ELSEVIER

Journal of Molecular Structure 479 (1999) 13–19

Journal of
MOLECULAR
STRUCTURE

E-2-Benzylidenebenzocycloalkanones. Stereostructure and NMR spectroscopic investigation

P. Perjési[a], T. Nusser[b], Gy. Tarczay[c], P. Sohár[c,*]

[a]*Department of Medical Chemistry, University Medical School, POB 99, H-7601 Pécs, Hungary*
[b]*Chinoin Pharmaceuticals, POB 110, H-1325 Budapest, Hungary*
[c]*Department of General and Inorganic Chemistry, Loránd Eötvös University, POB 32, H-1518 Budapest, Hungary*

Received 24 July 1998; received in revised form 20 October 1998; accepted 20 October 1998

Abstract

Series of *E*-2-benzylideneindanones (**a**), -tetralones (**b**) and -benzosuberones (**c**) with OCH_3 (**2**–**4**), NO_2 (**5**–**7**) and F (**8**–**10**) substitutions (*ortho*, *meta* and *para*) on their benzylidene moiety were synthesized by aldol condensation of the appropriate aldehydes and benzocyclanones. The stereostructure (configuration and conformation) and the electronic properties (conjugation of the enone moiety with the aromatic rings) of the compounds were studied by IR, ^1H and ^{13}C NMR spectroscopy including also 2D-HSC, DNOE and DEPT measurements. Ab initio calculations were carried out to corroborate the experimental findings. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: *E*-2-benzylideneindanones -tetralones -benzosuberones; Stereostructure; IR, H and C NMR spectra; Ab initio geometry optimisation

---

1. Introduction

Numerous synthetic and natural α,β-unsaturated carbonyls exhibit remarkable biological activity [1]. Among others, several chalcones and related benzylidene ketones have been reported to possess antifungal [2], antibacterial [3] and cytotoxic (antitumor) [4] activities.

Recently we have stated antifungal [5,6] and cytotoxic (antitumor) [7] activities of some *E*-2-benzylideneindanones (**a**), -tetralones (**b**), and -benzosuberones (**c**, see Scheme 1). A number of the investigated derivatives were found to be more active than the reference compounds used in the different in vitro test systems. The observed biological activities have been found to be affected by both the ring size and the substitution pattern of the benzylidene moiety [5–7].

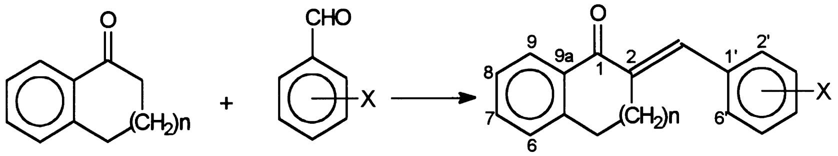
The biological activity of the α,β-unsaturated carbonyl (enone) compounds is considered to be associated with their reactivity with the thiol moiety of the critical peptides and/or proteins [1]. Is this mechanism true, then electronic and steric factors should affect the reactivity, i.e. their biological activity. In order to support this assumption, we have performed a comparative IR, ^1H NMR, and ^{13}C NMR study on compounds **1a**-**c**–**10a**-**c** (Scheme 1).

The aim of this study was to investigate the stereostructure (configuration and conformation) and the electronic properties (conjugation of the enone moiety with the conjugated and the condensed benzene rings) of our compounds, which determine their reactivity with nucleophilic reagents [8].

---

* Corresponding author (Spectroscopy). Tel.: + 36-1-209-0599; Fax: + 36-1-209-0602; E-mail: sohar@para.chem.elte.hu

PII: S0022-2860(98)00805-9



1a-c — 10a-c

n=0(**a**), 1(**b**) or 2(**c**); X=H (**1**), OCH_3 (**2-4**), NO_2 (**5-7**) or F (**8-10**),
Pos. of X: *ortho* (**2**, **5**, **8**), *meta* (**3**, **6**, **9**) or *para* (**4**, **7**, **10**)

Scheme 1.

2. Materials and methods

The *E*-2-benzylideneketones **1**–**10** were prepared according to the methods described in the literature [9,10]. Elemental analysis data (C, H) of the previously unpublished compounds were within 0.4% of the calculated values. The melting points (°C) and (yields (%)) of unreported compounds are as follows. **2a**: 131–133 (81), **8a**: 134–136 (73), **9a**: 127–129 (88), **2b**: 108–110 (83), **8b**: 56–58 (72), **9b**: 89–91 (89), **2c**: 85–87 (78), **5c**: 130–132 (69), **6c**: 113–15 (85), **7c**: 172–174 (93), **8c**: 59–61 (71) and **9c**: 75–77 (88).

