STEREOCHEMISTRY OF NITROGENOUS HETEROCYCLES. 71.* ISOMERIZATION — EQUILIBRATION OF STEREOISOMERIC ETHINYLCARBINOLS EPIMERIC AT THE CARBINOL CENTER†

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Equilibration of stereoisomeric cyclic ethinylcarbinols, epimeric at the carbinol center, was conducted for the first time and it was shown that the equilibrium is shifted toward the equatorial alcohol (at 50°C for 2e-methyl-4-hydroxy-4-phenylethinyl-trans-decahydroquinoline, 2e-methyl-4-hydroxy-4-ethinyl-trans-decahydroquinoline, 4-hydroxy-4-ethinyl-trans-decahydroquinoline — (78±1)% equatorial and (22±1)% axial alcohol, for 1,2e,5e-trimethyl-4-ethinylpiperidol-4 (74±1)% equatorial and (26±1)% axial alcohol). The epimerization of stereoisomeric ethinylcarbinols can be used as a method for determination of the configuration of the quaternary carbinol center.

We previously elaborated the conditions of the Favorskii exchange reaction [3]. It was shown in the present article that these conditions can be used for mutual conversion and equilibration of stereoisomeric ethinylcarbinols epimeric at the carbinol center.

The Favorskii reaction — condensation of carbonyl compounds with acetylene or its monosubstituted derivatives under the effect of KOH — is reversible [4, 5]. The equilibrium is shifted toward ethinylcarbinols at low temperatures (−30-+20°C) [6], and toward decomposition of ethinylcarbinols into the starting carbonyl and acetylene components at high temperatures (100-150°C) (reverse Favorskii reaction) [6, 7]. A temperature in the 20-150°C range is considered unsuitable for both the forward and the reverse reaction and is especially undesirable in conducting condensation with unsubstituted acetylene, since the probability of formation of glycols increases due to the decrease in the solubility of acetylene at a high temperature. This temperature range, not recommended, remained poorly investigated for many years as a result.

Conversion of ethinylcarbinols into each other with a good yield by exchange of carbonyl components was only known for exchange of aliphatic ketones into aromatic ketones (KOH, 0°C) [8], but the yield of ethinylcarbinols did not exceed 20% in exchange of aliphatic ketones for other aliphatic components [9, 10].

We previously [3] elaborated the conditions for exchange of acetone for other aliphatic carbonyl components (methyl ethyl, methyl propyl, methyl hexyl ketones, cyclohexanone) with 60-80% yields of the product of the reaction using dimethylvinylethinylcarbinol. Exchange was conducted with KOH at 25-60°C. It was thus shown that the low-temperature part of the range unsuitable for the forward and reverse reactions can be used for the preparative Favorskii exchange reaction. The possibility of mutual conversions and thermodynamic equilibration of stereoisomeric ethinylcarbinols epimeric at the carbinol center in conditions of exchange of the carbonyl or acetylene component is the logical consequence of this exchange reaction.

Although higher stability of cyclic ethinylcarbinols with an equatorial ethinyl group was proposed in the literature [11], mutual conversion of the isomers could not be detected for a long time. Nevertheless, the results of the forward Favorskii reaction have frequently been attributed to the lower stability of equatorial alcohols and their conversion into axial alcohols epimeric to them in the conditions of the reaction [12, 13]. Only one case of demonstrated mutual conversion of isomeric ethinylcarbinols has been described. It was shown in [14] that the epimer with an axial hydroxyl is formed in an insignificant amount in condensation of 1,2*e*,5*e*-trimethyl-4*e*-ethinylpiperidol-4*e* with 3-methyl-3-hydroxy-2-butanone with KOH at 20-25°C for 3 days in addition to the normal, predicted ethinylcarbinol. Since the final ethinylcarbinols were not converted into each other in the reaction conditions, the possibility of conversion of the starting ethinylcarbinols was investigated. It was found that the 1,2*e*,5*e*-trimethyl-4*a*-ethinylpiperidol-4*e* isomer with an equatorial hydroxyl is 30% converted into an isomer with

*See [1] for Communication 70.

