Monatshefte für Chemie 132, 1081–1093 (2001)

**Monatshefte für Chemie**
**Chemical Monthly**


# Special Reactions of α,β-Unsaturated Ketones III [1]. Formation and Structure Elucidation of Dimers of 2-Aryl-methyleneketones: (5*E*)-5-Benzylidene-9β-phenyl-*trans*-4a-1,2,3,4,4a,5,6,7,8,9a-decahydroxanthen-4aα-ol and 3β,5β-*Bis*-(4-methoxyphenyl)-2α,4β,6α-trimethyl-4α-propionyl-cyclohexanone [2]

**Edith Gößnitzer*, Winfried Wendelin, Karl Schermanz,** and **Karin Frieberger**

Institute of Pharmaceutical Chemistry and Pharmaceutical Technology, Karl-Franzens-University Graz, A-8010 Graz, Austria

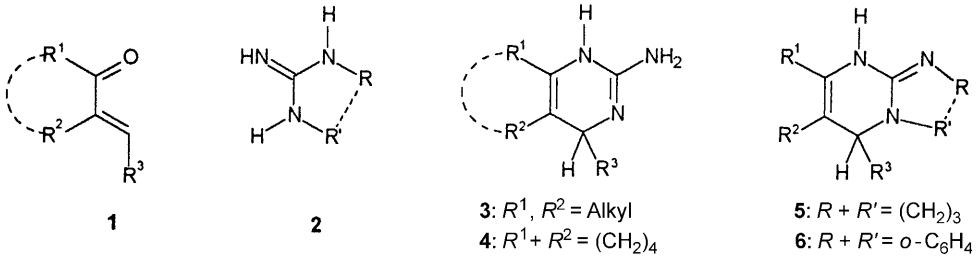
**Summary.** The reaction of 2-benzylidenecyclohexanone and 1-(4-methoxyphenyl)-2-methyl-1-penten-3-one with guanidine did not yield the expected 4-phenylhexahydro-2-quinazolinamine and 4-(*p*-methoxyphenyl)-dihydro-2-pyrimidinamine, respectively, but nitrogen-free products which turned out as [3+3]- and [4+2]-cycloadducts of two molecules of the applied vinylogous ketone each. According to elemental analyses, mass spectra, and, in particular, NMR analyses ($^1$H and $^{13}$C NMR, HH-COSY, *gs*-HSQC, *gs*-HMBC, 1D TOCSY, NOESY, and 1D NOE difference spectra), the prepared dimers were identified as racemic (5*E*)-5-benzylidene-9β-phenyl-*trans*-4a-1,2,3,4,4a,5,6,7,8,9a-decahydroxanthen-4aα-ol and 3β,5β-*bis*-(4-methoxyphenyl)-2α,4β,6α-trimethyl-4α-propionylcyclohexanone, respectively. Structure and stereochemistry of the dimers are elucidated, and mechanisms for their formation are proposed.

**Keywords.** Decahydroxanthen-4a-ol, 5-benzylidene-9-phenyl-*trans*-4a-; Cyclohexanone, 3,5-*bis*-(4-methoxyphenyl)-2,4,6-trimethyl-4-propionyl; Dimers of 2-benzylidene ketones; NMR spectroscopy; Structure elucidation.

## Introduction

As previously reported, dihydropyrimidinamines **3** and fused derivatives, *e.g.* hexahydroquinazolinamines **4**, tetrahydropyrimidopyrimidines **5**, and pyrimidobenz-

* Corresponding author. E-mail: edith.goessnitzer@uni-graz.ac.at




**Scheme 1**

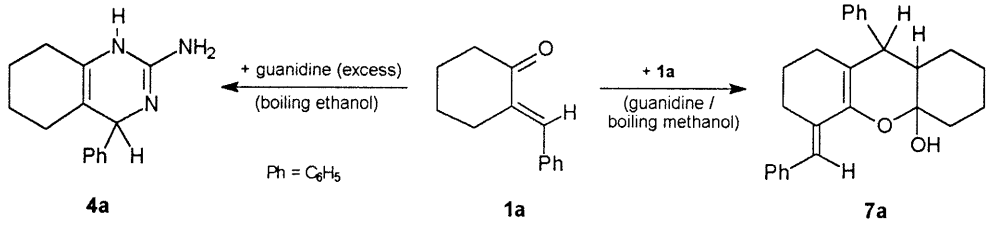
imidazoles **6**, can be prepared by reaction of acyclic and bridged $\alpha,\beta$-unsaturated ketones **1** with guanidines and bridged guanidines **2**, respectively [3–8].

In some special cases, the vinylogous ketones **1** did not react with the guanidines **2** but with a second molecule of enone **1** to yield nitrogen-free products which turned out to be dimers of the employed ketones **1** [1, 8]. In this paper we report on the dimerization reactions of 2-benzylidenecyclohexanone (**1a**) and 1-(4-methoxyphenyl)-2-methyl-1-penten-3-one (**1b**), which afforded 5-benzylidene-9-phenyldecahydroxanthen-4a-ol (**7a**) and 3,5-*bis*-(4-methoxy-phenyl)-2,4,6-trimethyl-4-propionylcyclohexanone (**12b**). The structure elucidations of **7a** and **12b** were accomplished mainly by means of one- and two-dimensional NMR spectroscopy.