IR spectra were taken in KBr discs with a Bruker IFS-55 instrument, controlled by OPUS 2.0 software. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at room temperature, on a Bruker DRX-500 spectrometer at 500.13 (^1H) and 125.76 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. The standard Bruker microprogram NOEMULT.AU to generate NOE [11,12] was used. DEPT spectra [13] were run in a standard manner [14], using only the $\Theta = 135°$ pulse to separate CH/CH_3 and CH_2 lines phased ‘up’ and ‘down’, respectively. The 2D-HSC spectra [15] were obtained by using the standard Bruker pulse program HXCO.AU.

The ab initio geometry optimisation was carried out using the GAUSSIAN 94 [16] program package at RHF level. The Dunning–Huzinaga full double zeta basis set was used [17] with polarisation functions for all atoms. The criteria of convergence were the standard values of GAUSSIAN 94.

3. Structure

The IR, ^1H and ^{13}C NMR data (Tables 1 and 2) proved the expected structures of the compounds investigated, hence, only their stereostructures and the feature of conjugation in them will be briefly discussed here.

Theoretically, *E* and *Z* geometric isomers can be equally formed in the reaction used for synthesis of our compounds. The *Z* configuration, however, is highly unfavourable because of strong steric interaction between the aryl and carbonyl groups. Nevertheless, for one member of the three series **a**, **b** and **c** (**3a**,**c** and **4b**) the *E* configuration was proved by DNOE experiments directly. The steric close arrangement of H-2′,6′ atoms of the aryl group and the methylene hydrogens vicinal to the C_α (C-2) atom were confirmed by significant NOE: by saturating the signal of one of the interacting groups, intensity enhancement was observed on the signal of the other group (Table 3).

The carbonyl IR-frequency of the compounds investigated is decisively determined by the ring size. The ring strain reveals in higher frequencies [18] for series **a**, relative to series **b** and **c** by 35 and 34 cm^{-1} (mean values), respectively (Table 4).

The mean value of the $\nu C{=}O$ frequencies in the series **a**–**c** are 1698, 1663 and 1664 cm^{-1}. Expansion of electron delocalization including also the aryl group in the side chain causes lowering in the $\nu C{=}O$ frequency for the *meta*- and *para*-substituted derivatives as compared to the *ortho*-analogues in series **a** to an increasing extent (by 5, 11 and 13 cm^{-1}, respectively) in order of substituents F, NO_2 and OMe.

Table 1
^{1}H-NMR data[a] and characteristic IR-frequencies[b] of compounds **1a-c–10a-c**[c]

