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Studies of photoinduced addition of water and alcohols to substituted dihydroquinolines

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Steady-state photolysis products of 6- and 8-substituted 2,2,4-trimethyl-1,2-dihydroquinolines in water and lower alcohols were identified by ^{1}H NMR. In the case of electron-donor substituents, the solvent molecule is added to the double bond of the heterocycle affording the corresponding 4-hydroxy- or 4-alkoxytetrahydroquinolines. Nitro-substituted dihydroquinolines are photostable. The addition of EtOH and Pr^{n}OH occurs only in the presence of water to give a mixture of alkoxy- and hydroxy-adducts. A reaction scheme is suggested.

Key words: 1,2-dihydroquinolines, photoaddition of alcohols to the double bond, steady-state photolysis, ^{1}H NMR spectroscopy.

The Markownikoff rule, one of the longest known empirical rules in organic chemistry, finds its theoretical basis in the fact that the ionic addition of a nonsymmetrical reagent to a non-symmetrical olefin proceeds *via* the more stable of two carbenium ions, namely, that with a positive charge on the carbon atom bearing a substituent. The photoinduced addition of water, methanol, and ethanol to the double bond of 2,2,4,6-tetramethyl-1,2-dihydroquinoline presents yet another example of the fulfillment of the Markownikoff rule.[1] Irradiation with light with the wavelength 300—400 nm affords the corresponding 4-hydroxy- and 4-alkoxy-2,2,4,6-tetramethyl-1,2,3,4-tetrahydroquinolines. In the present work, we continued the study of this reaction with dihydroquinolines (DHQ) with various substituents in the benzene ring and heterocycle using water and various alcohols as reaction media as an example (Scheme 1). The starting compounds (**1—8**) studied in this work and the adducts (**9—21**) are listed in Table 1.

Table 1. The starting dihydroquinolines and their photolysis products in water and alcohols

Compound	R^1	R^2	R^3	Product	R^4	M.p. /°C	Yield (%)
1	H	H	H	**9**	Me	—	—
2	H	Me	H	**10**[a]	H	149—151	73
				11[b]	Me	78—80	75
				12	Et	[c]	—
				13	Pr^n	[c]	—
3	Me	Me	H	**14**	Me	Yellow oil	—
4	H	EtO	H	**15**	H	[c]	—
				16	Me	Yellow oil	—
				17	Et	[c]	—
5	H	OH	H	**18**	Me	[d]	—
6	H	NO$_2$	H	—	—	—	—
7	H	H	MeO	**19**[e]	H	109—111	70
				20[f]	Me	81—83	75
				21	Et	[c]	—
8	H	H	NO$_2$	—	—	—	—

[a] Found (%): C, 76.21; H, 9.20; N, 6.80. $C_{13}H_{19}NO$. Calculated (%): C, 76.10; H, 9.27; N, 6.83.

[b] Found (%): C, 76.90; H, 9.50; N, 6.35. $C_{14}H_{21}NO$. Calculated (%): C, 76.71; H, 9.59; N, 6.39.

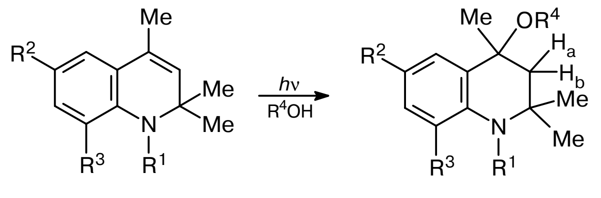
[c] Was not isolated in pure state.

[d] Unstable and decomposes during purification.

[e] Found (%): C, 70.65; H, 8.59; N, 6.40. $C_{13}H_{19}NO_2$. Calculated (%): C, 70.59; H, 8.60; N, 6.33.

[f] Found (%): C, 71.60; H, 8.90; N, 6.02. $C_{14}H_{21}NO_2$. Calculated (%): C, 71.49; H, 8.90; N, 5.96.

