SYNTHESIS OF 2,2-DIMETHYL-4-METHOXYCHROMANS[1]

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Abstract —— 2,2-Dimethyl-4-methoxychromans have been synthesized by the reduction of 2,2-dimethyl-4-chromanones with $NaBH_4$ followed by treatment with hydrochloric acid in methanol solution.

INTRODUCTION

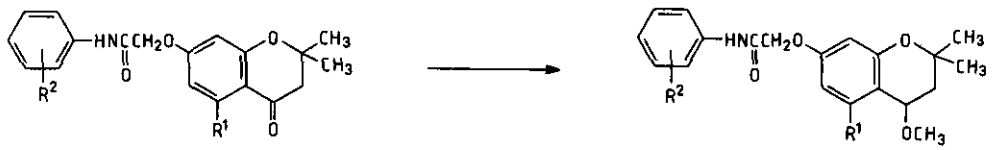
Owing to their bioactivity[2] 2,2-dimethyl-2H-chromenes became a well-known group of the benzopyran-type heterocycles during the past decade.[3] Their especially important representatives are precocene I (2,2-dimethyl-7-methoxy-2H-chromene) and precocene II (2,2-dimethyl-6,7-dimethoxy-2H-chromene) isolated from *Ageratum houstonianum*[4,5] as well as other plant sources.[6] Starting from 2,2-dimethyl-4-chromanones, various procedures have been worked out for their synthesis.[7-17] Very recently, in the course of the preparation of 2,2-dimethyl-2H-chromenes Teixidor et al.[17] isolated 2,2-dimethyl-4,6,7-trimethoxychroman in approx. 10% yield as a by-product on the reduction of 6,7-dimethoxy-2,2-dimethyl-4-chromanone with $NaBH_4$ in methanol. 2,2-Dimethyl-4-ethoxychroman was synthesized by Merten and Müller starting from salicylaldehyde.[18] To our knowledge, no other examples have hitherto been published for the formation of 2,2-dimethyl-4-alkoxychroman derivatives.

In recent years we have been engaged in the synthesis of precocene analogues as potential plant protecting agents.[1,14-16,19,20] In our experiments 2,2-dimethyl-4-chromanones were used as starting materials, and some of them were found to give 2,2-dimethyl-4-methoxychromans instead of 2,2-dimethyl-2H-chromenes on reduction with $NaBH_4$ followed by treatment with hydrochloric acid in methanol.

In the present paper our systematic investigation and the results on the synthesis of 2,2-dimethyl-4-methoxychromans are reported.

RESULTS AND DISCUSSION

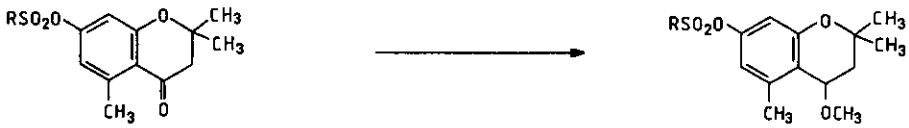
In order to enhance the "original precocene activity" or to consider the appearance of new bioactivities we prepared a series of 2,2-dimethyl-2H-chromenes[1,14-16,20] with a large variety of substituents in the aromatic ring. If 2,2-dimethyl-4-chromanones possessing a carboxamide moiety at position 7 (1-13) are allowed to react with $NaBH_4$ and then treated with hydrochloric acid in methanol, 2,2-dimethyl-4-methoxychromans (27 - 39) precipitate from the solution in good yield.



1 - 13 27 - 39

1, 27: $R^1 = R^2 = H$
2, 28: $R^1 = H$, $R^2 = 2\text{-}CH_3$
3, 29: $R^1 = H$, $R^2 = 4\text{-}CH_3$
4, 30: $R^1 = H$, $R^2 = 2\text{-}Cl$
5, 31: $R^1 = H$, $R^2 = 3\text{-}Cl$
6, 32: $R^1 = H$, $R^2 = 4\text{-}Cl$
7, 33: $R^1 = H$, $R^2 = 2\text{-}Br$
8, 34: $R^1 = H$, $R^2 = 3\text{-}Br$
9, 35: $R^1 = H$, $R^2 = 4\text{-}Br$
10, 36: $R^1 = CH_3$, $R^2 = H$
11, 37: $R^1 = CH_3$, $R^2 = 2\text{-}Cl$
12, 38: $R^1 = CH_3$, $R^2 = 3\text{-}Cl$
13, 39: $R^1 = CH_3$, $R^2 = 4\text{-}Cl$

We also investigated the reduction of alkyl- or arylsulfonyloxy-2,2-dimethyl-4-chromanones (14 - 17) with $NaBH_4$ which gave 2,2-dimethyl-4-hydroxychromans. When the dehydration of these latter substances was conducted, it was found that 4-methoxy-2,2,5-trimethylchroman derivatives (40 - 43) were formed from those chromanones having a methyl group in position 5.



