

Synthesis of Benzopyran Derivatives, XV [1] Preparation of Arylsulfonyloxy-2,2-dimethyl- 2*H*-chromenes

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Summary. Arylsulfonyloxy-2,2-dimethyl-2*H*-chromenes (**26–35**) have been synthesized by reduction of arylsulfonyloxy-2,2-dimethyl-4-chromanones (**6–15**) followed by dehydration.

Keywords. 2,2-Dimethyl-4-chromanones; Reduction with NaBH₄; 2,2-Dimethyl-4-hydroxychromans; Dehydration; Conformational analysis.

Synthese von Benzopyranderivaten. 15. Mitt.:

Darstellung von Arylsulfonyloxy-2,2-dimethyl-2*H*-chromenen

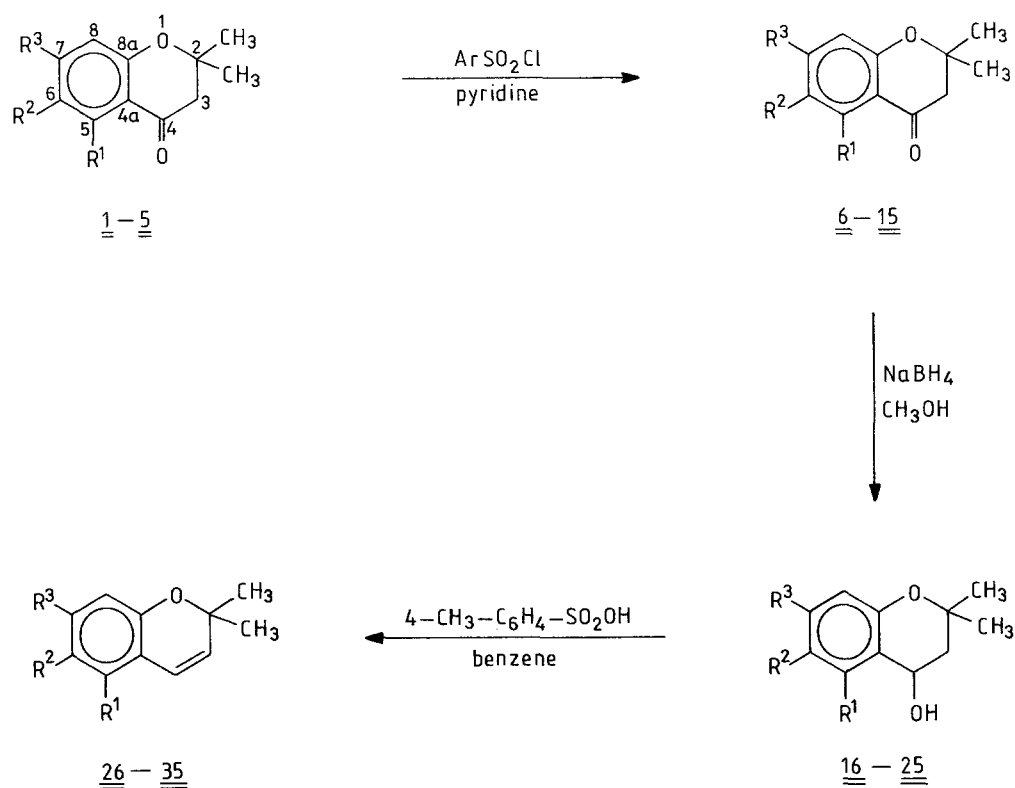
Zusammenfassung. Reduktion von Arylsulfonyloxy-2,2-dimethyl-4-chromanonen (**6–15**) und anschließende Dehydratisierung liefert Arylsulfonyloxy-2,2-dimethyl-2*H*-chromene (**26–35**).

