

Synthesis of Substituted Benzyl Ethers of 1-(4-Hydroxyphenyl)oct-2-en-1-one

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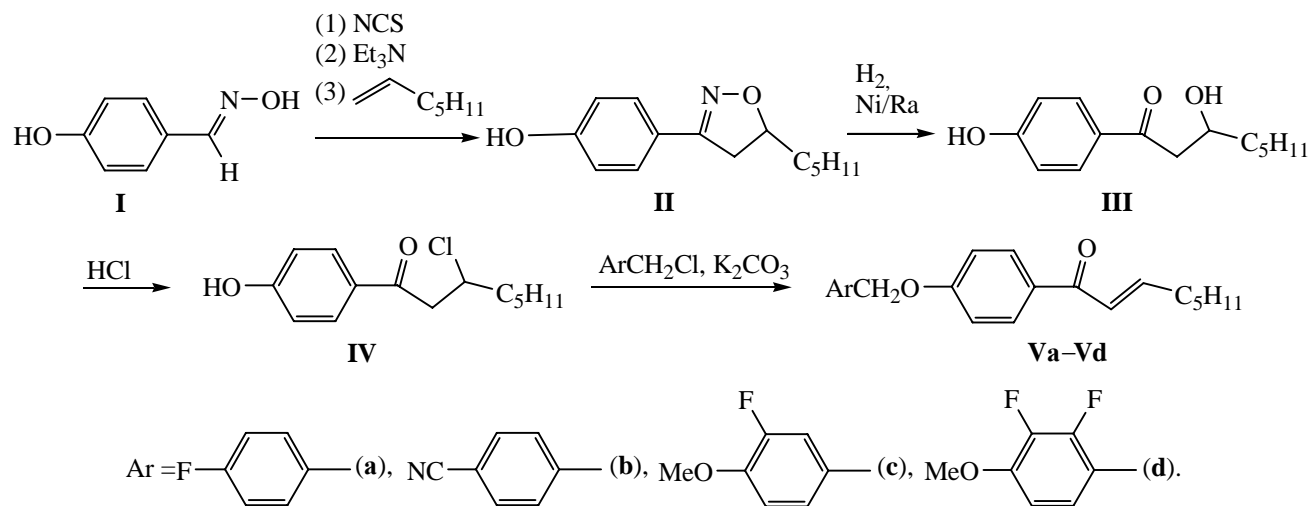
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Abstract—A preparation of substituted benzyl ethers of 1-(4-hydroxyphenyl)oct-2-en-1-one from 3-(4-hydroxyphenyl)-5-pentyl-2-isoxazoline was developed for the first time. These ethers can be used as promising additives and useful intermediates for synthesis of fluorine-containing liquid crystals.

Syntheses of liquid crystalline compounds basing on substituted 2-isoxazolines were formerly reported [1–5]. One of the preparation procedures [1] employed as an intermediate substituted 2-isoxazoline **II**. This compound can be obtained from the easily available 4-hydroxybenzaldehyde oxime **I**. In the first stage of the process compound **I** is subjected to successive treatment with *N*-chlorosuccinimide and triethylamine to afford the corresponding nitrile oxide that at subsequent reaction with 1-heptene furnishes substituted 2-isoxazoline **II**. The opening of the heterocycle in the substituted 2-isoxazolines is widely used in the organic synthesis for preparation of versatile bifunctional compounds, for instance, aminoalcohols, β -hydroxyketones, and enones [6, 7]. We believe that the opening of the 2-isoxazoline ring in compound **II** may be used in the synthesis of new liquid crystalline compounds with various functional groups in

the side chain. The phenol hydroxy group can be used to connect rigid fragments of the molecule through bridging ether groups. We report here on the possibility to use this approach to the synthesis of mesomorphous compounds by an example of preparation of substituted benzyl ethers from 1-(4-hydroxyphenyl)oct-2-en-1-one.

By hydrogenolysis of the heterocycle in 2-isoxazoline **II** on Raney nickel we obtained β -hydroxyketone **III** in 76% yield. At treating hydroxyketone **III** with hydrochloric acid β -chloroketone **IV** formed alongside a dehydration product; the former compound became the main reaction product at prolonged process time, and it was isolated in 70% yield. β -Chloroketone **IV** arises due to hydrogen chloride addition across the double bond of the dehydration product of compound **III**. We presumed that a double bond may form in the next benzylation stage, and therefore



β -chloroketone **IV** would be suitable for the synthesis of the target benzyl ethers.