	$CH_2(3)$	$CH_2(4)$	H-6	H-7	H-8	H-9	=CH[f]	H-2′		H-6′	H-3′		H-5′	H-4	νC=O band	γC_{Ar}H		
	m^{d}(2H)	m^{e}(2H)	$\sim d$(1H)	$\sim t$(1H)	$\sim t$(1H)	$\sim d$(1H)	s(1H)	Aromatic ring in side chain[g]								Band[h]		Band[i]
1a	3.91		7.47	7.53	7.35^{k}	7.84	7.59^{l}		7.59^{l}			7.39		7.35^{k}	1693	740		763
2a	3.91		7.48	7.54	7.36	7.87	8.12	–		7.62	6.90		6.99	7.32	1706	740		749
3a	3.96		7.50	7.57^{k}	7.38	7.86	7.58^{k}	7.13		7.22	–		7.33	6.91	1691	733		781
4a	3.86		7.46	7.52	7.34	7.82	7.55		7.53			6.89		–	1695	735		823
5a	3.83		7.46	7.60	7.41	7.89	7.94	–		7.66	8.08		7.70	7.56	1704		738	
6a	4.11		7.60	7.66	7.45	7.92	7.68	8.53		7.93	–		7.65	8.24	1692	744		809
7a	4.09		7.58	7.66	7.46	7.93	7.69		7.80			8.30		–	1695	740		751
8a	3.89		7.47	7.54	7.34	7.82^{k}	7.83^{k}	–		7.63	7.07		7.18	7.31	1700	736		752
9a	3.95		7.52	7.58	$\sim 7.4^{k}$	7.85	7.55	7.06		$\sim 7.4^{k}$	–		$\sim 7.4^{k}$	7.30	1700	737		775
10a	3.89		7.48	$\sim 7.55^{k}$	7.35	7.82	$\sim 7.55^{k}$		$\sim 7.55^{k}$			7.08		–	1690	734		836
1b	3.13	2.94	7.25	7.49	$\sim 7.45^{k}$	8.16	7.90		$\sim 7.45^{k}$			$\sim 7.45^{k}$		~ 7.45	1661	741		756
2b	3.02	2.89	7.21	7.44	$\sim 7.3^{k}$	8.15	8.04	–		$\sim 7.3^{k}$	6.91		6.97	$\sim 7.3^{k}$	1664	741		763
3b	3.11	2.92	7.23	7.47	7.34	8.12	7.83	6.96		7.02	–		7.32	6.89	1666	742		780
4b	3.13	2.93	7.23	7.46	7.34	8.11	7.84		7.42			6.94		–	1666	744		841
5b	2.87	2.78	7.18	7.43	7.29	$\sim 8.05^{k}$	7.94	–		7.34	$\sim 8.05^{k}$		7.64	7.48	1672	741		755
6b	3.10	2.97	7.26	7.50	7.36	8.11	7.82	8.25		7.71	–		7.59	8.18	1663	746		801
7b	3.11	2.99	7.28	7.53	7.39	8.14	7.85		7.57			8.27		–	1666	738		749
8b	2.94	2.88	7.19	7.43	$\sim 7.3^{k}$	8.11	7.83	–		$\sim 7.3^{k}$	7.07		7.14	$\sim 7.3^{k}$	1670	742		760
9b	3.07	2.92	7.22	7.46	7.33	8.11	7.78	7.10		7.18	–		7.36	7.02	1667	737		764
10b	2.98	2.83	7.13	7.37	7.25	8.02	7.71		7.30			6.99		–	1663	745		844
1c	2.61	2.08	7.20	7.47	7.37	7.80	7.86		7.51			7.43		7.36	1663	757		762
2c	2.53	2.02	7.17	7.44	7.33	7.76	8.12	–		7.37	6.92		6.98	7.33	1662		763	
3c	2.60	2.06	7.18	7.45	7.35	7.79	7.81	7.03		7.09	–		7.33	6.90	1661	744		772
4c	2.62	2.08	7.18	7.45	7.35	7.76	7.79		7.49			6.94		–	1666	757		838
5c	2.26	1.74	7.14	7.50	7.30	7.73	7.95	–		7.36	8.11		7.66	7.50	1665	728		766
6c	2.54	2.08	7.19	7.45	7.32	7.75^{k}	7.77	8.29		7.75^{k}	–		7.58	8.15	1663	735		815
7c	2.49	2.00	7.13	7.40	7.28	7.69	7.72		7.53			8.17		–	1663	750		776
8c	2.51	1.99	7.17^{k}	7.44^{l}	7.33^{m}	7.76	7.90	–		7.41^{l}	7.10		7.16^{k}	7.32^{m}	1670	750		761
9c	2.58	2.06	7.19	7.47	7.35	7.77^{k}	7.76^{k}	7.18		7.25	–		7.38	7.04	1664	750		774
10c	2.45	1.93	7.06	$\sim 7.35^{k}$	7.22	7.65^{l}	7.66^{l}		$\sim 7.35^{k}$			6.97		–	1665	764		831

[a] Chemical shifts (in ppm, $\delta_{TMS}=0$ ppm) and coupling constants (in Hz) at 500 MHz in $CDCl_3$ solution. The assignments were supported by 2D-HSC measurements (except for **4c**, **8c**, **9a**, **10a**,**b**) and for **3a**,**c** and **4b** also by DNOE experiments.

[b] In KBr discs (cm^{-1}).

[c] Further data, IR, NO_2 frequencies for **5a-c–7a-c**, $\nu_{as}NO_2$: 1522 ± 12, $\nu_{s}NO_2$: 1349 ± 9, ^{1}H-NMR, OCH_3: 3.83 ± 0.02 (**2a-c**, **3a-c**, **4b**,**c**), 3.77 (**4a**), CH_2(Pos. 5), $\sim t$(2H): 2.89±0.02 (**1c-4c**, **6c**, **8c**, **9c**), 2.82 (**5c**, **7c**), 2.75 (**10c**); ^{3}J(H-6,H-7): 7.5±0.1, 6.5 (**6b**), 7.1 (**9c**), ^{3}J(H-8,H-9): 7.7±0.1, 7.3 (**1c**, **4b**), 8.2 (**5b**);

[d] Singulet (s) for **1a-10a**, m or $\sim t$ for all other compounds.