Introduction

Precocene I (2,2-dimethyl-7-methoxy-2*H*-chromene) and precocene II (2,2-dimethyl-6,7-dimethoxy-2*H*-chromene) have been isolated from *Ageratum houstonianum* [2] and other plant sources [3]. These substances were found to induce precocious metamorphosis and, therefore, they were considered as a new generation of insecticides. In order to enhance their antijuvenile hormone activity numerous precocene analogue 2,2-dimethyl-2*H*-chromenes have been synthesized [4–15]. One part of our previous synthetic studies has been devoted to the preparation of such chromenes possessing various alkoxy groups on their aromatic ring [8–13]. The other part comprises the synthesis of 2,2-dimethyl-2*H*-chromenes having a substituted benzyloxy [8–10, 14] or carboxamide containing [1, 15] side chain in the aromatic moiety. The preparation of this large variety of precocene analogues made possible several biological and pharmacological trials. Quantitative studies of the role of the substituents of the aromatic ring in the bioactivity of these substances have also been performed [16]. In the present paper we report on the synthesis of precocene analogues with arylsulfonyloxy group(s) on the aromatic ring.

Results and Discussion

On the basis of the bioactivity data gained from our previously synthesized precocene analogues [17], it seemed expedient to prepare 2,2-dimethyl-2*H*-chromenes possessing an electron acceptor group on the aromatic ring. Arylsulfonyloxy group appeared to be convenient. As far as this kind of substituents is concerned, to our knowledge only 2,2-dimethyl-7-tosyloxy-2*H*-chromenes have hitherto been published [7]. We were now investigating the effect of substitution in the arylsulfonyloxy moiety too. For this reason benzenesulfonyloxy, *p*-bromobenzenesulfonyloxy, and



- 1: $R^1 = R^2 = \text{H}$, $R^3 = \text{OH}$
 2: $R^1 = \text{CH}_3$, $R^2 = \text{H}$, $R^3 = \text{OH}$
 3: $R^1 = \text{H}$, $R^2 = R^3 = \text{OH}$
 4: $R^1 = \text{H}$, $R^2 = \text{OH}$, $R^3 = \text{OCH}_3$
 5: $R^1 = \text{H}$, $R^2 = \text{OCH}_3$, $R^3 = \text{OH}$
 6, 16, 26: $R^1 = R^2 = \text{H}$, $R^3 = \text{C}_6\text{H}_5\text{SO}_2\text{O}$
 7, 17, 27: $R^1 = R^2 = \text{H}$, $R^3 = 4\text{-CH}_3\text{-C}_6\text{H}_4\text{SO}_2\text{O}$
 8, 18, 28: $R^1 = R^2 = \text{H}$, $R^3 = 4\text{-Br-C}_6\text{H}_4\text{SO}_2\text{O}$
 9, 19, 29: $R^1 = \text{CH}_3$, $R^2 = \text{H}$, $R^3 = \text{C}_6\text{H}_5\text{SO}_2\text{O}$
 10, 20, 30: $R^1 = \text{CH}_3$, $R^2 = \text{H}$, $R^3 = 4\text{-CH}_3\text{-C}_6\text{H}_4\text{SO}_2\text{O}$
 11, 21, 31: $R^1 = \text{CH}_3$, $R^2 = \text{H}$, $R^3 = 4\text{-Br-C}_6\text{H}_4\text{SO}_2\text{O}$
 12, 22, 32: $R^1 = \text{H}$, $R^2 = \text{C}_6\text{H}_5\text{SO}_2\text{O}$, $R^3 = \text{OCH}_3$
 13, 23, 33: $R^1 = \text{H}$, $R^2 = \text{OCH}_3$, $R^3 = \text{C}_6\text{H}_5\text{SO}_2\text{O}$
 14, 24, 34: $R^1 = \text{H}$, $R^2 = R^3 = \text{C}_6\text{H}_5\text{SO}_2\text{O}$
 15, 25, 35: $R^1 = \text{H}$, $R^2 = R^3 = 4\text{-Br-C}_6\text{H}_4\text{SO}_2\text{O}$

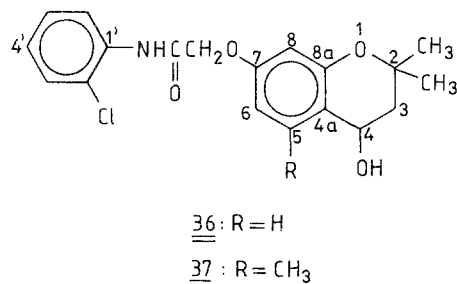
Scheme 1

p-toluenesulfonyloxy groups have been introduced. 2,2-Dimethylhydroxy-4-chromanones (**1–5**) were allowed to react with the appropriate arylsulfonyl chloride in anhydrous pyridine to afford arylsulfonyloxy-2,2-dimethyl-4-chromanones (**6–15**). Compounds **6–15** were reduced with NaBH₄ in hot methanol to obtain 2,2-dimethyl-4-hydroxychromans **16–25**.

