Synthesis, Physicochemical Properties, and Conformational Studies of (3-Alkoxymethyl-4-hydroxyphenyl)ethanones

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A homologous series of (3-alkoxymethyl-4-hydroxyphenyl)ethanones was prepared by the reaction of (3-chloromethyl-4-hydroxyphenyl)ethanone with the different alcohols in the presence of sodium hydrogen carbonate. The confirmation of structures was achieved by interpretation of IR, UV, and ^{1}H NMR spectra. Molecular modeling methods were used to establish conformations with global and local energetic minima. It was found that energetically the most stable conformations involved hydrogen bond formation between the hydrogen of phenolic group and the oxygen of alkoxyl group. Enthalpy values of hydrogen bonds of selected compounds were 24.86—30.51 kJ mol^{-1} and their distances were in the range 0.282—0.293 nm.

Organic compounds with phenolic groups possess various biological activities [1—3]. Many of them are used as intermediates of syntheses of biologically active compounds [4—6]. The reactivity of phenolic group in these syntheses can be changed due to present 2-positioned substituent forming the hydrogen bond with phenolic group [7, 8].

This paper is focused on the synthesis of the homologous series of (3-alkoxymethyl-4-hydroxyphenyl)-ethanones used as intermediates in the preparation of biologically active compounds [9, 10]. They were prepared by nucleophilic substitution reaction of (3-chloromethyl-4-hydroxyphenyl)ethanone with the corresponding alcohols in the presence of sodium hydrogen carbonate. The conformation arrangement of selected compounds was studied by the method of molecular modeling.

The starting product, (3-chloromethyl-4-hydroxyphenyl)ethanone, was prepared with a modification, in which paraformaldehyde was used instead of formaldehyde to obtain higher yield, 75 % instead of 57 %. This halo derivative with its primary benzylic moiety undergoes nucleophilic substitution reaction. According to the character of carbon rest to which the halogen is attached this compound is considered to belong to the halo derivatives with increased reactivity [11]. This increased reactivity by their nucleophilic substitution of halogen by alkoxyl group causes the formation of many by-products. For example, stilbenes were isolated using the stronger basic reagents than the alcoholates or hydroxides [12]. On the other hand, solute alcohols caused solvolysis according to [13]. For this reason less basic medium *e.g.* sodium hydrogen carbonate is suitable to use at the nucleophilic substitution reactions of this type of halo derivatives [14]. Reactions of (3-chloromethyl-4-hydroxyphenyl)ethanone with different alcohols in the presence of sodium hydrogen carbonate yielded a series of 18 (3-alkoxymethyl-4-hydroxyphenyl)ethanones with 1—9 carbons in the alkoxyl group, with branched alkyl groups having 3—5 carbons and cycloalkoxyl with 5 and 6 carbons. The purity of the formed compounds was assessed by thin-layer chromatography and R_F values were determined (Table 1). Confirmation of structures was achieved by the interpretation of IR, UV, and ^{1}H NMR spectra.

The UV spectra of the compounds displayed three typical absorption bands at 204 nm, 220 nm, and 274 nm (in methanol) and 202 nm, 218 nm, and 266 nm (in cyclohexane), associated with π—π^* transitions (Table 2). All of these absorption maxima had high values of molar extinction coefficients (log ε = 3.10—3.28). Comparison of these spectra with UV spectrum of phenylethanone, which possesses absorption bands at 246 nm, 280 nm, and 320 nm with log ε = 2.99, 2.04, 0.70 [15, 16] clearly indicates a strong hyperchromic effect of the II and III absorption bands according to the following resonance structure.

