Rearrangement products of some 1*R*,4*R*-2-arylidene-*p*-menthan-3-ones in acidic media, their structures, and conformational analysis

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1*R*,4*R*-2-(4-Phenylbenzylidene)-*p*-menthan-3-one in acidic media undergoes rearrangement with migration of the exocyclic double bond to the cyclohexane ring to form three 2-(4-phenylbenzyl) derivatives of *p*-menthen-3-ones. The reaction products differ in the location of the endocyclic double bond (Δ^1 or Δ^4) and in the configuration of the new chiral C(2) center in the resulting *p*-menth-4-en-3-ones. The configurations of the 1*R*,2*R*- and 1*R*,2*S*-2-(4-phenylbenzyl)-*p*-menth-4-en-3-ones were established based on analysis of their ^{1}H NMR spectra in combination with calculations by molecular mechanics. The molecular conformations of these compounds as well as of some racemic 2-benzyl-*p*-menth-1-en-3-one derivatives were studied.

Key words: 1*R*,4*R*-2-(4-phenylbenzylidene)-*p*-menthan-3-one, rearrangement, isomeric 2-(4-phenylbenzyl)-*p*-menthen-3-ones, IR spectra, ^{1}H NMR spectra, conformational analysis, molecular mechanics.

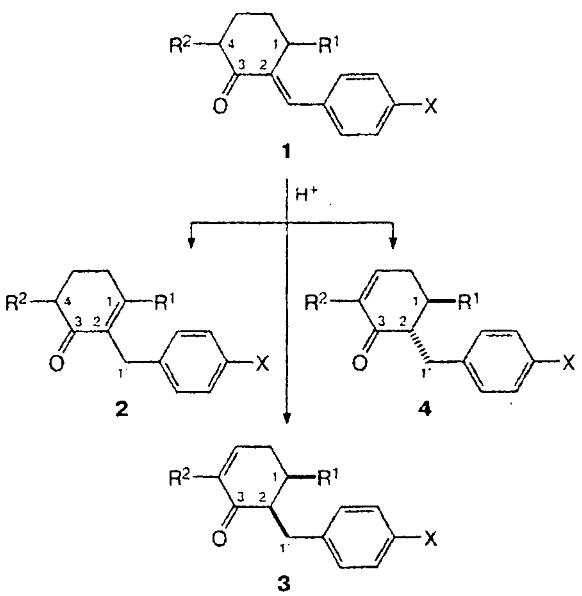
1*R*,4*R*-2-Arylidene-*p*-menthan-3-ones[1,2] are known as efficient chiral additives for liquid-crystal materials.[3,4] Studies of procedures for their chemical modifications with the aim of preparing new chiral and, probably, liquid-crystal compounds are of considerable interest.

Previously,[5] in attempting to perform demethylation of 1*R*,4*R*-2-(4-methoxybenzylidene)-*p*-menthan-3-one (**1a**) by fusing with pyridine hydrochloride, it was found that this process was accompanied by isomerization of the alicyclic fragment of the molecule to form a racemic 2-(4-hydroxybenzyl) derivative of 6-isopropyl-3-methylcyclohex-2-en-1-one (**2a**) in high yield (Scheme 1). The structure of the latter was confirmed by X-ray diffraction analysis of its 4-benzoyl derivative **2b**. Analogous conversions in acidic media were also observed[6] for some 2-arylidenecyclohexanones containing a hydrogen atom at the α′ position with respect to the carbonyl group (**1c** → **2d**, Scheme 1).

Studies of these rearrangements and investigations of the structures and conformational behavior of their products are of importance in the chemistry and stereochemistry of cyclic enone systems.

In this work, we studied the structures of rearrangement products of 1*R*,4*R*-2-(4-phenylbenzylidene)-*p*-menthan-3-one (**1b**), which were prepared both as described previously[5] and upon catalysis with strong acid ($HClO_4$), by IR and ^{1}H NMR spectroscopy in combination with conformational analysis by molecular mechanics (MM).[7] For comparison, we performed the conformational analysis of compound **2a** (a rearrange-

Scheme 1



Compound	R¹	R²	X
1a	Me	Prⁱ	OMe
1b	Me	Prⁱ	Ph
1c	H	Me	H
2a	Me	Prⁱ	OH
2b	Me	Prⁱ	OCOPh
2c	Me	Prⁱ	Ph
2d	H	Me	H
1*R*,2*R*-*cis*-**3**	Me	Prⁱ	Ph
1*R*,2*S*-*trans*-**4**	Me	Prⁱ	Ph
4a	Me	Prⁱ	H

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ment product of **1a**) and its benzoyl derivative **2b**, which were prepared according to procedures described previously,[5] using analogous methods. The use of magnetically anisotropic solvents (C_6D_6 and DMSO-d_6) in ^{1}H NMR spectral studies of compound **2b** allowed us to obtain more informative spectra due to specific changes in the chemical shifts caused by these solvents.[8]

Identification of rearrangement products. Treatment of compound **1b** with Py · HCl or a catalytic amount of $HClO_4$ in CCl_4 afforded compound **2c** as well as two compounds with close elution times (**3** and **4**, HPLC data, see the Experimental section) in approximately equal yields. The spectral characteristics (IR and ^{1}H NMR) of these products and (for comparison) of compounds **2a** and **2b** prepared previously[5] are given in Tables 1—3. Based on the data of IR spectroscopy and taking into account generalizations made previously,[9,10] it can be concluded that rearrangement products **2c**, **3**, and **4** (like **2b**, which was studied by X-ray diffraction analysis[5]) contain the *s-trans*-enone fragment. This is evidenced by the ν(C=O) stretching vibration frequencies of the carbonyl groups of these products (see Table 1), which are close to those for compound **2b**, but are substantially lower than those for the starting *s-cis*-α,β-unsaturated ketones (1674 and 1676 cm^{-1} for **1a** and **1b**, respectively[1,11]), as well as by (as distinct from compounds containing the *s-cis*-enone fragment[9,10]) the higher frequencies and very low intensities of the ν(C=C) stretching vibration bands of the double bond and of the ν(Ar) skeletal vibrations of the benzene ring. The latter characteristic feature is typical primarily of weakly polarized benzene rings.

Although compounds **2c** and **4** were isolated by preparative liquid chromatography only as fractions containing 80—86% of the major compound (see the Experimental section), the ^{1}H NMR spectral studies made it possible to unambiguously identify all major rearrangement products. Thus, the ^{1}H NMR spectra (see Tables 2 and 3) indicate that products **2c**, **3**, and **4** have isomeric structures, which differ in the position of the endocyclic double bond. In the case of compound **2b**, whose structure was established by X-ray diffraction analysis,[5] a singlet of the methyl group observed in the ^{1}H NMR spectrum (in $CDCl_3$) at δ 1.96 corresponds to the double bond Δ^1. According to the ^{1}H NMR spectral data (see Table 2), product **2c** contains the endocyclic double bond in the analogous position. Unlike the above-mentioned spectrum, the spectra of **3** and **4** have a doublet of the methyl group at higher field (like different derivatives of *p*-menthan-3-ones and *p*-menth-4-en-3-one[11,12]) and a multiplet at δ 6.48 corresponding to the proton of the double bond, whereas the signal for the H(4) proton is absent, which indicates that the double bond in these compounds is located in the Δ^4 position.