## Results and Discussion

*Formation and structure elucidation of decahydroxanthenol* **7a**

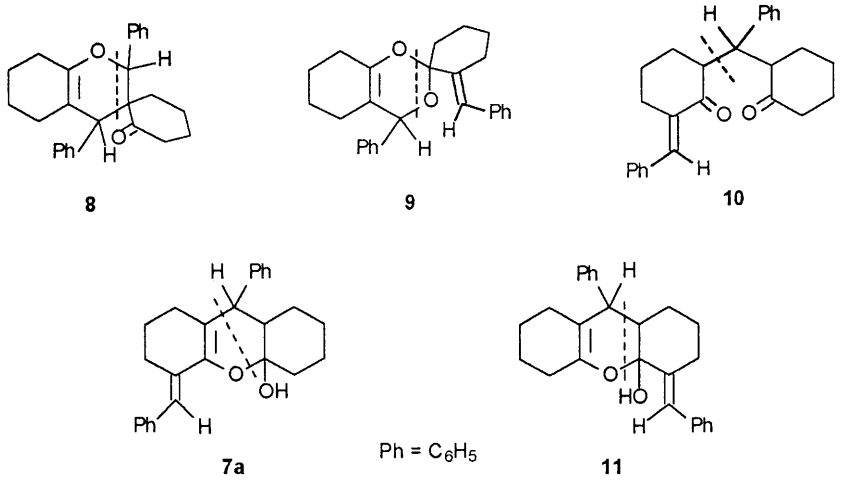
Heating of 2-benzylidenecyclohexanone (**1a**) with an excess of guanidine in ethanol yielded 4-phenylhexahydro-2-quinazolinamine **4a** [4]. In contrast, in boiling methanol under the influence of guanidine enone **1a** was transformed into a nitrogen-free product in a yield of 41%. According to the following structure analysis, this product represents 5-benzylidene-9-phenyldecahydroxanthen-4a-ol (**7a**).




**Scheme 2**

Elemental analysis and the mass spectrum of condensate **7a** revealed a molecular formula of $C_{26}H_{28}O_2$ ($m/z = 372$), pointing towards a dimer of the starting material generated by reaction of two molecules of **1a** without loss of water.

Inspection of the IR spectrum of **7a** showed no absorption bands for CO groups, but OH-stretching frequencies at $\nu = 3480\,\mathrm{cm}^{-1}$. Thus, the primarily



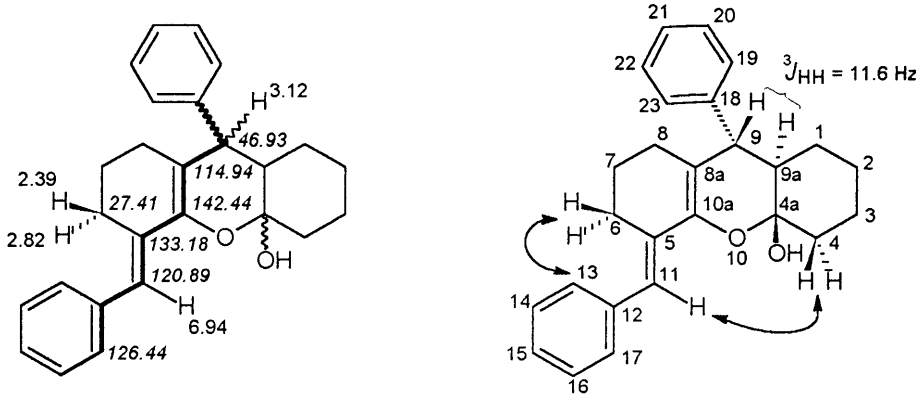

**Scheme 3**

expected structures of *Diels-Alder* dimers **8**, **9**, both spiro compounds, and also of a *Michael* adduct **10** (Scheme 3) had to be ruled out. However, an absorption band at $\nu = 1630\,\mathrm{cm}^{-1}$ pointed towards the existence of a conjugated enol ether, which guided from dione **10** to xanthenol **7a** and was not consistent with the isomeric structure **11** (the IR absorption of the non-conjugated enol ether moiety of **11** is expected at $\nu > 1650\,\mathrm{cm}^{-1}$ [9]).

The final proof of the structure of **7a** was obtained from NMR spectroscopic analysis. The complete assignment of all proton and carbon signals was carried out on the basis of one- and two-dimensional techniques ($^1$H and $^{13}$C, HH-COSY, NOESY, *gs*-HSQC, *gs*-HMBC, 1D TOCSY, 1D NOE).

The $^{13}$C spectrum of the dimer **7a** showed only 19 signals instead of 22 which were expected due to the symmetry of the two monosubstituted phenyl groups. This resulted from the accidental isochrony of additional two carbon atoms of the decahydroxanthene moiety (C-2 and C-7) and of the *para* and *meta* carbons of the two phenyl groups (C-14/16 and C-15; C-20/22 and C-21) each (Scheme 4). The evaluation of the *gs*-HSQC contour plots allowed the assignment of all proton-bearing carbons as listed in Table 1. Additionally, it confirmed the olefinic nature of the proton appearing as a broad singlet at $\delta = 6.94$ in the $^1$H NMR spectrum, relating it to the methine carbon atom at 120.89 ppm with the typical chemical shift of olefinic carbons [10].

The final decision between the dimers **7a** and **11** was made straightforward on the basis of the *gs*-HMBC experiments optimized for C–H coupling constants of 4, 8, and 10 Hz. The evaluation of the non-overlapping $^{13}$C–$^1$H long-range correlations of the benzyl proton H-9 ($\delta = 3.12$) with C-8a, C-10a, C-5, and C-11, as well as of the benzylidene proton H-11 ($\delta = 6.94$) with the carbon atoms C-5 and C-10a as well as with C-14/16 of the phenyl group at C-11, and, over six bonds, with C-18 of the phenyl residue at C-9 (see Table 1) resulted in the establishment of the diphenylpentadiene moiety with two conjugated C=C double bonds (highlighted in Scheme 4), which applies only to xanthenol **7a** (Scheme 3).




**7a**, diphenylpentadiene moiety **7a**, numbering and significant NOEs

**Scheme 4**

By inspection of the $^1$H spectrum together with the HH-COSY contour plots the resonances of the methylene group in position 6 of the cyclohexene moiety were identified by the transoid allylic long-range correlation of H-6*ax* with the olefinic proton H-11. Moreover, an observed $^6J_{HH}$ correlation between H-11 and H-9 indicated a zig-zag arrangement of the C–H and C–C/C=C bonds connecting these protons. This fact was in accordance with the above deduced conjugation of double bonds found in IR and HMBC spectra and confirmed structure **7a**.