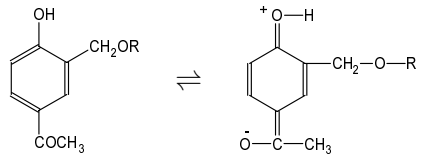


Table 1. Characterization of Prepared (3-Alkoxymethyl-4-hydroxyphenyl)ethanones *I*—*XVIII*

Compound	R	Formula M_r	w_i(calc.)/% w_i(found)/% C	 H	Yield/% R_F	M.p./℃ Solvent
I	CH_3	$C_{10}H_{12}O_3$ 180.21			64 0.26	86—88[a] *b*
II	C_2H_5	$C_{11}H_{14}O_3$ 194.23	68.02 68.23	7.27 7.39	54 0.29	64—65 *b*
III	C_3H_7	$C_{12}H_{16}O_3$ 208.28	69.21 69.25	7.74 7.87	60 0.38	52—53 *c*
IV	$CH(CH_3)_2$	$C_{12}H_{16}O_3$ 208.28	69.21 69.35	7.74 7.85	70 0.55	70—73 *d*
V	C_4H_9	$C_{13}H_{18}O_3$ 222.29	70.24 70.34	8.16 8.18	60 0.42	53—54 *c*
VI	$CH_2CH(CH_3)_2$	$C_{13}H_{18}O_3$ 222.29	70.24 70.05	8.16 8.12	64 0.56	39—41 *c*
VII	$CH(CH_3)CH_2CH_3$	$C_{13}H_{18}O_3$ 222.29	70.24 70.15	8.16 8.08	58 0.60	40—43 *c*
VIII	$C(CH_3)_3$	$C_{13}H_{18}O_3$ 222.29	70.24 70.34	8.16 8.24	62 0.61	44—46 *c*
IX	C_5H_{11}	$C_{14}H_{20}O_3$ 236.31	71.16 71.28	8.53 8.60	64 0.48	34—35 *c*
X	i-C_5H_{11}	$C_{14}H_{20}O_3$ 236.31	71.16 71.27	8.53 8.65	65 0.57	47—48 *c*
XI	cyclo-C_5H_9	$C_{14}H_{18}O_3$ 234.30	71.77 71.58	7.74 7.62	63 0.58	61—63 *c*
XII	C_6H_{13}	$C_{15}H_{22}O_3$ 250.34	71.97 71.87	8.86 8.82	57 0.54	41—43 *c*
XIII	cyclo-C_6H_{11}	$C_{15}H_{20}O_3$ 248.31	72.55 72.77	8.12 8.05	61 0.66	64—66 *c*
XIV	C_7H_{15}	$C_{16}H_{24}O_3$ 264.37	72.69 72.83	9.15 9.21	58 0.61	60—62 *c*
XV	C_8H_{17}	$C_{17}H_{26}O_3$ 278.19	73.35 73.27	9.41 9.20	63 0.65	44—45 *c*
XVI	C_9H_{19}	$C_{18}H_{28}O_3$ 292.42	73.93 73.77	9.65 9.55	66 0.68	45—47 *c*
XVII	CH_2—C_6H_5	$C_{16}H_{16}O_3$ 256.30	74.98 74.87	6.29 6.23	60 0.57	52—53 *c*
XVIII	CH_2—CH═CH_2	$C_{12}H_{14}O_3$ 206.24	69.89 69.73	6.84 6.89	62 0.47	30—31 *c*

a) Ref. [14] gives m.p. = 87—88 ℃, *b*) methanol, *c*) heptane, *d*) cyclohexane.

The IR spectra of the compounds displayed characteristic bands associated with C═O, C═C, and O—H stretching vibrations (Table 2). Further examination of the OH stretching vibration showed that its position at about 3340 cm^{-1} was not influenced by the decreasing concentration of the CCl_4 solutions and thus highlighted the lack of intermolecular hydrogen bond according to [17, 18].

The ^1H NMR spectra showed signals at $\delta = 7.50$—7.80 of aromatic protons with a multiplet for $H^{2,6}$ hydrogens and at $\delta = 6.65$—6.87 for H^5 hydrogen. Protons of methyl group in $COCH_3$ give the singlet at $\delta = 2.40$—2.50 and protons of methylene groups in $ArCH_2O$ at $\delta = 4.60$—4.70 and at $\delta = 3.40$—3.90 due to the OCH_2R. The signal at $\delta = 8.20$—8.88 as singlet is due to the OH hydrogen (Table 3).