The structure of compounds **III** and **IV** was proved by the data obtained by analysis of IR, UV, and ^1H NMR spectra. In the IR spectrum of β -hydroxyketone **III** the absorption band of the stretching vibrations of the carbonyl group is observed at 1664 cm^{-1} . This shift of the $\text{C}=\text{O}$ frequency as compared with its usual position in alkyl aryl ketones in the region $1680\text{--}1700\text{ cm}^{-1}$ is caused by involvement of the carbonyl group of compound **III** into an intramolecular hydrogen bond with a hydroxy group attached to C^3 atom. In the ^1H NMR spectrum the β -hydroxyketone fragment of compound **III** gives rise to two doublets of doublets of protons from C^2H_2 at δ 2.95 and 3.11 ppm and to a multiplet of the proton C^3H at δ 4.16–4.25 ppm. In the IR spectrum of β -chloroketone **IV** the absorption band of the carbonyl stretching vibrations appears at 1675 cm^{-1} . A specific feature of the ^1H NMR spectrum of compound **IV** consists in the downfield shift of proton signals from the β -chloroketone moiety as compared to the corresponding signals in the spectrum of β -hydroxy-ketone **III**. Protons of C^2H_2 group give rise to doublets of doublets δ 3.18 and 3.50 ppm, and proton C^3H appears as a multiplet at δ 4.48–4.57 ppm.

In reaction of compound **IV** with substituted benzyl chlorides in the presence of potassium carbonate benzyl ethers **Va–Vd** were obtained in 50–80% yields. As we have presumed the hydrogen chloride is eliminated in the course of the reaction, and a double bond is formed. The latter fact is confirmed by the presence in the IR spectra of compounds **Va–Vd** of strong absorption bands from $\text{C}=\text{C}$ bond vibrations at $1610\text{--}1620\text{ cm}^{-1}$. The vibrations of the conjugated carbonyl group in the IR spectra of compounds **Va–Vd** are observed in the range $1660\text{--}1670\text{ cm}^{-1}$. In the ^1H NMR spectra of benzyl ethers **Va–Vd** vinyl protons C^2H and C^3H appear as multiplets at δ 6.84 and 7.05 ppm with a vicinal coupling constant 15.6 Hz. This value of the coupling constant indicates the formation of a *trans*-disubstituted double bond.

We established by measuring the temperature of phase transitions in benzyl ethers **Va–Vd** that none of the compounds formed a mesophase. This may be due in particular to insufficient number of ring structures in the central part of the molecule. However compounds **Va–Vd** have a structure typical for many nematic liquid crystals. Therefore it is possible to use the compounds as various isotropic additives to nematic liquid crystal mixtures. For instance, the application of two-ring benzyl

ethers as chiral additives to nematic mixtures was described in [8]. We believe that among compounds we obtained the most promising for this application is benzyl ether **Vb** with a terminal cyano group. This compound of low melting point can be used as isotropic additive for reducing the temperature of mesophase formation in nematic liquid crystal mixtures.

It should also be mentioned that the enone moiety present in the molecules of compounds **Va–Vd** can be used to introduce some practically important structural elements of the liquid crystal compounds, for instance, fluorine atoms [9–12].

Thus proceeding from 3-(4-hydroxyphenyl)-5-pentyl-2-isoxazoline a synthetic procedure was developed for benzyl ethers of 1-(4-hydroxyphenyl)oct-2-en-1-one which may be interesting as components of liquid crystal compositions. The report on application of the approach we developed to the synthesis of more complex liquid crystalline compounds with a functionally modified side chain will be published elsewhere.

EXPERIMENTAL

Phase transition temperature was measured on a heating block coupled with a polarization microscope. IR spectra were recorded from solutions in chloroform on a spectrophotometer Specord 75-IR in a cell of potassium bromide. UV spectrum was taken on a spectrophotometer Specord M40 from a methanol solution. ^1H NMR spectra were registered on spectrometer Bruker Avance 400 (400 MHz), from solutions in deuteriochloroform, internal reference HMDS. Reactions progress was monitored and the purity of compounds obtained was checked by TLC on Kiesel-gel 60 F₂₅₄ plates (Merck).

