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STEREOCHEMISTRY OF ETHYNYLATION OF 2,7-DIALKYL- AND 1,2,7-TRIALKYL-trans-DECAHYDRO-4-QUINOLONES*

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UDC 547.831.3:541.634

The effect of the nature of the acetylide, the temperature, and the character of the solvent on the stereochemistry of ethynylation of isomeric 2,7-dialkyl- and 1,2,7-trialkyldecahydro-4-quinolones was investigated. Acetylenic alcohols that have an axially oriented ethynyl grouping were synthesized. Conditions for the stereospecific synthesis of epimeric (with respect to C_4) acetylenic alcohols were found. The isomers of acetylenic alcohols obtained were incapable of interconversions under the reaction conditions.

We have previously [2] described the stereochemistry of the nucleophilic addition of sodium acetylide in liquid ammonia and of ethynylmagnesium bromide and acetylene in the presence of powdered potassium hydroxide to the carbonyl group of sterically unhindered 2,7-dialkyl- and 1,2,7-trialkyldecahydro-4-quinolones (the 2-CH_3 group is equatorial). These ketones behave unusually: Under the influence of the first two reagents they form only isomers of the acetylenic alcohol with an equatorial orientation of the ethynyl substituent, whereas epimerization of the starting ketones with respect to the C_2 center to give their axial epimers occurs under the conditions of the Favorskii reaction.

In order to synthesize the missing epimers of the acetylenic alcohols that have an axial orientation of the ethynyl group we continued our study of the stereochemistry of the ethynylation of sterically unhindered 2,7- and 1,2,7-alkyl-substituted decahydro-4-quinolones (I-III) with other ethynylating agents under various conditions. The reaction of ketones I and II with lithium, potassium, calcium, and barium acetylides in liquid ammonia, in contrast to the reaction with sodium acetylide [2], proceeds nonstereospecifically with the formation in each case of a mixture of two isomers containing, in addition to alcohols VI and VIII,

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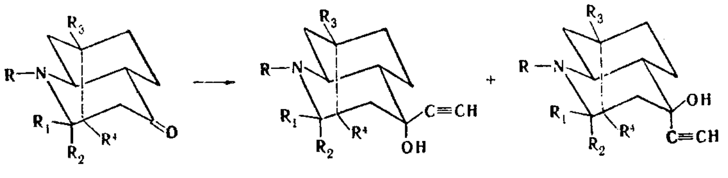
*See [1] for our preliminary communication.

Institute of Bioorganic Chemistry, Academy of Sciences of the Belorussian SSR, Minsk 220600. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1086-1091, August, 1980. Original article submitted December 17, 1979.

0009-3122/80/1608-0843$07.50

which have an equatorial ethynyl substituent, their epimers with respect to C_4 with an axial ethynyl group (VII, IX); the stereoselectivity of the investigated acetylides decreases on passing from lithium acetylide to calcium, potassium, and barium acetylides. In the latter case the fraction of epimers VII and IX with an axial ethynyl substituent is ~50%. However, the reactivities of the investigated acetylides are just the opposite of their stereoselectivities (Table 1).



I–V VI, VIII, X, XII, XIV VII, IX, XI, XIII, XV

I, VI, VII $R=R_2=R_3=H$, $R_1=R_4=CH_3$; II, VIII, IX $R=R_1=R_4=CH_3$; $R_2=R_3=H$; III, X, XI $R=R_1=CH_3$, $R_2=R_4=H$, $R_3=t\text{-Bu}$; IV, XII, XIII $R=R_1=R_3=H$, $R_2=R_4=CH_3$; V, XIV, XV $R=R_2=R_4=CH_3$; $R_1=R_3=H$

A study of the effect of the reaction temperature on the ratios of the epimers in the mixtures showed that when the temperature of the acetylene synthesis was raised from −76°C to +20°C, there was a gradual increase in the percentages of epimers VII and IX formed as a result of axial approach of the ethynyl grouping. Whereas alcohols VI and VIII with an equatorial ethynyl substituent clearly predominate in the mixtures at −76°C, epimers VI and VII and VIII and IX are formed in approximately equal amounts at −30 to −15°C, while inversion of the stereochemistry of the reaction occurs at and above 0°C, and epimers VII and IX with an axial ethynyl group predominate in the mixtures of products. This tendency is displayed particularly clearly in the reactions of ketones I and II with lithium and potassium acetylides. The reaction with barium acetylide, the stereochemistry of which does not depend on the temperature, constitutes an exception.