Table 1. Selected physicochemical characteristics of rearrangement products **2—4**

Compound	M.p. /°C	Elution time/min[a]	IR, ν/cm^{-1}		
			ν(C=O)[b]	ν(C=C)	ν(Ar)
2a	87—89	—	1665[c]	1632[c]	1600[c]
2b	96—97.5	—	1664	1632	1602
2c	—	5.23	1658	1630	1600[d]
3	59.5—60.5	3.10	1672	1600	1600
4	—	3.37	1666	1600	1600

[a] See the Experimental section.

[b] The ν(C=O) values for the menthenone fragment are given; for compound **2b**, ν(C=O) for the ester is observed at 1742 cm^{-1}.

[c] The spectrum was measured in CCl_4. The ν(OH) absorption band of the hydroxyl group is observed at 3440 cm^{-1}. [d] Inflection in the low-frequency shoulder of the ν(C=C) band.

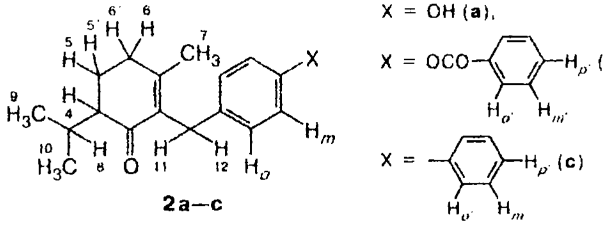
Other characteristic features of the ^{1}H NMR spectra are also consistent with the above-mentioned structural differences. In all cases, the protons of the methyl groups of the isopropyl fragment are magnetically nonequivalent and give two doublets with a vicinal spin-spin coupling constant of 6.8 Hz, as in the case of 2-arylidene derivatives of *p*-menthan-3-one[11] and nonsubstituted *p*-menth-4-en-3-one[12] studied previously (see Table 2). The signals for the methine proton of the isopropyl group in the spectra of compounds **2a—c**, **3**, and **4** differ in position and multiplicity in accordance with the above-mentioned difference in the position of the endocyclic double bonds.

The magnetic nonequivalence of the benzyl protons observed in the spectra of all the compounds under study (see Table 2) reflects the asymmetry of their molecular structures.[13]

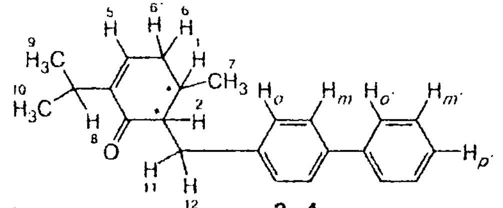
Therefore, the analysis of the spectral data demonstrated that the cyclic fragment of rearrangement product **2c** has a structure analogous to those of compounds **2a** and **2b** studied previously.[5] Apparently, products **3** and **4**, which were found for the first time in the case of the rearrangement of compound **1b**, are stereoisomeric 2-(4-phenylbenzyl) derivatives of *p*-menth-4-en-3-one, which differ in the configuration of the new chiral C(2) center (*i.e.*, these compounds are the 1*R*,2*R*-*cis* and 1*R*,2*S*-*trans* diastereomers). A change in the configuration of the C(1) atom in the course of the rearrangement seems to be unlikely taking into account the possibility for the process to proceed through the formation of the dienol form[6] involving only the C(4) center.

Determination of configurations of diastereomeric products. The configurations of products **3** and **4** were established based on their ^{1}H NMR spectra in combination with conformational analysis by the MM method for model structures **3a** and **4a** (see Scheme 1, X = H).

The calculated steric energies (E_{st}) for the most probable conformations of compounds **3a** and **4a**, which differ both in the orientation of the methyl group with respect to the cyclohexenone ring and in the rotation of the exocyclic isopropyl and benzyl fragments (see the Newman projections), are given in Table 4. The methyl group in conformers *A—C* of diastereomer **3a** and in conformers *A—D* of diastereomer **4a** is in the equatorial



2a—c



3, 4

Table 2. Chemical shifts (δ) in the ^{1}H NMR spectra of rearrangement products **2**, **3**, and **4**

Compound	Solvent	H(1)	H(2)	H(4)	H(5)	H(5′)	H(6)	H(6′)	H(11)	H(12)	H(8)	CH$_3$(7)	CH$_3$(9,10)	H$_o$	H$_m$	H$_{o'}$	H$_{m'}$	H$_{p'}$
2a	CD$_2$Cl$_2$	—	—	2.02	1.91	1.76	2.37	2.32	3.56	3.53	2.29	1.92	0.79; 0.83	6.93	6.62	—	—	—
2b	CDCl$_3$	—	—	2.08	1.97	1.81	2.42	2.39	3.72	3.67	2.37	1.96	0.84; 0.90	7.07	7.20	8.19	7.50	7.61
2b	DMSO-d$_6$	—	—	2.13	1.96	1.77	2.48	2.48	3.69	3.67	2.31	2.00	0.83; 0.90	7.19	7.23	8.17	7.65	7.80
2b	C$_6$D$_6$	—	—	1.85	1.52	1.40	1.76	1.74	3.71	3.68	2.46	1.45	0.83; 0.86	7.09	7.20	8.17	7.03	7.12
2c	CDCl$_3$	—	—	2.09	1.98	1.82	2.42	2.40	3.74	3.70	2.38	1.98	0.85; 0.90	7.21	7.46	7.55	7.40	7.30
3	CDCl$_3$	2.26	2.77	—	6.48	—	2.54	2.21	2.62	3.28	2.87	0.97	1.01; 1.04	7.25	7.51	7.58	7.43	7.32
4	CDCl$_3$	2.02	2.44	—	6.54	—	2.59	2.11	2.98	3.00	2.90	1.04	1.01; 1.03	7.27	7.50	7.57	7.42	7.32
2b	Δδ*	—	—	0.23	0.46	0.41	0.66	0.65	0.01	−0.01	−0.09	0.51	0.01; 0.04	0.02	−0.00	0.02	0.47	0.50

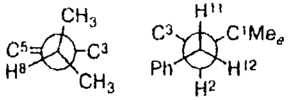
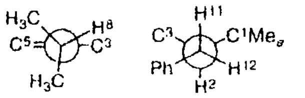
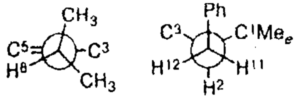
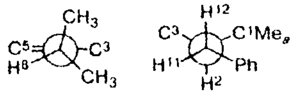
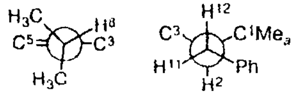
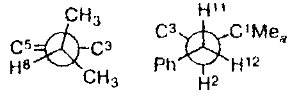
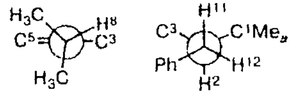
* $\Delta\delta = \delta(CDCl_3) - \delta(C_6D_6)$.