1-(4-Hydroxyphenyl)-3-hydroxyoctan-1-one (III). A dispersion of 2 g of Raney nickel in 20 ml of methanol and 12 ml of water was saturated with hydrogen at stirring for 1 h. Then a solution of 3.58 g (15.4 mmol) of 3-(4-hydroxyphenyl)-5-pentyl-2-isoxazoline (**II**) prepared by procedure [1] and 9.3 g (150 mmol) of boric acid in 80 ml of methanol was added. The reaction mixture was stirred under hydrogen atmosphere till consumption of hydrogen ended. The catalyst was filtered off, washed on the filter with 100 ml of dichloromethane, 150 ml of saturated solution of NaCl was added, and then the organic layer was separated. The products were additionally extracted from the water layer into dichloromethane (2×50 ml). The combined organic solutions were washed in succession with 50 ml of

saturated sodium hydrogen carbonate solution and 50 ml of saturated solution of NaCl, dried with sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was recrystallized from a mixture toluene–petroleum ether. Yield 2.77 g (76%), mp 76.5–77.5°C (toluene–petroleum ether). IR spectrum, cm^{-1} : 3575, 3460–3100 (OH), 3010 (C–H_{arom}), 2950, 2925, 2850 (C–H_{alkyl}), 1664 (C=O), 1600, 1590, 1505 (C=C_{arom}). ¹H NMR spectrum, δ , ppm: 0.88 t (3H, C⁸H₃, *J* 7 Hz), 1.16–1.66 m (8H, CH₂, H_{alkyl}), 2.95 d.d (1H, *J*₁ 9, *J*₂ 18 Hz), 3.11 d.d (1H, *J*₁ 2.4, *J*₂ 18 Hz) (C²H₂), 3.65 br.s (1H, C³OH), 4.16–4.25 m (1H, C³H), 6.80–6.98 m (1H, C⁴OH), 6.85 d (2H, *J* 9 Hz), 7.85 d (2H, *J* 9 Hz) (arom. protons).

1-(4-Hydroxyphenyl)-3-chlorooctan-1-one (IV).

To a solution of 0.766 g of β -hydroxyketone **III** in 20 ml of dioxane was added 1.5 ml of concn. hydrochloric acid. The mixture obtained was stirred for 22.5 h at 20°C. Then 40 ml of toluene and 50 ml of saturated sodium chloride solution were added to the reaction mixture. The organic layer was separated. The products were additionally extracted from the water layer into toluene (2×20 ml). The combined toluene solutions were washed in succession with 30 ml of saturated sodium hydrogen carbonate solution and 30 ml of saturated solution of NaCl, dried with sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was crystallized from a mixture toluene–petroleum ether. Yield 0.577 g (70%), mp 56–57°C (toluene–petroleum ether, decomp.). UV spectrum, λ_{max} , nm: 221.1, 279.8. IR spectrum, cm^{-1} : 3585, 3100–3500 (O–H), 3025, 3010 (C–H_{arom}), 2960, 2930, 2875, 2865 (C–H_{alkyl}), 1675 (C=O), 1605, 1585, 1510 (C=C_{arom}). ¹H NMR spectrum, δ , ppm: 0.88 t (3H, C⁸H₃, *J* 6.8 Hz), 1.20–1.38 m (4H, C⁶H₂, C⁷H₂), 1.40–1.62 m (2H, C⁵H₂), 1.69–1.89 m (2H, C⁴H₂), 3.18 d.d (1H, *J*₁ 5.6, *J*₂ 16.4 Hz), 3.50 d.d (1H, *J*₁ 8, *J*₂ 16.4 Hz) (C²H₂), 4.48–4.57 m (1H, C³HCl), 5.74 br.s (1H, C⁴OH), 6.88 d (2H, *J* 8.8 Hz), 7.89 d (2H, *J* 8.8 Hz) (arom. protons).

4-Fluorobenzyl ether of 1-(4-hydroxyphenyl)-oct-2-en-1-one (Va). To a solution of 0.1 g (0.39 mmol) of β -chloroketone **IV** and 0.052 ml (0.43 mmol) of 4-fluorobenzyl chloride in 50 ml of methyl ethyl ketone was added 3 g of potassium carbonate. The reaction mixture was heated at reflux while stirring for 15 h. Then the inorganic precipitate was filtered off and washed on the filter with 50 ml of methyl ethyl ketone. The solvent was distilled off at reduced pressure, the residue was recrystallized from 2-propanol. Yield 59%, mp 96–97°C (2-propanol).

