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Acid-Catalyzed Dehydration of Hydroxy-Substituted Perhydroindenyl(perhydronaphthyl)ethanones and Perhydroindene-(perhydronaphthalene)carboxylates

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Abstract—Perhydroindenyl(perhydronaphthyl)ethanones and perhydroindene(naphthalene)carboxylates differing in the size of the fused ring (C_5, C_6) and in the nature of carbonyl-containing substituent (acetyl, ethoxycarbonyl) undergo dehydration on heating in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid. The process is accompanied by complete enolization of the endocyclic oxo group. Depending on the size of the fused ring, individual partially hydrogenated naphthylethanones and naphthalene-carboxylates or mixtures of isomeric partially hydrogenated indenylethanones and indenecarboxylates are formed.

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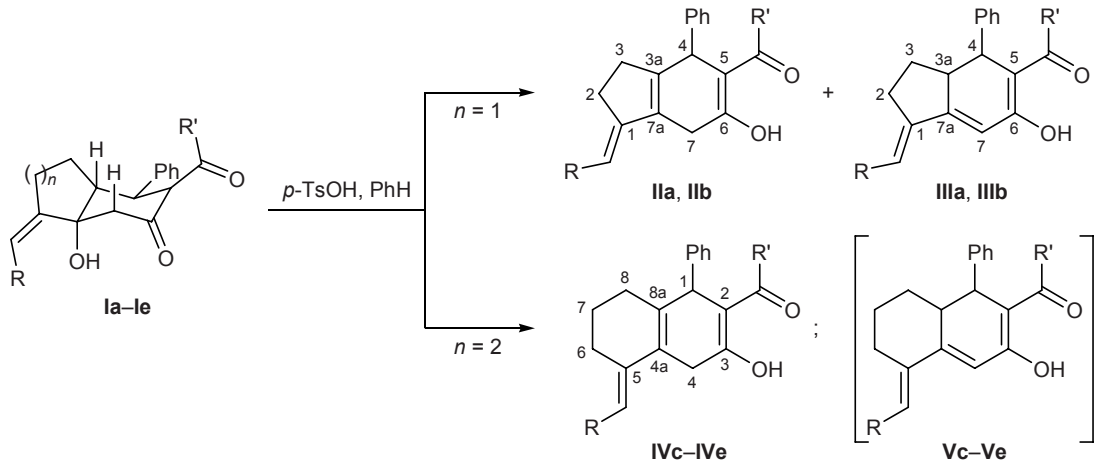
Up to now, the chemistry of monocyclic hydroxycyclohexanones like 3-substituted 2,4-diacetyl[bis-(ethoxycarbonyl)]-5-hydroxy-5-methylcyclohexanones has been well documented. These compounds are available via condensation of aldehydes with CH acids such as acetylacetone and acetoacetic acid esters [1]. The use of acid catalysts ensures their selective dehydration with formation of α,β-unsaturated enones. Acetyl-substituted systems were found to undergo enolization [2, 3].

In the present article we report on acid-catalyzed dehydration of related bicyclic systems differing in the size of the fused carbocycle (five- or six-membered), nature of the carbonyl-containing substituent (acetyl or ethoxycarbonyl), and ylidene fragment (benzylidene or furfurylidene). The initial compounds, 1-(1-benzylidene-7a-hydroxy-6-oxo-4-phenylperhydroinden-5-yl)-ethan-1-one (**Ia**), ethyl 1-benzylidene-7a-hydroxy-6-oxo-4-phenylperhydroindene-5-carboxylate (**Ib**), 1-(5-benzylidene-4a-hydroxy-3-oxo-1-phenylperhydronaphthalen-2-yl)ethan-1-one (**Ic**), ethyl 5-benzylidene-4a-hydroxy-3-oxo-1-phenyl-perhydronaphthalene-2-carboxylate (**Id**), and ethyl 5-furfurylidene-4a-hydroxy-3-oxo-1-phenyl-perhydronaphthalene-2-carboxylate (**Ie**), were synthesized by us previously by Michael condensation of diphenylmethylidene-, benzylidene-, and furfurylidene-substituted cyclopentanones and cyclohexanones with acetylacetone and ethyl acetoacetate. Compounds **Ia**–**Ie** were shown to have the structure with *trans*-junction of the carbocycles, axial orientation of the hydroxy group, and equatorial orientation of the other substituents [4].