The dehydration of substances **16–21** was attempted with 4 *N* HCl (cf. Refs. [8–15]) but the reaction was too slow. In the case of compounds **16–18** the conversion was not higher than 70% even after three months. Dehydration was distinctly accelerated by the presence of a methyl group in position 5; 2,2-dimethyl-4-hydroxychromans **19–21** gave **29–31** in approx. 80% yield within one month. But for a preparative purpose this is also too slow.

Therefore, the 2,2-dimethyl-4-hydroxychromans (**16–25**) have been dehydrated in hot benzene with *p*-toluenesulfonic acid catalyst to afford 2,2-dimethyl-2*H*-chromenes **26–35** in good yields.

To elucidate the role of the methyl group in position 5 on the dehydration detailed NMR spectroscopic investigations have been performed concerning the stereochemistry of 2,2-dimethyl-4-hydroxychromans **16–21**. Substances **36** and **37** were used as model compounds to corroborate the results obtained with **16–21**.



Scheme 2

The tetrahydropyran ring of 2,2-dimethyl-4-hydroxychromans may exist in two halfchair conformations (**I** and **II**), interconversion of which is quite fast at room temperature (Fig. 1). Although this ring inversion results in complete averaging of the axial and equatorial signals, in the case of compounds **16–21**, **36**, and **37**, owing to the presence of the OH-4, groups H_β-3/H_α-3 and Me_β-2/Me_α-2 are diastereotopic; but despite of the fast inversion different chemical shift values are observed. Characteristic ¹H chemical shift data and coupling constants are summarized in Table 1. Although all compounds studied are racemates, only the enantiomer possessing

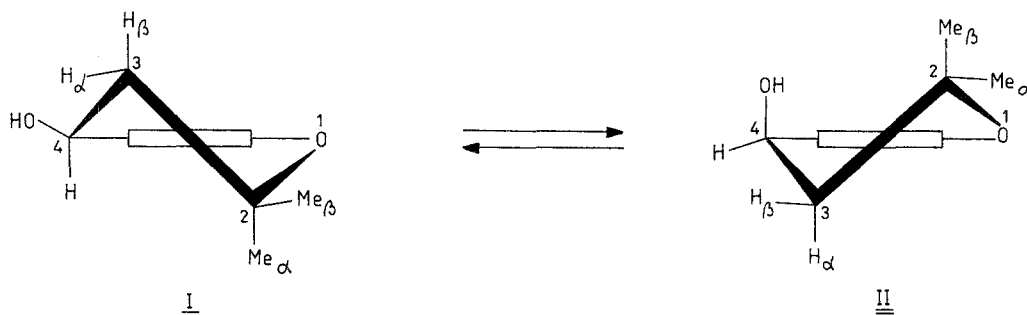


Fig. 1. Conformations I and II of the tetrahydropyran ring

Table 1. ¹H chemical shift and coupling constant data, and **I/II** conformer ratios (%) of 2,2-dimethyl-4-hydroxychromans

Compound	H _β -3	H _α -3	H-4	H-5	H-6	H-8	Me _β -2	Me _α -2	OH-4	Me-5	J(H _β -3,H-4)	J(H _α -3,H-4)	I/II
16	1.79	2.11	4.76	7.34	6.51	6.45	1.38	1.25	2.19	—	9.1	6.3	91/9
19^a	2.02	2.04	4.81	—	6.43	6.30	1.33	1.37	1.84	2.33	4.7	4.1	27/73
17^a	1.80	2.12	4.77	7.34	6.52	6.47	1.39	1.26	2.07	—	9.1	6.1	91/9
20^a	2.04	2.05	4.84	—	6.47	6.32	1.35	1.39	1.73	2.35	4.8	4.0	28/72
18	1.79	2.11	4.76	7.36	6.53	6.46	1.39	1.26	2.42	—	9.1	6.1	91/9
21	2.06	2.06	4.84	—	6.47	6.31	1.36	1.40	1.66	2.37	—	—	—
36	1.84	2.16	4.80	7.40	6.59	6.42	1.44	1.31	2.05	—	8.8	6.1	87/13
37	2.05	2.09	4.85	—	6.45	6.31	1.38	1.45	2.40	2.44	4.8	3.1	28/72

