

## Molecular and crystal structures of stereoisomeric 2*R*,3*R*,6*S*-2-(1'*S*-hydroxy-1'-biphenyl)- and 2*R*,3*R*,6*S*-2-(1'*R*-hydroxy-1'-biphenyl)methyl-3-methyl-6-isopropylcyclohexanones

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It was established by X-ray diffraction analysis that 2-(1'-hydroxy-1'-biphenyl)methyl-3-methyl-6-isopropylcyclohexanone, one of the minor products of the directed aldol reaction of (–)-menthone bromomagnesium enolate with 4-phenylbenzaldehyde, has the 2*R*,3*R*,6*S*,1'*R* configuration. The characteristic features of the spatial structure of this β-hydroxyketone were compared with those of the major stereoisomeric product of the above-mentioned reaction. The latter has the 2*R*,3*R*,6*S*,1'*S* configuration. In the crystals, both stereoisomers have the cyclohexanone ring in a chair-like conformation with the three substituents in equatorial positions and are characterized by the presence of the annelated (*cis*-fused) pseudoring with an –OH...O=C< intramolecular hydrogen bond. The structures of the stereoisomers differ in the orientation of the aryl group and the hydrogen atom at the C(1') chiral center with respect to the cyclohexanone ring. The results of X-ray diffraction analysis were compared with the data of molecular mechanics calculation for the energetically most favorable conformations of the isolated molecules of β-hydroxyketones under study.

**Key words:** stereoisomeric 2-(1'-hydroxy-1'-biphenyl)methyl-3-methyl-6-isopropylcyclohexanones, configuration, molecular structure, X-ray diffraction analysis, conformational analysis, molecular mechanics, hydrogen bond.

Studies of molecular structures of chiral poly-substituted cyclohexanones, in particular, of 2-(α-hydroxy-α-aryl)methyl-substituted 3-methyl-6-isopropylcyclohexanone ((–)-menthone), are of great interest in organic stereochemistry and crystal chemistry. The hindered rotation of the α-hydroxybenzyl substituent in these compounds with respect to the cyclohexanone fragment makes possible the existence of stable conformers, which differ in the character of hydrogen bonds with the participation of the hydroxyl group. This, in turn, may lead to fundamental differences in the crystal structures of these compounds.

Examples of these compounds are stereoisomeric β-hydroxyketones, derivatives of (–)-menthone (3*R*,6*S*-3-methyl-6-isopropylcyclohexanone). These compounds are the products of the directed aldol condensation of (–)-menthone with aromatic aldehydes.<sup>1</sup> It was demonstrated<sup>1,2</sup> that the performance of the reaction of selectively generated (–)-menthone bromomagnesium enolates with 4-phenylbenzaldehyde under conditions of thermodynamic control<sup>3</sup> provides its regioselectivity (introduction of the hydroxybenzyl substituent at position 2) as well as the retention of the configuration of the 3*R*,6*S*-3-methyl-6-isopropylcyclohexanone fragment. Generally, the appearance of two new chiral centers in the course of condensation provides the possibility of preparing four

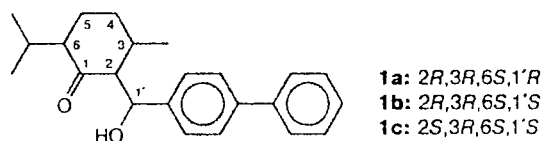
stereoisomeric β-hydroxyketones. Two of them, the 2*R*,3*R*,6*S*,1'*S* and 2*S*,3*R*,6*S*,1'*S* stereoisomers,\* have been studied by X-ray diffraction analysis, <sup>1</sup>H NMR spectroscopy, and molecular mechanics.<sup>1,2,4,5</sup> The opposite configurations of the C(2) chiral centers in these stereoisomers lead to the difference in their molecular conformations and to the difference in the character of H bonds formed by the hydroxyl group (a strong intramolecular –OH...O=C< hydrogen bond in the first case<sup>1,5</sup> and an intermolecular cooperative –OH...OH...OH hydrogen bond in the second case<sup>4</sup>).

We succeeded in isolating one more β-hydroxyketone from a mixture of stereoisomeric products of the above-mentioned reaction of (–)-menthone bromomagnesium enolate by preparative liquid chromatography (see the Experimental section). The relatively small retention time of this stereoisomer suggests the presence of intramolecular hydrogen bonds in its molecules.

The aim of this work was to establish the structure and the absolute configuration of the resulting new stereoisomer of 2-(1'-hydroxy-1'-biphenyl)methyl-3-methyl-6-isopropylcyclohexanone (**1a**) by X-ray dif-

\* Ketol with the 2*S*,3*R*,6*S*,1'*S* configuration was prepared by the reaction of (–)-menthone triisopropoxytitanium enolate with 4-phenylbenzaldehyde<sup>4</sup>.

fraction analysis, to study the conformations of its *p*-menthanone,  $\alpha$ -hydroxybenzyl, and biphenyl fragments in the crystal, to compare these conformations with those in the 2*R*,3*R*,6*S*,1'*S* (**1b**) and 2*S*,3*R*,6*S*,1'*S* isomers (**1c**), and to compare the character of the hydrogen bonds formed in these hydroxy compounds.



Taking into account the possible difference in molecular conformations in crystals and solutions, which has been experimentally observed in the case of  $\beta$ -hydroxyketone **1c**,<sup>4</sup> we modeled the spatial structures of the isolated molecules of stereoisomeric ketols **1a** and **1b**, which differ in the configuration of the exocyclic chiral center, by molecular mechanics.