Table 3. Experimental spin-spin coupling constants (*J*) in the ^{1}H NMR spectra of rearrangement products **2a—c**, **3**, and **4**

Compound	Solvent	*J*/Hz										
		H(6),H(6′)	H(5),H(5′)	H(11),H(12)	H(4),H(5)	H(4),H(5′)	H(4),H(8)	H(5),H(6)	H(5),H(6′)	H(5′),H(6)	H(5′),H(6′)	H(8),CH$_3$(9,10)
2a	CD$_2$Cl$_2$	−17.2	−12.5	−13.7	4.5	10.7	5.3	4.3	4.4	9.2	4.6	6.8
2b	CDCl$_3$	−17.6	−13.2	−14.4	4.5	10.6	5.2	4.4	4.9	9.6	4.2	6.9
	DMSO-d$_6$	−17.5	−12.9	−15.5	4.5	10.6	5.1	4.3	4.8	9.7	4.3	6.8
	C$_6$D$_6$	−17.1	−13.0	−15.3	4.5	10.8	5.3	4.2	4.8	9.7	4.2	6.9
2c	CDCl$_3$	−17.8	−12.8	−14.9	4.5	10.5	5.0	4.6	4.9	9.5	4.2	6.8
		H(6),H(6′)	H(11),H(12)	H(1),H(2)	H(1),H(6)	H(1),H(6′)	H(2),H(11)	H(2),H(12)	H(5),H(6)	H(5),H(6′)	H(8),CH$_3$(9,10)	H(1),CH$_3$(7)
3	CDCl$_3$	−18.2	−14.0	3.5	4.1	4.9	8.8	5.7	3.0	4.9	6.7	6.8
4	CDCl$_3$	−18.6	−14.1	6.9	4.8	5.9	5.4	7.9	3.9	3.9	6.8	6.6

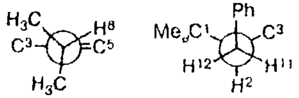
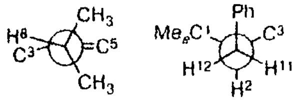
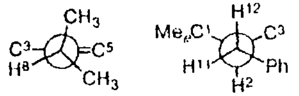
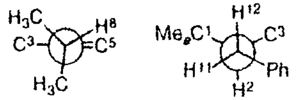
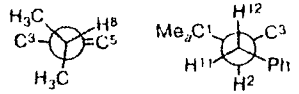
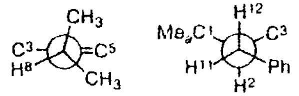
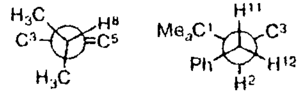
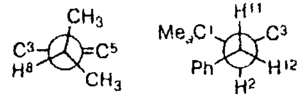
Note. For the multiplets of the H(5) and H(8) protons in compounds **3** and **4** and for the multiplet of the H(6) proton in compound **3**, the long-range spin-spin coupling constants $J_{H(5),H(8)}$ = 1.3 Hz and $J_{H(6),CH3(7)}$ = 1.5 Hz are observed.

Table 4. Steric energies (E_{st}/kJ mol^{-1}) and the H—C—C—H torsion angles (φ(H,H)/deg) for the most probable conformers of model structures **3a** and **4a** based on the results of calculations by molecular mechanics and the vicinal spin-spin coupling constants of the protons (^3J/Hz) calculated according to Eqs. (1)—(3)

Conformer	Conformation	E_{st}	Conformation (%)	φ(1,2)	$^3J_{H(1),H(2)}$			φ(1,6)	$^3J_{H(1),H(6)}$			φ(1,6′)	$^3J_{H(1),H(6')}$		
					(1)	(2)	(3)		(1)	(2)	(3)		(1)	(2)	(3)
					Compound **3a** (1*R*,2*R*)										
A		79.4	29.8	54	3.4	4.3	3.5	−53	3.6	4.8	4.4	−170	10.0	11.8	11.4
B		80.3	21.2	55	3.3	4.2	3.4	−53	3.6	4.8	4.4	−170	10.0	11.8	11.4
C		85.3	2.8	48	4.1	5.1	4.4	−55	3.3	4.5	4.1	−173	10.1	12.0	11.6
D		81.1	15.1	−63	2.5	3.2	2.4	49	4.0	5.3	4.4	−68	2.1	2.8	2.4
E		81.9	10.8	−62	2.6	3.3	2.5	51	3.8	5.1	4.3	−67	2.2	3.0	2.5
F		82.3	9.1	−61	2.7	3.4	2.6	49	4.0	5.3	4.5	−68	2.1	2.8	2.4
G		83.2	6.5	−61	2.7	3.4	2.6	50	3.9	5.2	4.3	−67	2.1	2.9	2.5
	$^3J^{av}$				3.1	3.9	3.1		3.7	5.0	4.4		6.7	8.1	7.7

(*To be continued*)

Table 4. (*Continued*)

Confor-mer	Conformation	E_{st}	Confor-mation (%)	φ(1,2)	$^3J_{H(1),H(2)}$			φ(1,6)	$^3J_{H(1),H(6)}$			φ(1,6′)	$^3J_{H(1),H(6')}$		
					(1)	(2)	(3)		(1)	(2)	(3)		(1)	(2)	(3)
					Compound **4a** (1*R*,2*S*)										
A		77.7	39.8	172	10.1	11.2	11.1	−59	2.9	4.0	3.5	−177	10.2	12.1	11.8
B		80.7	11.4	173	10.0	11.1	11.1	−58	3.0	4.1	3.7	−176	10.2	12.1	11.8
C		81.9	6.7	176	10.2	11.3	11.3	−55	3.4	4.5	4.1	−173	10.1	11.9	11.7
D		82.3	5.9	169	9.9	11.0	10.9	−58	3.0	4.0	3.6	−177	10.2	12.1	11.8
E		80.3	14.9	70	2.0	2.5	1.7	47	4.3	5.7	4.9	−70	1.9	2.6	1.9
F		81.5	8.1	69	2.0	2.6	1.8	47	4.3	5.7	4.9	−70	1.9	2.6	1.8
G		83.2	4.3	72	1.8	2.4	1.5	51	3.8	5.1	4.3	−67	2.2	3.0	2.2
H		84.0	3.1	71	1.9	2.4	1.6	48	4.1	3.5	4.6	−69	2.0	2.8	2.0
	$^3J^{av}$				7.3	8.2	7.9		3.4	4.6	4.0		7.4	8.9	8.5

Note. The notations of the protons are analogous to those used in Table 2. The characteristics are given only for the conformers whose contents in the equilibrium system at 298 K were higher than 2.5%.

position (the C(CH$_3$)C(1)C(2)C(3) torsion angle (φ_1) is close to 180°), whereas this group in the remaining above-mentioned conformers is in the axial position (φ_1 are 65—67°). Correspondingly, the 2-benzyl substituent in conformers *A*—*C* of diastereomer **3a** is in the axial position (the C(1')C(2)C(3)C(4) torsion angle (φ_2) is close to 90°), whereas this substituent in the remaining forms of **3a** is in the pseudoequatorial position (φ_2 are 161—166°). In the case of *trans*-diastereomer **4a**, the 2-benzyl group is in the pseudoequatorial orientation in conformers *A*—*D* (φ_2 are 130—159°) and in the axial orientation in the remaining conformers (φ_2 are 91—100°). The orientations of the methyl substituent in alternative conformations of this diastereomer are analogous to those in the corresponding forms of **3a**.

According to the results of calculations by the MM method, the cyclohexenone ring in all alternative conformers of both diastereomers **3a** and **4a** adopts a twisted sofa-C(1) conformation as evidenced by small absolute values of the endocyclic C(2)C(3)C(4)C(5) and C(3)C(4)C(5)C(6) torsion angles (see also Figs. 1 and 2).