Diketones **Ia** and **Ic** and keto esters **Ib**, **Id**, and **Ie** underwent dehydration and complete enolization of the endocyclic carbonyl group on heating in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid (Scheme 1). Depending on the size of the fused ring, the products were either isomer mixtures **IIa**/**IIIa** and **IIb**/**IIIb** (overall yield 68–74%) with different positions of the double bond in the bicyclic system or individual compounds **IVc**–**IVe** (70–75%). All the isolated compounds showed a positive color test for enolic hydroxy group (violet color) with an alcoholic solution of iron(III) chloride.

Taking into account the presence of a hydrogen atom in both α-positions with respect to the hydroxy group in molecules **Ia**–**Ie**, the dehydration process could involve abstraction of hydrogen from C^7 or C^{3a} in **Ia** and **Ib** or from C^4 or C^{8a} in **Ic**–**Ie**. By analogy with hydroxycyclohexanones [2, 3], dehydration with formation of double bond conjugated with the carbonyl group might be expected. However, in our case the dehydration direction depended on the size of the fused ring. Naphthalene substrates **Ic**–**Ie** underwent regioselective dehydration involving hydrogen atom in the bridgehead position (*trans*-elimination) with formation

Scheme 1.



I–IV, R = Ph, R′ = Me (**a**, **c**), OEt (**b**, **d**); R = Fu, R′ = OEt (**e**); *n* = 1 (**a**, **b**), 2 (**c**–**e**).

of exhaustively substituted double bond. Dehydration of perhydroindene analogs **Ia** and **Ib** having a five-membered fused ring gave rise to formation of both C^{3a}=C^{7a} and C^{7}=C^{7a} double bond, presumably due to more planar structure of the fused ring.

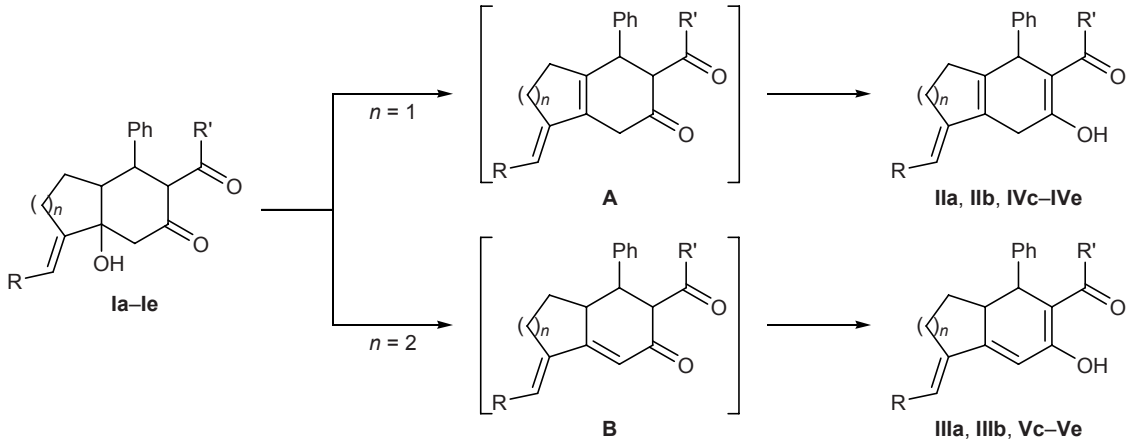
Unlike monocyclic analogs [2], both acetyl-, and ethoxycarbonyl-substituted bicyclic compounds **IIa**, **IIb**, **IIIa**, **IIIb**, and **IVc**–**IVe** were found to exist in the enol form. Their IR spectra contained a broad absorption band at 3065–3568 cm^{-1} due to enolic hydroxy group. The C=O stretching vibration band is displaced to lower frequencies by ~30–80 cm^{-1} relative to the corresponding band in the spectra of initial compounds **Ia**–**Ie** (1726–1748 cm^{-1}) due to conjugation [4]. The C=C absorption is not informative: it appears as a set of poorly resolved bands in the region 1590–1665 cm^{-1}. In the ^{1}H NMR spectra of **IVc**–**IVe**, the most characteristic are signals from magnetically nonequivalent methylene protons on C^4, δ 3.23–3.40 ppm, d (4-H_{ax}), and δ 3.51–3.54 ppm, d (4-H_{eq}), ^2J = 20.5–22.2 Hz; the exocyclic C^5=CH proton resonated as a singlet at δ 6.31–6.52 ppm (1H), signal from the enolic hydroxy proton appeared at δ 12.25–16.01 ppm (1H), and the chemical shift of 1-H was equal to 4.11–4.37 ppm.