The nature of the solvent (Table 1) also has a substantial effect on the stereospecificity of the ethynylation of ketones I and II. For example, the reaction with the acetylides of monovalent metals in the strongly polar and high-donor solvent hexametapol (HMPT) proceeds extremely readily with the stereospecific or preponderant formation of alcohols VII and IX, which have an axial orientation of the ethynyl group. On the other hand, a slow reaction and the primary formation of equatorial ethynyl derivatives VI and VIII are characteristic for an aprotic solvent, viz., dimethylformamide (DMF).

Thus, as a result of a study of the effect of the nature of the acetylide, the temperature, and the character of the solvent on the stereochemistry of the ethynylation of sterically unhindered 2,7-dialkyl- and 1,2,7-trialkyldecahydro-4-quinolones, we synthesized previously unknown acetylenic alcohols that have an axial orientation of the ethynyl group. The conditions for the stereospecific synthesis of epimeric (with respect to C_4) acetylenic alcohols of this series were found. It was established that the isomers of acetylenic alcohols obtained are incapable of interconversions under the conditions of the synthesis.

We also studied the ethynylation of ketones I and II in the presence of powdered potassium hydroxide in solution in liquid ammonia; in contrast to the results obtained under the conditions of the Favorskii reaction [2], isomerization of starting ketones I and II at the C_2 center in ketones IV and V is not observed. In addition to this, acetylenic alcohols VI and VII and VIII and IX, which correspond to the structures of the starting ketones, are formed in high yields. This result is evidently explained by the mild reaction conditions, viz., the low temperature and the high degree of donor properties of the solvent.

In addition to the ethynylation of ketones I–III, we investigated the ethynylation of sterically hindered 2,7-dimethyl- and 1,2,7-trimethyldecahydro-4-quinolones IV and V (with an axial 2-CH_3 group), which gave acetylenic alcohols with an equatorial ethynyl group as the only products in reactions with sodium acetylide in liquid ammonia and with ethynylmagnesium bromide, as well as under the conditions of the Favorskii reaction [3]. We obtained the same result in the reaction of ketones IV and V with barium and calcium acetylides in liquid ammonia. However, in ether, tetrahydrofuran (THF), and benzene at various temperatures, in addition to the known alcohols XII and XIV with an equatorial ethynyl group, which predominate

TABLE 1. Effect of the Nature of the Metal Acetylide, the Temperature, and the Solvent on the Stereochemistry of the Ethynylation of 2e,7a-Dimethyl- (I) and 1,2e,7a-Trimethyl-trans-decahydro-4-quinolones (II)