^a Measured at 500 MHz**Table 3.** ¹³C chemical shifts of 2,2-dimethyl-4-hydroxychromans

Compound	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	Me-2(α/β)	Me-5	C-1'	C-2'	C-3'	C-4'
16	76.1	42.4	63.0	123.4	128.5	113.8	149.7	110.9	154.0	25.7/28.7	—	135.4	128.3	129.1	134.1
19	74.1	42.2	61.6	120.4	140.5	115.9	149.6	109.0	154.4	26.0/28.9	19.1	135.6	128.3	129.1	134.1
17	76.1	42.0	62.7	123.4	128.6	113.7	149.6	110.7	153.9	25.6/28.7	—	132.2	128.2	129.7	145.3 (21.5)
20	74.1	42.2	61.6	120.4	140.6	115.9	149.6	109.0	154.5	26.1/29.0	19.2	132.6	128.4	129.7	145.3 (21.7)
18	76.2	42.1	62.9	123.6	128.7	113.6	149.5	110.7	154.1	25.7/28.7	—	134.3	129.7	132.9	129.5
21	74.3	42.3	61.8	120.7	140.8	115.9	149.6	109.0	154.6	26.2/29.0	19.3	134.8	129.9	132.5	129.5
36	75.9	42.7	63.2	116.8	129.1	107.4	157.6	102.9	154.5	25.9/28.8	—	—	—	—	—
37	74.0	42.4	61.1	116.2	140.7	109.3	157.0	100.7	154.7	26.1/28.6	19.2	—	—	—	—

Table 2. ^1H NOE data of 2,2-dimethyl-4-hydroxychromans

Compound	Irradiated	Measured NOE (%)
16	$Me_{\alpha}-2$	$H_{\alpha}-3$ (2.4), H-4 (3.7)
	$H_{\beta}-3$	$Me_{\beta}-2$ (1.2), $H_{\alpha}-3$ (5.8)
	H-4	$Me_{\alpha}-2$ (4.3), $H_{\alpha}-3$ (5.5), $H_{\beta}-3$ (1.5), H-5 (2.8)
19	H-4	H_2-3 (5.5), OH-4 (2.5), $Me-5$ (5.5)
	$Me-5$	H-4 (6.4), H-6 (6.7)
17	$Me_{\alpha}-2$	$H_{\beta}-3$ (0.8), $H_{\alpha}-3$ (3.8), H-4 (4.3)
	$H_{\alpha}-3$	$Me_{\alpha}-2$ (1.4), $Me_{\beta}-2$ (0.9), $H_{\beta}-3$ (11.3), H-4 (3.1)
	$H_{\beta}-3$	$Me_{\beta}-2$ (1.0), $H_{\alpha}-3$ (13.6), OH-4 (1.4), H-4 (0.7)
	H-4	$Me_{\alpha}-2$ (2.4), $H_{\alpha}-3$ (2.4), $H_{\beta}-3$ (0.6), OH-4 (3.4)
20	$Me_{\alpha}-2$	H_2-3 (5.7), H-4 (1.4)
	H-4	H_2-3 (4.9), OH-4 (3.9), $Me-5$ (5.4)
36	$Me_{\alpha}-2$	$H_{\alpha}-3$ (4.3), H-4 (6.4)
	$H_{\alpha}-3$	$Me_{\alpha}-2$ (3.4), $Me_{\beta}-2$ (3.4), $H_{\beta}-3$ (17.0), H-4 (9.4)
	$H_{\beta}-3$	$Me_{\beta}-2$ (2.1), $H_{\alpha}-3$ (18.2), H-4 (5.1)
	H-4	$Me_{\alpha}-2$ (3.0), $H_{\alpha}-3$ (2.0), H-5 (2.2)
37	$Me_{\alpha}-2$	H_2-3 (7.0), H-4 (1.3)
	H-4	H_2-3 (6.9), H-5 (8.9)

β OH-4 group is depicted. This convention is used in the course of the assignment of the ^1H and ^{13}C signals as well.