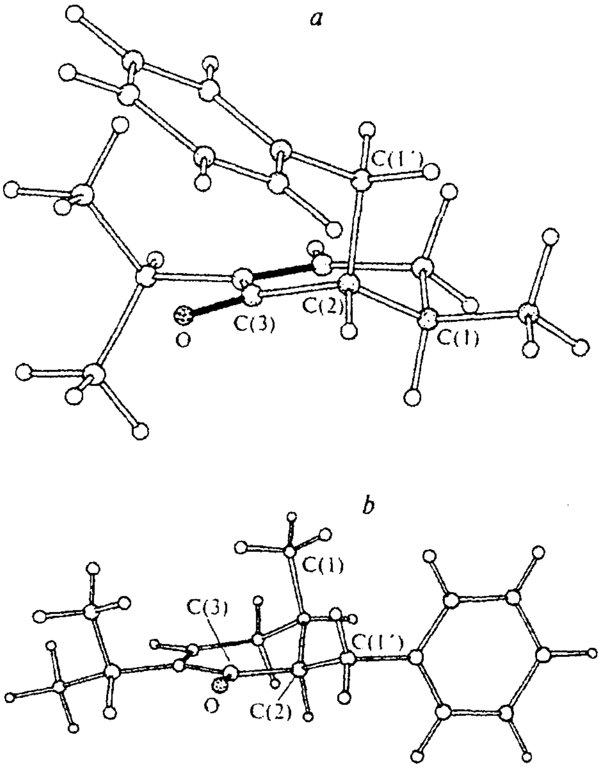


Fig. 1. The most probable alternative conformations of two types of model compound **3a** containing 1,2-substituents in different orientations: *a*, the methyl and benzyl groups are in the equatorial and axial positions, respectively; *b*, the methyl and benzyl groups are in the axial and equatorial positions, respectively (conformations *A* and *D* are given in Table 4).

The vicinal spin-spin coupling constants $^3J_{H,H}$ for the protons of the cyclohexene ring in the most probable alternative conformers of isomers **3a** and **4a** (Table 4) were determined based on the interproton torsion angles calculated by the MM method according to three modified forms of Karplus—Conroy's equation, *viz.*, accord-

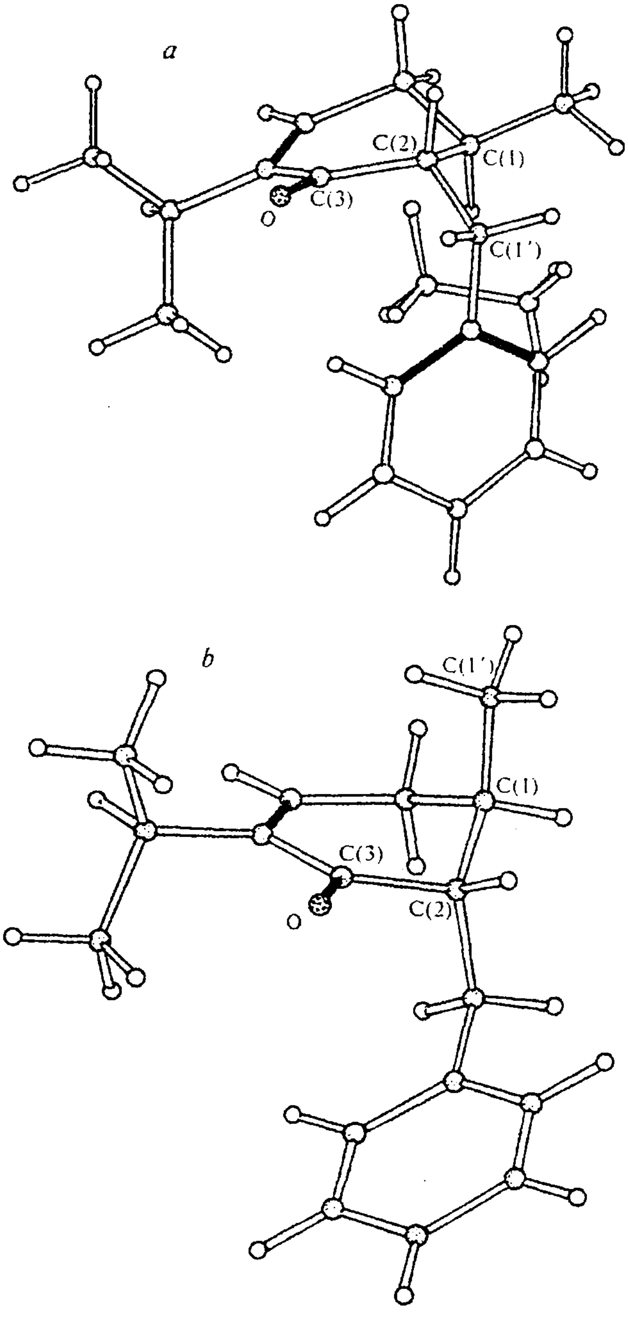


Fig. 2. The most probable alternative conformations of two types of model compound **4a** containing the methyl and benzyl substituents in the equatorial (*a*) and axial (*b*) orientations (conformations *A* and *E* are given in Table 4).

ing to Eq. (1) using empirical coefficients optimized previously,[14] according to Durette—Horton's equation (2) taking into account the electronegativities of α-substituents,[15] and according to Eq. (3) taking into consideration also the orientations of α-substituents with respect to the pair of coupling protons and the electronegativities of β-substituents[14]:

$$^{3}J_{\mathrm{H,H}} = 7.76\cos^2\varphi - 1.10\cos\varphi + 1.40, \qquad (1)$$

$$^{3}J_{\mathrm{H,H}} = (7.8 - \cos\varphi + 5.6\cos2\varphi)\cdot(1 - 0.1\Sigma\Delta\chi_i), \qquad (2)$$

$$^{3}J_{\mathrm{H,H}} = \mathrm{P}_1\cos^2\varphi + \mathrm{P}_2\cos\varphi + \mathrm{P}_3 + \\ + \Sigma\Delta\chi_i[\mathrm{P}_4 + \mathrm{P}_5\cos^2(\xi_i\varphi + \mathrm{P}_6|\Delta\chi_i|)], \qquad (3)$$

where φ is the torsion angle, $\Sigma\Delta\chi_i$ is the sum of the differences between the electronegativities of the substituents of the ethane fragment and the hydrogen atom according to Huggins,[16] P_1—P_6 are empirical coefficients,[14] ξ is the coefficient characterizing the orientation of the α-substituent relative to the pair of coupling protons, and $\Delta\chi_i$ is the electronegativity of the α-substituent calculated taking into account the electronegativity of the β-substituent.[14]

The weighted-mean values ($^{3}J^{\mathrm{av}}$) for each type of spin-spin coupling constants were calculated according to the following equation:

$$^{3}J^{\mathrm{av}} = \sum {^{3}J_i m_i}, \qquad (4)$$

where m_i is the mole fraction of the i-th conformer determined from the E_{st} values calculated by the MM method.

It can be seen from Table 4 that the $^{3}J_{\mathrm{H(1),H(2)}}$ constant is sensitive to the configurations of compounds **3** and **4** under study. The average calculated values of this constant ($^{3}J^{\mathrm{av}}$) for structure **3a** (3.1—3.9 Hz) are approximately half as large as those in the case of **4a** (7.3—8.2 Hz, see Table 4), which agrees satisfactorily with the experimental difference in the $^{3}J_{\mathrm{H(1),H(2)}}$ constants for compounds **3** and **4** (see Table 3). This fact as well as the fact that the calculated values $^{3}J^{\mathrm{av}}$ for the above-mentioned protons in compound **3a** agree closely with the experimental value (3.5 Hz) for compound **3** indicate that the products **3** and **4** are undoubtedly 1*R*,2*R*-*cis*-2-(4-phenylbenzyl)-*p*-menth-4-en-3-one and its 1*R*,2*S*-*trans* diastereomer, respectively.