[e] m or $\sim t$ for **1b-10b**, qi for **1c-10c**. Splits are 6.8±0.2, where determinable.

[f] Side chain.

[g] Three signals for **1a-c**, $\sim d$(2H), $\sim t$(2H) and $\sim t$(1H), four signals, two $\sim d$ (H-3′,6′) and two $\sim t$(H-4′,5′) for **2a-c** and **5a-c**, three $\sim t$(H-3′,5′,6′) and one qa (H-4′) for **8a-c**, two $\sim d$ (H-4,6′), one $\sim t$ (H-5′) and one $\sim s$ (H-2′) for **3a-c**, and **6a-c**, two $\sim d$ (H-2′,6′) and two $\sim t$ (H-4′,5′) for **9a-c**, two signal, 2x$\sim d$ (2x2H) for **4a-c** and **6a-c** and dd (H-2′,6′) and t (H-3′,5′) for **10a-c**. Coupling constants are ^{3}J(H,H): 7.6±0.2, ^{4}J(H,H): 2.3±0.2, except for the following cases: 8.2±0.2 (**2a-c**, **5a-c**, H-3′,4′ and **3a-c**, **6a-c**, H-4′,5′), 8.7 (**4a-c**, **7a-c**, H-2′,3′ and **10a-c**, H-2′,3′ and F,H-3′), 9.6±0.2 (**8a-c**, F,H-3′ and **9a-c**, F,H-4′).

[h] Condensed ring.

[i] Side chain. For the phenyl substituents, γ$C_{Ar}C_{Ar}$: 691 (**1a**,**c**), 697 (**1b**).

[k,l,m] Overlapping signals.

Table 2
^{13}C-NMR chemical shifts (in ppm, $\delta_{TMS} = 0$ ppm) of compounds **1a-c–10a-c** in $CDCl_3$ solution at 125.7 MHz[a]