14 - 17 40 - 43

14, 40: R = CH_3 16, 42: R = 4-CH_3-C_6H_4

15, 41: R = C_6H_5 17, 43: R = 4-Br-C_6H_4

Similar results were obtained with compounds possessing either benzyloxy or aminoalkoxy substituents on the aromatic ring, and 2,2-dimethyl-4-methoxychromans 44 - 46 and 47 - 52, respectively, were formed on the acidification of the reduction product in methanol.

18 - 20 44 - 46

18, 44: R^1 = R^2 = H

19, 45: R^1 = CH_3, R^2 = H

20, 46: R^1 = H, R^2 = 4-NO_2-$C_6H_4CH_2O$

21 - 26 47 - 52

21, 47: R^1 = R^2 = H, X = CH_2

22, 48: R^1 = R^2 = H, X = O

23, 49: R^1 = CH_3, R^2 = H, X = CH_2

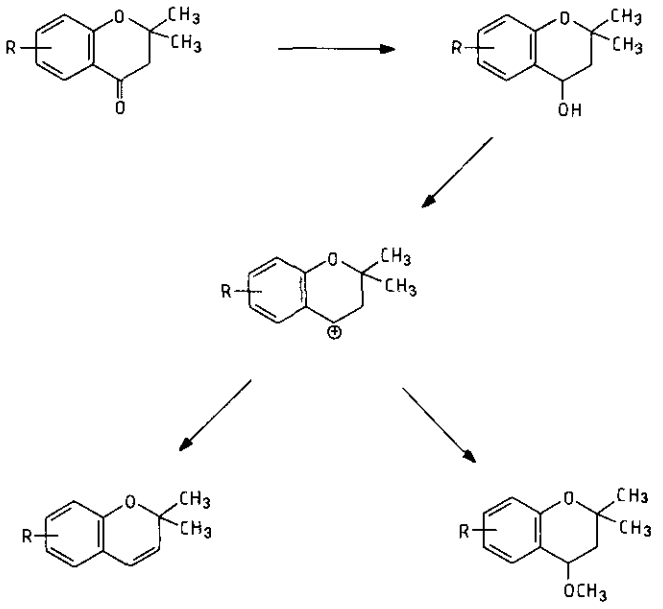
24, 50: R^1 = CH_3, R^2 = H, X = O

25, 51: R^1 = H, R^2 = CH_3, X = CH_2

26, 52: R^1 = H, R^2 = CH_3, X = O

2,2-Dimethyl-4-methoxychromans 27 - 46 are stable white crystalline materials while substances 47 - 52 are oily products which decompose quickly. Structures of all the compounds prepared were elucidated by ^{1}H-nmr spectroscopy and in the case of 27 - 46 by microanalysis as well. A singlet ^{1}H signal characteristic for the methoxy group at position 4 is found at about 3.4 ppm. Another characteristic signal in each spectrum is a triplet at approx. 4.5 ppm assigned to the hydrogen at C-4. All other proton signals could be assigned to the appropriate hydrogen atoms of the molecules.

A reasonable explanation for the formation of the 2,2-dimethyl-4-methoxychromans is that elimination and nucleophilic substitution are two concurrent reactions in acidic methanol solution leading either to 2,2-dimethyl-2H-chromenes or to 2,2-dimethyl-4-methoxychromans.



EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. ^{1}H-Nmr spectra in $CDCl_3$ (TMS as int. ref.) were recorded with a Bruker WP 200 SY spectrometer at 200 MHz. Tlc was performed on a Kieselgel 60 F_{254} (Merck) layer using hexane-acetone (7:3 v/v) as eluant.