The ^{1}H NMR spectra of dehydration products **IIa**/**IIb** and **IIIa**/**IIIb** obtained from perhydroindene derivatives contained sets of signals corresponding to both isomers. Signals at δ 3.07–3.21 (d, 1H, 7-H_{ax}), 3.23–3.36 (d, 1H, 7-H_{eq}; ^2J = 19.2–22.2 Hz), 4.04–4.15 (s, 1H, 4-H), and 11.06 (16.51) ppm (s, 1H, OH) were assigned to isomers **IIa** and **IIb**; isomers **IIIa** and **IIIb** displayed signals at δ 6.48–6.79 (s, 1H, 7-H), 4.00–4.11 (d, 1H, 4-H, J = 8.5–8.8 Hz), and 12.62 (16.72) ppm (s, 1H, OH). In addition, broadened signals from olefinic protons in the benzylidene substituent were present at δ 6.12 (**IIa**/**IIIa**) and 6.26 ppm (**IIb**/**IIIb**).

The ^{13}C NMR spectra of the products confirmed formation of isomer mixtures **IIa**/**IIb** and **IIIa**/**IIIb** and individual compounds **IVc**–**IVe**. In all cases, the number of signals from sp^3-hybridized carbon atoms in the cyclic fragments was consistent with the enol structure of these compounds.

The dehydration direction and enol structure of the products were interpreted in terms of heats of formation of possible intermediates **A** and **B** and isomeric systems **II**/**III** and **IV**/**V** containing five- and six-membered fused rings, respectively (Scheme 2). The calculations were performed in the PM3 approximation using MOPAC software. The results showed that the formation of compounds **IIa**, **IIb**, and **IVc**–**IVe** is thermodynamically more favorable than the formation of isomeric structures **IIIa**, **IIIb**, and **Vc**–**Ve**. The difference in the ΔH_f values for the corresponding intermediates **A** and **B** was 2.3–3.75 kcal/mol for the perhydronaphthalene derivatives and 1.0–1.1 kcal/mol for the perhydroindenes. The latter value implies almost equally probable formation of intermediates **A** and **B**. Enolization of both acetyl- and ethoxycarbonyl-substituted intermediates to give compounds **II**–**V** is accompanied by a gain in energy of 2.7–6 kcal/mol. The geometric parameters were optimizes so as to minimize the heat of formation. The observed stability of the cyclohexadiene fragment in molecules **IIa**, **IIb**, and **IVc**–**IVe** may be rationalized assuming that it

Scheme 2.



n = 1: $\Delta\Delta H_f$(**A** – **B**) = 1.0–1.1 kcal/mol; n = 2: $\Delta\Delta H_f$(**A** – **B**) = 2.3–3.7 kcal/mol; n = 1, 2: $\Delta\Delta H_f$ = 4.2–5.4 kcal/mol.

adopts a *boat* conformation with pseudoaxial orientation of the phenyl substituent on C^4 (**IIa**, **IIb**) or C^1 (**IVc**–**IVe**), where skewed interaction with the substituent on C^5 (C^2) is minimized. However, X-ray diffraction study is necessary to rigorously prove this assumption. The newly synthesized compounds attract interest from the viewpoint of their subsequent transformation into heterocyclic systems.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer at 200 MHz using tetramethylsilane as internal reference. The IR spectra were measured on an FSM-1201 spectrophotometer with Fourier transform. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using hexane–diisopropyl ether–acetone (3 : 1 : 1) as eluent; spots were detected by treatment with iodine vapor or water.

Initial perhydroindenyl(perhydronaphthyl)ethanones and perhydroindene(perhydronaphthalene)carboxylates **Ia**–**Ie** were synthesized as described in [4].