	C=O	C-2	CH_2(3)	CH_2(4)	C-5a	C-6	C-7	C-8	C-9	C-9a	=CH[b]	C-1′	C-2′		C-6′	C-3′		C-5′	C-4′
1a	194.6	150.0	32.8		138.4	126.6	135.0[c]	128.1	124.7	135.7[c]	134.2	135.1[c]		131.1			129.3		130.1
2a	194.6	150.1	32.7		138.7	126.5	134.7	127.9	124.7	135.0	128.9	124.9	159.5		130.0	111.5		120.9	131.5
3a	194.1	149.5	32.2		137.8	126.1	134.5	127.5	124.2	134.8	133.6	136.5	116.0		123.1	159.6		129.7	115.0
4a	194.0	149.3	32.2		138.0	125.9	134.1	127.3	124.0	132.2	133.5	127.9		132.3			114.2		160.6
5a	193.5	149.3	31.5		138.4[c]	126.6	135.4	128.3	125.1	138.6[c]	129.9[d]	131.7	149.9		131.0	125.5		133.6	129.9[d]
6a	193.6	149.3	32.2		137.5[c]	126.3	135.2	128.0	124.7	137.4[c]	130.8	137.0[c]	124.2		136.4	148.7		130.0	123.8
7a	193.6	149.3	32.3		138.5	126.3	135.3	128.1	124.8	137.5	130.8	141.7		131.0			124.1		147.7
8a	193.6	149.4	32.1		137.7	126.0	134.6	127.5	124.3	136.4	125.2	123.3	161.6		129.8	115.9		124.1	131.1
9a	193.9	149.4	32.2		137.6	126.1	134.7	127.7	124.3	135.7	126.6	137.3	116.6		132.2	162.8		130.3	116.4
10a	193.9	149.3	32.1		137.7	126.0	134.5	127.5	124.2	134.1[d]	134.1[d]	131.4		132.4			115.9		163.1
1b	187.7	143.1	27.0	28.7	135.7[c]	128.4[e]	133.1	126.9	128.1[d,e]	133.3	136.5	135.3[c]		129.7			128.3		128.1[d,e]
2b	188.2	143.8	28.0	29.5	135.9	128.7	133.6	127.3	128.6	134.1	133.1	125.3	158.7		130.1[d]	111.2		120.5	130.1[d]
3b	187.7	143.1	27.1	28.7	137.0[c]	128.1[d]	133.2	126.9	128.1[d]	133.3	136.4	135.6[c]	115.2		122.1	159.4		129.3	113.9
4b	187.7	143.0	27.1	28.7	133.6[c]	128.0[d]	133.0	126.9	128.0[d]	133.4[c]	136.6	128.3		131.7			113.9		159.9
5b	187.5	143.9	27.6	29.3	137.4	128.9	134.8	127.5	128.6	133.5	133.1	132.2	148.6		131.7	125.3		133.8	129.6
6b	187.1	143.0	27.1	28.6	137.4[c]	128.3[d]	133.6[e]	127.2	128.3[d]	133.0	133.4[e]	137.8[c]	124.1		135.6	148.2		129.5	123.0
7b	187.2	143.1	27.3	28.7	138.5	128.3	133.7	127.3	128.4	133.0	133.6	142.5		130.4			123.7		147.3
8b	187.6	143.9	28.0	29.3	138.1	128.7	133.8	127.4	129.5	133.7	128.6	124.2	161.1		131.1	116.2		124.3	130.8
9b	187.3	143.0	27.0	28.6	136.4	128.1[d]	133.3	126.9	128.1[d]	133.2	134.9	137.8	116.2		125.5	162.5		129.9	115.2
10b	187.6	143.0	27.0	28.7	135.1	128.1[d]	133.2	127.0	128.1[d]	133.3	135.4	131.8		131.7			115.4		162.5
1c	197.9	139.6[c]	24.7	26.5	138.6[c]	128.9	132.3	126.9	129.0	137.9[c]	137.8	135.7		129.4			128.5[d]		128.5[d]
2c	198.2	140.0	25.3	27.5	139.6[c]	129.2	132.6	127.4	129.4	138.0[c]	134.9	125.4	158.8		129.8	111.2		120.6	130.5
3c	197.7	139.5[c]	24.7	26.5	138.5[c]	128.8	132.3	126.9	129.0	136.9[c]	137.7	138.0[c]	114.8		121.7	159.5		129.4	114.1
4c	199.0	139.5[c]	24.9	26.4	139.0[c]	128.8[e]	132.2	126.9	129.0[e]	135.7	137.7	128.2		131.3			114.1		160.1
5c	197.5	140.2[c]	24.8	26.9	139.8[c]	129.5[d]	133.1	127.4	129.5[d]	138.6[c]	135.2	132.7[c]	148.5		131.3	125.3		133.9	129.5[d]
6c	196.9	140.3	24.6	26.2	139.4	129.0	132.6	126.9	129.1	137.8[c]	134.7	137.2[c]	123.5		135.1	148.1		129.5	122.9
7c	197.1	141.0[c]	24.8	26.4	139.4	129.0	132.8	127.1	129.2	137.9	135.0	142.4[c]		129.9			123.7		147.3
8c	197.8	140.4[c]	25.4	26.8	140.1[c]	129.4	132.9	127.4	129.5	139.0[c]	131.1	124.3	161.4		130.4	116.2		124.4	130.7
9c	197.6	139.5[c]	24.7	26.4	138.9[c]	129.0	132.5	127.0	129.2	138.4[c]	136.4	137.9	115.8		125.3	162.7		130.0	115.4
10c	197.5	139.5[c]	24.6	26.3	138.5[c]	128.8	132.3	126.9	129.0	137.5[c]	136.5	131.7		132.2			115.5		162.6

[a] The assignments were supported by DEPT (except for **7a)** and 2D-HSC measurements (except for **4c**, **8c**, **9a** and **10a**,**b**). Further signals: OCH_3: 56.0 (**2a**), 55.2 (**3a**, **4b**), 55.1 (**4a**, **3b**,**c**), 55.9 (**2b**,**c**), 55.3 (**4c**); CH_2 (Pos. 5): 31.5 ± 0.1 (**1c**, **3c**, **5c**, **6c**, **7c**, **9c**, **10c**), 32.0 (**2c**), 31.7 (**4c**) 31.9 (**8c**); J(F,C): coupling constants in Hz, ^{1}J: 253.6 (**8a**), 250.2 (**8b**), 249.6 ± 0.2 (**8c**, **10b**,**c**), 246.5 (**9a**,**c**), 245.8 (**9b**), 252.0 (**10a**), $^{2}J(F,C_{quat.})$: 11.9 (**8a**), 14.2 (**8b**,**c**), ^{2}J(F,CH): 22.0 ± 0.1 (**8a-c**, for C-2 in **9c**), 21.0 ± 0.2 (for both couplings in **9a**,**b**, and for C-4 in **9c**), 21.5 (**10a-c**), $^{3}J(F,C_{quat})$: 7.7 (**9a-c**), ^{3}J(F,CH): 8.6 (for C-4 in **8a**), 2.3 (for C-6 in **8a**), >1 (for C-6 in **8b**,**c**), 9.1 (**10a**), 8.2 ± 0.1 for all other cases (except for C-4 in **8c** where undefined due to signal overlap), $^{3}J(F,CH_{olefinic})$: 5.6 (**8a**), <1 (**8b**,**c**, **9a-c)**, ^{4}J: 3.6 (**8a**), 3.0 ± 0.2 (**8b**,**c**, **9b**, **10a-c**), 2.2 (**9a**), <1 (**9c**).