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TABLE 1. Thermodynamic Equilibrium of Epimeric Ethinylcarbinols (50°C)*

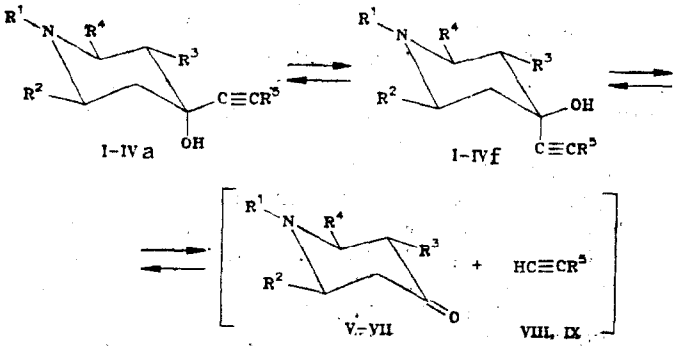
Equilibrium	Solvent	SC	EC : KOH : K : RC≡CH : S **	t_e, min	ERA, %		K	$-\Delta G°$, kal/mole
					a	f		
Ia⇄If	Dioxane	I	1:2:2:0:4,5	10	22	78	3,54	0,81
	Dioxane	I	1:2:0:2:4,5	10	22	78	3,54	0,81
	Benzene	I	1:2:2:0:7,5	15	23	77	3,34	0,78
	THF	I	1:2:2:0:4,5	10	22	78	3,54	0,81
IIa⇄IIf	Dioxane	II	1:2:2:0:16	15	23	77	3,34	0,78
IIIa⇄IIIf	Dioxane	III	1:2:0:x***:11	25	22	78	3,54	0,81
	Benzene	III	1:2:0:x***:16	25	22	78	3,54	0,81
	THF	III	1:2:0:x***:11	25	22	78	3,54	0,81
IVa⇄IVf	Dioxane	IV	1:2:0:x***:7,5	30	26	74	2,85	0,67

*SC: starting carbinol, EC: ethinylcarbinol, K: ketone, S: solvent; t_e: time of establishment of equilibrium; ERA: equilibrium ratio of alcohols.
**Ratio of EC:KOH:K:RC≡CH, mole, solvent, liter. Equilibrium was attained beginning with each isomer.
***Saturation with acetylene at atmospheric pressure.

an axial hydroxyl in very long contact with a base (12 days at 20-25°C); the reverse conversion by 15-20% takes place after 8 days. A conclusion was then drawn concerning the possibility of isomerization of ethinylcarbinols into each other and the higher thermodynamic stability of the axial alcohol. It was hypothesized in [15] that isomerization does not take place by reversible decomposition—synthesis of ethinylcarbinols, but in the catalytic action of alcoholate of the enol form of a keto alcohol on the ethinylcarbinols, but the mechanism of the conversions was not reported.

No cases of mutual conversions of ethinylcarbinol isomers have been observed in recent studies. It was concluded in [16] that the isomers of acetylenic alcohols are incapable of mutual conversions.

We used the isomers of 2*e*-methyl-4-hydroxy-4-phenylethinyl-*trans*-decahydroquinoline (If and Ia), in which *trans*-coupling of the rings guaranteed their conformational homogeneity, as the model compounds for studying our proposed mutual conversion of isomeric ethinylcarbinols in the conditions of the Favorskii exchange reaction. Phenylacetylene was selected as the acetylene component as this allowed avoiding the formation of glycols at high temperatures on one hand and preventing loss of the acetylene component by evaporation on the other hand. Instead of a base, which is a catalyst of the reaction, carbonyl or acetylene components were additionally added to accelerate exchange and shift the equilibrium at high temperatures toward ethinylcarbinol. The course of the reaction was monitored by GLC.



Ia,f R^1=H, R^2=Me, $R^3-R^4=(CH_2)_4$, R^5=Ph; IIa,f $R^1=R^5$=H, R^2=Me, $R^3-R^4=(CH_2)_4$; IIIa,f $R^1=R^2=R^5$=H, $R^3-R^4=(CH_2)_4$; IVa $R^1=R^2$=Me, $R^3-R^4=R^5$=H; V R^1=H, R^2=Me, $R^3-R^4=(CH_2)_4$; VI $R^1=R^2$=H, $R^3-R^4=(CH_2)_4$; VII $R^1=R^2$=Me, R^3-R^4=H; VIII R^5=Ph; IX R^5=H

The study showed that ethinylcarbinols Ia, f are actually rapidly isomerized into each other in these conditions; the reaction in dioxane at 50°C ends after 10 min with a 1:1:2 ethinylcarbinol:KOH:ketone ratio. The

same equilibrium position corresponding to 78±7% of equatorial alcohol If and 22±1% axial alcohol Ia is attained for both isomers (see Table 1).