Conformational state of the 1R,2R-cis diastereomer. The conformation of the cyclohexenone ring and the orientations of the methyl and benzyl groups in compound **3** are characterized by the spin-spin coupling constant $^{3}J_{\mathrm{H(1),H(6')}}$. The calculated values of the latter are substantially different for the conformers containing the H(1) atom in the axial (10.0—12.0 Hz) and equatorial (2.1—3.0 Hz) orientations (correspondingly, containing the equatorial and axial methyl group, see Table 4). A comparison of the calculated and experimental values of this spin-spin coupling constant (see Table 3) confirmed that compound **3** exists in solutions as an equilibrium mixture of the above-mentioned conformers. Based on the results of calculations by the MM method, the conformers with the equatorial methyl and axial benzyl substituents are slightly preferential (58% of the total amount). However, taking into account that the calculated value of $^{3}J^{\mathrm{av}}{}_{\mathrm{H(1),H(6')}}$ is substantially overestimated compared to the experimental value, we corrected the ratio of the conformers in the equilibrium system using the experimental value of $^{3}J_{\mathrm{H(1),H(6')}}$ and Eq. (4) for the weighted-mean spin-spin coupling constants, which were calculated according to either Eq. (2) or (3) for the conformations of each of the two above-mentioned types. This correction was based on the fact that the calculated values of the conformationally independent constants $^{3}J_{\mathrm{H(1),H(2)}}$ (for **3a**) and $^{3}J_{\mathrm{H(1),H(6)}}$ (for **3a** and **4a**) determined according to any of Eqs. (1)—(3) differ from the experimental values by less than 1 Hz (*cf.* the data in Tables 3 and 4). Consequently, the spin-spin coupling constants calculated according to the above-mentioned equations (as well as the geometries of the molecular conformations according to the results of MM calculations) have reliable values. Hence, the fact that the calculated values of the conformationally sensitive constant $^{3}J^{\mathrm{av}}{}_{\mathrm{H(1),H(6')}}$ for both model structures are larger than the corresponding experimental values indicates that calculations for these structures by the MM methods give overestimated contents of the conformers with the high spin-spin coupling constant $^{3}J_{\mathrm{H(1),H(6')}}$, *i.e.*, these calculations inadequately reproduce the relative energies of alternative conformations of the molecular systems under study. When corrections were applied, the contents of the conformers with the equatorial methyl and axial benzyl groups were evaluated at 22—23% (using Eq. (2)) and 26—27% (using Eq. (3)).

Therefore, it can be concluded that compound **3** exists in solutions as a mixture of conformers containing 1,2-substituents in different orientations. Examples of the most probable inverted conformations are shown in Fig. 1. According to analysis of the ^{1}H NMR spectral data, in distinction to the results of calculations by the MM method, the conformers containing the axial methyl substituent and the equatorial bulkier 4-phenylbenzyl group at position 2 are noticeably preferential (they account for no less than 70%; see, for example, Fig. 1, *b*), which corresponds to the general regularities of the conformational behavior of six-membered cyclic systems.[17]

Conformational state of the 1R,2S-trans diastereomer. In the case of *trans*-diastereomer **4**, two spin-spin coupling constants, *viz.*, $^{3}J_{\mathrm{H(1),H(2)}}$ and $^{3}J_{\mathrm{H(1),H(6')}}$, are conformationally sensitive. According to estimations analogous to those described above for compound **3**, the contents of the conformers with the equatorial methyl group and the pseudoequatorial benzyl fragment in solutions are 40—50%, *i.e.*, two conformational types of the cyclohexenone fragment (see Fig. 2) are virtually equally probable. Calculations by the MM method gave a somewhat overestimated content (64%) of the conformers of this type and, correspondingly, overestimated $^3J^{av}_{H(1),H(2)}$ and $^3J^{av}_{H(1),H(6')}$ values (see Table 4).

Conformations of the exocyclic benzyl group in diastereomeric compounds. The calculated vicinal spin-spin coupling constants for the H(2) proton with the nonequivalent benzyl protons and their values, averaged in accordance with the contents of different conformers based on the results of MM calculations for model compounds **3a** and **4a**, are given in Table 5. The calculated values $^3J^{av}_{H(2),H(11)}$ and $^3J^{av}_{H(2),H(12)}$ for structure **3a** (particularly, calculated with the use of Eqs. (2) and (3)) are in good agreement with the experimental values for compound **3** (see Table 3), which is indicative of the preferential occurrence of several approximately equally probable conformers containing one of the benzyl protons in the *trans* orientation with respect to the H(2) atom (see Tables 4 and 5, the Newman projections). In the conformations with the axial methyl group, the phenyl group is in the *gauche* orientation with respect either to the C(2)—C(1) bond (see Fig. 1, *b*) or to the C(2)—C(3) bond (see Table 4). In the case of the equatorial orientation of the methyl group, only conformers with the transoid orientation of the phenyl group with respect to the C(2)—C(1) bond, *i.e.*, conformers in which the phenyl group is maximally remote from the methyl group, occur in noticeable amounts (see Fig. 1, *a*, Table 4). Therefore, the rotamer equilibrium for the benzyl fragment in compound **3** is determined primarily by nonbonded interactions between the 1-methyl group and the phenyl fragment.

In the case of stereoisomer **4**, the contents of the conformers with the transoid orientation of the H(2) proton relative to either H(11) or H(12) (see, for example, Fig. 2, *b*) are smaller than those in the case of compound **3**, which can be judged from the observed tendency to a decrease in both the corresponding experimental and calculated spin-spin coupling constants (see Tables 3 and 5).

Conformational state of 2-benzyl-p-menth-1-en-3-one derivatives. In the case of compounds **2a—c** containing one chiral center (racemates), the ^{1}H NMR spectral data (for compound **2b** in solvents with different magnetic anisotropy, see Table 2) in combination with the results of MM calculations for model structure **2e** (X = H) allowed us to characterize the conformational states of their molecules in detail. The endocyclic torsion angles indicate (the small values of these angles relative to the C(1)—C(2) and C(2)—C(3) bonds, Table 6) that the cyclohexenone fragments in all alternative conformers of **2e** adopt in principle the same conformation, *viz.*, the twisted sofa-C(5) (see also Fig. 3). This conformation of the ring and the preferential equatorial orientation of the isopropyl substituent (according to the results of MM calculations, the C(2)C(3)C(4)C(8) torsion angles in conformers *A—E* are in the range of 162—171°) are confirmed by a comparison of the experimental spin-spin coupling constants $^3J_{H(4),H(5)}$ and $^3J_{H(5),H(6)}$ for compounds **2a—c** (see Table 3) with the corresponding weighted-mean calculated values for model structure **2e** ($^3J^{av}_{H,H}$, Table 7). The spin-spin coupling constants $^3J_{H(4),H(5')}$ and $^3J_{H(5'),H(6)}$ are most sensitive to ring inversion and, correspondingly, to a change in the orientation of the isopropyl substituent. The experimental values of these spin-spin coupling constants agree satisfactorily with the corresponding calculated mean-weighted values, which indicates that the results of calculations by the MM method (see Table 6) adequately describe the conformational equilibrium and the spatial structure of the cyclohexenone fragment of compound **2**. In the case of these compounds, the conformations with the axial orientation of the H(4) proton and, correspondingly, with the equatorial orientation of the isopropyl group prevail (see Fig. 3, *a*). This result agrees with the general concepts of conforma-