[b] Side chain

[c,e] Interchangeable assignments.

[d] Overlapping signals, in case of **1b**, **2b**, **4b**, **5c** and **10a** there are differences in the second decimal of chemical shifts within the limit of error.

Table 3
Results of DNOE measurements on compounds **3a,c** and **4b**

Saturated signal	Responses 3-CH_2 [a]	H-2′	H-6′	H-2′,6′	H-6	=C_βH
3-CH_2 [b,c]		**3a,c**	**3a,c**		**3a**	
H-2′	**3c**					**3a,c**
H-6′ [d]						**3a,c**
H-2′,6′ [e]	**4b**					**4b**
=C_βH		**3a,c**	**3a,c**	**4b**		
5-CH_2 [b]					**3c**	

[a] Vicinal to =C(α). Further responses:
[b,c] 4-CH_2 (**3c**, **4b**)
[d] H-5′ (**3a,c**)
[e] H-3′,5′ (**4b**).

In the fluoro compounds the ring size did not influence the frequency difference of positional isomers. The slightly higher νC=O frequency of the *ortho*-fluoro compounds is due to the $-I$ effect of the substituents [19] being more effective in this position instead of a change in the conformational equilibrium corresponding to the rotation around the $C_\beta - C_{Ar}^{-1}$ bond.

The same is valid for the methoxy-analogues in series **b** and **c** (including six- and seven-membered rings). In series **a**, however, a spectacular change is observable in the νC=O frequency, hence in the participation of the aryl group in the conjugation; the conjugation spreads into the aryl group, which reveals itself in a lowering of the νC=O frequency by 15 and 11 cm^{-1}, respectively, for **3a** and **4a** as compared to **2a**.

Nitro compounds represent an intermediate case between the fluoro and methoxy derivatives. The influence of changes in ring size or the position of the substituent (and simultaneously in equilibriums of rotamers corresponding to rotations around the $C_\beta - C_{Ar}^{-1}$ or C_{Ar}^{subset}–N(O_2) bonds) on the νC=O frequency operates in different proportions; the difference in frequencies between positional isomers **5a** and **6a**/**7a** (5-ring series) is high (11 cm^{-1}), while it is small for benzosuberones (**c** series), thus the spread of conjugation changes significantly in the case of **a**-type compounds, while only scarcely in series **c**.

In series **b** (in the tetralones), both rotational equilibrium differ for the individual compounds influencing equally the νC=O frequency.

Very large differences were observed in the ^{1}H NMR spectra of *ortho*- and *meta/para*-substituted compounds for the chemical shifts H_β in series **a**, the mean downfield shift is 0.56, 0.26 and 0.28 ppm in the cases of OMe, NO_2 and F substituents. In the **b** and **c** series much smaller and scarcely different from one another shift differences (0.09–0.22 ppm) were measured. The delocalization in the enone system and consequently the bond polarization, thus causes the paramagnetic shifts [20] of the H_β signal to be diminished by the buffering effect of the aryl group of electron-reservoir nature in coplanar arrangement, possible for *meta*- and *para*-substituted derivatives.

From the above data, in accord with the IR frequencies, it may be concluded, that:

1. the enone moiety is planar in series **a** and non-planar for series **b** and **c**.
2. in series **a** the aryl group is also coplanar with the enone moiety, thus for this series a fully planar molecular skeleton is characteristic, while in series

Table 4
Spectral data on compounds **1a**–**10a**, **1b**–**10b** and **1c**–**10c** relevant to electron distribution (conjugation) and stereostructure (conformational equilibrium)

