

## Synthesis and Properties of Benzylidene Derivatives of Terpenoid Ketones

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**Abstract**—Optically active benzylidene derivatives of camphor and menthone were obtained in preparative yields by condensation of the ketones with aromatic aldehydes in DMSO in the presence of *t*-BuOLi. The synthesized  $\alpha,\beta$ -unsaturated ketones show high specific rotation and thus are suitable to bedoping component to liquid-crystalline compositions.

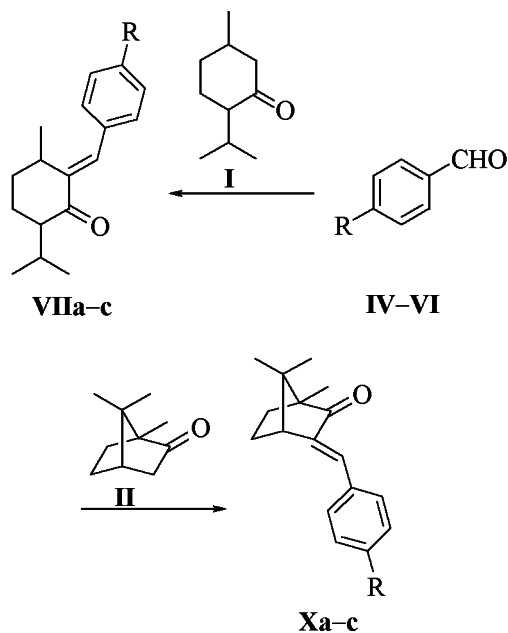
In the chemistry and physics of mesomorphic systems, nematic liquid crystals doped with optically active organic compounds attract special interest. The specific feature of these system lies in their spiral hypomolecular structure analogous to the cholesterol mesophase. This behavior is associated with the capability of the optically active compounds to induce ordering into helix in the nematic phase. Chiral  $\alpha,\beta$ -unsaturated ketones prepared by crotonic condensation from *l*-menthone and aromatic aldehydes exhibited such activity [1].

The goal of this study was to develop of a more efficient preparation procedure for menthone (**I**) derivatives, and synthesis of optically active benzylidene derivatives of camphor (**II**). As a model for

refining the synthetic procedure 2-cyclohexylcyclohexanone (**III**) was used.

To the synthesis of benzylidene derivatives we applied bezaldehyde (**IV**), anisaldehyde (4-methoxybenzaldehyde) (**V**), and 4-phenylbenzaldehyde (**VI**). Since the crotonic condensation does not affect the asymmetrical atom in camphor (**II**) and at least one of the asymmetrical centers in menthone (**I**) molecule we believed that the derivatives synthesized would also be optically active. Although the aromatic aldehydes are more reactive than aliphatic ones, they virtually cannot be brought into crotonic condensation under the standard conditions of the reaction (with alkali as catalyst and ethanol as solvent). In a patent [2] the condensation was described of ketone **II** with tetramethylterephthalaldehyde performed by boiling in anhydrous toluene with sodium hydroxide for 96 h; the yield was 38%. The yields of the same order of magnitude (30–50%) were attained by condensation of ketone **I** with aldehydes **IV** and **V** in the presence of potassium hydroxide in polar aprotic solvents: DMF, DMSO, HMPA, and dimethylacetamide [3]. The yield of condensation products with ketones **II** and **III** under these conditions was low. Potassium and sodium ethylates turned out to be inefficient catalysts in condensation carried out in anhydrous ethanol. The use of *t*-BuOK in DMSO resulted in 30–60% yields.

Organolithium compounds are known to be applied as basic catalysts. Camphor condensation with *trans*-4-(4-methylphenyl)-3-buten-2-one in the presence of BuLi occurs at  $-78^{\circ}\text{C}$  to afford the condensation product in hardly 7% yield [7]. We attempted to use *t*BuOLi as catalyst. The use of lithium as counterion with a large solvate radius leaves room for better results. The experimental data are presented in a table.



R = H (**IV**), OCH<sub>3</sub> (**V**), Ph (**VI**); **VII**, **X**, R = H (**a**), OCH<sub>3</sub> (**b**), Ph (**c**).

Yields and characteristics of condensation products of ketones **I–III** with aromatic aldehydes **IV–VI**

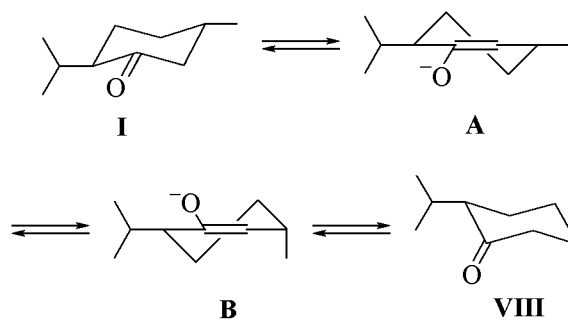
Initial ketone no.	Aldehyde no.	Reaction time, min	Yield, %	mp, °C	$[\alpha]_D^{20}$ (c, solvent)
<b>I</b>	<b>IV</b>	60	62	–	–217° (2.6, chloroform)
	<b>V</b>	60	83	115–117	–253° (4.3, acetone)
	<b>VI</b>	75	78	105	–274° (1.7 chloroform)
<b>II</b>	<b>IV</b>	60	70	92–94	+361° (2.7, acetone)
	<b>V</b>	40	85	128	+498° (3.2, acetone)
	<b>VI</b>	30	82	160	+476° (2.3, chloroform)
<b>III</b>	<b>IV</b>	45	67	102	–
	<b>V</b>	40	88	113	–
	<b>VI</b>	60	85	137	–