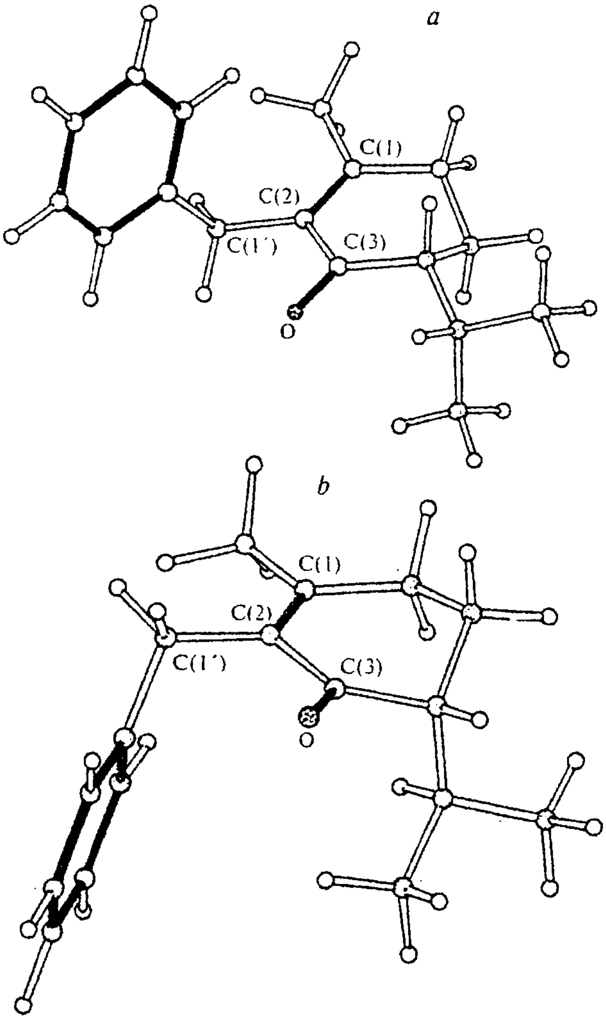
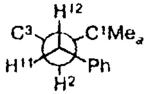
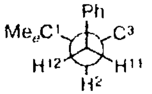
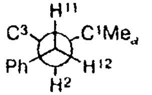
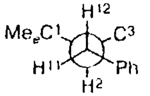
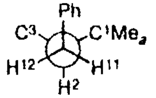
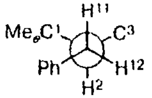
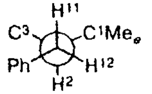
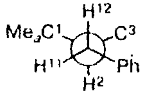
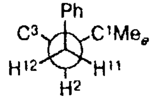
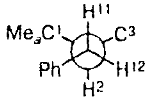
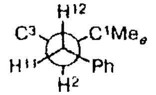
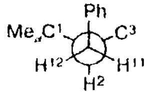


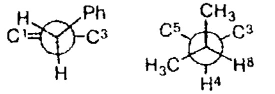
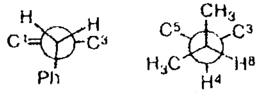
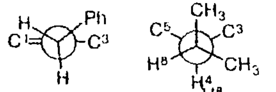
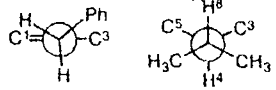
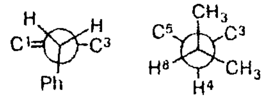
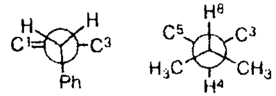
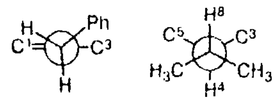
Fig. 3. The most probable alternative conformations of two types of model compound **2e** containing the isopropyl substituent in the equatorial (*a*) and axial (*b*) positions (conformations *A* and *F* are given in Table 6).

Table 5. Vicinal spin-spin coupling constants for the benzyl protons (^3J/Hz) for alternative conformations of model diastereomeric structures **3a** and **4a** calculated by Eqs. (1)—(3)

Confor-mation	Fraction (%)	$\varphi(2,11)$	$^3J_{H(2),H(11)}$			$\varphi(2,12)$	$^3J_{H(2),H(12)}$			Confor-mation	Fraction (%)	$\varphi(2,11)$	$^3J_{H(2),H(11)}$			$\varphi(2,12)$	$^3J_{H(2),H(12)}$		
			(1)	(2)	(3)		(1)	(2)	(3)				(1)	(2)	(3)		(1)	(2)	(3)
				Structure **3a**										Structure **4a**					
	25.9	−59	3.1	4.2	3.8	−173	10.2	12.0	11.7		51.2	56	3.3	4.4	3.5	−58	3.0	4.1	3.2
	15.6	−172	10.0	11.8	11.5	72	1.7	2.4	1.6		12.6	68	2.1	2.9	2.4	167	9.8	11.6	11.2
	0.4	53	3.5	4.7	3.8	−60	2.8	3.8	3.3		2.6	179	10.3	12.1	11.8	65	2.4	3.2	2.8
	51.0	−177	10.2	12.1	11.7	59	2.9	3.9	3.0		23.0	66	2.3	3.1	2.7	177	10.3	12.1	11.8
	4.8	60	2.7	3.7	2.9	−53	3.5	4.7	4.2		7.4	174	10.2	12.0	11.8	58	3.0	4.1	3.7
	2.5	−63	2.5	3.3	3.0	−178	10.2	12.1	11.8		3.3	56	3.2	4.4	3.5	−59	2.9	4.0	3.1
	$^3J^{av}$		7.8	9.4	9.0		4.8	6.0	5.3		$^3J^{av}$		3.6	4.7	4.0		5.5	6.9	6.2

Note. The fractions of the conformers, which contain the methyl group in the same orientation and the benzyl substituent adopting the same conformation along the C(2)—C(1′) bond, but which differ in rotamery of the isopropyl fragment, are summed in each row.

Table 6. Steric energies (E_{st}/kJ mol^{-1}) and selected torsion angles for the most probable conformers of model compound **2e** based on the results of calculations by molecular mechanics

Confor-mer	Conformation	E_{st}	Fraction (%)	Torsion angles/deg					
				C(1)C(2)C(3)C(4)	C(2)C(3)C(4)C(5)	C(3)C(4)C(5)C(6)	C(4)C(5)C(6)C(1)	C(5)C(6)C(1)C(2)	C(6)C(1)C(2)C(3)
A		81.1	29.9	1	−34	57	−52	18	8
B		83.2	13.9	4	−34	57	−52	21	3
C		84.5	8.7	4	−37	59	−51	17	7
D		85.3	5.3	7	−40	59	−49	14	7
E		86.5	3.5	8	−39	59	−51	19	3
F		81.1	28.9	−11	43	−59	47	−12	−6
G		86.5	3.4	−10	40	−59	50	−18	−3

Note. The data for conformers whose contents were higher than 2.5% are given.

tional analysis,[17] according to which conformations of the cyclohexane systems containing a bulky axial substituent (the isopropyl group) are destabilized due to nonbonded 1—3 interactions (with the axial C(6)—H(6) bond in the case of the compound under study).

It should be noted that in the crystals of compound **2b** (according to the data of X-ray diffraction analysis),[5] the cyclohexenone fragment containing the equatorial isopropyl substituent also adopts the twisted sofa-C(5) conformation The experimental values of the endocyclic torsion ang[illegible]nd the C(3)C(2)C(1')C(Ph) torsion angle[5] are i[illegible]d agreement with the calculated values for model structure **2e** (see Table 6). This is circumstantial evidence that the use of the calculated (MM) molecular geometries of the compounds under study for the estimation of the spin-spin coupling constants of particular conformers is justified.