The connection of the second phenyl group with C-9 followed from the long-range correlation between C-9 and the *o*-protons H-19/23 as well as from the observed NOE between these *o*-protons and H-9 (Fig. 1). Further heteronuclear correlations starting from H-6*ax* and H-8*ax* as described in Table 1 enabled to complete the cyclohexene ring. Analogously, $CH_2$-1 and $CH_2$-4 were found as the terminal links of the tetramethylene bridge furnishing the cyclohexane ring. The 1D TOCSY experiment described below with irradiation of H-9 (Fig. 2) allowed to assign the protons of $CH_2$-2 and $CH_2$-3.

The carbon atom C-4a at 96.39 ppm, with a chemical shift characteristic of *hemi*-acetal carbons [10], bears the hydroxylic group and is the starting point for the oxygen bridge to the enol carbon C-10a, which completes the central dihydropyrane ring.

### *Stereochemistry of xanthenol* **7a**

The orientation of the phenyl group in the benzylidene substituent at C-5, *i.e.* 5*E* (*trans* to the central pyrane ring) as shown in Scheme 5, became evident by the dipolar interactions of both H-6*ax* and H-6*eq* with the *o*-phenyl protons H-13/17 on the one hand, and the NOE between H-11 and H-4*eq* on the other. The lack of deshielded *ortho* protons H-13/17 suggested that the coplanar arrangement of the phenyl group at C-11 and the pentadiene moiety of **7a** is probably lost.

The magnitude of $^3J_{(H\text{-}9,H\text{-}9a)}$ of the H-9 doublet (11.6 Hz) is significant for its *anti* conformation with respect to the bridgehead proton H-9a and reveals at the same time the equatorial position of the phenyl group at C-9 (see Scheme 5) [11].

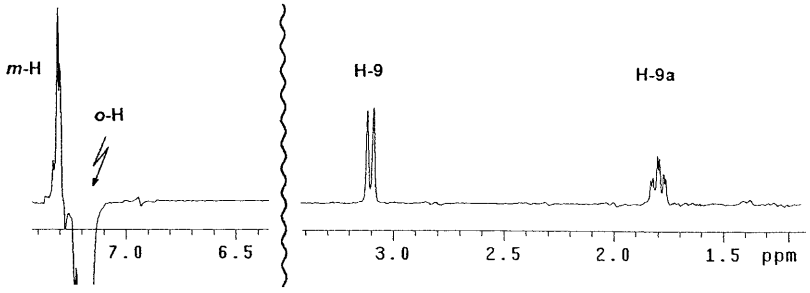



**Fig. 1.** 1D NOE difference spectrum of **7a** (irradiation of the *o*-protons of the phenyl group at C-9)

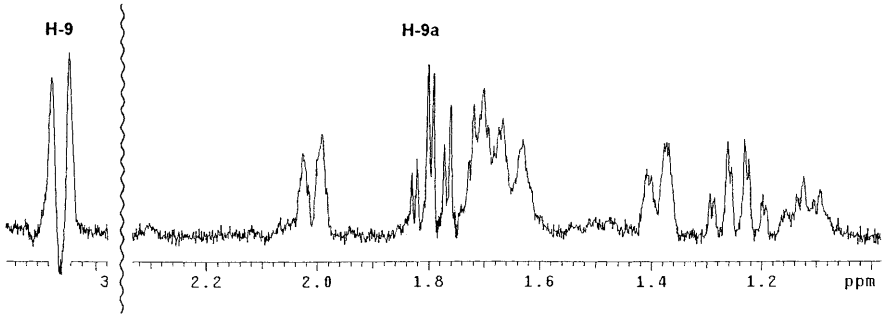


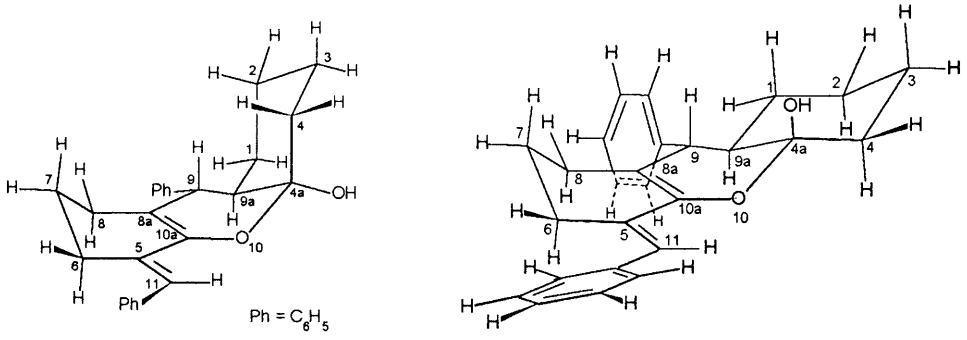

**Fig. 2.** 1D TOCSY spectrum of **7a** (irradiation of H-9; mixing time: 0.2 s)

Connected with the question of the orientation of the hydroxy group at C-4a was the type of junction, *cis* or *trans*, of the dihydropyrane and cyclohexane ring of **7a**. As can be seen from Scheme 5, the signal pattern of the bridgehead proton H-9a is indicative of the relevant type of ring junction. In the case of *trans* fusion, the resonance of H-9a should appear as a doublet of a doublet or a *pseudo*-triplet with a $^{3}J_{\text{H-9a/H-1}ax,\text{H-9}}$ of *ca.* 10–12 Hz, whereas in the *cis*-type compound the signal should show only one large antiperiplanar ($^{3}J_{\text{H-9a/H-9}}$) and two smaller synclinal couplings with $^{3}J_{\text{H-9a/H-1}ax,\text{H-1}eq} \approx 3$–4 Hz.

The partly overlapped signal of H-9a ($\delta = 1.80$ ppm) became visible in a 1D NOE difference experiment with irradiation of the *o*-protons H-19/23 ($\delta =$ 7.18 ppm) of the phenyl ring at C-9. The signal of H-9a appeared as a triplet of doublets ($J = 11.6$ and 3.2 Hz; see Fig. 1).

The same signal pattern of H-9a could be observed in the 1D TOCSY experiment with irradiation of H-9, in which the connectivities from H-9 through the cyclohexane ring to both H-4*ax* and H-4*eq* could be derived (Fig. 2).