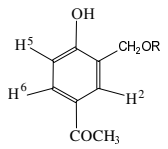
On the basis of molecular modeling it was found out that the most suitable conformations of these compounds were stabilized by the intramolecular hydrogen bond between hydrogen of the phenolic group and oxygen in the alkoxy group O—H···O. The distances between neighbouring atoms involved in the hydrogen bond are in all cases considerably smaller than the sum of their van der Waals radii of present atoms and these are middle strong in comparison to weaker hydrogen bond. There is not the same opinion in the literature on the relationship between the energy of the hydrogen bond and its length. The hydrogen bond O—H···O with the distance d(O···O) up to 0.265 nm is considered as strong, in the range 0.265—0.280 nm as middle strong, and over 0.280 nm as weak [19—21]. The strength of the hydrogen bond was expressed

Table 2. Values of Stretching Vibrations of Prepared Compounds and Values of λ_{max} and $\log \varepsilon$ in UV Spectra of Prepared Compounds

Compound	$\tilde{\nu}$(OH)	$\tilde{\nu}$(C═O)	$\tilde{\nu}$(C═C)	$\lambda_{1\,max}$		$\lambda_{2\,max}$		$\lambda_{3\,max}$	
	cm^{-1}	cm^{-1}	cm^{-1}	nm	$\log(\varepsilon/(m^2\ mol^{-1}))$	nm	$\log(\varepsilon/(m^2\ mol^{-1}))$	nm	$\log(\varepsilon/(m^2\ mol^{-1}))$
I	3369	1682	1615 1590	204	3.16	224	3.12	276	3.17
II	3339	1680	1614 1590	202	3.23	218	3.21	266	3.19[a]
				204	3.17	224	3.13	276	3.17
III	3338	1680	1613 1591	202	3.26	218	3.23	266	3.23[a]
				204	3.16	224	3.12	276	3.15
IV	3330	1681	1614 1590	202	3.29	218	3.26	266	3.23
V	3339	1681	1614 1590	202	3.26	218	3.22	266	3.20[a]
				204	3.17	224	3.14	276	3.17
VI	3342	1681	1614 1590	202	3.22	218	3.19	266	3.16[a]
				204	3.14	224	3.10	276	3.13
VII	3326	1681	1614 1590	202	3.19	218	3.16	266	3.13[a]
				204	3.13	224	3.10	274	3.13
VIII	3304	1682	1614 1590	206	3.12	224	3.13	274	3.14
IX	3341	1681	1614 1590	202	3.26	224	3.22	276	3.26
X	3342	1682	1615 1590	202	3.13	218	3.10	266	3.08[a]
				204	3.18	224	3.14	276	3.17
XI	3330	1681	1614 1590	204	3.10	224	3.11	274	3.10
XII	3343	1682	1614 1589	204	3.12	224	3.10	274	3.11
XIII	3319	1681	1614 1590	204	3.18	224	3.16	274	3.15
XIV	3341	1681	1614 1590	202	3.23	218	3.19	266	3.17[a]
				204	3.29	224	3.25	276	3.28
XV	3339	1681	1614 1590	204	3.14	224	3.11	274	3.12
XVI	3342	1682	1614 1590	204	3.13	224	3.10	276	3.13
XVII	3369	1682	1614 1588	204	3.23	222	3.20	276	3.22
XVIII	3353	1682	1614 1590	204	3.23	224	3.22	274	3.23

a) In cyclohexane.