Table 1. Physical constants and analytical data of compounds 27 - 52

Compound	mp °C	Yield %	Overall formula	Calculated C%	Calculated H%	Found C%	Found H%
27	124-125	70.5	$C_{20}H_{23}NO_4$	70.36	6.79	70.60	6.74
28	117-118	79.6	$C_{21}H_{25}NO_4$	70.96	7.09	70.93	7.15
29	142-143	84.2	$C_{21}H_{25}NO_4$	70.96	7.09	71.03	7.23
30	144-145	73.6	$C_{20}H_{22}ClNO_4$	63.91	5.90	63.89	6.01
31	63-64	58.0	$C_{20}H_{22}ClNO_4$	63.91	5.90	63.72	6.07
32	152-153	73.2	$C_{20}H_{22}ClNO_4$	63.91	5.90	63.93	5.83
33	132-133	53.1	$C_{20}H_{22}BrNO_4$	57.15	5.27	57.20	5.35
34	77-78	63.8	$C_{20}H_{22}BrNO_4$	57.15	5.27	57.17	5.26
35	154-155	72.4	$C_{20}H_{22}BrNO_4$	57.15	5.27	57.24	5.39
36	134-135	76.4	$C_{21}H_{25}NO_4$	70.96	7.09	70.91	7.13
37	159-160	75.7	$C_{21}H_{24}ClNO_4$	64.69	6.20	64.75	6.31
38	109-110	60.6	$C_{21}H_{24}ClNO_4$	64.69	6.20	64.23	6.09
39	119-120	55.5	$C_{21}H_{24}ClNO_4$	64.69	6.20	64.14	6.08
40	84-85	62.8	$C_{14}H_{20}O_5S$	56.04	6.72	56.07	6.74
41	102-103	52.4	$C_{19}H_{22}O_5S$	63.14	5.85	63.09	5.88
42	93-94	76.5	$C_{20}H_{24}O_5S$	63.98	6.17	64.01	6.29
43	94-95	78.4	$C_{19}H_{21}BrO_5S$	51.71	4.79	52.21	4.77
44	98-99	53.8	$C_{19}H_{21}NO_5$	66.47	6.12	66.53	6.03
45	113-114	65.4	$C_{20}H_{23}NO_5$	67.39	6.22	67.36	6.27
46	181-182	75.5	$C_{26}H_{22}N_2O_8$	63.27	5.10	63.37	5.25
47	oil	87.5	$C_{19}H_{29}NO_3$	-	-	-	-
48	oil	91.0	$C_{18}H_{27}NO_4$	-	-	-	-
49	oil	77.7	$C_{20}H_{31}NO_3$	-	-	-	-
50	oil	86.9	$C_{19}H_{29}NO_4$	-	-	-	-
51	oil	87.6	$C_{20}H_{31}NO_3$	-	-	-	-
52	oil	96.7	$C_{19}H_{21}NO_4$	-	-	-	-