Consequently, the *trans* fusion of the dihydropyrane and cyclohexane rings as well as the axial orientation of the hydroxy group in position 4a (*trans* to H-9a) were proved (Scheme 5). Additional and independent confirmation of the axially oriented HO-4a could be obtained from the *vice versa* NOE between H-9 and the OH group, showing their location on the same side of the molecule.




*cis*-**7a** ((4a*R*,9*S*,9a*R*)-enantiomer) *trans*-**7a** ((4a*S*,9*S*,9a*R*)-enantiomer)

**Scheme 5**

Conclusions concerning preferred conformations of the three fused rings of xanthenol **7a** could be drawn from further NOE spectra and the typical signal patterns of particular $-CH_2-CH_2-$ ring moieties. The signal multiplicities and coupling constants of H-1*ax*/H-1*eq* and H-4*eq*, which are not overlapped, are in agreement with the chair form of the fused cyclohexane ring. H-1*ax* exhibits a quartet of doublets arising from the geminal and two axial couplings ($^2J_{\text{H-1}ax,\text{H-1}eq} = {}^3J_{\text{H-1}ax,\text{H-2}ax} = {}^3J_{\text{H-1}ax,\text{H-9a}} = 12.4\,\text{Hz}$) and one equatorial coupling ($^3J_{\text{H-1}ax,\text{H-2}eq} = 2.4\,\text{Hz}$). Furthermore, significant NOEs between H-1*ax* and H-3*ax* as well as H-2*ax* and H-9a/H-4*ax* show their pairwise arrangement above and below the plane of the chair, respectively.

On account of the three $sp^2$ carbon atoms C-5, C-10a, and C-8a, the fused benzylidene-substituted cyclohexene ring adopts predominantly a sofa conformation with $CH_2$-7 as out-of-plane group [12]. The methylene protons H-6*ax*/H-6*eq* obviously experience deshielding effects of both the neighbouring 5(11) double bond and the spatially near phenyl group, resulting in downfield shifts of their signals to 2.39 and 2.82 ppm.

As follows from considerations using *Dreiding* models and according to Ref. [12] and literature cited therein, the central dihydropyrane ring prefers a half-chair form, which is slightly distorted towards a sofa. Weak NOEs between H-11 and HO-4a/H-4*eq* indicate a certain steric proximity and are consistent with the proposed intermediate half-chair/sofa conformation of the dihydropyrane ring (Scheme 5).

The above mentioned findings led finally to the correct structure of the isolated dimer **7a**, racemic (5*E*)-5-benzylidene-9$\beta$-phenyl-*trans*-4a-1,2,3,4,4a,5,6,7,8,9a-decahydroxanthen-4a$\alpha$-ol [13]. The stereoformula of **7a** shown in Scheme 5 is in good accordance with the observed spectroscopic data.

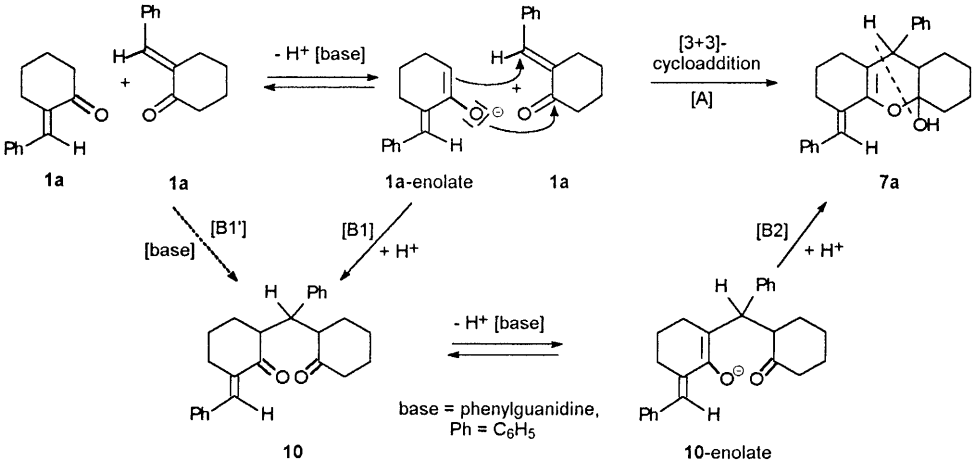
### *Mechanism of formation of xanthenol* **7a**

Dimer **7a** could easily be generated *via* partly base-induced transformation of benzylidenecyclohexanone **1a** into **1a**-enolate and nucleophilic [3+3]-cycloaddition of this enolate to enone **1a** in one (Scheme 6, route A) or two steps. In case of a two step reaction, the already mentioned *Michael* adduct **10** might be generated

**Table 1.** NMR data of decahydroxanthenol **7a** (400 MHz $^{1}$H/100 MHz $^{13}$C, $CDCl_3$, 300 K; numbering of **7a**: see Scheme 4)