1-(1-Benzylidene-6-hydroxy-4-phenyl-2,3,4,7-tetrahydro-1*H*-inden-5-yl)ethan-1-one (IIa) and 1-(1-benzylidene-6-hydroxy-4-phenyl-2,3,3a,4-tetrahydro-1*H*-inden-5-yl)ethan-1-one (IIIa). *p*-Toluenesulfonic acid, 0.01 g (0.07 mmol), was added to a solution of 1 g (2.77 mmol) of compound **Ia** in 25 ml of benzene, the mixture was heated for 30 min under reflux and cooled, and the precipitate was filtered off, washed with benzene, and recrystallized from hexane. Yield 0.65 g (68%), a mixture of yellow and orange crystals; R_f 0.324, 0.405; mp 179–185°C. IR spectrum, ν, cm^{-1}: 3161–3568 (OH); 3024, 3065 (C–H$_{arom}$); 2924, 2849 (CH$_{aliph}$); 1664 (C=O); 1593 (C=C–C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: **IIa**: 3.21 d and 3.37 d (1H each, 7-H, ^2J = 22.2 Hz), 4.15 s (1H, 4-H), 16.51 s (1H, OH); **IIIa**: 6.48 s (1H, 5-H), 4.00 d (1H, 2-H, J = 8.8 Hz), 16.72 s (1H, OH); **IIa**/**IIIa**: 6.12 br.s (2H, =CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: **IIa**: 145.70 s (C^1), 29.06 t (C^2), 31.07 t (C^3), 142.98 s (C^{3a}), 45.28 d (C^4), 116.98 s (C^5), 180.01 s (C^6), 33.32 t (C^7), 137.92 s (C^{7a}), 200.00 s (C=O), 125.60 d (Ph**C**H=), 27.06 q (CH_3); **IIIa**: 138.90 s (C^1), 29.06 t (C^2), 29.58 t (C^3), 42.11 d (C^{3a}), 45.10 d (C^4), 108.06 s (C^5), 159.27 s (C^6), 136.29 d (C^7), 142.98 s (C^{7a}), 191.05 s (C=O), 126.54 d (Ph**C**H=), 25.76 q (CH_3). Found, %: C 84.84; H 6.80. $C_{24}H_{22}O_2$. Calculated, %: C 84.82; H 6.43.

Ethyl 1-benzylidene-6-hydroxy-4-phenyl-2,3,4,7-tetrahydro-1*H*-indene-5-carboxylate (IIb) and ethyl 1-benzylidene-6-hydroxy-4-phenyl-2,3,3a,4-tetrahydro-1*H*-indene-5-carboxylate (IIIb) were synthesized in a similar way from 1 g (2.56 mmol) of compound **Ib**. Yield 0.71 g (74%), a mixture of yellow and orange crystals; R_f 0.356, 0.420; mp 130–136°C. IR spectrum, ν, cm^{-1}: 3065–3568 (OH); 3025, 3065 (C–H$_{arom}$); 2926, 2854 (C–H$_{aliph}$); 1712 (C=O); 1653 (C=C–C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: **IIb**: 3.07 d and 3.23 d (1H each, 7-H, ^2J = 19.2 Hz), 4.14 s (1H, 4-H), 11.06 s (1H, OH); **IIIb**: 6.79 s (1H, 7-H), 3.98 d (1H, 2-H, J = 8.5 Hz), 12.62 s (1H, OH); **IIb**/**IIIb**: 6.26 s (2H, =CH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: **IIb**: 141.13 s (C^1), 30.27 t (C^2), 32.16 t (C^3), 141.16 s (C^{3a}), 47.03 d (C^4), 110.03 s (C^5), 154.96 s (C^6), 32.13 t (C^7), 139.96 s (C^{7a}), 168.00 s (C=O), 126.83 d (Ph**C**H=), 60.83 t (OCH_2), 14.32 q (CH_3); **IIIb**: 139.92 s (C^1), 30.27 t (C^2), 30.15 t (C^3),

41.43 d (C^{3a}), 47.15 t (C^4), 111.27 s (C^5), 150.53 s (C^6), 137.21 d (C^7), 141.08 s (C^{7a}), 168.69 s (C=O), 127.92 d (Ph**C**H=), 60.83 t (OCH_2), 14.32 q (CH_3). Found, %: C 80.48; H 6.63. $C_{25}H_{24}O_3$. Calculated, %: C 80.64; H 6.45.