### Results and Discussion

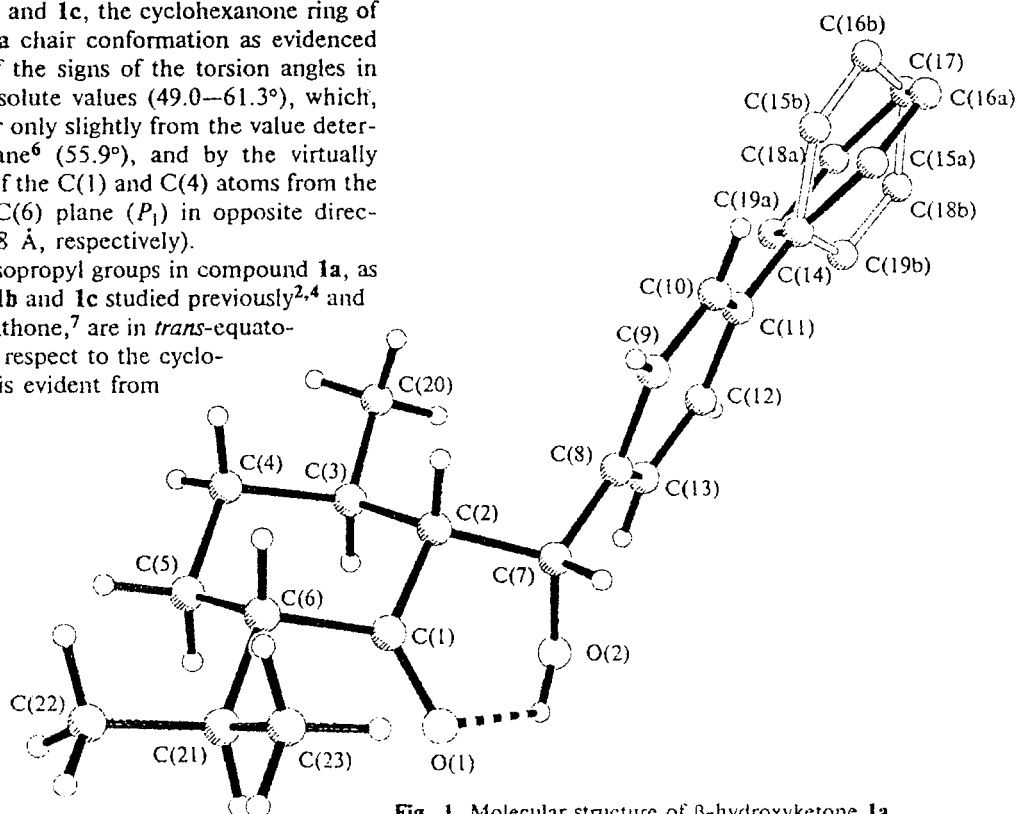
The molecular structure of  $\beta$ -hydroxyketone **1a** under study, which we established by X-ray diffraction analysis, and the atomic numbering scheme are shown in Fig. 1. The bond lengths and bond angles are given in Tables 1 and 2, respectively. As in the case of stereoisomeric compounds **1b** and **1c**, the cyclohexanone ring of molecule **1a** adopts a chair conformation as evidenced by the alternation of the signs of the torsion angles in the ring, by their absolute values (49.0–61.3°), which, on the average, differ only slightly from the value determined for cyclohexane<sup>6</sup> (55.9°), and by the virtually identical deviations of the C(1) and C(4) atoms from the mean C(2)C(3)C(5)C(6) plane ( $P_1$ ) in opposite directions (–0.66 and 0.68 Å, respectively).

The methyl and isopropyl groups in compound **1a**, as in the case of ketols **1b** and **1c** studied previously<sup>2,4</sup> and in the initial (–)-menthone,<sup>7</sup> are in *trans*-equatorial orientations with respect to the cyclohexanone ring. This is evident from

**Table 1.** Bond lengths (*d*) in the structure of **1a**

Bond	<i>d</i> /Å	Bond	<i>d</i> /Å
C(1)–O(1)	1.192(9)	C(10)–C(11)	1.393(6)
C(1)–C(2)	1.557(7)	C(11)–C(12)	1.394(7)
C(1)–C(6)	1.532(9)	C(11)–C(14)	1.480(6)
C(2)–C(3)	1.546(7)	C(12)–C(13)	1.402(7)
C(2)–C(7)	1.535(8)	C(14)–C(15a)	1.36(1)
C(3)–C(4)	1.57(1)	C(14)–C(15b)	1.36(1)
C(3)–C(20)	1.490(8)	C(14)–C(19a)	1.36(1)
C(4)–C(5)	1.551(9)	C(14)–C(19b)	1.36(1)
C(5)–C(6)	1.501(9)	C(15a)–C(16a)	1.34(1)
C(6)–C(21)	1.562(7)	C(15b)–C(16b)	1.34(1)
C(21)–C(22)	1.46(1)	C(16a)–C(17)	1.35(1)
C(21)–C(23)	1.46(1)	C(16b)–C(17)	1.35(1)
C(7)–C(8)	1.499(7)	C(17)–C(18a)	1.35(1)
C(7)–O(2)	1.411(7)	C(17)–C(18b)	1.35(1)
C(8)–C(9)	1.430(7)	C(18a)–C(19a)	1.44(1)
C(8)–C(13)	1.362(7)	C(18b)–C(19b)	1.44(1)
C(9)–C(10)	1.377(6)		

the values of the torsion angles  $\varphi_1$ ,  $\varphi_2$ ,  $\varphi_3$ , and  $\varphi_4$ , which are close to 180° (Table 3), and from the small deviations of the C(20) and C(21) atoms from the above-mentioned mean plane  $P_1$  in opposite directions (0.80 and –0.56 Å, respectively). Therefore, as in the case of compounds **1b** and **1c** studied previously,<sup>1,2</sup> the 3*R*,6*S* configuration that corresponds to the initial (–)-menthone is retained in