Scheme 1



1—8 **9—21**

Experimental

2,2,4,6-Tetramethyl-1,2-dihydroquinoline (**2**), m.p. 42 °C, 6-ethoxy-2,2,4-trimethyl-1,2-dihydroquinoline (**4**), b.p. 161 °C (12 Torr), and 2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline (**22**), m.p. 41 °C, (Reakhim, Russia) were used. 2,2,4-Trimethyl-1,2-dihydroquinoline (**1**), m.p. 18 °C, was synthesized[2,3] by condensation of acetone with aniline, yield 65%; 1,2,2,4,6-pentamethyl-1,2-dihydroquinoline (**3**), b.p. 150—152 °C (12 Torr), was synthesized[3] in the reaction of compound **2** with MeI, yield

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75%. 6-Hydroxy-, 6-nitro-, 8-methoxy, and 8-nitro-2,2,4-trimethyl-1,2-dihydroquinolines (**5**—**8**),[2,3] m.p. 174, 123, 54, and 120 °C, respectively, and 6-hydroxy- and 8-methoxy-2,2,4-trimethyl-1,2,3,4-tetrahydroquinolines (**23**, **24**),[2] m.p. 189 and 43—45 °C, respectively, were kindly provided by Yu. A. Ivanov (I. M. Gubkin Oil and Gas University, Moscow). Physicochemical constants of all starting compounds corresponded to the literature data. Before use, compounds **1**, **2**, **5**, and **7** were sublimed *in vacuo*, and compounds **3** and **4** were distilled *in vacuo*. Bidistilled water, MeOH (Merck, for chromatography), EtOH, Pr^{n}OH, and Pr^{i}OH (Reakhim, special purity) were used as reagents and solvents.

The conditions of the preparative-scale, steady-state photolysis and the isolation of products were described in detail elsewhere.[1] The reaction was followed by monitoring changes in the UV absorption spectra with a Specord UV—VIS spectrophotometer (Germany) in the range of long-wave absorption of the starting DHQ (330—360 nm) and the adducts (280—330 nm). After photolysis, the solvent was removed *in vacuo*, and the residue was dissolved in $(CD_3)_2SO$ or CD_3OD for registration of the ^1H NMR spectra on a Bruker WM-250 NMR spectrometer. Since the products are unstable,[1] neither purification no separation in the case of water-alcohol solutions were carried out. The ^1H NMR spectra of the products (**9**—**21**) are listed in Table 2; for comparison those of 2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline (**22**) and its 6-hydroxy- and 8-methoxy-derivatives (**23** and **24**) are given.

Results and Discussion

The photolysis of dihydroquinolines **1**—**4** and **7** in water and MeOH affords the corresponding adducts **9**—**11**, **14**—**16**, **19**, and **20** with the yields close to quantitative as followed from the presence of the isosbestic points in the absorption spectra recorded during the reaction. Only in the case of compound **5**, the reaction is complicated by the formation of noticeable amounts of side products. However, the product of MeOH addition **18** is the major product (>80%) in this case, too. This allowed us to register its ^1H NMR spectrum. Since we failed to purify adduct **18** from impurities, its elemental analysis and determination of its melting point were not carried out. Compounds **6** and **8** were photostable and did not enter in the reaction under study.

When EtOH and Pr^{n}OH are used as the reagents and the solvents, the photoaddition occured only in the presence of water to give a mixture of hydroxy- and

Table 2. The ^1H NMR spectra (DMSO-d_6) of the addition products of water and alcohols to DHQ[a]