Assignment	Spectrum	Position of aryl substituent	Series (x-membered ring) **a** (5)	**b** (6)	**c** (7)
νC=O	IR		1698 ± 8	1663 ± 3	1664 ± 3
=CH(Ar)		*m, p*	7.62 ± 0.07	7.80 ± 0.10	7.76 ± 0.10
[H_β]	^{1}H NMR	*o*	8.12	8.02	8.12
H-9			7.87 ± 0.05	8.09 ± 0.07	7.73 ± 0.07
C=O			194.1 ± 0.5	187.4 ± 0.3	197.6 ± 0.6
	^{13}C NMR	*m, p*	16	8	2
$\Delta\delta$[C(α)-C(β)]		*o*	21	11	4

Table 5
Calculated dihedral angles Θ_1, Θ_2 and Θ_3 [a] in compounds **1a-c**

	Θ_1	Θ_2	Θ_3
1a	0	0	0
1b	10.4	12.7	43.5
1c	− 32.0	− 15.3	40.8

[a] c.f. text.

b and **c**, the conformers with out-of-plane aryl group to the enone plane are preferred, except for compounds **9c** and **10c**, where the aryl group is coplanar with the C=C bond of the non-planar enone group in the dominant conformer.

For the H-9 atom of the condensed benzene ring, in *peri* position to the carbonyl group, the following mean chemical shift values were measured in series **a**, **b** and **c**: 7.87, 8.09 and 7.73 ppm, respectively (Table 4). Consequently, the coplanar arrangement of the carbonyl to the condensed ring in series **a** did not change significantly in the tetralones (in series **b**), and the anisotropic effect of the carbonyl [21] causes an even larger downfield shift on the H-9 signal. The higher paramagnetic shift can be explained by the backforced polarization of the C=O bond in the non-planar enone group; the anisotropy of the carbonyl group becomes stronger due to enhanced bond order.

After all, these facts refer to an essentially unaltered C(9)–C(9a)–C=O dihedral angle, which deviated only slightly from 0° also in series **b**. On the other hand, from the stronger shielding of H-9 in series **c** it may be concluded that this dihedral angle significantly changes.

From the ^{13}C NMR shifts further conclusions can be drawn, supporting the above statements:

1. the chemical shift difference of C_α and C_β atoms ($\Delta\delta C_\alpha C_\beta$) is characteristic of the polarization in the enone moiety (the extension of delocalization [22]): the more polarized is the enone group the higher is $\Delta\delta C_\alpha C_\beta$. The mean value of $\Delta\delta C_\alpha C_\beta$ is 16, 8 and 2 ppm in the 5-, 6- and 7-membered alkanone ring containing series **a**, **b** and **c** for *meta*- and *para*-substituted compounds, while for *ortho*-analogues more enhanced data were observed (21, 11 and 4 ppm, respectively). Hence, enone polarization is most pronounced in series **a** (full planar structure) and even stronger for the *ortho*-substituted compounds where the buffering effect of the out-of-plane aryl group cannot be effective (c.f. Table 4).
2. the mean shift of carbonyl carbons with only slight fluctuation is 187.4 ppm in the tetralones (series **b**). Due to ring strain [15] this value is higher in series **a** (194.1 ± 0.5 ppm) and a further increase can be observed for series **c**, the seven-membered alkanone ring containing benzosuberones (197.6 ± 0.6 ppm). The latter enhancement in the C=O shift is due to the moderate bond polarization as compared to series **a** and **b**, which results from its localization to the C=O bond in the non-planar enone moiety.

Quantum chemical calculations were carried out to support our suggestions from IR and NMR spectroscopic investigations concerning the conformational behaviours of series **a**, **b** and **c** containing 5-, 6- and 7-membered alkanone rings and different substituents in different positions on the benzene ring of the aryl group.

Ab initio geometry optimisation on compounds **1a**-**c** lead to results (Table 5) which are in excellent agreement with our spectroscopic conclusions. They support

1. the fully planar structure of type **a** compounds (the three dihedral angles relevant to conformations are equally 0°);
2. the moderate and considerable distortion of dihedral angle Θ_1: C(9)–C(9a)–C=O in series **b** and **c**, respectively;
3. the moderate and commensurable change in dihedral angle Θ_2: O=C–C(α)=C(β)—deviation of the enone moiety from coplanar arrangement—in series **b** and **c**; and
4. the similar and significant distortion in dihedral angle Θ_3: C(α)=C(β)–C(1,Ar)–C(2,Ar) in both series **b** and **c**: the preference of the non-planar arrangement of the aryl group and the enone moiety.

Acknowledgements

The authors are indebted to Dr A Csámpai and Mrs. A. Böszin-Nagy for skilled technical assistance.