Epimeric composition of the products of ethynylation of ketone I		Ethynylation conditions				Epimeric composition of the products of ethynylation of ketone II	
(—C≡CH), VI, *e*, %	(—C≡CH) VII, *a*, %	Reagent	Solvent	Temp., °C	Time, h	(—C≡CH), VIII, *e*, %	(—C≡CH), IX, *a*, %
100	0	NaC≡CH	Liq. NH_3	−76	3.0	100	0
88	12		Ether	+20	1.5	88	12
			Ether	+20	1.5	86^{a}	14^{a}
57	43		C_6H_6	+20	1.5	58	42
27	73		HMPT^{b}	+20	0.5	26	74
20^{c}	0^{c}		DMF	+20	4.0	20^{c}	0^{c}
78	22	LiC≡CH	Liq. NH_3	−76	1.5	77	23
64	36		Liq. NH_3	−50	1.0	63	37
58	42		" "	−30	0.5	58	42
52	48		" "	−15	0.5	53	47
51	49		Ether	−15	0.5	52	48
44	56		Ether	0	0.3	43	57
35	65			+20	0.4	35	65
52	48		THF	−15	0.25	53	47
43	57		THF	0	0.2	43	57
33	67			+20	0.2	34	66
30	70		C_6H_6	+20	0.5	27	73
0	100		HMPT	+20	>1 min	0	100
63	37		DMF	+20	1.2	62	38
			C_6H_6	+20	0.5	21^{a}	79^{a}
60	40	KC≡CH	Liq. NH_3	−76	0.1	59	41
44	56		C_6H_6	+20	0.2	45	55
34	66		THF	+20	0.2	33	67
20	80		HMPT	+20	>1 min	20	80
72	28		DMF	+20	0.5	72	28
54	46	$Ba(C\equiv CH)_2$	Liq. NH_3	−45	0.5	54	46
57	43		THF	+20	0.25	56	41
80	0		DMF	+20	1.5	79	0
55	45		HMPT	+20	0.2	55	45
72	28	$Ca(C\equiv CH)_2$	Liq. NH_3	−76	6.0	69	31
63	37		Liq. NH_3/THF	−45	1.0	62	38
58	42		Liq. NH_3/HMPT	−45	0.5	57	43
0	0		Liq. NH_3/DMF	−45	2.0	0	0
88	12	KOH	Liq. NH_3	−40	0.5	86	14
55	45			−25	0.5	54	46
40	60			−15	0.5	40	60
0	0	$HC\equiv CLi\cdot NH_2CH_2{-}CH_2{-}NH_2$	THF	+20	12	0	0
54	46		Dioxane	+100	10	52	48
58	42		THF	+60	12	55	45

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[a] Ethynylation of 1,2-dimethyl-7-tert-butyldecahydro-4-quinolone (III). Epimers X and XI. [b] The abbreviation "HMPT" stands for hexamethylphosphoric triamide (hexametapol). [c] The starting ketone is present.

in the mixtures, their axial epimers XIII and XV are formed in small amounts. When the indicated solvents are replaced by hexametapol, the latter are obtained in preponderant amounts (Table 2).

Consequently, by substantially changing the reaction conditions, even in the case of sterically hindered 2,7- and 1,2,7-substituted decahydro-4-quinolones, one can direct the reaction to favor the formation of the difficult-to-obtain epimers of acetylenic alcohols XIII and XV with an axial ethynyl group.

The structures of the synthesized acetylenic alcohols were established by spectral and chemical methods. The presence of a triple bond in alcohols VII, IX, XI, XIII, and XV was confirmed by a positive qualitative reaction for acetylene, exhaustive hydrogenation to the corresponding 4-ethyl-substituted derivatives, and by hydration to ketones (Table 3). The orientation of the hydroxy and ethynyl groups in alcohols VII, IX, XI, XIII, and XV was determined on the basis of a study of the relative rates of their etherification and oxidation and their basicity constants, as well as on the basis of a study of the IR spectra of the alcohols and the configurationally related ketols.

TABLE 2. Effect of the Nature of the Metal Acetylide, the Temperature, and the Solvent on the Stereochemistry of the Ethynylation of 2a,7a-Dimethyl- and 1,2a,7a-Trimethyl-trans-decahydro-4-quinolones (IV, V)