Compound	δ										J_{H_a,H_b} /Hz
	R^1	C(2)Me_2	C(3)H_a	C(3)H_b	C(4)Me	R^4	C(5)H	C(6)R^2	C(7)H	C(8)R^3	
9	5.57 (s)	1.15 (s); 1.20 (s)	1.53 (d)	2.03 (d)	1.42 (s)	2.95 (s)	7.15 (dd)	6.48 (t)	6.92 (t)	6.50 (dd)	13.9
10	5.09 (s)	1.13 (s); 1.18 (s)	1.68 (d)	1.84 (dd)[b]	1.38 (s)	4.39 (s)	7.09 (d)	2.14 (s)	6.69 (dd)	6.37(d)	13.7
11	5.32 (s)	1.12 (s); 1.17 (s)	1.49 (d)	2.05 (d)	1.40 (s)	2.94 (s)	6.96 (d)	2.14 (s)	6.74(dd)	6.40 (d)	13.8
12	5.29 (s)	1.15 (s); 1.19 (s)	1.50 (d)	2.06 (d)	1.41 (s)	0.98 (t); 3.19 (q)	6.97 (d)	2.14 (s)	6.73 (dd)	6.40 (d)	14.0
13	5.28 (s)	1.13 (s); 1.19 (s)	1.52 (d)	2.06 (d)	1.42 (s)	0.80 (t); 1.38 (m); 3.09 (t)[c]; 3.2 (t)[c]	6.98 (d)	2.14 (s)	6.74 (dd)	6.41 (d)	14.3
14	2.68 (s)	1.16 (s); 1.20 (s)	1.69 (d)	2.15 (d)	1.42 (s)	2.95 (s)	7.07 (d)	2.18 (s)	6.91 (dd)	6.50 (d)	14.1
15	5.03 (s)	1.12 (s); 1.17 (s)	1.67 (d)	1.82 (dd)[b]	1.38 (s)	4.59 (s)	6.89 (d)	1.27 (t); 3.88 (q)	6.55 (dd)	6.41 (d)	13.2
16	5.08 (s)	1.13 (s); 1.18 (s)	1.57 (d)	2.05 (d)	1.42 (s)	2.95 (s)	6.73 (d)	1.26 (t); 3.89 (q)	6.60 (dd)	6.45 (d)	13.7
17	5.15 (s)	1.12 (s); 1.16 (s)	1.51 (d)	2.04 (d)	1.42(s)	0.99 (t); 3.11 (q)[c]; 3.22 (q)[c]	6.73 (d)	1.27 (t); 3.88 (q)	6.59 (dd)	6.44 (d)	14.1
18	5.25 (s)	1.10 (s); 1.15 (s)	1.48 (d)	2.03 (d)	1.38 (s)	2.93 (s)	6.60 (d)	8.30 (s)	6.44 (dd)	6.35 (d)	13.7
19	4.55 (s)	1.19 (s); 1.21 (s)	1.78 (d)	1.89 (dd)[b]	1.40 (s)	4.54 (s)	6.97 (dd)	6.51 (t)	6.66 (dd)	3.74 (s)	13.6
20	4.63 (s)	1.18 (s); 1.23 (s)	1.55 (d)	2.10 (d)	1.43 (s)	2.94 (s)	6.84 (dd)	6.51 (t)	6.69 (dd)	3.75 (s)	13.9
21	4.65 (s)	1.17 (s); 1.24 (s)	1.56 (d)	2.10 (dd)	1.44(s)	0.97 (t); 3.15 (q)[c]; 3.20 (q)[c]	6.85 (dd)	6.51 (t)	6.69 (dd)	3.75 (s)	13.9
22	5.39 (s)	1.08 (s); 1.17 (s)	1.28 (d)	1.68 (ddd)[d]	1.24 (d)	2.80 (m)	7.03 (dd)	6.44 (t)	6.83 (t)	6.42 (dd)	12.7
23	4.68 (s)	1.04 (s); 1.12 (s)	1.24 (d)	1.64 (ddd)[d]	1.19 (d)	2.74 (m)	6.51 (d)	8.18 (s)	6.34 (dd)	6.27 (d)	12.7
24	4.48 (s)	1.07 (s) 1.22 (s)	1.30 (d)	1.72 (ddd)[d]	1.24 (d)	2.84 (m)	6.73 (dd)	6.46 (t)	6.62 (dd)	3.73 (s)	12.7

[a] The integral intensities of the signals correspond to those expected. For ethyl and aromatic protons, the characteristic spin-spin coupling constants are observed: $J_{CH_2,CH_3} \approx 7$, $J_o = 7$—8 and $J_m = 1$—2 Hz.