| | | $\delta$(C)/ppm | $\delta$(H)/ppm$^{\text{multiplicity}}$ | $J_{HH}$/Hz | long-range CH correlations | relevant $^{1}$H,$^{1}$H-NOE interactions |
|---|---|---|---|---|---|---|
| 1 | $CH_2$ | 27.13 | *ax*: 1.25$^{qd}$ | 12.4/2.4 | 46.93; 47.16; 96.39 | H-3*ax*; HO-4a; H-9 |
| | | | *eq*: 1.39$^{dm}$ | 12.4 | | H-9; *o*-H-19/23 |
| 2 | $CH_2$ | 23.03 | *ax*: 1.13$^{m}$ | | 46.93; 47.16 | H-4*ax*; H-9a |
| | | | *eq*: 1.70$^{d1}$ | 13.6 | | |
| 3 | $CH_2$ | 25.48 | *ax*: 1.62$^{m1}$ | | | |
| | | | *eq*: 1.69$^{m1}$ | | | |
| 4 | $CH_2$ | 38.15 | *ax*: 1.76$^{td1}$ | 12.8/4.0 | 25.48; 46.93; 47.16; 96.39 | |
| | | | *eq*: 2.01$^{dm}$ | 12.8 | | HO-4a; H-11 |
| 4a | C | 96.39 | – | | | |
| 5 | C | 133.18 | – | | | |
| 6 | $CH_2$ | 27.41 | *ax*: 2.39$^{tm}$ | 14.4 | 23.03; 28.01; 120.89; 133.18 | *o*-H-13/17 |
| | | | *eq*: 2.82$^{dt}$ | 14.4/2.0 | | *o*-H-13/17 |
| 7 | $CH_2$ | 23.03 | *ax*: 1.49$^{m}$ | | | |
| | | | *eq*: 1.55$^{m1}$ | | | |
| 8 | $CH_2$ | 28.01 | *ax*: 1.73$^{m1}$ | | 114.94; 142.52 | |
| | | | *eq*: 1.93$^{m1}$ | | | |
| 8a | C | 114.94 | – | | | |
| 9 | CH | 46.93 | 3.12$^{d}$ | 11.6 | 27.13; 114.94; 120.89; 133.18; 142.52 | H-1*ax*; HO-4a; H-8*eq*; *o*-H-19/23 |
| 9a | CH | 47.16 | 1.80$^{td1}$ | 11.6/3.2 | | |
| 10a | C | 142.44 | – | | | |
| 11 | CH | 120.89 | 6.94$^{s,broad}$ | | 27.41; 129.33; 133.18; 138.12; 142.52 | H-4*eq*; HO-4a |
| 12 | C | 142.52 | – | | | |
| 13/17 | CH | 126.44 | 7.30 | | | |
| 14/16 | CH | 129.33 | 7.33 | | | |
| 15 | CH | 129.33 | 7.33 | | | |
| 18 | C | 138.12 | – | | | |
| 19/23 | CH | 126.06 | 7.18$^{d}$ | 6.8 | | H-9; H-9a |
| 20/22 | CH | 127.94 | 7.28 | | 120.89; 126.06; 138.12 | |
| 21 | CH | 127.94 | 7.28 | | 46.93 | |
| | | OH | 2.31$^{s,broad}$ | | | H-1*ax*; H-4*eq*; H-9; H-11; |

[1] (Partly) overlapped




**Scheme 6**

as intermediate. Transformation of the benzylidene-substituted cyclohexanone ring of **10** into an enolate and ring closure between the enolate oxygen and the carbonyl group affords again xanthenol **7a** (Scheme 6, route B1,2).

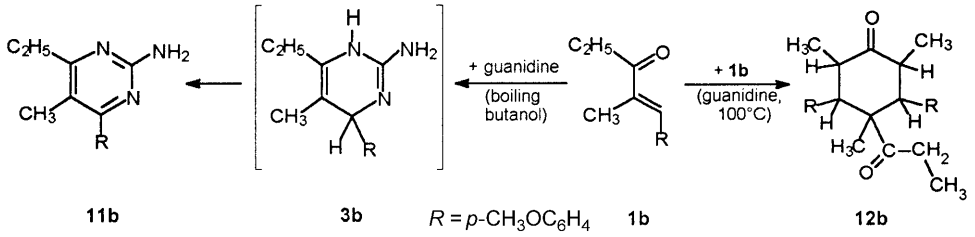
A literature search showed that there are many reports on dimerization reactions of $\alpha,\beta$-unsaturated ketones occurring in the course of the preparation of enones from aldehydes and ketones [14,15]. In particular, *Oszbach et al.* [16] have prepared the dimer **7a** from enone **1a** by treatment with ethanolic sodium hydroxide solution and postulated the correct constitution on the basis of UV, IR, and some $^1$H NMR data. However, an unequivocal proof of the structure and stereochemistry of xanthenol **7a** has not been published so far.

*Structure elucidation of propionylcyclohexanone* **12b**

The reaction of 1-(*p*-methoxyphenyl)-2-methyl-1-penten-3-one (**1b**) with guanidine in boiling butanol yields, probably *via* 1,4-dihydropyrimidinamine **3b** as intermediate, 6-ethyl-5-methyl-4-(*p*-methoxyphenyl)-2-pyrimidinamine (**11b**) [17]. In contrast, heating of the low-melting pentenone **1b** (m.p.: 50°C) with guanidine without solvent under a nitrogen atmosphere furnished exclusively a nitrogen-free product of m.p. 205°C. Together with the very lipophilic behaviour in TLC, the elemental analysis of compound **12b** led to the assumption that a dimerization of enone **1b** in the presence of guanidine had occurred. The evaluation of the IR and NMR spectra revealed structure and stereochemistry of 3,5-*bis*-(4-methoxyphenyl)-2,4,6-trimethyl-4-propionylcyclohexanone **12b** (Scheme 7). So far, **12b** as well as its analogues are unknown in literature.

A first glance at the IR spectrum proved that the conjugated keto function of educt **1b** at 1661 cm$^{-1}$ is no longer existent in the isolated compound **12b**, whereas two intense absorption bands at $\nu = 1709$ and 1697 cm$^{-1}$ indicated the presence of two carbonyl groups.

The $^1$H NMR spectrum (Fig. 3) showed nine different types of protons in two sets of fragments with an intensity ratio of 1:2, indicating symmetry in the cyclohexanone moiety. The HH-COSY revealed the $ABX_3$ system of the two equivalent




**Scheme 7**

-CH(Ar)–CH–$CH_3$ fragments of the cyclohexane ring, *i.e.* a doublet at $\delta =$ 3.30 ppm, a doublet of a quartet at $\delta = 2.97$ ppm, and a doublet for the methyl protons at $\delta = 0.83$ ppm.

The evaluation of the *gs*-HSQC spectrum afforded the assignment of all C–H resonances (Table 2). The heteronuclear long range shift correlation (*gs*-HMBC) confirmed the assignment and linkage of the quarternary carbons. In detail, the connectivities of the carbonyl C-1 (211.87 ppm) with H-2/6 and H-3/5 and the protons of $CH_3$-11/12 as well as of C-4 (57.19 ppm) with H-3/5 led to the establishment of the cyclohexanone ring. Correlations of the second carbonyl C-7 (216.02 ppm) with the methylene and methyl protons of $CH_2$-8 and $CH_3$-9 allowed to complete the propionyl residue. The location of the propionyl residue and of $CH_3$-10 at C-4 as well as the linkage of the two 4-methoxyphenyl substituents with C-3/5 followed from the long-range correlations described in Table 2, which also provides further details for the structural analysis of **12b** (Scheme 9).