**Fig. 1.** Molecular structure of  $\beta$ -hydroxyketone **1a**.

**Table 2.** Bond angles ( $\omega$ ) in the structure of **1a**

Angle	$\omega/\text{deg}$	Angle	$\omega/\text{deg}$	Angle	$\omega/\text{deg}$
O(1)—C(1)—C(2)	122.6(6)	C(22)—C(21)—C(23)	102.5(6)	C(11)—C(14)—C(15b)	124.2(6)
O(1)—C(1)—C(6)	122.9(5)	C(2)—C(7)—C(8)	116.3(4)	C(11)—C(14)—C(19a)	114.4(6)
C(2)—C(1)—C(6)	114.1(5)	C(2)—C(7)—O(2)	111.5(5)	C(11)—C(14)—C(19b)	124.1(6)
C(1)—C(2)—C(3)	111.1(4)	O(2)—C(7)—C(8)	107.2(4)	C(15a)—C(14)—C(19a)	123.0(6)
C(1)—C(2)—C(7)	106.7(4)	C(7)—C(8)—C(9)	118.2(4)	C(15b)—C(14)—C(19b)	111.6(6)
C(3)—C(2)—C(7)	117.8(5)	C(7)—C(8)—C(13)	124.3(5)	C(14)—C(15a)—C(16a)	124.8(6)
C(2)—C(3)—C(4)	111.4(5)	C(9)—C(8)—C(13)	117.3(4)	C(14)—C(15b)—C(16b)	128.3(6)
C(2)—C(3)—C(20)	114.7(4)	C(8)—C(9)—C(10)	119.8(4)	C(15a)—C(16a)—C(17)	119.4(6)
C(4)—C(3)—C(20)	107.2(6)	C(9)—C(10)—C(11)	122.8(4)	C(15b)—C(16b)—C(17)	116.0(6)
C(3)—C(4)—C(5)	110.1(7)	C(10)—C(11)—C(12)	116.9(4)	C(16a)—C(17)—C(18a)	113.1(6)
C(4)—C(5)—C(6)	112.8(5)	C(10)—C(11)—C(14)	122.9(4)	C(16b)—C(17)—C(18b)	125.0(6)
C(1)—C(6)—C(5)	106.6(6)	C(12)—C(11)—C(14)	120.1(4)	C(17)—C(18a)—C(19a)	132.5(6)
C(1)—C(6)—C(21)	110.2(5)	C(11)—C(12)—C(13)	120.6(4)	C(17)—C(18b)—C(19b)	113.0(6)
C(5)—C(6)—C(21)	116.3(4)	C(8)—C(13)—C(12)	122.5(5)	C(14)—C(19a)—C(18a)	107.2(6)
C(6)—C(21)—C(22)	112.1(4)	C(11)—C(14)—C(15a)	122.5(6)	C(14)—C(19b)—C(18b)	126.1(6)
C(6)—C(21)—C(23)	111.9(5)				

$\beta$ -hydroxyketone **1a** under the reaction conditions used. Based on this fact, it was determined that the new C(2) and C(1') chiral centers\* in the molecule under study have the *R* configurations. Therefore,  $\beta$ -hydroxyketone **1a** differs from compound **1b** studied previously<sup>2</sup> in the configuration of only one exocyclic C(7) chiral center.

The conformations of the saturated rings in ketols **1a** and **1b** are virtually identical (see Table 3). In both stereoisomers, all three substituents are in equatorial orientations (see the values of the torsion angles  $\varphi_1$ – $\varphi_6$  in Table 3), which agrees with the general regularities of conformational analysis of cyclohexane derivatives.<sup>8</sup> It should be noted that the degrees of puckering<sup>9</sup> of the saturated carbocycles in **1a** and **1b** are close to the corresponding value calculated for cyclohexane.<sup>10</sup>

Puckering parameter	<b>1a</b>	<b>1b</b>
S	1.15	1.18
$\theta$	4.2	3.2
$\psi$	25.1	29.7

In all the cases, the isopropyl group is in the *ap* conformation with respect to the C(6)—H(6) bond (in all the structures, the torsion angle  $\varphi_7$  is close to  $180^\circ$ , see Table 3 and Ref. 4).