[b] Spin-spin coupling constant $^4J = 1.2$ Hz.

[c] The duplication of the proton signals for the OCH_2 fragment, the ratio of isomers is 1 : 1.

[d] Spin-spin coupling constants $^3J = 5.5$—5.9 Hz, $^4J_{NH,H_b} = 1.5$ Hz.

Table 3. The yield of products **10** and **13** in the photolysis of dihydroquinoline **2** in the H_2O—Pr^nOH mixtures of different compositions*

$[H_2O]$ /mole fraction	Yield (%)	
	10	**13**
0	0	0
0.08	17	83
0.45	64	36
0.80	69	31
1	100	0

* Determined from ^1H NMR data; the concentration of dihydroquinoline **2** is $3 \cdot 10^{-3}$ mol L^{-1}.

alkoxy-adducts, their ratio depending on the water : alcohol ratio (Table 3). Pr^iOH gives no adducts with DHQ under study, probably, because of steric hindrances. We used this fact to increase the solubility of DHQ in water in the synthesis of hydroxy derivatives. The reaction was carried out in water—Pr^iOH mixtures (3 : 1). Earlier,[1] we used the water—EtOH mixtures (3 : 1) for this purpose.

Comparison of the ^1H NMR spectra of the adducts (see Table 2) allowed us to make some conclusions about their structures. Noticeable changes are observed in the shifts of $C(3)H_a$ and $C(3)H_b$ protons of the adducts depending on the nature of the OR group. For the hydroxy derivatives, the difference in the shifts of these protons is less than that for the alkoxy derivatives (see Table 2) ($\Delta\delta$ 0.11—0.16 and 0.43—0.56 ppm, respectively) with the centers of gravity of the doublet pairs for hydroxy- and alkoxy-compounds being close. The value of the geminal constant of spin-spin coupling $^2J_{H_a,H_b}$ depends also on the bulk of the substituent R, all factors being the same, and increases in the order: H < Me < Et ≤ Pr^n. For the analogues containing the hydrogen atom instead of the OR group in position 4, 2,2,4-trimethyl-1,2,3,4-tetrahydroquinolines with the corresponding substituents in positions 6 and 8 (see Table 2, compounds **22**—**24**), the signals of the $C(3)H_a$ and $C(3)H_b$ protons are shifted upfield by 0.3 ppm, the distance between the doublets being intermediate ($\Delta\delta$ ~0.40 ppm). The decrease in the constant of spin-spin coupling (J_{gem} = 12.7 Hz) indicates a decrease in the angle between the C—H_a and C—H_b bonds. The changes in the ^1H NMR spectra of the hydroxy- and alkoxy-adducts in comparison with those of 2,2,4-trimethyl-1,2,3,4-tetrahydroquinolines show that the structures of the products are strained. This is also confirmed by the comparative analysis of the NMR spectra of compounds **11** and **14**. When the NH group is replaced by NMe, the downfield shift of the signals for the C(5)H and C(7)H protons is observed, rather than their expected shielding due to the exit of the NMe group out of the plane.