Table 3. ^{1}H NMR Spectral Data of Prepared Compounds



Compound	δ_i											
	OH		$H^{2,6}$		H^5		$ArCH_2$		OCH_2 OCH		$COCH_3$	
I	8.20	1H, s	7.75	2H, m	6.68	1H, d	4.72	2H, s	3.47[a]	2H, s	2.55	3H, s
II	8.37	1H, s	7.70	2H, m	6.75	1H, d	4.62	2H, s	3.50	2H, q	2.40	3H, s
III	8.37	1H, s	7.70	2H, m	6.75	1H, d	4.63	2H, s	3.42	2H, t	2.40	2H, s
IV	8.50	1H, s	7.70	2H, m	6.75	1H, d	4.60	2H, s	3.62	1H, m	2.40	2H, s
V	8.35	1H, s	7.70	2H, m	6.75	1H, d	4.62	2H, s	3.45	2H, t	2.40	3H, s
VI	8.60	1H, s	7.77	2H, s	6.70	1H, d	4.75	2H, s	3.50	2H, d	2.50	3H, s
VII	8.62	1H, s	7.90	2H, m	6.75	1H, d	4.62	2H, s	3.45	2H, t	2.40	3H, s
VIII	8.88	1H, s	7.74	2H, m	6.87	1H, d	4.74	2H, s	1.56	9H, s	2.40	3H, s
IX	8.37	1H, s	7.52	2H, m	6.57	1H, d	4.65	2H, s	3.47	2H, t	2.45	3H, s
X	8.31	1H, s	7.72	2H, m	6.77	1H, d	4.62	2H, s	3.45	2H, t	2.40	3H, s
XI	8.53	1H, s	7.76	2H, m	6.95	1H, d	4.73	2H, s	4.10	1H, m	2.53	3H, s
XII	8.35	1H, s	7.80	2H, m	6.85	1H, d	4.75	2H, s	3.50	2H, t	2.50	3H, s
XIII	8.60	1H, s	7.70	2H, m	6.78	1H, d	4.80	2H, s	3.95	1H, m	2.50	3H, s
XIV	8.40	1H, s	7.72	2H, m	6.77	1H, d	4.62	2H, s	3.45	1H, t	2.42	3H, s
XV	8.35	1H, s	7.72	2H, m	6.77	1H, d	4.69	2H, s	3.50	2H, t	2.47	3H, s
XVI	8.40	1H, s	7.80	2H, m	6.85	1H, d	4.65	2H, s	3.50	2H, t	2.50	3H, s
XVII	8.37	1H, s	7.20	7H, m	6.70	1H, d	4.60	2H, s	3.90	2H, s	2.50	3H, s
XVIII	8.33	1H, s	7.70	2H, m	6.65	1H, d	4.65	2H, s	3.90	2H, s	2.40	3H, s

a) OCH_3.

Table 4. Values of Distances and Energies of Hydrogen Bond

Compound	d(H···OR) / nm	ΔH_h / J mol^{-1}
I	0.284	29.6522
III	0.284	30.3009
IV	0.289	28.1533
VII	0.293	27.5297
VIII	0.283	28.9992
IX	0.284	30.4060
XII	0.283	30.2825
XIV	0.282	30.5118
XVII	0.296	24.8694
XVIII	0.288	29.3742

as the enthalpy difference between present hydrogen bond and the same conformation without the hydrogen bond. The calculated enthalpy values of the hydrogen bonds of the selected compounds were 24.86—30.51 J mol^{-1} and the corresponding distances were in the range 0.282—0.293 nm. Comparing these 10 compounds, only smaller differences of the calculated enthalpy are shown between branched derivatives with four carbons of alkoxyl group (*sec*-butyl *VII* and *tert*-butyl *VIII*) and benzyl derivative (*XVII*), which has the smallest value of hydrogen bond energy (Table 4, Fig. 1).