The difference in the configuration of the exocyclic chiral centers in the molecules of ketols **1a** and **1b** determines the difference in the conformation of the hydroxybenzyl fragments. This complex substituent in molecule **1a** has the +*sp* conformation along the C(2)—C(7) bond (the H(2)C(2)C(7)H(7) torsion angle  $\varphi_8$  is  $62(2)^\circ$  and the H(2)—C(2) and H(7)—C(7) bonds are in the *gauche* orientations). In the crystal of stereoisomeric ketol **1b**, which differs in the configuration of the exocyclic C(7) chiral center, the hydroxybenzyl

**Table 3.** Selected torsion angles ( $\varphi_i/\text{deg}$ ) in the molecules of  $\beta$ -hydroxyketones **1a** and **1b** determined by X-ray diffraction analysis

Torsion angle	$\varphi_i$	<b>1a</b>	<b>1b</b>
C(1)C(2)C(3)C(20)	$\varphi_1$	171.0(5)	176.5(2)
C(5)C(4)C(3)C(20)	$\varphi_2$	–177.8(6)	–178.1(2)
C(2)C(1)C(6)C(21)	$\varphi_3$	–174.2(4)	–171.1(2)
C(4)C(5)C(6)C(21)	$\varphi_4$	175.3(8)	178.4(2)
C(4)C(3)C(2)C(7)	$\varphi_5$	172.5(5)	177.0(2)
C(6)C(1)C(2)C(7)	$\varphi_6$	176.0(4)	172.4(2)
H(6)C(6)C(21)H(21)	$\varphi_7$	–167.0(2)	–171.4(5)
H(2)C(2)C(7)H(7)	$\varphi_8$	62.2(2)	–59.2(6)
C(1)C(2)C(7)C(8)	$\varphi_9$	–171.7(4)	–63.6(3)
C(3)C(2)C(7)C(8)	$\varphi_{10}$	–62.6(6)	174.4(2)
C(3)C(2)C(7)O(2)	$\varphi_{11}$	–60.7(6)	–57.6(3)
C(1)C(2)C(7)O(2)	$\varphi_{12}$	64.9(5)	64.4(2)
C(2)C(7)O(2)H(O(2))	$\varphi_{13}$	–70.4(9)	–53.9(10)
C(7)O(2)H(O(2))...O(1)	$\varphi_{14}$	27.0(7)	11.8(11)
O(2)H(O(2))...O(1)C(1)	$\varphi_{15}$	19.0(8)	30.1(10)
H(O(2))...O(1)C(1)C(2)	$\varphi_{16}$	–20.9(8)	–18.2(10)
O(1)C(1)C(2)C(7)	$\varphi_{17}$	–11.1(8)	–14.7(3)
O(2)C(7)C(8)C(13)	$\varphi_{18}$	10.4(7)	2.6(3)
C(12)C(11)C(14)C(19a)	$\varphi_{19a}$	27.0(1)	–26.0(3)
C(12)C(11)C(14)C(19b)	$\varphi_{19b}$	–19.1(1)	—

fragment adopts the –*sp* conformation (the torsion angle  $\varphi_8$  is  $-59.2^\circ$ ).<sup>2</sup> Correspondingly, these diastereomers differ in the orientation of the aryl group relative to the cyclohexanone ring, which is characterized by the torsion angles  $\varphi_9$  or  $\varphi_{10}$  (see Table 3). In stereoisomer **1a**, the aryl substituent is in the *ap* orientation relative to the C(1)—C(2) bond and in the –*sp* orientation with respect to the C(2)—C(3) bond of the cyclohexanone ring. In the case of **1b**, the orientation of the aryl substituent relative to the above-mentioned bonds in the ring is opposite to that observed in **1a**.

The *gauche* orientations of the C(7)—O(2) bonds with respect to the cyclohexanone ring in both diastere-

\* Hereinafter, the C(1') chiral center is denoted C(7) (according to the numbering scheme shown in Fig. 1) for the sake of convenience.

omers **1a** and **1b** are identical (see the torsion angles  $\varphi_{11}$  and  $\varphi_{12}$  in Table 3) and lead to the formation of the O(2)H(O(2))...O(1) intramolecular hydrogen bond. In both compounds, the six-membered pseudoring, which is formed through an intramolecular hydrogen bond and is *cis*-annulated with the cyclohexanone ring (the dihedral angle between the mean C(1)C(2)C(4)C(5) and C(1)C(2)O(2)H(O(2)) planes is 57 and 54° in ketols **1a** and **1b**, respectively), adopts a O(1),C(7)-*twist-boat* conformation (see the torsion angles  $\varphi_{12}$ – $\varphi_{17}$  in Table 3). The C(1), C(2), O(2), and H(O(2)) atoms are in a single plane to within 0.01 Å. The O(1) and C(7) atoms deviate from this plane in the same direction by 0.29 and 0.72 Å, respectively.

In the case of ketol **1a**, the geometric parameters of the intramolecular hydrogen bond (H...O is 2.14 Å and the O–H...O angle is 126°) indicate that this bond is weaker than that in the crystal of diastereomeric **1b** (H...O, 2.039 Å; O–H...O, 145°).<sup>2</sup> Unlike the crystals of **1a** and **1b**, in the crystal of  $\beta$ -hydroxyketone **1c** the C(7)–O and C(1)–C(2) bonds are in the transoid orientation ( $\varphi_{12} = 165.4^\circ$ ),<sup>4</sup> which excludes the possibility of formation of an intramolecular hydrogen bond. Previously,<sup>4</sup> it has been demonstrated that this conformation of **1c** is stabilized by intermolecular cooperative hydrogen bonds OH...OH...OH...