Recently,[1] we have shown that the chemical properties of compound **11** differ substantially from those of tetrahydroquinolines with the H atom in position 4, for example, from compound **22**. Unlike compound **22** and the parent DHQ, compound **11** does not react with free radicals and, consequently, does not inhibit the reactions of chain oxidation. Probably, a lone pair of the N atom partly comes out from the conjugation with the aromatic ring due to the strained state of the heterocycle resulting in the strengthening of the N—H bond with respect to reactions with free radicals. This conclusion is confirmed by the analysis of the IR spectra of compounds **10** and **11** given in our previous publication.[1] Instead of two bands belonging to the pulse modes of the aromatic ring in compound **22** at 1581 and 1603 cm^{-1}, only one band at 1618 cm^{-1} was observed in compounds **10** and **11**. An increase in the frequency of this band points to a decrease in conjugation in the benzene ring.[4] A decrease in the frequency of the stretching mode of the N—H bond in comparison to tetrahydroquinoline **22** and especially to dihydroquinoline **2** is yet another characteristic feature of these compounds (3309, 3330, 3351, and 3360 cm^{-1} for compounds **10**, **11**, **22**, and **2**, respectively). It is worth noting that the decrease in the stretching mode of the N—H bond on going from compound **2** to compound **22** correlates with a decrease in the antioxidant properties of tetrahydroquinolines in comparison to DHQ.

The introduction of bulkier EtO and Pr^nO substituents causes their restricted rotation resulting in the duplication of the signals for the protons of the OCH_2 groups. As mentioned above, the attempt to synthesize more sterically hindered isopropyl ether failed.

For the hydroxy derivatives, we observed a long-range spin-spin coupling of the hydroxy proton with one of the protons in position 3 (for example, for adduct **19** δ 1.89, ^4J = 1.22 Hz). This coupling is stereospecific and typical of the protons in transoid configuration. This allows one to make the spatial assignment of the signals for the two protons in position 3 relative to the substituent OR in position 4.

The reaction under study resembles the photoaddition of MeOH to the double bond of 1-methylcyclohexenes and especially of 3- and 4-phenyl-1,2-dihydronaphthalenes, which is being investigated over the last three decades.[5—10] The mechanism accepted involves the proton transfer from a solvent to the double bond to give a carbocation, for which several routes of transformation are possible. In the case of cyclohexenes, this is the isomerization to the *exo* isomer and the nucleophilic addition of the alcohol. For 3- and 4-phenyl-1,2-dihydronaphthalenes, the adduct with MeOH was isolated along with numerious other products.[10] In the case of 4-phenyl-1,2-dihydronaphthalene, the addition product is not the major one. A fundamental difference of DHQ under study from cyclohexenes and naphthalenes is that the photolysis of DHQ results in selective addition of alcohols or water, and virtually no other products are formed.

The key problem discussed in the literature is the state of cyclohexene to which the proton is transferred, *viz.*, to the excited singlet or triplet states or to the socalled strained *trans*-cyclohexene formed from them as a result of *cis-trans* isomerization. The experimental data presented in the works cited counts in favor of formation of *trans*-cyclohexene,[6—8] although the protonation of the triplet excited state cannot be ruled out for cyclohexenones.[9] Our preliminary data[11] on pulse photolysis of compound **2** demonstrated the formation of an active transient species as a result of photolysis with a lifetime of several ms. The formation of this species is independent of the presence of oxygen in the system. Therefore, we assume that this is a *trans*-isomer, which is then protonated to give a carbocation.

It follows from the ^{1}H NMR spectra of the photolysis products of compounds **2** and **7** in MeOD that the addition results in a mixture of isomers with one deuterium atom in position 3, but in different orientation (axial and equatorial) approximately in equal amounts, as it was in the photolysis of 1-methylcyclohexene.[5] This argues that in this case there is no spatially more preferable direction of addition, as it was observed for an exotic cyclohexenone, the Pumperer ketone.[7]