IR spectrum, cm^{-1} : 3025, 3015 (C–H_{arom}), 2955, 2930, 2870, 2855 (C–H_{alkyl}), 1660 (C=O), 1610 (C=C), 1595, 1570, 1510 (C=C_{arom}). ¹H NMR spectrum, δ , ppm: 0.89 t (3H, C⁸H₃, *J* 6.8 Hz), 1.16–1.40 m (4H, C⁶H₂, C⁷H₂), 1.51 quintet (2H, C⁵H₂, *J* 7 Hz), 2.29 q (2H, C⁴H₂, *J* 7 Hz), 5.08 s (2H, OCH₂), 6.87 d (1H, C²H, *J* 15.6 Hz), 6.94–7.14 m (1H, C³H), 6.99 d (2H, *J* 8.8 Hz), 7.04–7.14 m (2H), 7.40 m (2H), 7.93 d (2H, *J* 8.8 Hz) (arom. protons).

4-Cyanobenzyl ether of 1-(4-hydroxyphenyl)-oct-2-en-1-one (Vb). Yield 49%, mp 43°C (2-propanol). IR spectrum, cm^{-1} : 3025, 3015 (C–H_{arom}), 2960, 2930, 2860 (C–H_{alkyl}), 2235 (C≡N), 1665 (C=O), 1610 (C=C), 1600, 1570, 1500 (C=C_{arom}). ¹H NMR spectrum, δ , ppm: 0.89 t (3H, C⁸H₃, *J* 7 Hz), 1.16–1.39 m (4H, C⁶H₂, C⁷H₂), 1.51 quintet (2H, C⁵H₂, *J* 7 Hz), 2.29 distorted q (2H, C⁴H₂, *J* 7 Hz), 5.18 s (2H, OCH₂), 6.84 distorted d (1H, C²H, *J* 15.2 Hz), 7.05 t.d (1H, C³H, *J*₁ 7, *J*₂ 15.2 Hz), 6.99 d (2H, *J* 9 Hz), 7.54 d (2H, *J* 8 Hz), 7.68 d (2H, *J* 8 Hz), 7.94 d (2H, *J* 9 Hz) (arom. proton \hat{u}).

4-Methoxy-3-fluorobenzyl ether of 1-(4-hydroxyphenyl)oct-2-en-1-one (Vc). Yield 58%, mp 59–60°C (2-propanol). IR spectrum, cm^{-1} : 3035, 3030, 3020 (C–H_{arom}), 2965, 2935, 2860 (C–H_{alkyl}), 1670 (C=O), 1620 (C=C), 1600, 1575, 1520, 1510 (C=C_{arom}). ¹H NMR spectrum, δ , ppm: 0.89 t (3H, C⁸H₃, *J* 6.8 Hz), 1.17–1.38 m (4H, C⁶H₂, C⁷H₂), 1.51 quintet (2H, C⁵H₂, *J* 7.2 Hz), 2.29 d.q (2H, C⁴H₂, *J*₁ 1.6, *J*₂ 7.2 Hz), 3.89 s (3H, OCH₃), 5.03 s (2H, OCH₂), 6.87 t.d (1H, C²H, *J*₁ 1.6, *J*₂ 15.6 Hz), 7.04 t.d (1H, C³H, *J*₁ 7.2, *J*₂ 15.6 Hz), 6.93–7.00 m (3H), 7.12 m (1H), 7.16 m (1H), 7.93 d (2H, *J* 8.8 Hz) (arom. protons).

4-Methoxy-2,3-difluorobenzyl ether of 1-(4-hydroxyphenyl)oct-2-en-1-one (Vd). Yield 78%, mp 76–77°C (2-propanol). IR spectrum, cm^{-1} : 3025, 3010 (C–H_{arom}), 2960, 2930, 2875, 2860 (C–H_{alkyl}), 1660 (C=O), 1610 (C=C), 1595, 1570, 1510 (C=C_{arom}). ¹H NMR spectrum, δ , ppm: 0.89 t (3H, C⁸H₃, *J* 7 Hz), 1.12–1.38 m (4H, C⁶H₂, C⁷H₂), 1.51 quintet (2H, C⁵H₂, *J* 7 Hz), 2.29 d.q (2H, C⁴H₂, *J*₁ 1, *J*₂ 7 Hz), 3.90 C (3H, OCH₃), 5.11 C (2H, OCH₂), 6.87 t.d (1H, C²H, *J*₁ 1, *J*₂ 15.6 Hz), 7.04 t.d (1H, C³H, *J*₁ 7, *J*₂ 15.6 Hz), 7.00 d (2H, *J* 8.8 Hz), 7.94 d (2H, *J* 8.8 Hz), 6.72–6.78 m (1H), 7.10–7.18 m (1H) (arom. protons).

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