In the crystals of **1a** and **1b**, the molecular conformations differ also in the orientation of the substituent at the C(7) atom with respect to the cyclohexanone ring. In **1a**, the aryl substituent is in an approximately eclipsed position relative to the methyl group at the C(3) atom (see Fig. 1). Evidently, the spatial proximity of these groups determines the steric hindrance of molecule **1a**. Unlike **1a**, the conformation that is realized in the crystal of stereoisomeric ketol **1b** is apparently characterized by minimum nonbonded interactions of the sub-

stituents at the C(3) and C(7) atoms due to the fact that the C(7)–H bond is in an approximately eclipsed position with respect to the equatorial methyl group and the bulky aryl substituent is most remote<sup>2</sup> from the >C(3)HCH<sub>3</sub> fragment. It should be noted that in the structure of **1a** the C(8)...C(13) phenyl ring and the C(7)–O(2) bond are virtually in a single plane (the corresponding torsion angle  $\varphi_{18}$  is 10.4(7)°). Apparently, this orientation is stabilized by weak attractive interactions between the O(2) and H(13) atoms (the O(2)...H(13) distance is 2.37 Å; the sum of the van der Waals radii<sup>11</sup> of the O and H atoms is 2.45 Å). The second ring of the biphenyl fragment is disordered over two equally probable conformations (see Fig. 1). In both cases, this fragment is nonplanar (see the torsion angles  $\varphi_{19a}$  and  $\varphi_{19b}$  in Table 3) and is characterized by shortened intramolecular contacts between the *ortho* hydrogen atoms H(10)...H(15a) (2.24 Å; the sum of the van der Waals radii is 2.32 Å), H(10)...H(15b) (2.17 Å), H(12)...H(19a) (2.04 Å), and H(12)...H(19b) (2.11 Å).

In the crystal, molecules of compound **1a** are packed in stacks along the OZ axis (Fig. 2). In stacks, substantially shortened (up to 0.6 Å) H...H intermolecular contacts (Table 4) are observed between the molecules related by the translation along the OY axis. A crystal packing with such strong repulsions between atoms cannot exist. Therefore, these contact can be considered as forbidden,<sup>12,13</sup> which is indicative of the statistical character of the disorder of the biphenyl fragment. On this basis, it can be concluded that in the crystal of compound **1a** the adjacent stacks along the OY axis are formed by molecules with different conformations of the biphenyl group.

The results of conformational analysis of the model stereoisomeric structures **2a** and **2b** by molecular mechanics (Table 5) reflect the conformational features of

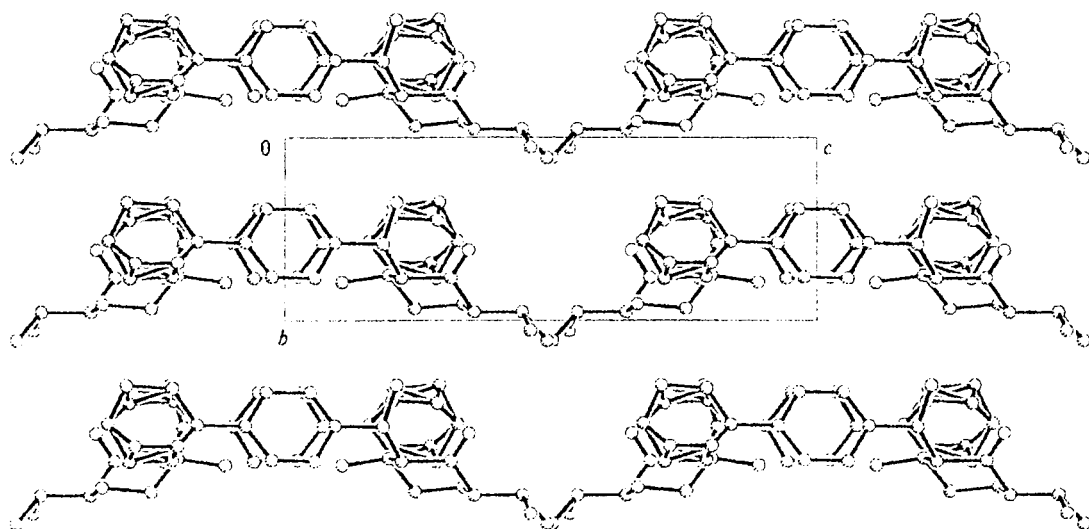


Fig. 2. Crystal packing for compound **1a**.

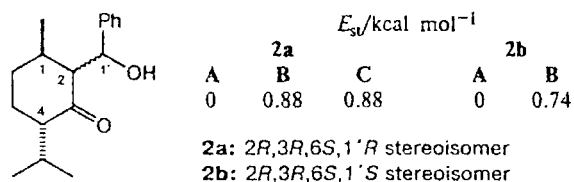
**Table 4.** Intermolecular shortened A...B' contacts in the crystal of **1a** (*d* is the distance and *d*<sub>vdw</sub> is the sum of the van der Waals radii)

A	B'	Symmetry operation	<i>d</i> /Å	<i>d</i> <sub>vdw</sub> /Å
H(2O)	H(6)	<i>x</i> , <i>y</i> -1, <i>z</i>	2.11	2.32
H(2O)	H(16a)	0.5- <i>x</i> , -0.5+ <i>y</i> , - <i>z</i>	2.02	2.32
H(15a)	C(7)	0.5- <i>x</i> , 0.5+ <i>y</i> , <i>z</i>	2.77	2.87
H(15a)	C(8)	0.5- <i>x</i> , 0.5+ <i>y</i> , <i>z</i>	2.83	2.87
H(15b)	H(19b)	<i>x</i> , 1+ <i>y</i> , <i>z</i>	1.92	2.32
H(15b)	C(19b)	<i>x</i> , 1+ <i>y</i> , <i>z</i>	2.70	2.87
H(16b)	C(18b)	<i>x</i> , 1+ <i>y</i> , <i>z</i>	2.58	2.87
H(16b)	H(18b)	<i>x</i> , 1+ <i>y</i> , <i>z</i>	1.79	2.32
C(15b)	H(4b)	- <i>x</i> , <i>y</i> , - <i>z</i>	2.70	2.87
H(18b)	C(16b)	<i>x</i> , <i>y</i> -1, <i>z</i>	2.59	2.87
H(18b)	H(16b)	<i>x</i> , <i>y</i> -1, <i>z</i>	1.79	2.32
H(18b)	H(22a)	<i>x</i> , <i>y</i> -1, <i>z</i>	2.24	2.32
H(19b)	C(15b)	<i>x</i> , <i>y</i> -1, <i>z</i>	2.74	2.87