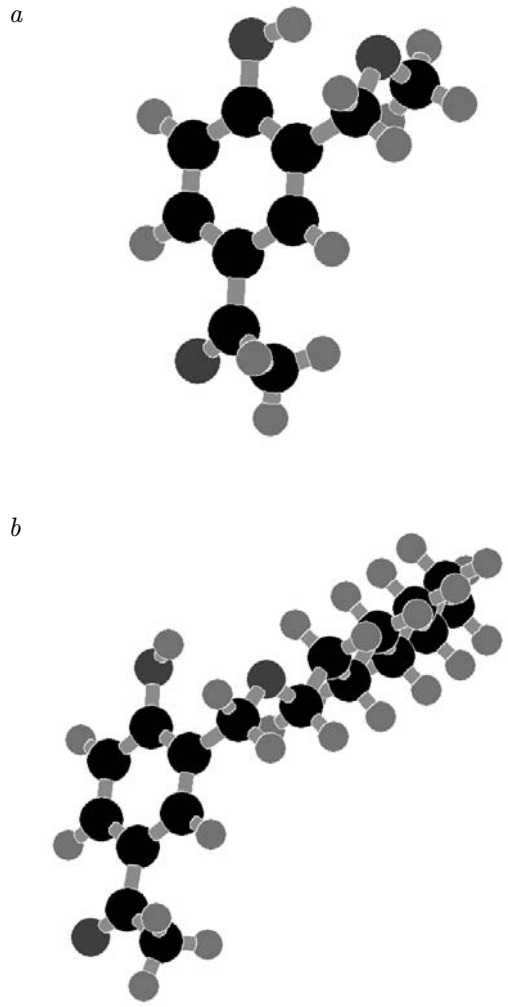


Fig. 1. The stereo view representing hydrogen bond of (4-hydroxy-3-methoxymethylphenyl)ethanone (*a*) and (4-hydroxy-3-nonyloxymethylphenyl)ethanone (*b*).

EXPERIMENTAL

Melting points were determined using a Kofler micro hot stage. Elemental analysis was performed using the elemental analyzer Model 1108 (Erba). The purity of the formed compounds was assessed using thin-layer chromatography SILUFOL® UV-254 (Kavalier) plates in a solvent system of cyclohexane—ethyl acetate (φ_r = 9:1). UV spectra were run on a spectrometer Hewlett—Packard 8452. IR spectra were recorded using FTIR IMPACT 400 D (Nicolet) spectrophotometer in CCl_4. ^{1}H NMR spectra of the prepared compounds dissolved in deuterochloroform were recorded on a Tesla BS-487 A spectrometer at a frequency 80 MHz and TMS was used as internal standard.

The conformation analysis was performed using potential field MM2 [22] in the program Molgen and the founded conformations were entirely optimized by the semiempiric method AM1 [23]. Strength of the hydrogen bonds was expressed as the enthalpy difference between the optimal conformation and the nonbonded conformation [24, 25].

(3-Chloromethyl-4-hydroxyphenyl)ethanone

To a sulfonation flask, set up with mechanical stirring, contact thermometer, and powder funnel, 0.15 mol of 4-hydroxyphenylethanone and 90 cm^3 of concentrated HCl were added. The temperature was raised to 45—50 ℃ and 7.5 g of paraformaldehyde was gradually added. The temperature was subsequently maintained, the mixture was stirred and the reaction was allowed to proceed for 4.5 h. Following the precipitation, the solid product was collected using suction filtration, washed with water and crystallized from benzene or ethyl acetate. Yield 75 % $C_9H_9O_2Cl$, m.p. = 159—161 ℃ (Ref. [26] gives m.p. = 160—162 ℃, yield 57 %).

(3-Alkoxymethyl-4-hydroxyphenyl)ethanones *I*—*XVIII*

To a sulfonation flask, set up with a mechanical stirrer, reflux condenser, and thermometer, 0.12 mol of (3-chloromethyl-4-hydroxyphenyl)ethanone and 100 cm^3 of the dried corresponding alcohol was added. The temperature was raised to 40—50 ℃ and 19.2 g (0.23 mol) of sodium hydrogen carbonate was added grad-

ually during 1 h. The temperature was maintained, the mixture was stirred and the reaction was allowed to proceed for 6 h. Subsequently sodium hydrogen carbonate was filtered and the excess of alcohol was removed by vacuum distillation. Residues were crystallized from hexane or cyclohexane. The solid compounds were obtained after standing in fridge.

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