The use of *t*-BuOLi instead of potassium hydroxide did not significantly affect the yield of 2-benzylidene-menthone (**VIIa**), but the reaction time notably reduced (1 h against 4 h by procedure [3]). Reaction with the other aldehydes provided higher yields. 2-(4-methoxybenzylidene)menthone (**VIIb**) was obtained in 83% yield, and 2-(4-phenylbenzylidene)menthone (**VIIc**) in 78% yield.

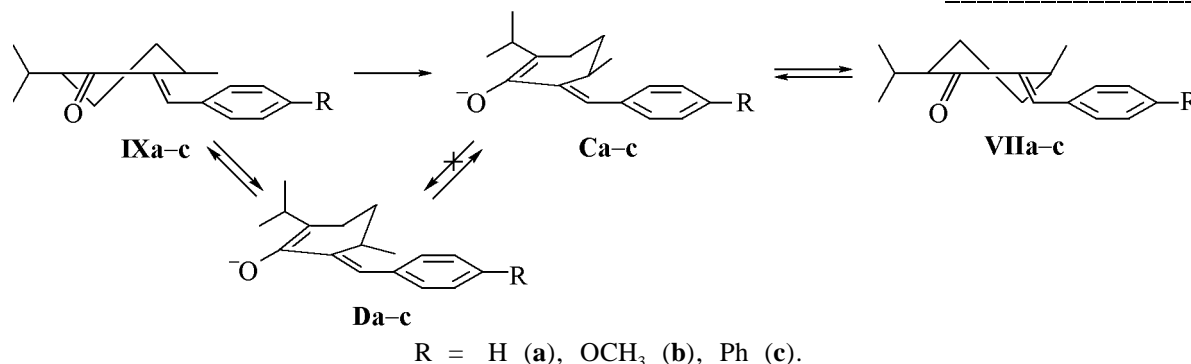
Under conditions of crotonic condensation of aromatic aldehydes with *trans*-3-menthone (**I**) arise benzylidene derivatives of *cis*-3-menthone, isomenthone (**VIII**). The formation of ketone **VIII** derivatives from the initial ketone **I** was not unexpected. In the basic medium *trans*-isomer **I** is in equilibrium with *cis*-isomer **VIII** due to keto-enol tautomerism. We checked it experimentally. As showed the GLC of the reaction mixture before visible crystallization both ketones **I** and **VIII** were present therein in the ratio 70:30 in agreement with the data from [5]. It is also seen from the changed optical activity of ketones: the optical activity of the initial menthone was  $[\alpha]_D^{20} -27.8^\circ$ , and that of the equilibrium mixture was  $[\alpha]_D^{20} +8.5^\circ$ . The specific rotation of ketone **VIII** calculated by Biot law amounts to  $+92^\circ$  in agreement with the known data [5, 6].

However the lack of menthone **I** derivatives among the reaction products was unexpected. It is believed

that crotonic condensation undergoes only one epimer, namely (+)-isomenthone [7], but the reasons of this selectivity have not been explained. This statement seems dubious: hardly the spatial orientation of the methyl group would affect the formation of enolate ion by proton abstraction from the C<sup>4</sup> of the six-membered menthone ring; it is also unlikely that the reactivity of the epimeric enolate-ions would be influenced. The difference in the total energy of ions **A** and **B** originating respectively from ketones **I** and **VIII** calculated in the MM2 approximation equals only to 1.4 kcal mol<sup>-1</sup>, and thus the conformational transitions are quite probable.



We believe that more logical is an assumption of epimerization of the arising  $\alpha,\beta$ -unsaturated ketones



(IX). The geometry optimization for ions originating from ketones IX during enolization at C<sup>4</sup> atom shows that in both cases forms the same ion C. The proton addition causing minimum changes in the orientation of the substituents and resulting in the low-energy conformation of the six-membered ring should afford benzyldene derivatives of isomenthone VIIa-c.

The hypothetical ion D with a pseudoequatorial methyl group that may lead to menthone derivatives IXa-c is more strained than ion C because the methyl group adjacent to the aromatic ring should cause distortion of coplanarity in the double bonds system. The torsional angle C(O<sup>-</sup>)C=CPh for ions Da-c equals to 10.4, 10.1, and 9.9° respectively whereas for ions Ca-c it is 2.8, 2.7, and 2.8°. The calculated energy difference for the corresponding pairs of ions Da-c and Ca-c is 6.61, 6.33, and 6.63 kcal mol<sup>-1</sup>. Thus the conformational transition C→D is a lot less probable than A→B transition.