The knowledge of the correct structure of dimer **12b** allowed to discuss a [4+2]-cycloaddition of two molecules of the phenylmethylpentenone **1b** as a possible way of formation. In the probably occurring *Diels-Alder* reaction the tautomeric **1b**-enolate served as diene and added at postions 1,4 to the second vinylogous ketone **1b** (Scheme 8, route A). However, **12b** could also be formed by means of two consecutive *Michael* additions *via* the acyclic 1-nonen-3,7-dione **13b** as intermediate (route B1,2).

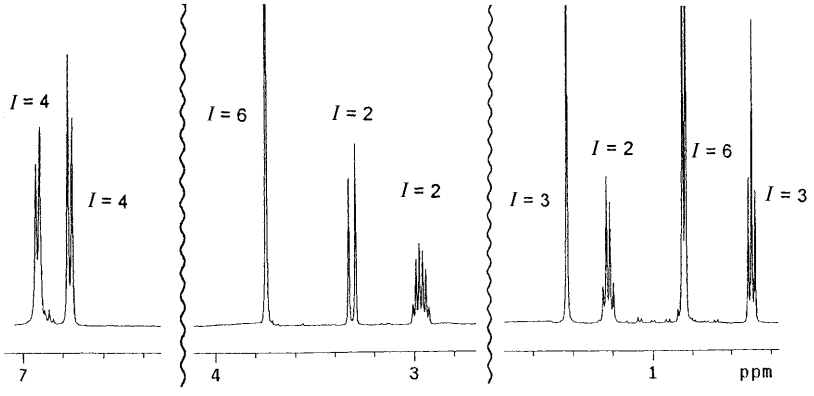
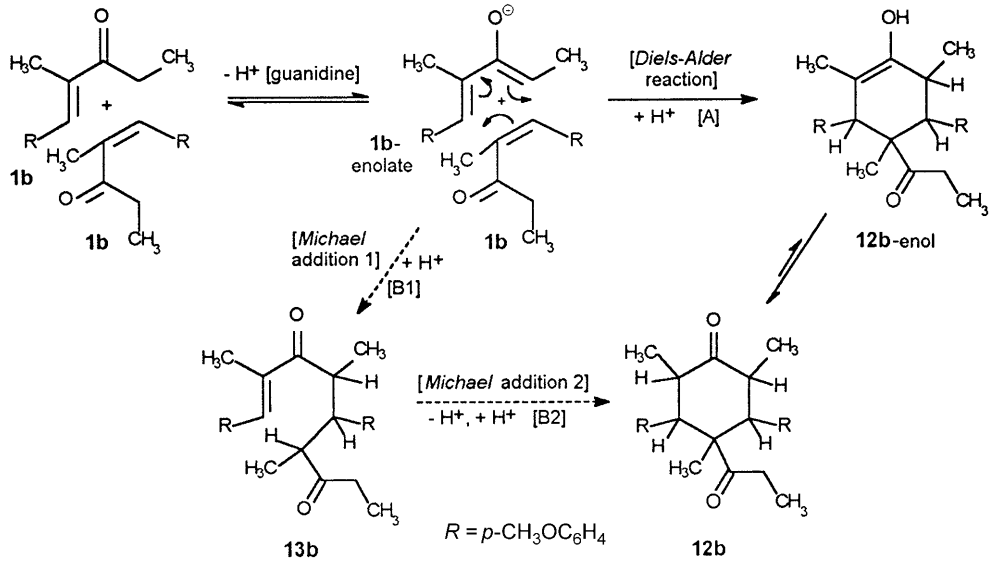



**Fig. 3.** 400 MHz $^1$H NMR spectrum of dimer **12b** in $CDCl_3$ (*I*: intensity in units of protons)

**Table 2.** NMR data of propionylcyclohexanone **12b** (400 MHz $^{1}$H/100 MHz $^{13}$C, $CDCl_3$, 300 K; numbering of **12b**: see Scheme 9)

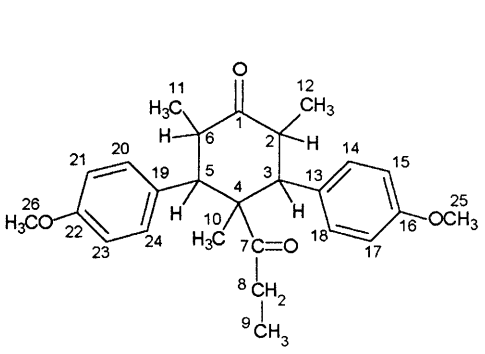
| | | $\delta$(C)/ppm | $\delta$(H)/ppm$^{multiplicity}$ | $J_{HH}$/Hz | Long-range CH correlations | Relevant $^{1}$H,$^{1}$H-NOE interactions |
|---|---|---|---|---|---|---|
| 1 | C=O | 211.87 | – | | | |
| 2/6 | CH | 43.89 | 2.97$^{dq}$ | 13.2/6.0 | 11.09; 57.26; 211.87 | |
| 3/5 | CH | 57.26 | 3.30$^{d}$ | 13.2 | 11.09; 12.65; 43.89; 57.19; 130.27; 211.87; 216.02 | $CH_3$-10; H-14/18,H-20/24 |
| 4 | C | 57.19 | – | | | |
| 7 | C=O | 216.02 | – | | | |
| 8 | $CH_2$ | 34.72 | 1.21$^{q}$ | 7.2 | 6.88; 216.02 | |
| 9 | $CH_3$ | 6.88 | 0.49$^{t}$ | 7.2 | 34.72; 216.02 | |
| 10 | $CH_3$ | 11.09 | 1.43$^{s}$ | | 57.26; 216.02 | H-2/6; $CH_2$-8; H-14/18,H-20/24 |
| 11/12 | $CH_3$ | 12.65 | 0.83$^{d}$ | 6.0 | 43.89; 57.26; 211.87 | H-3/5; H-14/18,H-20/24 |
| 13/19 | C | 130.58 | – | | | |
| 14/18 | CH | 130.27 | 6.92$^{d}$ | 8.8 | 57.26; 130.27; 158.27 | H-2/6; H-3/5; $CH_3$-10 |
| 20/24 | CH | | | | | |
| 15/17 | CH | 113.34 | 6.75$^{d}$ | 8.8 | 113.34; 130.27; 158.27 | |
| 21/23 | CH | | | | | |
| 16/22 | C | 158.27 | – | | | |
| 25/26 | $CH_3$ | 55.11 | 3.74$^{s}$ | | 158.27 | |