Assignment of the ^1H -NMR signals was corroborated by 1D NOE difference measurements: If the H-4 proton is defined α then $Me_{\alpha}-2$ can easily be differentiated; i.e. irradiation of H-4 results in an intensity enhance only of the signal of this methyl group. Spatial proximity necessary for such an interaction is present only in conformer **I** and, therefore, the measured NOE data prove the dominance of conformer **I** as well. In the case of compounds **16–18** and **36** irradiation of H-4 results in considerably higher NOE on $H_{\alpha}-3$ than on $H_{\beta}-3$ signal. At the same time, however, saturation of $Me_{\alpha}-2$ causes a selective intensity enhancement only on the $H_{\alpha}-3$ signal. All these allowed an unambiguous assignment of the ^1H signals and confirmed the dominance of conformer **I** in these cases. The latter was further corroborated by the $J(H_{\beta}-3, H-4)$ and $J(H_{\alpha}-3, H-4)$ coupling constants. The measured $J(H_{\beta}-3, H-4)$ coupling constants (9.1, 9.1, 9.1, and 8.8 Hz) show that conformer **II** should also be present in the conformation equilibrium. On the basis of the Karplus equation taking the electronegativity of the substituents into account [18] coupling constant $J(H_{ax}, H_{ax})$ should be 9.7 and $J(H_{eq}, H_{eq})$ 2.9 Hz.

These data made possible a semiquantitative description of the **I/II** conformation equilibrium as well (Table 1). From these observations it may be deduced that in the case of compounds without a methyl group in position 5 the conformation with an equatorial OH-4 group is preferred. Although the NOE data (Table 2) do not allow a semiquantitative description of the conformation equilibrium, they prove that conformer **II** should also be present in the equilibrium and, therefore, irradiation of H-4 should result in the intensity enhancement on the $H_{\beta}-3$ signal as well. In the case of substance **17** irradiation of $Me_{\alpha}-2$ resulted in a small but distinct (0.8%) effect on $H_{\beta}-3$ which also confirms the presence of conformer **II**.

Introduction of a methyl group into position 5 results in a characteristic change of the NMR spectra. The most apparent feature is the decrease of the difference of the chemical shifts of Me_α -2, Me_β -2 and H_α -3, H_β -3 signals, respectively. As a result methylene protons show highly coupled AB(X) spectra, moreover in the case of compound **21** a complete isochronism appears and, therefore, a simple calculation of $J(H$ -3, H -4) coupling constant is impossible.

Since in the case of compounds **19**, **20**, and **37** $J(H_\beta$ -3, H -4) and $J(H_\alpha$ -3, H -4) coupling constants are quite similar (3.1–4.8 Hz), the ratio of conformer **I** should be low. The conformer **II** should amount to 72–78% as calculated from the coupling constants. Irradiation of Me -5 resulted in intensity enhancement on the H -6 signal and this effect was used to differentiate the close H -6 and H -8 signals. From all these observations it can be deduced that, owing to the unfavourable steric interaction between Me -5 and OH_{eq} -4, the conformation equilibrium is changed, thus conformer with an axial OH group predominates.

Beside the steric effects a so-called “anomeric effect” may also play a role since a favourable energetic interaction may exist between the π -sextet of the aromatic ring and the antibonding σ^* orbital of the axial C–O moiety which was observed in the case of vincamine derivatives as well [19]. Change of the conformation equilibrium as a result of the Me -5 group makes understandable our observation that in the case of 2,2,5-trimethyl-4-hydroxychromans (**19–21** and **37**) the rate of dehydration is enhanced which may be a consequence of a stereoelectronic effect favourable for an E_2 elimination.

The above-discussed structures were further supported by the ^{13}C -NMR data summarized in Table 3.