The mechanism of isomerization in our opinion consists of decomposition of ethinylcarbinols into carbonyl and acetylene components and reverse synthesis, and the equilibrium position of the ethinylcarbinol isomers is determined by the ratio of the rate constants of formation and decomposition of each isomeric ethinylcarbinol.

Isomeric ethinylcarbinols If and Ia were preparatively isolated after isomerization with a total yield of 90%, separated, and their authenticity was demonstrated by the test of mixing with known samples [17] to reliably demonstrate the mutual conversions.

Almost the same results were obtained in equilibration of isomers If and Ia in tetrahydrofuran and benzene (see Table 1).

If we use a conformational energy of the hydroxyl group in 4-hydroxy-*trans*-decahydroquinoline in ultrabasic medium equal to 1.05 kcal/mole, as found for 4-butylcyclohexanol in [18], the conformational energy of the phenylethinyl substituent will be equal to 0.24±0.03 kcal/mole, which is close to the value of 0.18 kcal/mole found for the ethinyl group in conformational equilibrium of 1-ethinylcyclohexanol [19].

As noted above [14], 30% axial, and 20% equatorial alcohol from the axial (leading to the erroneous conclusion concerning the higher stability of the *a*-epimer) was obtained in isomerization of 1,2*e*,5*e*-trimethyl-4-ethinylpiperidol-4 isomers from the equatorial alcohol. Although equilibrium was not explicitly attained from both sides, the percentage conversion of the equatorial alcohol into axial alcohol differed significantly from what we obtained for ethinylcarbinols Ia and If (22±1%). This could have been due to the structure of the compounds, which had a different type of ethinyl substituent and the number of axial substituents in the piperidine ring. We thus investigated the effect of these factors on the equilibrium position.

Equilibration of isomers of 2*e*-methyl-4-hydroxy-4-ethinyl-*trans*-decahydroquinoline IIa and IIf, which differed from ethinylcarbinols Ia and If only by the character of the ethinyl substituent, was conducted with continuous passage of an acetylene current to compensate for losses of acetylene at the high temperature. As the study showed (see Table 1), almost the same equilibrium of the isomers as for the phenylethinyl derivative was established during isomerization: 77% equatorial alcohol IIf and 23% axial alcohol IIa, $-\Delta G^0 = 0.78 \pm 0.03$ kcal/mole, which indicates equal conformational energies of the phenylethinyl and ethinyl groups ($-\Delta G^0_{CH \equiv C} = 0.27 \pm 0.03$ kcal/mole).

The same results were obtained in equilibration of isomers of 4-hydroxy-4-ethinyl-*trans*-decahydroquinoline (IIIa and IIIf) in dioxane, tetrahydrofuran, and benzene (78% equatorial IIIf and 22% axial alcohol IIIa), which suggests that the equatorial methyl in the β position to the carbinol group does not affect the equilibrium position of ethinylcarbinols.

The study of equilibration of 1,2*e*,5*e*-trimethyl-4-ethinylpiperidol-4 isomers (IVa and IVe) in the same conditions produced results (74% equatorial alcohol IVf and 26% axial IVa, $-\Delta G^0 = (0.67 \pm 0.03)$ kcal/mole) slightly different from both those that we previously obtained for other ethinylcarbinols (78% equatorial and 22% axial alcohol) and from those obtained for isomer IVf (30% axial alcohol) [14]. We can hypothesize that the differences in the results in [14] and our results could be due to a difference in the conditions of isomerization and methods of determining the composition of the mixture (preparative TLC, R_f of equatorial alcohol IVf of 0.66, of axial IVa of 0.74).