In the ^{1}H NMR spectrum of compound **2b**, the magnetic nonequivalence of the benzyl protons and their geminal spin-spin coupling constant depend on the solvent (see Tables 2 and 3). Since this spin-spin coupling constant depends on the mutual orientation of the methylene unit and the π-orbitals of the adjacent unsaturated bonds,[13] the observed change in this value may be indicative of the effect of the solvent on the conformational equilibrium of this exocyclic fragment of the molecules. The nonequivalence of the benzyl protons may be a consequence, primarily, of the asymmetric structure of the cyclohexenone fragment in molecules of compounds **2**. In addition, the hindrance to rotation of the bulky 4-benzoyloxybenzyl fragment, which depends on the solvation of the adjacent carbonyl group (due to the formation of H-complexes with chloroform, π-complexes with benzene, and, probably, dipole-dipole interactions with DMSO), may also be of importance.

The calculations for compound **2e** demonstrated that the phenyl group of the benzyl fragment adopts preferentially the +*sp* or −*sp* conformation along the C(2)—C(1') bond (the C(3)C(2)C(1')C(Ph) torsion angles are in the range of 68—69 or vary from −107 to −109°; see also the Newman projections, Table 6). Apparently, this conformation and the virtually planar structure[5] of the maximum substituted *s-trans*-enone fragment minimize unfavorable nonbonded interactions of the benzene ring with the carbonyl and methyl groups. In the crystal, the benzene ring of compound **2b** is virtually perpendicular to the C(2)—C(1') bond (the C(3)C(2)C(1')C(Ph) torsion angle is 95.8°),[5] as distinct from the calculated data for model structure **2e**. In this case, the differences between the experimental and calculated data are consistent with the concept of the dependence of the conformation of the benzyl fragment on the environment (solvation with solvents of different nature and the packing of molecular fragments in the crystal).

Table 7. Interproton torsion angles (φ(H,H)/deg) and spin-spin coupling constant ($^3J_{\mathrm{H,H}}$/Hz) for alternative conformations of model compound **2e** calculated by Eqs. (1)—(3)

Conformer	Fraction (%)	φ(4,5)	$^3J_{\mathrm{H(4),H(5)}}$			φ(4,5')	$^3J_{\mathrm{H(4),H(5')}}$			φ(5,6)	$^3J_{\mathrm{H(5),H(6)}}$		
			(1)	(2)	(3)		(1)	(2)	(3)		(1)	(2)	(3)
Conformations with the equatorial isopropyl group													
A	29.9	66	2.2	3.1	2.6	−175	10.2	12.0	11.7	−52	3.7	5.2	4.5
B	13.9	65	2.3	3.2	2.7	−175	10.2	12.0	11.7	−53	3.5	5.1	4.3
C	8.7	67	2.2	3.0	2.5	−174	10.2	12.0	11.7	−51	3.8	5.4	4.7
D	5.3	65	2.4	3.3	2.8	−176	10.2	12.1	11.7	−50	3.9	5.5	4.9
E	3.5	64	2.2	3.0	2.5	−173	10.1	12.0	11.6	−51	3.8	5.4	4.7
Conformations with the axial isopropyl group													
F	28.9	−55	3.3	4.5	3.6	61	2.7	3.7	2.8	49	4.0	5.7	5.1
G	3.4	−55	3.3	4.5	3.6	61	2.7	3.7	2.8	52	3.7	5.2	4.5
$^3J^{\mathrm{av}}$			2.7	3.6	3.0		7.5	9.0	8.4		3.8	5.4	4.7

Conformer	Fraction (%)	φ(5,6')	$^3J_{\mathrm{H(5),H(6')}}$			φ(5',6)	$^3J_{\mathrm{H(5'),H(6)}}$			φ(5',6')	$^3J_{\mathrm{H(5'),H(6')}}$		
			(1)	(2)	(3)		(1)	(2)	(3)		(1)	(2)	(3)
Conformations with the equatorial isopropyl group													
A	29.9	64	2.4	3.5	2.3	−169	10.0	12.5	13.2	−52	3.7	5.2	4.5
B	13.9	64	2.4	3.5	2.4	−170	10.0	12.6	13.2	−53	3.5	5.1	4.3
C	8.7	65	2.3	3.4	2.2	−168	9.9	12.4	13.1	−52	3.7	5.2	4.5
D	5.3	66	2.2	3.3	2.0	−167	9.8	12.3	13.0	−50	3.9	5.5	4.9
E	3.5	65	2.3	3.4	2.2	−169	10.0	12.5	13.2	−51	3.8	5.4	4.7
Conformations with the axial isopropyl group													
F	28.9	165	9.7	12.2	12.8	−67	2.2	3.1	1.9	49	4.0	5.7	5.1
G	3.4	168	9.9	12.4	13.1	−64	2.4	3.5	2.3	51	3.7	5.3	4.6
$^3J^{\mathrm{av}}$			5.0	6.6	6.1		7.1	9.1	9.1		3.8	5.4	4.7

Note. The calculated data are given only for conformations whose contents in the equilibrium system at room temperature were higher than 2.5%. The $^3J^{\mathrm{av}}$ values were obtained taking into account the data for all possible conformations.

The conformation of the isopropyl group in compounds **2a—c** along the C(8)—C(4) bond can be determined from the mode of splitting of the signals for the H(8) and H(4) protons. The multiplet for the H(8) proton in the spectra of these compounds contains eight broadened lines, which is in agreement with the close values of the vicinal spin-spin coupling constants with the protons of the methyl groups and with H(4) (see Table 3). The experimental value of $^3J_{\mathrm{H(4),H(8)}}$ confirms the results of calculations (see Table 6, the Newman projections), according to which different mutual orientations of these protons (the *trans* and two *gauche* forms) are virtually equally probable.

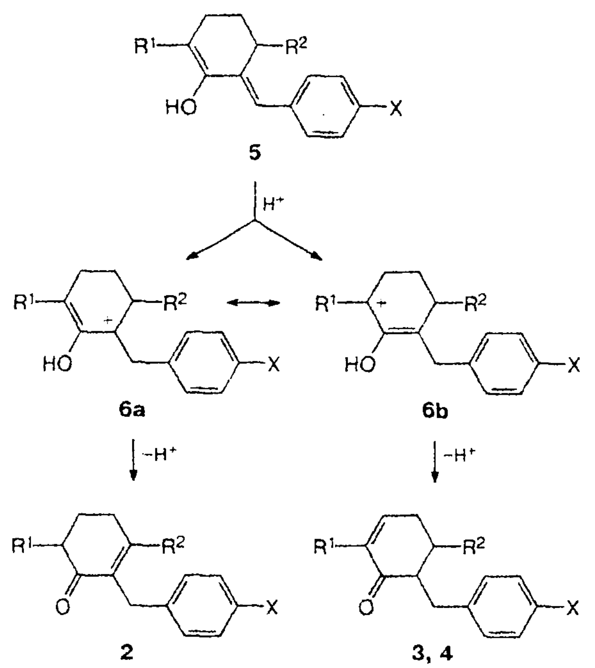
Changes in the chemical shifts of the protons for compound **2b** on going from $CDCl_3$ to C_6D_6 are of interest. It can be seen from Table 2 ($\Delta\delta$ values) that shielding of the protons of the isopropyl and benzyl fragments and of the *ortho*-protons of the benzoyl group changes only slightly. For the remaining protons, shielding is substantially increased, the effect of the aromatic solvent being maximum for the H(6) and H(6´) protons and the protons of the methyl group. Apparently, in accordance with the character of polarization of the *s-trans*-enone fragment of ketones **2** (positive charges on the C(1) and C(3) atoms), the solvating benzene molecules are oriented so that the H(6) and H(6´) protons and the protons of the methyl group are substantially shielded by the π-electron system of the benzene ring. This effect is noticeably weakened for the somewhat more remote H(5) and H(5´) protons (see Table 2). A flattened structure of the *s-trans*-enone fragment in the compounds under study[5] may be favorable for efficient interactions between its π-electron system and benzene molecules. Evidently, this is responsible for the fact that the $\Delta\delta$ values observed for compound **2b** upon complexation with benzene are 1.5—2 times larger than the values obtained for 2-(4-chlorobenzylidene)-*p*-menthan-3-one (**1**, X = Cl, see Scheme 1), containing the substantially twisted *s-cis*-enone group.[11]