Beside the substituent effects semiselective INEPT [20] and 2D C/H correlation measurements were used for the assignment. Starting from an unambiguous ^1H assignment of Me_α -2 and Me_β -2 signals, on the basis of 2D C/H correlation measurements chemical shift of Me_α -2 was found the lower one in each case. In compounds **16–18** and **36** this is in accordance with the axial arrangement of Me_α -2. Owing to the change of the conformation equilibrium in the case of compounds **19–21** and **37** Me_β -2 is axial, decrease of its chemical shift is, therefore, expected. Taking into account that in conformer **II** OH and Me_β -2 are 1,3-*syn* diaxial and the δ -effect appearing in such a case may result in an increase of the chemical shift [21]. The two effects compensate each other and, therefore, the chemical shift of Me_β -2 remains almost unchanged. Characteristic alterations were observed for the C-2 chemical shift of compounds **16–18** and **36** with an upfield shift of approx. 2 ppm. This effect is a consequence of the presence of different conformations. It is known that a γ -*gauche* effect induced by an OH group on a quaternary carbon atom is approx. -0.5 ppm while the γ -*anti* is about $+1.0$ ppm [22]. The measured chemical shift values support that the introduction of a Me -5 group results in the dominance of conformer **II**. The C-4 chemical shifts are different in compounds with or without a methyl group in position 5 which is a consequence of various effects present (Me -5 γ -*gauche*, Me_β -2 and Me_α -2 γ , OH_{ax} -4 and OH_{eq} -4) and, therefore, less applicable for conformational analysis.

Different substituent effects of ArSO_2O or AlkO moieties are shown in chemical shift values of C-4a, C-6, C-7, and C-8 [23] of model compounds **36** and **37**. Correct assignments of the quaternary C-7 and C-8a signals were possible from the observation that in the case of a semiselective INEPT experiment from the OCH_2

Table 4. Physical constants of compounds **6–35**

Com- pound	M.p. °C	Yield ^a %	Molecular formula ^e	Com- pound	M.p. °C	Yield ^a %	Molecular formula ^e
6	57–58	77.2	C ₁₇ H ₁₆ O ₅ S	21	135–136	81.6	C ₁₈ H ₁₉ BrO ₅ S
7	82–83 ^b	72.2	C ₁₈ H ₁₈ O ₅ S	22	118–119	69.8	C ₁₈ H ₂₀ O ₆ S
8	119–120	97.3	C ₁₇ H ₁₉ BrO ₅ S	23	141–142	90.1	C ₁₈ H ₂₀ O ₆ S
9	97–98	93.8	C ₁₈ H ₁₈ O ₅ S	24	116–117	68.3	C ₂₃ H ₂₂ O ₈ S ₂
10	120–121	69.3	C ₁₉ H ₂₀ O ₅ S	25	190–191	69.2	C ₂₃ H ₂₀ Br ₂ O ₈ S ₂
11	130–131	96.4	C ₁₈ H ₁₇ BrO ₅ S	26	95–96	85.1	C ₁₇ H ₁₆ O ₄ S
12	127–128	96.6	C ₁₈ H ₁₈ O ₆ S	27	101–102 ^d	86.2	C ₁₈ H ₁₈ O ₄ S
13	116–117	88.9	C ₁₈ H ₁₈ O ₆ S	28	68–69	84.2	C ₁₇ H ₁₅ BrO ₄ S
14	139–140	87.3	C ₂₃ H ₂₀ O ₈ S ₂	29	77–78	74.5	C ₁₈ H ₁₈ O ₄ S
15	186–187	88.2	C ₂₃ H ₁₈ Br ₂ O ₈ S ₂	30	91–92	85.1	C ₁₉ H ₂₀ O ₄ S
16	93–94	58.3	C ₁₇ H ₁₈ O ₅ S	31	96–97	83.3	C ₁₈ H ₁₇ BrO ₄ S
17	107–108 ^c	94.3	C ₁₈ H ₂₀ O ₅ S	32	94–95	65.2	C ₁₈ H ₁₈ O ₅ S
18	oil	86.4	C ₁₇ H ₁₇ BrO ₅ S	33	89–90	63.1	C ₁₈ H ₁₈ O ₅ S
19	98–99	93.4	C ₁₈ H ₂₀ O ₅ S	34	108–109	90.2	C ₂₃ H ₂₀ O ₇ S ₂
20	109–110	91.8	C ₁₉ H ₂₂ O ₅ S	35	141–142	82.2	C ₂₃ H ₁₈ Br ₂ O ₇ S ₂