With respect to the small differences from the results that we obtained for other ethinylcarbinols, since the isomers of 2*e*-methyl-4-hydroxy-4-ethinyl-*trans*-decahydroquinoline and 1,2*e*,5*e*-trimethyl-4-ethinylpiperidol-4 are similar with respect to the type of C substitution of the piperidine ring [(at one equatorial α-methyl (methylene) substituent with respect to the carbinol group, equatorial β-substituents do not affect the equilibrium], we can hypothesize that the small differences in the equilibrium constants are due to the different conformational energy of the hydroxyl and ethinyl groups (especially the polar hydroxyl group) in the piperidine rings with tertiary and secondary nitrogen atoms (they differ strongly, for example, in the orientation of the free electron pair of the nitrogen and the basicity of the amino group).

Both carbo- and heterocyclic ketones are known to participate in the Favorskii reaction. As a consequence, we can hypothesize that epimerization is a common property of ethinylcarbinols and can be used to determine the configuration of the quaternary carbinol center, which usually presents significant difficulties.

We thus conducted the reaction of isomerization—equilibration of stereoisomeric ethinylcarbinols epimeric at the carbinol center for the first time and showed that the alcohol with an equatorial hydroxyl group is thermodynamically more stable; equilibration of ethinylcarbinols can be used for determining the configuration of a quaternary carbinol center.

EXPERIMENTAL

Synthesis and demonstration of the configuration of isomers of *trans*-decahydroquinolines If-IIIf and Ia-IIIa, ethinylpiperidols-4 IVf and IVa and the corresponding ketones were described previously in [12, 17, 20-22].

GLC analysis was conducted on a Khrom-41 chromatograph with a flame-ionization detector in glass columns 3 mm in diameter. Helium was the carrier gas. In the case of phenylethinylcarbinols, the column (1.2 m) was packed with Chromaton N-super (0.20-0.25 mm) with application of 5% Se-30 + 1% OV-225. The retention time of the isomers of decahydroquinoline I at 190°C for a carrier gas flow rate of 48 ml/min was: 13.2 for If and 15.4 min for Ia. In the case of ethinylcarbinols, the column (2.4 m) was packed with Chromaton N (0.20-0.25 mm) with 5% PEG-6000. The retention times of the isomers of decahydroquinoline II and III were (170°C, 34 ml/min): 11.2 for IIa; 13.6 for IIf; 9.2 for IIIa; 11.4 min for IIIf; isomers of ethinylpiperidol-4 IV (140°C, 38 ml/min): 11.2 for IVa; 12.6 min for IVf. The standard deviations of the analyses did not exceed 1%.

General Method of Investigation of Isomerization—Equilibration of Ethinylcarbinols. The study of isomerization—equilibration of ethinylcarbinols was conducted in a reactor thermostated with a water jacket and equipped with a reflux condenser, thermometer, and stirrer with a valve in which petrolatum was used as the locking liquid. Then 2.5 mmole of ethinyl- or phenylethinylcarbinol and 5 mmole of the corresponding ketone or R—C≡CH with a solvent (see Table 1) were added to a mixture of 5 mmole of powdered KOH and 2 ml of anhydrous solvent and the mixture was stirred at 50.0±0.2°C in an argon (phenylethinylcarbinols) or acetylene current (ethinylcarbinols). Samples for GLC analysis were take with a 0.1 ml glass tube, treated with a small amount of water (0.1-0.2 ml), extracted with chloroform, dried with magnesium sulfate, and analyzed.

Isomerization of 2*e*-methyl-4*a*-hydroxy-4*e*-phenylethinyl-*trans*-decahydroquinoline (Ia). Here 13.5 g (50 mmole) of 2*e*-methyl-4*a*-hydroxy-4*e*-phenylethinyl-*trans*-decahydroquinone Ia with T_m of 147-148°C and 10.2 g (100 mmole) of phenylacetylene in 10 ml of dioxane were added to a mixture of 5.6 g of powdered KOH in 30 ml of anhydrous dioxane. The mixture was stirred for 1 h at 50°C (the equilibrium position of the isomers was attained according to GLC analysis: 78% If and 22% Ia), treated with 8 ml of water, and the product of the reaction was extracted with chloroform. After drying of the extract with magnesium sulfate and distillation of the solvent and phenylacetylene, 12.1 g (90%) of a mixture of isomers If and Ia was obtained. Using the method in [17, 23], 8.9 g (66%) of 2*e*-methyl-4*e*-hydroxy-4*a*-phenylethinyl-*trans*-decahydroquinoline (If) with T_m of 127-128°C and 2.4 g (18%) of the isomer of decahydroquinoline Ia with T_m of 147-148°C, which did not depress the melting point in samples mixed with known samples, were separated from the mixture.