B' is the atom of the adjacent molecule.

the isolated molecules of the compounds under study in the gaseous phase and provide an idea of their relative stability. Besides, these data are useful in the analysis of a number of aspects of the stereochemistry of formation of β-hydroxyketones, derivatives of (-)-menthone.<sup>14</sup>

First, it should be noted that of two stereoisomeric 2*R*,3*R*,6*S*-ketols, the energetically more favorable conformation **A** of model structure **2b** (the aryl substituent at the C(7) atom is in the transoid orientation with respect to the C(2)—C(3) bond of the cyclohexanone ring) is characterized by the lowest steric energy (*E*<sub>st</sub>).



The geometric characteristics of this conformation agree well with the data of X-ray diffraction analysis for

compound **1b**.<sup>2</sup> On this basis, it can be suggested that the conformation of the *p*-menthanone fragment in the structure under study does not undergo substantial distortions under the effect of intermolecular interactions in the crystal. However, according to the results of molecular mechanics,<sup>5</sup> conformer **A** of ketol **2b** exists in the equilibrium with conformer **B**, which is also stabilized by an intramolecular hydrogen bond but whose aryl substituent at the C(7) atom is in the *gauche* orientation with respect to the C(2)—C(3) bond of the cyclohexanone ring (see the torsion angle φ<sub>10</sub> in Table 5). The content of the minor conformer **B** of compound **2b** was estimated<sup>5</sup> from the obtained values of *E*<sub>st</sub> and was shown to be 22% at 25 °C. The results of modeling of compound **2b** agree well with the data of <sup>1</sup>H NMR spectroscopy for ketol **1b**.<sup>5</sup>

For the model structure **2a**, the theoretically determined conformation **B**, which corresponds to the geometry that is realized in the crystalline phase of ketol **1a**, is not the energetically most favorable one. According to calculations, conformer **A**, which differs from conformer **B** in the orientation of the aryl substituent (see the torsion angles φ<sub>9</sub>, φ<sub>10</sub>, and φ<sub>20</sub> in Tables 3 and 5), is preferred. In this conformation, the aryl group, which is in the transoid orientation with respect to the C(2)—H(2) bond and is in the virtually eclipsed position relative to the axial C(3)—H bond, is maximum remote from the equatorial methyl group at the C(3) atom (Fig. 3). Apparently, in the case of the above-described configurations of the chiral centers, these structural characteristics are responsible for the fact that conformation **A**, like the most favorable conformer **A** for ketol **2b**, is energetically favorable.

In conformation **A** of model ketol **2a**, as in the case of crystals of **1a**, an intramolecular hydrogen bond is realized. However, the conformation of the pseudoring that is formed through this bond is different (see Fig. 3). Instead of the *twist*-boat conformation observed in the crystals of ketols **1a** and **1b**, the distorted C(7)-sofa conformation is realized in conformer **A** of compound **2a**. Besides, the H-bonded pseudoring is virtually coplanar with the base plane of the cyclohexanone ring,

**Table 5.** Selected torsion angles (φ<sub>*i*</sub>/deg) in molecules **2a** and **2b** calculated by molecular mechanics

Torsion angle	φ <sub><i>i</i></sub>	Structure <b>2a</b>			Structure <b>2b</b>	
		<b>A</b>	<b>B</b>	<b>C</b>	<b>A</b>	<b>B</b>
H(2)C(2)C(7)H(7)	φ <sub>8</sub>	-49.1	63.7	-163.7	-63.4	-176.6
C(1)C(2)C(7)C(8)	φ <sub>9</sub>	78.5	-168.0	-43.9	-62.8	-168.5
C(3)C(2)C(7)C(8)	φ <sub>10</sub>	-52.0	69.3	-165.1	174.4	69.8
C(3)C(2)C(7)O(2)	φ <sub>11</sub>	-179.6	-58.7	74.2	-58.8	-169.5
C(1)C(2)C(7)O(2)	φ <sub>12</sub>	-49.0	64.0	-164.6	63.9	47.8
C(2)C(7)O(2)H(O(2))	φ <sub>13</sub>	68.9	-67.3	175.0	-64.3	73.4
C(7)O(2)H(O(2))...O(1)	φ <sub>14</sub>	-48.7	27.3	—	24.3	-44.7
O(2)H(O(2))...O(1)C(1)	φ <sub>15</sub>	7.6	20.1	—	22.1	-8.8
H(O(2))...O(1)C(1)C(2)	φ <sub>16</sub>	14.2	-22.9	—	-22.5	33.8
O(1)C(1)C(2)C(7)	φ <sub>17</sub>	6.5	-9.8	-14.2	-10.3	-10.2
H(2)C(2)C(7)C(8)	φ <sub>20</sub>	-169.3	25.6	159.2	-2.0	158.9