Table 2. ^{1}H-Nmr spectral properties of compounds 27-52

Compound	δ (ppm)
27	1.42 (s, 3H), 1.52 (s, 3H), 2.08 (m, 2H), 3.52 (s, 3H), 4.48 (t, 1H, J= 6.58 Hz), 4.66 (s, 2H), 6.50-7.68 (m, 8 aromatic protons), 8.32 (s, 1H)
28	1.40 (s, 3H), 1.48 (s, 3H), 2.06 (m, 2H), 2.28 (s, 3H), 3.48 (s, 3H), 4.45 (t, 1H , J=6.57 Hz), 4.65 (s, 2H), 6.46-8.02 (m, 7 aromatic protons), 8.22 (s, 1H)
29	1.40 (s, 3H), 1.48 (s, 3H), 2.04 (m, 2H), 2.35 (s, 3H), 3.48 (s, 3H), 4.43 (t, 1H, J=6.58 Hz), 4.58 (s, 2H), 6.42-7.52 (m, 7 aromatic protons), 8.18 (s, 1H)
30	1.40 (s, 3H), 1.46 (s, 3H), 2.02 (m, 2H), 3.36 (s, 3H), 4.44 (t, 1H, J= 6.48 Hz), 4.60 (s, 2H), 6.42-8.42 (m, 7 aromatic protons), 9.02 (s, 1H)
31	1.34 (s, 3H), 1.44 (s, 3H), 2.02 (m, 2H), 3.44 (s, 3H), 4.40 (t, 1H, J= 6.52 Hz), 4.52 (s, 2H), 6.38-7.66 (m, 7 aromatic protons), 8.26 (s, 1H)
32	1.35 (s, 3H), 1.46 (s, 3H), 2.02 (m, 2H), 3.44 (s, 3H), 4.38 (t, 1H, J= 6.58 Hz), 4.54 (s, 2H), 6.40-7.52 (m, 7 aromatic protons), 8.22 (s, 1H)
33	1.36 (s, 3H), 1.46 (s, 3H), 2.04 (m, 2H), 3.42 (s, 3H), 4.42 (t, 1H, J= 6.54 Hz), 4.60 (s, 2H), 6.44-8.46 (m, 7 aromatic protons), 9.06 (s, 1H)
34	1.35 (s, 3H), 1.43 (s, 3H), 2.02 (m, 2H), 3.44 (s, 3H), 4.38 (t, 1H, J= 6.56 Hz), 4.57 (s, 2H), 6.42-7.83 (m, 7 aromatic protons), 8.22 (s, 1H)
35	1.36 (s, 3H), 1.44 (s, 3H), 2.03 (m, 2H), 3.46 (s, 3H), 4.38 (t, 1H, J= 6.58 Hz), 4.54 (s, 2H), 6.40-7.48 (m, 7 aromatic protons), 8.22 (s, 1H)
36	1.42 (s, 6H), 1.83 (dd, 1H, J=14.4, 5.12 Hz), 2.26 (dd, 1H, J=14.4, 2.92 Hz), 2.30 (s, 3H), 3.42 (s, 3H), 4.27 (dd, 1H, J=4.75, 2.56 Hz), 4.54 (s, 2H), 6.32-7.58 (m, 7 aromatic protons), 8.24 (s, 1H)
37	1.42 (s, 6H), 1.82 (dd, 1H, J=14.2, 4.75 Hz), 2.28 (dd, 1H, J=14.2, 2.56 Hz), 2.32 (s, 3H), 3.42 (s, 3H), 4.25 (dd, 1H, J=4.75, 2.56 Hz), 4.60 (s, 2H), 6.35-8.42 (m, 6 aromatic protons), 9.04 (s, 1H)
38	1.43 (s, 6H), 1.84 (dd, 1H, J=14.0, 4.84 Hz), 2.25 (dd, 1H, J=14.0, 2.58 Hz), 2.33 (s, 3H), 3.40 (s, 3H), 4.26 (dd, 1H, J=4.76, 2.52 Hz), 4.54 (s, 2H), 6.28-7.72 (m, 6 aromatic protons), 8.22 (s, 1H)
39	1.42 (s, 6H), 1.82 (dd, 1H, J=14.6, 4.78 Hz), 2.24 (dd, 1H, J=14.6, 2.59 Hz), 2.32 (s, 3H), 3.42 (s, 3H), 4.24 (dd, 1H, J=4.78, 2.57 Hz), 4.56 (s, 2H), 6.28-7.54 (m, 6 aromatic protons), 8.24 (s, 1H)
40	1.38 (s, 3H), 1.40 (s, 3H), 1.80 (dd, 1H, J=13.8, 4.75 Hz), 2.20 (dd, 1H, J=13.8, 2.56 Hz), 2.32 (s, 3H), 3.06 (s, 3H), 3.38 (s, 3H), 4.25 (dd, 1H, J=4.75, 2.56 Hz), 6.56 (d, 1H, J=2.48 Hz), 6.68 (d, 1H, J=2.48 Hz)
41	1.36 (s, 3H), 1.39 (s, 3H), 1.80 (dd, 1H, J=14.0, 4.78 Hz), 2.20 (dd, 1H, J=14.0, 2.56 Hz), 2.24 (s, 3H), 3.32 (s, 3H), 4.21 (dd, 1H, J=4.78, 2.59 Hz), 6.28-7.88 (m, 7 aromatic protons)
42	1.32 (s, 3H), 1.38 (s, 3H), 1.78 (dd, 1H, J=14.4, 2.56 Hz), 2.20 (dd, 1H, J=14.4, 2.56 Hz), 2.24 (s, 3H), 2.42 (s, 3H), 3.38 (s, 3H), 4.22 (dd, 1H, J=4.76, 2.54 Hz), 6.28-7.78 (m, 6 aromatic protons)