^a In the case of **26–35** yields refers to *Method A*^{b–d} Lit. [7] m.p. ^b 79–80 °C, ^c 107 °C, and ^d 101–102 °C^e Elemental analyses (C, H) were in good agreement with calculated values**Table 5.** ¹H-NMR spectroscopic data of 2,2-dimethyl-2*H*-chromenes

Com- pound	δ (ppm)
26	1.34 (s, 6 H), 5.58 (d, 1 H), 6.23 (d, 1 H), 6.39–7.83 (m, 8 aromatic protons)
27	1.38 (s, 6 H), 2.42 (s, 3 H), 5.62 (d, 1 H), 6.23 (d, 1 H), 6.41–7.74 (m, 7 aromatic protons)
28	1.36 (s, 6 H), 5.57 (d, 1 H), 6.26 (d, 1 H), 6.45–7.74 (m, 7 aromatic protons)
29	1.38 (s, 6 H), 2.22 (s, 3 H), 5.63 (d, 1 H), 6.24 (d, 1 H), 6.40 (d, 1 H), 6.44 (d, 1 H), 7.48–7.90 (m, 5 aromatic protons)
30	1.37 (s, 6 H), 2.22 (s, 3 H), 2.45 (s, 3 H), 5.62 (d, 1 H), 6.22 (d, 1 H), 6.40 (d, 1 H), 6.42 (d, 1 H), 7.32 (d, 2 H), 7.74 (d, 2 H)
31	1.38 (s, 6 H), 2.20 (s, 3 H), 5.64 (d, 1 H), 6.25 (d, 1 H), 6.40 (d, 1 H), 6.42 (d, 1 H), 7.62–7.80 (m, 4 aromatic protons)
32	1.37 (s, 6 H), 3.38 (s, 3 H), 5.66 (d, 1 H), 6.34 (d, 1 H), 6.46 (s, 1 H), 6.94 (s, 1 H), 7.63–7.86 (m, 5 aromatic protons)
33	1.36 (s, 6 H), 3.39 (s, 3 H), 5.72 (d, 1 H), 6.34 (d, 1 H), 6.48 (s, 1 H), 6.80 (s, 1 H), 7.58–7.84 (m, 5 aromatic protons)
34	1.37 (s, 6 H), 5.66 (d, 1 H), 6.21 (d, 1 H), 6.62 (s, 1 H), 6.86 (s, 1 H), 7.42–7.76 (m, 10 aromatic protons)
35	1.42 (s, 6 H), 5.68 (d, 1 H), 6.20 (d, 1 H), 6.64 (s, 1 H), 6.90 (s, 1 H), 7.64–7.80 (m, 8 aromatic protons)

signal a polarization transfer appeared only on the C-7 signal. Since substitution of C-7 is without influence on the chemical shift of C-8a in *meta* position, the assignment of the ^{13}C signals of compounds **16–21** is unambiguous.

Structures of all new compounds synthesized have been elucidated by microanalysis (Table 4) and ^1H -NMR spectroscopy. ^1H -NMR spectroscopic data of 2,2-dimethyl-2*H*-chromenes (**26–35**) are summarized in Table 5.

Experimental Part

The NMR spectra were recorded on Bruker WP 200 SY, AC-250 and AM-500 spectrometers in CDCl_3 (internal standard *TMS*, $\delta = 0.0$ ppm) at room temperature. In the 1D measurements 32 K data points were used for the FID. For homonuclear NOE experiments a delay time of 3 s was applied. NOE difference and 2D carbon-proton correlated experiments were recorded by using the Bruker software package. The semiselective INEPT experiment was optimized for $J(\text{H}, \text{C})$ 7 Hz long-range coupling.

TLC was performed on Kieselgel 60 F_{254} (Merck) layer using hexane : acetone (7 : 3 v/v) as eluant.

2,2-Dimethyl-4-chromanones **6–15**

A mixture of compounds **1–5** (10 mmol), appropriate arylsulfonyl chloride (30 mmol), and anhydrous pyridine (30 ml) was allowed to stand in the refrigerator for 24 h and then poured onto crushed ice. The precipitate was filtered off, washed with water, dried, and crystallized from methanol to yield substances **6–15**.