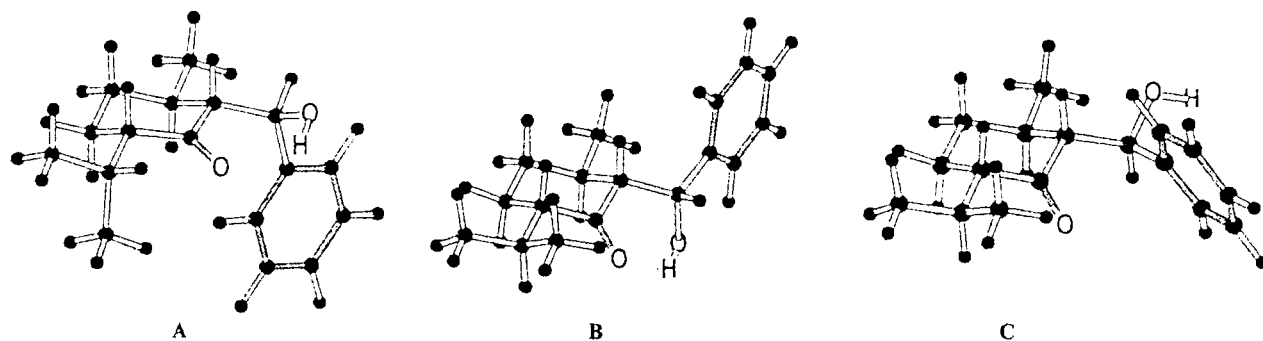


Fig. 3. Alternative molecular conformations of compound 2a.

unlike conformation B and the crystal structures of **1a** and **1b**, in which the dihedral angles between these rings have significant values.

The third possible conformer of molecule **2a** (C), which is formed as a result of rotation about the C(2)—C(7) bond, is characterized by the *anti* orientation of the aryl fragment with respect to the C(2)—C(3) bond (see the torsion angle  $\varphi_{10}$  in Table 5) and, correspondingly, by the absence of essential nonbonded interactions with the methyl group at the C(3) atom (see Fig. 3). In this case, an intramolecular hydrogen bond cannot be formed. Moreover, the equatorial methyl group that is located in proximity to the hydroxyl group would be expected to exert a shielding effect upon formation of molecular associates. Therefore, the characteristic feature of the isolated molecules of ketol **1a** as well of its stereoisomer **1b** is that their preferred conformations are characterized by an intramolecular hydrogen bond and by the orientation of the aryl substituent at the C(7) atom such that it provides minimum nonbonded interactions of the substituent with the methyl group at the C(3) atom.

The difference in the energy of alternative conformations A and B of model ketol **2a** is not so significant and does not evidently preclude the existence of conformation B, which possesses the larger value of  $E_{st}$  in the crystal but is apparently more favorable for the packing of molecules in stacks.

### Experimental

Diastereomeric 2-[1'-hydroxy-1'-(4-biphenyl)methyl]-*p*-menthan-3-ones (**1a**—**c**) and mixtures containing these compounds were analyzed by HPLC (KAKh-3 column, normal phase, 10 vol.% BuOAc solution in octane as eluent, flow rate 100  $\mu$ L min<sup>-1</sup>). The retention times (min) were as follows: 4.30 (4-phenylbenzaldehyde); 5.67 (**1a**); 6.77 (**1b**); 8.48 (ketol, which was not preparatively isolated, was presumably, the 2*S*,3*R*,6*S*,1'*R* stereoisomer)\*; and 12.47 (**1c**).

The IR spectra were recorded on a Specord 75IR instrument.

\* The compound was assigned to the class of ketols based on the analysis of the spectral relations in the course of HPLC and the configuration was ascribed by the exclusion method.

**The directed aldol reaction of (–)-menthone bromo-magnesium enolate with 4-phenylbenzaldehyde.** A solution of  $\text{Pr}_2\text{NH}$  (dried over Na) (3.2 mL, 22.9 mmol) in ether (3 mL) was added to an ethereal solution (15 mL) of butylmagnesium bromide, which was prepared from a magnesium powder (0.525 g, 21.6 mmol), under an atmosphere of argon at 25 °C. The reaction mixture was stirred for 10 min and then a solution of (–)-menthone (3 mL, 17.3 mmol) in  $\text{Et}_2\text{O}$  (5 mL) was added dropwise. The mixture was stirred for 20 min and cooled to +10 °C. A solution of 4-phenylbenzaldehyde (2.83 g, 15.6 mmol) in  $\text{Et}_2\text{O}$  (26 mL) was added dropwise. The reaction mixture was kept for 20 h and decomposed with an aqueous solution of  $\text{NH}_4\text{Cl}$  (300 mL). The organic compounds were extracted with  $\text{CHCl}_3$ , washed with water, dried with  $\text{CaCl}_2$ , filtered through a short silica gel layer, and concentrated. An oil was obtained in a yield of 5.82 g (80% of the theoretically calculated value), which crystallized out upon storage. According to the HPLC data, the resulting product contained  $\beta$ -hydroxyketones **1a**, **1b**, and **1c** in yields of 12%, 65%, and 15%, respectively. The sample (0.1 g) was taken for the analysis. Recrystallization of the residue from hexane afforded crystals of compound **1b** in a yield of 2.4 g, m.p. 94–97 °C. After additional crystallization from hexane, the m.p. was 99–100 °C (corresponding to the data in Ref. 2). Ketol **1a** was isolated from the mother liquor, which was obtained after first crystallization of ketol **1b**, by preparative column chromatography (silica gel Woelm, 5–40 mm fraction, 60×3 cm column, 10% EtOAc solution in hexane as eluent, 12–15-mL fractions were collected) in a yield of 196 mg. Crystallization from hexane afforded ketol **1a** in a yield of 43 mg, m.p. 99.5–100 °C. IR (KBr pellets),  $\nu/\text{cm}^{-1}$ : 1695 (CO), 3480 (OH). A mixed sample of **1a** and **1b** gave a melting point depression of 71–73 °C. Crystals of **1a** suitable for X-ray diffraction analysis were prepared by slow evaporation of a solution in a mixture of octane and toluene.