1-(5-Benzylidene-3-hydroxy-1-phenyl-1,4,5,6,7,8-hexahydronaphthalen-2-yl)ethan-1-one (IVc) was synthesized in a similar way from 1 g (2.67 mmol) of compound **Ic**. Yield 0.67 g (70%), yellow crystals, R_f 0.624, mp 157–158°C. IR spectrum, ν, cm^{-1}: 3078–3568 (OH); 3044, 3078 (C–H_{arom}); 2947, 2855 (C–H_{aliph}); 1645 (C=O); 1596 (C=C–C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.40 d and 3.54 d (1H each, 4-H, ^2J = 20.5 Hz), 4.37 s (1H, 1-H), 16.01 s (1H, OH), 6.52 s (1H, =CH), 2.15 m (2H, 6-H), 1.50 m (2H, 7-H), 2.52 (2H, 8-H), 7.30 m (10H, H_{arom}), 1.07 s (3H, CH_3). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 49.17 d (C^1), 110.35 s (C^2), 178.78 s (C^3), 32.70 t (C^4), 130.03 s (C^{4a}), 138.49 s (C^5), 27.60 t (C^6), 26.91 t (C^7), 29.46 t (C^8), 137.27 s (C^{8a}), 200.90 s (C=O), 123.44 d (Ph**C**H=), 26.32 q (CH_3). Found, %: C 84.55; H 6.57. $C_{25}H_{24}O_2$. Calculated, %: C 84.23; H 6.74.

Ethyl 5-benzylidene-3-hydroxy-1-phenyl-1,4,5,6,7,8-hexahydronaphthalene-2-carboxylate (IVd) was synthesized in a similar way from 1 g (2.47 mmol) of compound **Id**. Yield 0.72 g (75%), yellow crystals, R_f 0.605, mp 149°C. IR spectrum, ν, cm^{-1}: 3159–3568 (OH); 3078, 3026 (C–H_{arom}); 2962, 2866 (C–H_{aliph}); 1665 (C=O); 1618 (C=C–C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.38 d and 3.51 d (1H each, 4-H, ^2J = 22.0 Hz), 4.11 s (1H, 1-H), 12.29 s (1H, OH), 6.43 s (1H, =CH), 2.01 m (2H, 6-H), 1.54 m (2H, 7-H), 2.56 m (2H, 8-H), 7.28 m (10H, H_{arom}), 4.09 t (2H, CH_2, J = 8.0 Hz), 1.15 t (3H, CH_3, J = 8.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 48.75 d (C^1), 100.88 s (C^2), 169.84 s (C^3), 31.50 t (C^4), 124.73 s (C^{4a}), 138.57 s (C^5), 27.72 t (C^6), 23.29 t (C^7), 29.73 t (C^8), 137.78 s (C^{8a}), 171.82 s (C=O), 122.93 d (Ph**C**H=), 60.81 t (OCH_2), 14.42 q (CH_3). Found, %: C 80.68; H 6.90. $C_{26}H_{26}O_3$. Calculated, %: C 80.83; H 6.79.

Ethyl 5-furfurylidene-3-hydroxy-1-phenyl-1,4,5,6,7,8-hexahydronaphthalene-2-carboxylate (IVe) was synthesized in a similar way from 0.7 g (1.78 mmol) of compound **Ie**. Yield 0.47 g (71%), yellow crystals, R_f 0.70, mp 179–180°C. IR spectrum, ν, cm^{-1}: 3102–3568 (OH); 3064, 3028 (C–H_{arom}); 2952, 2875 (C–H_{aliph}); 1702 (C=O); 1618 (C=C–C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.23 d and 3.52 d (1H each, 4-H, ^2J = 21.4 Hz), 4.27 s (1H, 1-H), 12.25 s (1H, OH), 6.31 s (1H, =CH), 2.17 m (2H, 6-H), 1.55 m (2H, 7-H), 2.52 m (2H, 8-H), 7.18 m (5H, H_{arom}), 7.72 m (1H, 5′-H), 6.41 m (2H, 3′-H, 4′-H), 4.29 t (2H, CH_2, J = 8.2 Hz), 1.07 t (3H, CH_3, J = 8.2 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 48.59 d (C^1), 100.72 s (C^2), 169.95 s (C^3), 31.04 t (C^4), 128.91 s (C^{4a}), 138.98 s (C^5), 27.79 t (C^6), 22.59 t (C^7), 29.21 t (C^8), 135.37 s (C^{8a}), 171.58 s (C=O), 112.72 d (C^5=**C**H), 61.11 t (OCH_2), 14.59 q (CH_3). Found, %: C 76.02; H 6.52. $C_{24}H_{24}O_4$. Calculated, %: C 76.59; H 6.38.

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