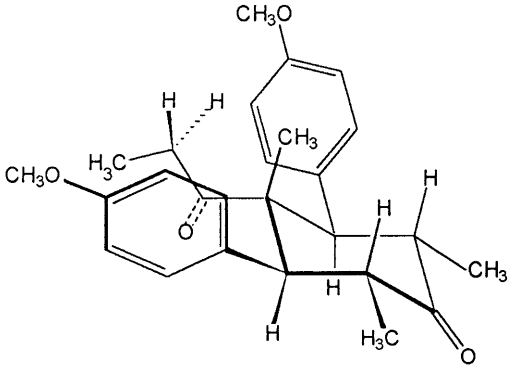

**Scheme 8**

*Stereochemistry of dimer* **12b**

Statements concerning the stereochemistry of dimer **12b** could be made by means of the $^{1}$H signal analysis and significant NOESY correlations. Thus, the chair



Constitution of dimer **12b**



Stereoformula of *meso*-**12b**

**Scheme 9**

conformation of the cyclohexanone with both equatorially oriented methyl groups at C-2/6 and *p*-methoxyphenyl substituents at C-3/5 was evidenced by the vicinal coupling constants of the equivalent proton pairs H-2/6 and H-3/5. The large value of $^3J_{HH} = 13.2$ Hz is significant for their pairwise antiperiplanar arrangement. The NOESY spectra proved the axial position of $CH_3$-10 *via* the dipolar interactions with the axially oriented H-2/6. Moreover, the NOESY cross peaks between $CH_2$-8 and $CH_3$-10 argued for a time average gauche conformation of the methylene protons of $CH_2$-8 with respect to $CH_3$-10 (Scheme 9). The carbonyl C-7 might be directed parallely to H-3/5. On account of steric hindrance by the vicinal methyl groups at C-2/6 and C-4, the methoxyphenyl substituents in position 3 and 5 should be approximately perpendicularly arranged with respect to the plane of the cyclohexanone ring.

In accordance with these findings, the remarkable highfield shift of about 1.2 ppm for the signals of the methyl and methylene protons ($\delta = 0.49$ and 1.21 ppm) of the propionyl residue can be clearly attributed to the anisotropic effects of the facing phenyl groups. Studies on *Dreiding* molecular models showed that no anisotropic effect of the phenyl groups towards $CH_2$-8 could be expected if the methylene protons would be oriented parallely to H-3/5. The $^{13}C$ resonance of $CH_3$-10 experienced a significant upfield shift of about 8 ppm from 19.80 to 11.09 ppm caused by the $\gamma$-effect also due its axial position [10].

Because of the mirror image equivalence of the substitutents in positions 2/6 and 3/5, the dimer **12b** has a plane of symmetry in the molecule and represents *meso*-3$\beta$,5$\beta$-*bis*-(4-methoxyphenyl)-2$\alpha$,4$\beta$,6$\alpha$-trimethyl-4$\alpha$-propionylcyclohexanone.

## Experimental

Melting points were determined on a Kofler melting point apparatus and are uncorrected. Thin-layer chromatograms (TLC) were run on TLC plastic sheets silica gel 60 F254 (E. Merck, Darmstadt); elution systems: $C_6H_6$:MeOH = 90:10 (ES 1), toluene-$Et_2O$ = 90:10 (ES 2). The spots were detected by visual examination under UV light (254 and 366 nm). Infrared spectra were recorded with Perkin-

Elmer 881 and 2000 FTIR spectrophotometers in KBr disks; frequencies are reported in $cm^{-1}$ (s = strong, m = middle, w = weak). NMR spectra were acquired on a Varian 400 MHz Unity Inova NMR spectrometer equipped with a Sun Sparc 5 computer system and operating at an observation frequency of 399.98 MHz for $^1H$ and 100.59 MHz for $^{13}C$. 1D and 2D NMR experiments were performed using a reverse geometry 5 mm broad-band probehead and a pulsed field gradient unit. The HH-COSY [18], *gs*-HSQC [19], *gs*-HMBC [20], NOESY [21], 1D NOE difference [22], and 1D TOCSY [23] experiments were performed using the pulse programs supplied by the manufacturer. The *gs*-HMBC experiments were optimized for 4, 8, and 10 Hz (delays of 125.0, 62.5, and 50.0 ms, respectively). All NOEs were measured in degassed samples. For the 1D NOE experiments, 3 s pre-irradiation times were used. FIDs were exponentially multiplied prior to *Fourier* transformation. The mixing time in the NOESY experiments was 0.8 s. 1D TOCSY spectra were achieved in series with arrayed mixing times (0.02, 0.04, 0.06, 0.08, 0.10, 0.12, 0.16, 0.20, 0.24 s). 15–25 mg of the substances were dissolved in 0.5 $cm^3$ of deuterated solvents and measured at 300 K. All chemical shifts are reported in $\delta$ units (ppm) with *TMS* as internal standard. Mass spectra were taken with a Finnigan Mat 212 spectrometer (EI, 120 EV, $R = 1000$) by Dr. *R. Saf*, Institute of Chemical Technology of Organic Materials, Technical University Graz. Elemental analyses were performed by *J. Theiner*, Institute of Physical Chemistry, University of Vienna; they agreed favourably with the calculated values.