**X-ray diffraction study.** Crystals of **1a** ( $\text{C}_{23}\text{H}_{28}\text{O}_2$ ) are monoclinic. At –120 °C  $a = 20.409(5)$  Å,  $b = 5.677(2)$  Å,  $c = 16.795(4)$  Å,  $\beta = 98.29(2)^\circ$ ,  $V = 1925.5(9)$  Å<sup>3</sup>,  $d_{\text{calc}} = 1.161$  g cm<sup>-3</sup>, space group  $C2$ ,  $Z = 4$ . The unit cell parameters and intensities of 3076 independent reflections ( $R_{\text{int}} = 0.025$ ) were measured on an automated Siemens P3/PC diffractometer ( $\lambda$ -Mo-K $\alpha$  radiation, graphite monochromator,  $\theta/2\theta$  scanning technique,  $2\theta_{\text{max}} = 60^\circ$ ). We carried out the profile analysis of the X-ray diffraction data using the PROFIT program.<sup>15</sup>

The structure was solved by the direct method with the use of the SHELXTL PLUS program package.<sup>16</sup> The positions of the hydrogen atoms, except for the H atoms of the benzene ring, were located from the difference electron density synthe-

**Table 6.** Coordinates ( $\times 10^4$ ) and equivalent isotropic thermal parameters ( $U_{eq} \times 10^3$ ) of nonhydrogen atoms in the structure of **1a**

Atom	x	y	z	$U_{eq}/\text{\AA}^2$
O(1)	1705(5)	1164(10)	3470(3)	165(3)
O(2)	1448(3)	-1457(8)	2106(3)	113(2)
C(1)	1367(3)	2669(12)	3128(3)	76(2)
C(2)	1170(3)	2699(10)	2197(3)	52(1)
C(3)	411(3)	2537(13)	1963(3)	79(2)
C(4)	43(3)	4360(21)	2447(4)	132(3)
C(5)	290(4)	4124(25)	3361(4)	173(4)
C(6)	1020(3)	4553(13)	3570(3)	83(2)
C(7)	1598(3)	831(10)	1857(3)	63(2)
C(8)	1564(2)	770(9)	959(3)	41(1)
C(9)	1844(2)	2694(9)	575(3)	38(1)
C(10)	1858(2)	2630(9)	-242(2)	37(1)
C(11)	1599(2)	763(9)	-727(2)	34(1)
C(12)	1322(2)	-1095(9)	-348(3)	48(1)
C(13)	1317(2)	-1066(9)	486(3)	50(1)
C(14)	1613(1)	692(1)	-1605(2)	39(1)
C(17)	1652(1)	640(2)	-3252(3)	99(3)
C(15a)	2079(1)	1847(2)	-1960(1)	55(3)
C(16a)	2109(1)	1854(2)	-2750(1)	74(3)
C(18a)	1202(1)	-467(5)	-2866(1)	131(7)
C(19a)	1119(1)	-606(4)	-2026(1)	48(3)
C(15b)	1710(1)	2613(3)	-2060(1)	41(3)
C(16b)	1736(1)	2711(3)	-2851(2)	67(4)
C(18b)	1552(2)	-1467(4)	-2913(2)	216(16)
C(19b)	1537(2)	-1308(4)	-2056(2)	100(6)
C(20)	170(2)	2924(15)	1092(4)	76(2)
C(21)	1303(1)	4547(12)	4485(2)	129(3)
C(22)	928(3)	6096(12)	4949(4)	230(8)
C(23)	1968(3)	5550(19)	4638(4)	141(4)

sis. For the disordered fragment of the molecule, the positions of the hydrogen atoms were calculated geometrically for each possible orientation. All hydrogen atoms were refined using the riding model with fixed values of  $U_{iso} = nU_{eq}$  of the nonhydrogen atoms to which the hydrogen atoms are attached ( $n = 1.5$  for the methyl groups and  $n = 1.2$  for the remaining hydrogen atoms). The angles of rotation for the methyl and hydroxy groups were refined. Because of the large correlations between the positional parameters of the atoms, the requirements of planarity of the phenyl groups (to within 0.005 Å) and of equality of the lengths of the equivalent C—C bonds (to within 0.003 Å) were imposed on the disordered fragment in the course of refinement. The full-matrix least-squares refinement (based on  $F^2$ ) with anisotropic thermal parameters for nonhydrogen atoms using 1468 reflections converged to  $wR_2 = 0.253$  ( $R_1 = 0.091$  based on 1061 reflections with  $F > 4\sigma(F)$ ,  $S = 1.10$ ). The coordinates of the nonhydrogen atoms are given in Table 6.

Molecular mechanics calculations<sup>17</sup> were carried out with the MMX force field.<sup>18</sup> X-ray diffraction studies were carried

out in the Center of X-ray Diffraction Studies (A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences).

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Received April 6, 1998