The developed condensation procedure turned out to be efficient also for preparation of optically active benzyldene derivatives of *d*-camphor. Under the described conditions the reaction with camphor occurs even readier than with menthone. In condensation of ketone II with aldehyde VI already several minutes after the mixing of reagents the crystalline reaction product starts to precipitate. Somewhat slower are reactions with aldehydes IV and V (see table).

As show <sup>1</sup>H NMR data, the cinnamoyl fragment in the obtained derivatives of ketone II possesses *E*-configuration as also in the respective derivatives of ketone I. To the olefin proton of these compounds corresponds the signal in the region 7.17–7.23 ppm; this value for a proton of a cinnamoyl fragment in a *Z*-configuration should be 6.3 ppm [8]. The same conclusion follows from the geometry optimization for these compounds in the MM2 approximation.

Note however that noncoplanarity of the C(O)C=CPh fragment in the derivatives of ketone II is considerably less than in derivatives of ketone I. If in the latter the torsion angle reaches 57–59°, in the molecules of camphor derivatives this value is only 3–4°. The α,β-unsaturated ketones obtained possess extremely high optical activity, apparently due to diastereomeric homogeneity. Thus they are promising as chiral doping components for liquid-crystal compositions.

The synthesized derivatives of ketones I–III are well soluble in acetone, ether, chloroform, somewhat less in alcohol, and therefore this solvent is suitable for recrystallization. They are relatively chemically

inert, and the attempts to prepare by standard procedures from the derivatives of ketones I–III epoxides, oximes, and Schiff bases have been unsuccessful.

## EXPERIMENTAL

GLC analysis of reaction mixtures and condensation products was carried out on chromatograph Chrom-4 equipped with flame-ionization detector, carrier gas nitrogen, flow rate 40 ml/min, column 1500×3 mm, stationary phase 5% XE-60 on Inerton AW-DMCS (0.2–0.25 mm), oven temperature programmed from 70 to 260°C at a rate 5 deg/min. <sup>1</sup>H NMR spectra were registered on spectrometer Tesla BS-567A in CDCl<sub>3</sub> and C<sub>6</sub>D<sub>6</sub>, internal reference HMDS.

Initial ketone I, [α]<sub>D</sub><sup>20</sup> -27.8°, was obtained by oxidation of the natural menthol. The derivatives of ketone II were prepared from natural Japanese camphor, [α]<sub>D</sub><sup>20</sup> +46.6° (*c* 5.7, ethanol).

**Condensation of ketones I–III with aromatic aldehydes.** In 15 ml of anhydrous DMSO were dissolved 3 g (0.02 mol) of ketone and 0.022 mol of aldehyde. To a mixture of 1.2 g (0.015 mol) of *t*-BuLi and 10 ml of anhydrous DMSO was added dropwise the solution of reagents controlling the rate of addition so as the temperature of the reaction mixture did not exceed 20°C; the reaction mixture was cooled with water bath. The stirring was continued till complete consumption of the ketone. Then the reaction mixture was poured into 250 ml of ice water containing 10 ml of acetic acid. The precipitate was filtered off, washed with water, and recrystallized from ethanol.

<sup>1</sup>H NMR spectra of compounds VIIa-c were consistent with the published data [7].

**3-Benzylidenecamphor (Xa).** <sup>1</sup>H NMR spectrum, δ, ppm: 0.83 s (3H, CH<sub>3</sub>), 1.00 s and 1.03 s [6H, (CH<sub>3</sub>)<sub>2</sub>C], 1.40–2.32 m (4H, 2CH<sub>2</sub>), 3.11 d (1H, HC, *J* 4 Hz), 7.23 s (1H, =CH), 7.25–7.51 m (5H arom).

**3-(4-Methoxybenzylidene)camphor (Xb).** <sup>1</sup>H NMR spectrum, δ, ppm: 0.78 s (3H, CH<sub>3</sub>), 0.98 s and 1.00 s [6H, (CH<sub>3</sub>)<sub>2</sub>C], 1.46–2.28 m (4H, 2CH<sub>2</sub>), 3.08 d (1H, HC, *J* 5 Hz), 7.17 s (1H, =CH), 6.92 d and 7.42 d (4H arom, *J* 9 Hz).

**3-(4-Phenylbenzylidene)camphor (Xc).** <sup>1</sup>H NMR spectrum, δ, ppm: 0.80 s (3H, CH<sub>3</sub>), 0.96 s and 1.00 s [6H, (CH<sub>3</sub>)<sub>2</sub>C], 1.44–2.23 m (4H, 2CH<sub>2</sub>), 3.16 d (1H, HC, *J* 7 Hz), 7.23 s (1H, =CH), 7.08–7.66 m (5H arom).

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