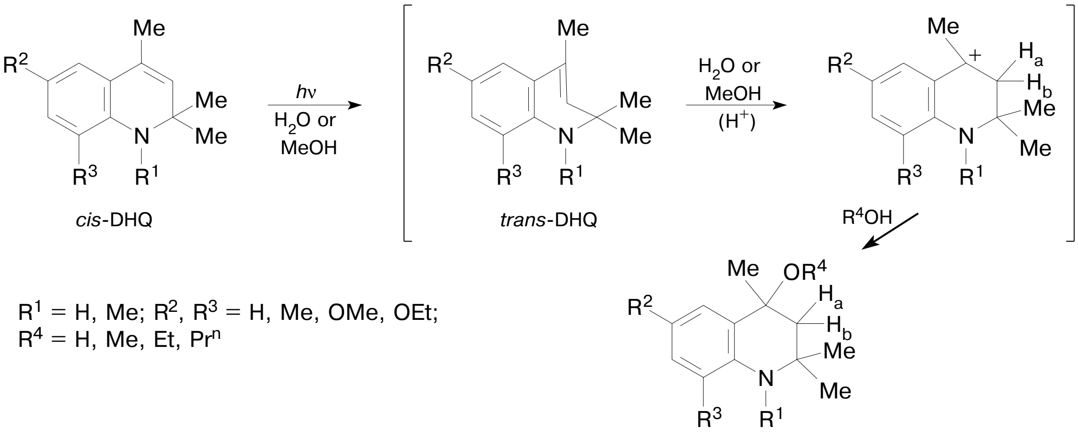
As mentioned above, the reaction with EtOH and Pr^{n}OH occurs only in the presence of small amounts of water. First, this can be due to insufficient acidities of these alcohols in comparison with water and methanol[12] and hence, due to impossibility of generation of carbocations in these solvents. Second, the analysis of the absorption spectra of DHQ in various solvents indicates that the character of their interactions with water and MeOH is different from those with EtOH and PrOH. In water and MeOH, the long-wave absorption band of DHQ is hypsochromically shifted by 15 and 8 nm, respectively, whereas in EtOH и PrOH it is shifted batochromically by 1—2 nm in comparison with its position in the spectrum in hexane. Final conclusions can be made after thorough study of the reaction kinetics.

As for the step of nucleophilic addition of an alcohol to the carbocation, the competition between the components of the solvent occurs in the water-alcohol solutions. This is reflected in the composition of the product (see, for example, Table 3). In addition to the solvent composition, the ratio of hydroxy- and alkoxy-adducts is determined by many other factors, *e.g.*, the nature of the alcohol and DHQ and the concentration of DHQ. For example, in the photolysis of compounds **2** and **7** in 95% EtOH, the yields of products **12** and **21** were 40 and 73%, respectively. When the concentration of EtOH was <25%, the only reaction products were compounds **10** and **19**, respectively. The experimental data on the composition of the photolysis products indicates unambiguously the higher rate constant for the addition of water than for the addition of EtOH and Pr^{n}OH.

Studies of photolysis of *N*-substituted DHQ **3** is of considerable interest to clarify the role of the hydrogen atom of the amino group in the reaction and to rule out the intramolecular hydrogen transfer. Contrary to the works[13,14] where it was shown that *N*-substituted DHQ underwent cleavage of the C(2)—N bond to give colored products in the photolysis in ether—isopentane—ethanol glasses at −196 °C [13] and in dioxane at ambient temperature,[14] our results show that the photolysis of **3** in MeOH affords adduct **14**. This is yet another experimental confirmation of the proton transfer from the solvent rather than from the amino group in the photolysis of DHQ in water and alcohols.

Thus, in this work we present new examples of the photoaddition of water and aliphatic alcohols to the double bond of various DHQ and the limitations of this reaction. A characteristic feature of the reaction with ethanol and propanol is that water was necessarily present. DHQ with electron-accepting substituents (compounds **6** and **8**) are photostable. The experimental results suggest that the reaction proceeds in three steps, the first of which is the photolysis of DHQ itself to afford an active transient species (probably, *trans*-DHQ), the second step involves proton transfer from water or methanol to this species, and the third step is a nucleophilic addition of an alcohol or water to the carbocation formed (Scheme 2).

Scheme 2



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