Thanks are also due to the Hungarian Research Foundation (OTKA) for financial support.

References

[1] J.R. Dimmock, M.L.C. Wong, Can. J. Pharm. Sci. 11 (1976) 35–53.

[2] T.M. Al-Nakib, V. Bezjak, M.J. Meegan, R. Chandy, Eur. J. Med. Chem. 25 (1990) 455–462.

[3] E. Erciyas, H.I. Erkaleli, G. Cosar, J. Pharm. Sci. 83 (1994) 545–548.

[4] R.J. Anto, K. Sukumaran, G. Kuttan, M.N. Rao, V. Subbaraju, R. Kuttan, Cancer-Lett. 97 (1995) 33–37.

[5] T.M. Al-Nakib, P. Perjési, R. Varghese, M.J. Meegan, Med. Princip. & Pract. 6 (1997) 14–21.

[6] P. Perjési, T.M. Al-Nakib, R. Varghese, Med. Princip. Pract., in preparation.

[7] P. Perjési et al., unpublished results.

[8] D. Duval, S. Geribaldi, Nucleophilic attacks on enones, in: S. Patai, Z. Rappoport (Eds.), The Chemistry of Enones, vol. 1, Wiley, Chichester, 1989, 355–469.

[9] A.T. Nielsen, W.J. Houlihan, The aldol condensation, in: Organic Reactions, vol. 16, Wiley, New York, 1968, 44–47.

[10] A. Hassner, N.H. Cromwell, J. Amer. Chem. Soc. 80 (1958) 893–900.

[11] J.K.M. Sanders, J.D. Mersch, Progr. Nucl. Magn. Reson. 15 (1982) 353 and references cited therein..

[12] P. Sohár, Nuclear Magnetic Resonance Spectroscopy, vol. 1, CRC Press, Boca Raton, Florida, 1983, 196–197.

[13] D.T. Pegg, D.M. Doddrell, M.R. Bendall, J. Chem. Phys. 77 (1982) 2745.

[14] M.R. Bendall, D.M. Doddrell, D.T. Pegg, W.E. Hull, High Resolution Multipulse NMR Spectra Editing and DEPT, Bruker, Karlsruhe, 1982.

[15] R.R. Ernst, G. Bodenhausen, A. Wokaun, Principles of Nuclear Magnetic Resonance in One and Two Dimension, Clarendon Press, Oxford, UK, 1987, 471–479.

[16] GAUSSIAN 94 (Revision B.2), M.J. Frisch, G.W. Trucks, H.B. Schlegel, P.M.W. Gill, B.G. Johnson, M.A. Robb, J.R. Cheeseman, T.A. Keith, G.A. Petersson, J.A. Montgomery, K. Raghavachari, M.A. Al-Laham, V.G. Zakrzewski, J.V. Ortiz, J.B. Foresman, J. Cioslowski, B.B. Stefanov, A. Nanayakkara, M. Challacombe, C.Y. Peng, P.Y. Ayala, W. Chen, M.W. Wong, J.L. Andres, E.S. Replogle, R. Gomperts, R.L. Martin, D.J. Fox, J.S. Binkley, D.J. Defrees, J. Baker, J.P. Stewart, M. Head-Gordon, C. Gonzales and J.A. Pople, Gaussian Inc., Pittsburgh Pa, 1995.

[17] T.H. Dunning Jr., P.J. Hay, in: H.F. Schaefer (Ed.), Modern Theoretical Chemistry, vol. 3, Plenum, New York, 1976, 1–28.

[18] S. Holly, P. Sohár, in: L. Láng, W.H. Prichard (Eds.), Theoretical and Technical Introduction to the Series ‘‘Absorption Spectra in the Infrared Region’’, Akadémiai Kiadó, Budapest, 1975, 97.

[19] S. Holly, P. Sohár, in: L. Láng, W.H. Prichard (Eds.), Theoretical and Technical Introduction to the Series ‘‘Absorption Spectra in the Infrared Region’’, Akadémiai Kiadó, Budapest, 1975, 96.

[20] P. Sohár, Nuclear Magnetic Resonance Spectroscopy, vol. 2, CRC Press, Boca Raton, Florida, 1983, 52.

[21] P. Sohár, Nuclear Magnetic Resonance Spectroscopy, CRC Press, Boca Raton, Florida, 1, 1983, 32–33 and 2, 51.

[22] P. Sohár, Nuclear Magnetic Resonance Spectroscopy, vol. 2, CRC Press, Boca Raton, Florida, 1983, 181, 182 and 197.