LITERATURE CITED

1. A. A. Espenbetov, Yu. T. Struchkov, N. Yu. Kuz'mina, and G. S. Litvinenko, Izv. Akad. Nauk SSSR, Ser. Khim., No. 5, 1056 (1988).
2. G. S. Litvinenko and T. K. Iskakova, VI International Conference on Organic Synthesis, Abstracts, Papers, Moscow (1986), p. 133.
3. G. S. Litvinenko, T. K. Iskakova, and D. G. Kim, Izv. Akad. Nauk Kaz. SSSR, Ser. Khim., No. 2, 67 (1987).
4. A. T. Babayan, Zh. Obshch. Khim., **10**, 480 (1940).
5. A. I. Zakharova, Zh. Obshch. Khim., **11**, 939 (1941).
6. I. L. Kotlyarevskii, M. S. Shvartsberg, and L. B. Fisher, Reactions of Acetylenic Compounds [in Russian], Novosibirsk (1967).
7. A. V. Shchelkunov, R. L. Vasil'eva, and L. A. Krichevskii, Synthesis and Mutual Transformations of Monosubstituted Acetylenes [in Russian], Alma-Ata (1970).
8. W. Chodkiewicz, Ann.Chim. (Paris), **13**, 819 (1957).
9. V. I. Nikitin and S. D. Savranskaya, Zh. Obshch. Khim., **23**, 1146 (1953).
10. V. I. Nikitin and S. D. Savranskaya, Zh. Obshch. Khim., **25**, 1106 (1955).
11. A. V. Kamernitskii and A. A. Akhrem, Usp. Khim., **30**, 145 (1961).
12. B. V. Unkovskii, Yu. F. Malina, I. P. Boiko, T. D. Sokolova, and M. T. Zaitseva, Zh. Org. Khim., **3**, 757 (1967).
13. A. A. Akhrem, L. I. Ukhova, and A. N. Sergeeva, Izv. Akad. Nauk BSSR, Ser. Khim., No. 6, 75 (1975).
14. V. I. Nikitin, E. M. Glazunova, G. S. Sanyukovich, I. N. Grigina, and I. I. Voropaeva, Zh. Org. Khim., **9**, 2484 (1973).
15. E. M. Glazunova and G. S. Sanyukovich, Proceedings of the All-Union Conference on the Chemistry of Acetylene [in Russian], Tbilisi (1975), p. 259.
16. L. I. Ukhova, A. N. Sergeeva, and A. A. Akhrem, Khim. Geterosikl. Soedin., No. 8, 1086 (1980).
17. G. S. Litvinenko and T. K. Iskakova, Izv. Akad. Nauk KazSSR, Ser. Khim., No. 6, 62 (1985).
18. G. Chiurdoglu and W. Masschelein, Bull. Soc. Chim. Belges, **70**, 767 (1961).
19. R. J. Ouelette, J. Am. Chem Soc., **84**, 3089 (1964).
20. I. N. Nazarov, I. A. Mokhir, B. V. Unkovskii, and G. S. Gusakova, Zh. Obshch. Khim., **29**, 1867 (1959).
21. A. A. Akhrem, L. I. Ukhova, G. P. Kukso, S. M. Volkov, N. I. Garbuz, and L. P. Solovei, Khim. Geterosikl. Soedin., No. 11, 1529 (1976).

22. K. D. Praliev, A. A. Andrusenko, T. T. Omarov, D. V. Sokolov, L. I. Ukhova, and A. A. Akhrem, Izv. Akad. Nauk KazSSR, Ser. Khim., No. 6, 49 (1967).
23. G. S. Litvinenko and T. K. Iskakova, Izv. Akad. Nauk KazSSR, Ser. Khim., No. 1, 73 (1984).