2,2-Dimethyl-4-hydroxychromans **16–25**

2,2-Dimethyl-4-chromanones **6–15** (10 mmol) were stirred and refluxed in methanol (150 ml) and NaBH_4 (50 mmol) was added in small portions. Stirring and reflux were continued until the disappearance of the starting material (approx. 2 h) as monitored by TLC. The solution was then cooled to room temperature and diluted with water. The precipitate was filtered off and crystallized from methanol to afford compounds **16–25**.

2,2-Dimethyl-2*H*-chromenes **26–35**

Method A

A mixture of substances **16–25** (5 mmol), *p*-toluenesulfonic acid (0.1 g), and benzene (50 ml) was refluxed for 30 min, cooled to room temperature, washed with NaHCO_3 solution, then with brine, and dried on MgSO_4 . The solvent was evaporated i.vac. and the residue crystallized from methanol to obtain compounds **26–35** (Tables 4 and 5).

Method B

Compounds **16–21** (5 mmol) were dissolved in acetone (150 ml) and the *pH* was adjusted to 2–3 with 4 *N* HCL. The mixture was left to stand at room temperature. Substances **19–21** gave 2,2-dimethyl-2*H*-chromenes **29–31** in approx. 80% yield within one month. In the case of compounds **16–18** the conversion was not more than 70% during three months according to TLC.

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References

- [1] Part XIV: Lévai A., Timár T. (1990) *Synth. Commun.* (in press)
- [2] Bowers W. S., Ohta T., Cleere J. S., Marsella P. (1976) *Science* **193**: 542
- [3] Kasturi T. R., Manithomas T. (1967) *Tetrahedron Lett.* 2573
- [4] Ohta T., Bowers W. S. (1977) *Chem. Pharm. Bull.* **25**: 2788
- [5] Banerji A., Goomer N. C. (1981) *Indian J. Chem.* **20B**: 144
- [6] Anastasis P., Brown P. E. (1982) *J. Chem. Soc., Perkin Trans. I* 2013
- [7] ApSimon J. W., Herman L. W., Huber C. (1985) *Can. J. Chem.* **63**: 2589
- [8] Timár T., Hosztafi S., Jászberényi J. Cs., Kövér K. E., Batta Gy. (1988) *Acta Chim. Hung.* **125**: 303
- [9] Timár T., Jászberényi J. Cs., Hosztafi S. (1988) *Acta Chim. Hung.* **125**: 457
- [10] Timár T., Hosztafi S., Jászberényi J. Cs. (1988) *Acta Chim. Hung.* **125**: 617
- [11] Timár T., Jászberényi J. Cs. (1988) *J. Heterocyclic Chem.* **25**: 871
- [12] Sebők P., Timár T., Jászberényi J. Cs., Batta Gy. (1988) *Heterocycles* **27**: 2595
- [13] Timár T., Jászberényi J. Cs., Hosztafi S. (1989) *Acta Chim. Hung.* **126**: 149
- [14] Lévai A., Timár T. (1990) *Pharmazie* (in press)
- [15] Lévai A., Timár T. (1990) *Pharmazie* (in press)
- [16] Dinya Z., Timár T., Hosztafi S., Fodor A., Deák P., Somogyi Á., Berényi M. (1985) In: *Strategies in Drug Design; Proc. Fifth Eur. Symp. on Quantitative Structure-Activity Relationships* (Seydel J. K., ed.), p. 403
- [17] Lévai A., Makleit S., Hajnal E., Timár T., Frank L., Bilkei-Gorzó A., Galamb V., Veres Á. R. (1989) *Hungarian Patent Application*, Budapest
- [18] Haasnoot L. A. G., DeLeeuw F. A. A. M., Altona C. (1980) *Tetrahedron* **36**: 3783
- [19] Moldvai I., Vedres A., Szántay, Jr. Cs., Tóth G., Szántay Cs. (1990) *Acta Chim. Hung.* (in press)
- [20] Bax A. (1984) *J. Magn. Reson.* **57**: 314
- [21] Grover S. H., Stothers J. B. (1974) *Can. J. Chem.* **52**: 870
- [22] Ayer W. A., Browne L. M., Fung S., Stothers J. B. (1978) *Org. Magn. Reson.* **11**: 73
- [23] Ewing D. F. (1979) *Org. Magn. Reson.* **12**: 499

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