*Racemic (5E)-5-benzylidene-9β-phenyl-trans-4a-1,2,3,4,4a,5,6,7,8,9a-decahydro-xanthen-4aα-ol* (**7a**; $C_{26}H_{28}O_2$)

A mixture of 9.30 g benzylidenecyclohexanone **1a** (50 mmol) and 2.95 g guanidine (50 mmol) in 20 $cm^3$ MeOH was heated to reflux for 2.5 h. Then, the reaction mixture was evaporated to dryness, and the residue was dissolved in benzene. After neutralization of the benzene solution with 2 *N* HCl and dilution with $H_2O$ the benzene layer was separated, dried over $Na_2SO_4$, and evaporated to dryness. The oily residue was triturated with MeOH and recrystallized from 2-PrOH to give colourless needles of **7a**.

Yield: 3.81 g (41%); m.p.: 121°C (Ref. [16]: 135–136°C); TLC (ES 1): $R_f = 0.65$; MS: *m/z* (%) = 372 ($M^+$, 30), 354 ($M^+$-18, 5), 275 ($M^+$-97, 100), 186 ($M^+$-186, 58), 117 (27), 115 (28), 91 (43); IR (KBr): $\nu = 3480$s, 2930s, 2860/2830m/w, 1630m, 1592m, 1490m, 1125s, 1065s, 955/948s/s $cm^{-1}$. $^1H$ ($CDCl_3$, $\delta$, 400 MHz) and $^{13}C$ NMR ($CDCl_3$, $\delta$, 100 MHz): see Table 1.

*meso-3β,5β-Bis-(4-methoxyphenyl)-2α,4β,6α-trimethyl-4α-propionylcyclohexanone* (**12b**; $C_{26}H_{32}O_4$)

Pentenone **1b** (8.17 g, 40 mmol) was melted under an $N_2$-atmosphere, and 2.36 g guanidine (40 mmol) were added. Within 1 h the reaction temperature was elevated to 100°C under stirring and held for 10 h till the melt became solid. After cooling, the reaction mixture was distributed between $CHCl_3$ and $H_2O$. The organic layer was separated, neutralized with 6% HBr, dried over $Na_2SO_4$, and evaporated to dryness. The residue was triturated with MeOH to give colourless needles of **12b**.

Yield: 3.27 g (40%); m.p.: 205°C; TLC (ES 2): $R_f = 0.67$; IR (KBr): $\nu = 2986$s, 2940s, 2838m, 1709/1697m/s, 1611s, 1579m, 1458/1444m/m, 1297s, 1187/1180s/s, 858m, 816s $cm^{-1}$. $^1H$ ($CDCl_3$, $\delta$, 400 MHz) and $^{13}C$ NMR ($CDCl_3$, $\delta$, 100 MHz): see Table 2.

## Acknowledgments

The authors express their thanks to Prof. Dr. *E. Breitmaier*, Kekulé Institute of Organic Chemistry and Biochemistry, Rheinische Friedrich-Wilhelms Universität Bonn, Germany, for recording some NMR spectra and for helpful discussions on the structure elucidation of xanthenol **7a**.

## References

[1] For part I, see Wendelin W, Schermanz K, Breitmaier E (1988) Monatsh Chem **119**: 355, for part II, Gößnitzer E, Wendelin W (2001) Magn Reson Chem **39**: 471
[2] Presented in part at the 14th International Congress of Heterocyclic Chemistry, Antwerp, Belgium 1993, Book of Abstracts PO-98
[3] Wendelin W, Kerbl H (1984) Monatsh Chem **115**: 309
[4] Wendelin W, Schermanz K, Blasi-Rabassa A, Gößnitzer E (1989) Scientia Pharmac **57**: 230
[5] Gößnitzer E, Wendelin W, Hocevar-Korosec M, Fellner H (1994) Scientia Pharmac **62**: 198
[6] Abou El Ella D, Gößnitzer E, Wendelin W (1996) J Heterocycl Chem **33**: 373
[7] Wendelin W, Gößnitzer E, Abou El Ella D (2000) Monatsh Chem **131**: 353
[8] Gößnitzer E (1994) PhD Thesis, Karl Franzens University Graz, Austria
[9] Williams DH, Fleming I (1991) Strukturaufklärung in der organischen Chemie. Thieme, Stuttgart, p 81
[10] Kalinowski KO, Berger S, Braun S (1984) $^{13}$C-NMR-Spektroskopie. Thieme, Stuttgart, pp 100, 118
[11] Günther H (1998) NMR Spectroscopy. Wiley, New York, p 115
[12] Rabideau PW (ed) (1989) The Conformational Analysis of Cyclohexenes, Cyclohexadienes, and Related Hydroaromatic Compounds. VCH, Weinheim
[13] International Union of Pure and Applied Chemistry, Commission on Nomenclature of Organic Chemistry (Rigandy J, Klesny SP) (1979) Nomenclature of Organic Chemistry, Section E-4.11 (Extension of the $\alpha$,$\beta$ system). Pergamon Press, Oxford New York Toronto Sydney Paris Frankfurt, p 482
[14] Otto HW, Ebner U (1976) Arch Pharm **309**: 969
[15] Lyle GG, Dziark JJ, Connor J, Saunderson-Huber C (1973) Tetrahedron **29**: 4039
[16] Oszbach G, Szabo D, Vitai ME (1976) Acta Chim Acad Sci Hung **90**: 51
[17] Wendelin W, Exner A, Egger P, Frahm AW (1989) Scientia Pharmac **57**: 232
[18] Bax A, Freeman R (1981) J Magn Reson **44**: 542
[19] Kay LE, Keifer P, Saarinen T (1992) J Am Chem Soc **114**: 10663
[20] Wilker W, Leibfritz D, Kerssebaum R, Bermel W (1993) Magn Reson Chem **31**: 287
[21] Bodenhausen G, Kogler H, Ernst RR (1984) J Magn Reson **58**: 370
[22] Kinns M, Sanders JKM (1984) J Magn Reson **56**: 518
[23] Kessler H, Oschkinat H, Griesinger C, Bermel W (1986) J Magn Reson **70**: 106

*Received April 11, 2001. Accepted (revised) May 18, 2001*