SPECIFIC C–H···N INTRAMOLECULAR INTERACTIONS IN THE VINYLOXY- AND VINYLTHIOPYRIDINE SERIES

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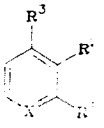
A weak hydrogen bond with the participation of the vinyl group α-hydrogen atom arises in 2-vinyloxypyridine and 2-vinylthiopyridine, which primarily exist in the s-trans-conformation, according to the ^1H and ^{13}C NMR data. This interaction does not take place in 2-vinyloxymethyl- and 2-vinyloxyethylpyridines, which primarily exist in the s-cis-conformation. The C—H...N intramolecular interaction also does not occur in o-vinyloxyaniline due to the specific features of the stereoelectronic state of the amino group nitrogen atom.

Examples of the appearance of C—H...X (X = heteroatom) specific intramolecular interactions of the weak hydrogen bond type are extremely limited [1-6]. This makes it difficult to determine the factors required for the appearance of this interaction. The parameters of the ^1H and ^{13}C NMR spectra of a systematically selected series of molecules were analyzed in the present study: 2-, 3-, 4-vinyloxypyridines (I-III), phenylvinyl ether (IV), 2-, 3,-, 4-vinylthiopyridines (V-VII), phenylvinyl sulfide (VIII), 2-, 3-, 4-vinyloxymethylpyridines (IX-XI), benzylvinyl ether (XII), 2-vinyloxyethylpyridine (XIII), and *o*-, *m*-, *p*-vinyloxyanilines (XIV-XVI). Compounds VI and VII were synthesized for the first time.



I-XVI

I, IV, XIV $R^1=OCH=CH_2$, $R^2=R^3=H$; II, XV $R^1=R^3=H$, $R^2=OCH=CH_2$; III, XVI $R^1=R^2=H$, $R^3=OCH=CH_2$; V, VIII $R^1=SCH=CH_2$, $R^2=R^3=H$; VI $R^1=R^3=H$; $R^2=SCH=CH_2$; VII $R^1=R^2=H$, $R^3=SCH=CH_2$; IX, XII $R^1=CH_2OCH=CH_2$, $R^2=R^3=H$; X $R^1=R^3=H$, $R^2=CH_2OCH=CH_2$; XI $R^1=R^2=H$, $R^3=CH_2OCH=CH_2$; XIII $R^1=C_2H_4OCH=CH_2$, $R^2=R^3=H$; I—III, V—VII, IX—XI, XIII X=N; IV, VIII, XII X=CH; XIV—XVI X=CNH_2

The parameters of the ^1H and ^{13}C NMR spectra (see Table 1) of the vinyl group in the series of vinyl ethers and sulfides are a function of the intensity of $p-\pi$ conjugation in the vinyloxy(vinylthio) group [7, 8]. The intensity of $p-\pi$ conjugation in the vinyloxy group of aryl-and hetarylvinyl ethers and sulfides is a function of the conditions of competitive $p-\pi$ conjugation with an unsaturated fragment [7-9]. The chemical shift of the β-carbon atom of the vinyl group is the criterion of efficiency of $p-\pi$ conjugation [9]. The character of the change in the position of the signal of the $C_{(\beta)}$ atom in vinylthiopyridines V-VII and phenylvinyl sulfide VIII is the same as in vinyloxypyridines I-III and phenylvinyl ether IV. The nucleus of the $C_{(\beta)}$ atom in phenylvinyl ether IV (95.1 ppm) and sulfide VIII (115.3 ppm) is most shielded. The resonance of this nucleus is successively shifted to the weak field in going to 2-vinyloxy(vinylthio)-, 3-vinyloxy(vinylthio)-, and 4-vinyloxy(vinylthio)pyridines (I-III, V-VII), respectively (see Table 1).

The chemical shifts of the vinyl group β-protons ($H_{(A)}$ and $H_{(B)}$) in ethers I-IV and sulfides V-VIII change symbatically with the chemical shift of the $C_{(\beta)}$ atom. The region of their change in these groups of compounds does not exceed 0.3 ppm, and the relative chemical shift of the $H_{(A)}$ and $H_{(B)}$ protons ($\Delta\delta = \delta H_{(A)} - \delta H_{(B)}$) for ethers

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