Therefore, the use of ^{1}H NMR spectroscopy in combination with conformational analysis by the MM method in the case of isomeric menthenones under study allowed us to establish the stereochemical configurations of diastereomeric structures and to characterize the conformational states of their molecules. This methodology can also be successfully applied to other diastereomeric structures.

* * *

The rearrangements of 2-arylidene derivatives of cyclohexanone **1a** and **1c**, which have been found previously,[5,6] afforded products only of type **2**. The mechanism of the process proposed previously[6] assumes the formation of dienol form **5**, its equilibrium protonation at the cyclic carbon atom of the double bond, and deprotonation of the resulting cation **6a** to form cyclohexenone derivatives **2a** and **2d** (Scheme 2).

Scheme 2



In this work, a diastereomeric mixture of *p*-menth-4-en-3-ones **3** and **4** was obtained for the first time along with product **2c** upon acid-catalyzed rearrangement of *s-cis*-ketone **1c**. In special experiments under conditions of the rearrangement, neither conversions of product **2c** into **3** or **4** nor transformations of diastereomers **3** and **4** into their structural isomer **2c** were detected by HPLC. The observed interconversion of diasteromers **3** and **4** is quite reasonable in connection with the possibility of their equilibrium enolization.

The results obtained require the refinement of the notions of the rearrangement pathways. On the one hand, protonation of the conjugated fragment of dienol **5** can be considered both as 1,2- and 1,4-processes with localization of a positive charge on the C(2) and C(4) atoms, respectively (see Scheme 2, cations **6a** and **6b**, respectively). When a proton is abstracted, these cations give isomers, which differ in position of the endocyclic double bond (**2** or **3** and **4**).

On the other hand, cations **6a** and **6b** can be represented (which is more likely) as resonance structures of the protonated form of dienol, which exhibits dual reactivity with respect to proton abstraction from the CH bonds at the α positions relative to the predominant localization of the positive charge to form isomeric cyclohexenone structures. Apparently, this stage of the process is kinetically controlled, the regiochemistry being strongly dependent on the electronic nature of the substituent.

Calculations of protonated forms **6a** and **6b** performed according to the PM3 method[18] demonstrated that the charge distributions as well as the energies of these cations are virtually identical. However, no noticeable effect of the X substituent on the charge distribution was revealed.

Elucidation of the reasons for the strong effect of the X substituent on the regiochemistry of deprotonation of cation **6** calls for further investigation. However, the revealed different paths of the rearrangement of 2-arylidene-*p*-menthan-3-ones to form isomeric cyclohexenone derivatives can be considered as a consequence of the characteristic features of the structures and reactivities of their protonated dienol forms.

Experimental

Analytical HPLC was carried out on a Milikhrom 2 chromatograph equipped with a KAKh-3 column (Silasorb 600 silica gel, 5 μm); a solution of AcOBu (3 vol.%) in octane as the eluent; detection was based on absorption at 260 nm. The IR spectra were measured on a Specord M80 spectrophotometer. The ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer (300 MHz) with Me_4Si as the internal standard. The interpretation of multiplets observed was carried out using the double resonance method and was confirmed by computer simulation of spin systems with the use of the NUTS 4.35 program.

Calculations of the spatial structures of the compounds under study were performed by molecular mechanics[7] with the MMX force field[19] using the PCMODEL program.

Acid-catalyzed rearrangement of 1*R*,4*R*-2-(4-phenylbenzylidene)-*p*-menthan-3-one (1b). A 60% $HClO_4$ solution (0.2 mL) was added to a solution of ketone **1b** (2 g, 6.3 mmol) in CCl_4 (25 mL). The reaction mixture was refluxed for 3 h, cooled, and neutralized with Na_2CO_3. Then C-80 silica gel was added and the mixture was concentrated *in vacuo*. The product was isolated from the residue by extraction with hot hexane. An oily substance was obtained in a yield of 1.7 g. According to the HPLC data, the resulting product contained three major components (in virtually equal amounts). The elution times are given in Table 1. The mixture was separated by preparative liquid chromatography (Woelm silica gel, 5—40 μm, 1×60-cm column, 2.5% AcOEt in hexane as the eluent, 8 mL min^{-1}) using the UV detector of the Milikhrom 2 chromatograph. Three fractions containing 80—86% of the major component were isolated (in the order of elution: 330, 213, and 215 mg). Crystallization of the first fraction from methanol (upon cooling to −20 °C) afforded 1*R*,2*R*-*cis*-2-(4-phenylbenzyl)menth-4-en-3-one (**3**) in a yield of 60 mg as a crystalline compound, m.p. 59.5—60.5 °C. Attempts to obtain the remaining components as crystalline compounds failed. According to the ^{1}H NMR spectral data, the second and third fractions contained 1*R*,2*S*-*trans*-2-(4-phenylbenzyl)menth-4-en-3-one (**4**) and racemic 2-(4-phenylbenzyl)menth-1-en-3-one (**2c**), respectively, as the major components.

Fusion of 1*R*,4*R*-2-(4-phenylbenzylidene)-*p*-menthan-3-one (1b) with pyridine hydrochloride. Ketone **1b** (4 g, 12.6 mmol) was added to Py · HCl (14.5 g, 126 mmol), which had been dried by azeotropic distillation of water with benzene. Then the benzene was distilled off. The reaction mixture was heated under argon at 200—210 °C for 2 h. The reaction mixture was cooled, diluted with water, extracted with benzene (3×40 mL), washed with water (3×150 mL), dried over $CaCl_2$, and concentrated *in vacuo*. An oily product was obtained in a yield of 3.7 g. According to the HPLC data, the composition of the mixture was identical to that obtained upon acid-catalyzed rearrangement.

Acid treatment of 1*R*,2*R*-*cis*-2-(4-phenylbenzyl)menth-4-en-3-one (3) and 2-(4-phenylbenzyl)menth-1-en-3-one (2c). Two drops of 60% $HClO_4$ were added to a solution of the corresponding compound (20 mg) in CCl_4 (10 mL). The reaction mixture was refluxed for 5 h, cooled, washed with water, and dried with $CaCl_2$. According to the HPLC data, the product obtained by treatment of compound **3** contained compounds **3** and **4** in virtually equal amounts. In the case of the product of acid treatment of compound **2c**, the composition of the mixture remained unchanged.

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