Table 2 continued

Compound	(ppm)
43	1.38 (s, 3H), 1.40 (s, 3H), 1.80 (dd, 1H, J=14.2, 4.75 Hz), 2.04 (dd, 1H, J=14.2, 2.56 Hz), 2.06 (s, 3H), 3.42 (s, 3H), 4.24 (dd, 1H, J= 4.75, 2.56 Hz), 6.26-7.70 (m, 6 aromatic protons)
44	1.36 (s, 3H), 1.44 (s, 3H), 2.04 (m, 2H), 3.46 (s, 3H), 4.40 (t, 1H, J= 6.58 Hz), 5.14 (s, 2H), 6.42-8.26 (m, 7 aromatic protons)
45	1.40 (s, 6H), 1.82 (dd, 1H, J=14.0, 4.75 Hz), 2.24 (dd, 1H, J=14.0, 2.56 Hz), 2.30 (s, 3H), 3.42 (s, 3H), 4.23 (t, 1H, J=6.56 Hz), 5.12 (s, 2H), 6.23-8.20 (m, 6 aromatic protons)
46	1.32 (s, 3H), 1.43 (s, 3H), 2.01 (m, 2H), 3.42 (s, 3H), 4.36 (t, 1H, J= 6.54 Hz), 5.16 (s, 4H), 6.42-8.26 (m, 10 aromatic protons)
47	1.34 (m, 2H), 1.46 (s, 6H), 1.58 (m, 4H), 2.01 (m, 2H), 2.46 (m, 4H), 2.76 (t, 2H, J=7.10 Hz), 5.45 (s, 3H), 4.06 (t, 2H, J=7.10 Hz), 4.38 (t, 1H, J=6.56 Hz), 6.34-7.30 (m, 3 aromatic protons)
48	1.36 (s, 3H), 1.42 (s, 3H), 2.02 (m, 2H), 2.56 (m, 4H), 2.80 (t, 2H, J= 6.84 Hz), 3.44 (s, 3H), 3.72 (m, 4H), 4.06 (t, 2H, J=6.84 Hz), 4.38 (t, 1H, J=6.59 Hz), 6.38-7.28 (m, 3 aromatic protons)
49	1.40 (s, 6H), 1.60 (m, 3H), 1.60 (m, 5H), 1.78 (dd, 1H, J=13.9, 2.58 Hz), 2.24 (dd, 1H, J=13.9, 2.59 Hz), 2.28 (s, 3H), 2.52 (m, 5H), 2.76 (t, 2H, J=6.26 Hz), 3.38 (s, 3H), 4.06 (t, 2H, J=6.26 Hz), 4.24 (dd, 1H, J=4.80, 2.54 Hz), 6.24 (d, 1H, J=2.42 Hz), 6.38 (d, 1H, J=2.42 Hz)
50	1.40 (s, 6H), 1.80 (dd, 1H, J=14.2, 2.56 Hz), 2.20 (dd, 1H, J=14.2, 2.58 Hz), 2.24 (s, 3H), 2.04 (m, 4H), 2.26 (t, 2H, J=6.42 Hz), 3.40 (s, 3H), 3.70 (m, 4H), 4.06 (t, 2H, J=6.42 Hz), 4.26 (dd, 1H, J=4.76, 2.52 Hz), 6.22 (d, 1H, J=2.48 Hz), 6.38 (d, 1H, J=2.48 Hz)
51	1.30 (s, 3H), 1.40 (m, 2H), 1.41 (s, 3H), 1.56 (m, 4H), 1.92 (m, 2H), 2.02 (s, 3H), 2.48 (m, 4H), 2.73 (t, 2H, J=6.26 Hz), 3.40 (s, 3H), 4.04 (t, 2H, J=6.26 Hz), 4.36 (t, 1H, J=6.18 Hz), 6.42 (d, 1H, J=5.48 Hz), 7.10 (d, 1H, J=5.48 Hz)
52	1.35 (s, 3H), 1.44 (s, 3H), 2.00 (m, 2H), 2.10 (s, 3H), 2.60 (m, 4H), 2.80 (t, 2H, J=6.16 Hz), 3.46 (s, 3H), 3.72 (m, 4H), 4.12 (t, 2H, J= 6.16 Hz), 4.42 (t, 1H, J=6.48 Hz), 6.48 (d, 1H, J=5.76 Hz), 7.18 (d, 1H, J=5.76 Hz)

General procedure for the preparation of the 2,2-dimethyl-4-methoxychromans

2,2-Dimethyl-4-chromanone (1 - 26; 10 mmol) was stirred and refluxed in methanol (200 ml), and $NaBH_4$ (50 mmol) was added in small portions. Stirring and reflux was continued until the disappearance of the starting material (approx. 2 h) according to tlc. The solution was cooled down, its pH adjusted to 2-4 with 4 N HCl and then left to stand at room temperature for 1-3 days. The mixture was diluted with water, the precipitated material filtered off, washed free of acid, and crystallized from methanol to give compounds 27 - 52 (Tables 1 and 2).

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