crude reaction mixture was poured into ice-water (50 g) and extracted with diethyl ether (3 × 25 ml). The combined ethereal fractions were washed with 1*N* sodium hydroxide, brine and dried (magnesium sulphate). The residue obtained after solvent removal was purified by flash column chromatography affording 0.25 g of **4b** (60% yield). Compound **4b** had mp 123-124°; ir (carbon tetrachloride): 2980, 2830, 1660, 1590, 1490, 1460, 1380, 1260, 1210, 1035 and 860 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.45 (s, 6H, CH_3), 2.80 (s, 2H, CH_2), 3.90 (s, 6H, OCH_3), 6.63 (s, 1H, H-8), 7.59 (s, 1H, H-5); ms: 252 (M^+, 17), 196 (M^+-56, 100).

Anal. Calcd. for $C_{13}H_{16}O_3S$: C, 61.90; H, 6.39; S, 12.72. Found: C, 62.22; H, 6.20; S, 12.65.

7-Methoxy-2,2-dimethyl-2*H*-1-benzothiopyran (**5a**).

A solution of **4a** (0.60 g, 2.7 mmoles) in anhydrous diethyl ether (50 ml) was treated with lithium aluminum hydride (0.10 g, 2.7 mmoles) and stirred for 1 hour at room temperature. After the careful addition of water, the mixture was filtered; the filtrate, containing the 4-thiochromanol was vigorously stirred with 6 *N* hydrochloric acid for 1 hour at room temperature. The organic fraction was washed with sodium bicarbonate solution, brine and dried (magnesium sulphate). After solvent removal, the residue was distilled bulb-to-bulb affording 0.43 g of **5a** (77% overall yield). Compound **5a** had bp 125-130°/0.4 torr; ir (carbon tetrachloride): 3050, 2990, 2820, 1590, 1550, 1485, 1460, 1430, 1265, 1225, 1050 and 905 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.39 (s, 6H, CH_3), 3.71 (s, 3H, OCH_3), 5.56 (d, J = 10 Hz, 1H, H-3), 6.30 (d, J = 10 Hz, 1H, H-4), 6.59 (dd, J = 8 Hz, 2.5 Hz, 1H, H-6), 6.74 (d, J = 2.5 Hz, 1H, H-8), 6.98 (d, J = 8 Hz, 1H, H-5); ms: 206 (M^+, 25), 191 (M^+-15, 100).

Anal. Calcd. for $C_{12}H_{14}OS$: C, 69.89; H, 6.84; S, 15.57. Found: C, 69.61; H, 6.50; S, 15.41.

6,7-Dimethoxy-2,2-dimethyl-2*H*-1-benzothiopyran (**5b**).

From 0.50 g (2.0 mmoles) of **4b**, the procedure above described afford-

ed 0.35 g of pure **5b** (75% yield). Compound **5b** had bp 140-145°/0.4 torr; ir (carbon tetrachloride): 3050, 2990, 2820, 1595, 1495, 1460, 1260, 1210, 1160, 1150 and 855 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.40 (s, 6H, CH_3), 3.84 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 5.60 (d, J = 10 Hz, 1H, H-3), 6.31 (d, J = 10 Hz, 1H, H-4), 6.66 (s, 1H, H-8), 6.72 (s, 1H, H-5); ms: 236 (M^+, 25), 221 ($M^+ - 15$, 100).

Anal. Calcd. for $C_{13}H_{16}O_2S$: C, 66.09; H, 6.83; S, 13.59. Found: C, 66.03; H, 6.87; S, 13.88.

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