Epimeric composition of the products of ethynylation of ketone V		Ethynylation conditions				Epimeric composition of the products of ethynylation of ketone IV	
(−C≡CH), XII, *e*, %	(−C≡CH), XIII, *a*, %	Reagent	Solvent	Temp., °C	Time, h	(−C≡CH), XIV, *e*, %	(−C≡CH), XV, *a*, %
100	0	NaC≡CH	Liq. NH_3	−76	3,5	100	0
91	9		Ether	+20	2,5	89	11
100	0		HMPT [a]	+20	0,5	100	0
0	0		DMF	+20	6,0	0	0
92	8	LiC≡CH	Liq. NH_3	−76	1,5	92	8
68	32		C_6H_6	+20	2,0	69	31
85	15		THF	+20	1,0	84	16
48	52		HMPT	+20	0,2	48	52
0	0		DMF	+20	4,0	0	0
74	26	KC≡CH	Liq. NH_3	−45	0,5	73	27
85	15		C_6H_6	+20	0,5	85	15
72	28		THF	+20	0,25	72	28
61	39		HMPT	+20	>1 min	60	40
100	0	$Ba(C{\equiv}CH)_2$	Liq. NH_3	−76	0,5	100	0
100	0		THF/Liq. NH_3	+20	0,5	100	0
56	44		HMPT/liq. NH_3	+20	0,25	56	44
100	0	$Ca(C{\equiv}CH)_2$	Liq. NH_3	−45	8,0	100	0
100	0		Liq. NH_3/THF	−45	4,0	100	0
100	0		Liq. NH_3/HMPT	−45	1,5	100	0
70[b]	0	KOH	Liq. NH_3	−45	1.0	70[b]	0
80[b]	0			−55	1.5	82[b]	0

[a] The abbreviation "HMPT" stands for hexamethylphosphoric triamide (hexametapol). [b] The starting ketone is present.

The correspondence between the orientation of the C_2 center in alcohols VIII, IX, XIV, and XV and in starting ketones II and V was confirmed by the PMR and IR spectra. Alcohols VIII and IX have 2-H signals at δ 2.45 ppm with $J_{2H,3He}$ = 3-4 Hz and $J_{2H,3Ha}$ = 10-11 Hz, while alcohols XIV and XV have signals at δ 2.90-2.98 ppm and spin–spin coupling constants of 6-6.5 and 2-3 Hz. Boltzmann bands, which are absent in the spectra of alcohols XIV and XV, are observed in the IR spectra of alcohols VIII and IX. The data presented above indicate an equatorial orientation the $2\text{-}CH_3$ group in alcohols VIII and IX and an axial orientation of the same group in alcohols XIV and XV.

EXPERIMENTAL

The melting points of the substances were determined with a Koffler apparatus. The IR spectra of KBr pellets, CCl_4 solutions, or films of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions in $CDCl_3$ were obtained with a Jeol JNM-PS-100 spectrometer with tetramethylsilane as the internal standard. Monitoring of the course of the ethynylation and confirmation of the individuality of the compounds obtained were realized by means of thin-layer chromatography (TLC) on Woelm (neutral) Al_2O_3 [elution with chloroform–ether–ethanol (3:1:0.5)]. The conditions for ethynylation of ketones I-V and the ratios of the epimers in the mixtures are presented in Tables 1 and 2. The crystalline "lithium acetylide–ethylenediamine" complex was obtained by the method in [4, 5]. The ethynylation with metal acetylides was carried out at a ketone:reagent ratio of 1:3 in the presence of powdered KOH (1:6 or 1:8) and with the "lithium acetylide–ethylenediamine" complex (1:6). The results of elementary analysis of VII, IX, XI, XIII, and XV-XXV are presented in Table 3. The epimeric compositions of the products were determined by gas–liquid chromatography (GLC). A Khrom-41 chromatograph with a flame-ionization detector was used for the separation. The glass capillary column was 50 m long and had an inner diameter of 0.3 mm, the column temperatures were 136 and 156°C, the carrier-gas (helium) flow rate was 4 ml/min, the division of the carrier gas stream (into the column and into the discharge) was 1:20, and the sample-vaporization temperature was 120°C. The basicity constants of the stereoisomeric alcohols

TABLE 3. 2,7-Dialkyl- and 1,2,7-Trialkyl-4-(ethynyl, ethyl, or acetyl)-decahydro-4-quinolols (VI-XXVII)

Compound	mp, °C	R_f	IR spectrum, ν, cm^{-1}				pK_a	Orient. of substits.		Found,%			Empirical formula	Calc., %		
			OH	≡CH	Acetate C—O	Boltzmann band		OH	4-R	C	H	N		C	H	N
VI	142—143	0,58	3615	3310	1240*	2790—2800	9,72	*a*	*e*							
VII	121—122	0,46	3611	3310	1220,* 1245, 1250	2800	9,41	*e*	*a*	75,4	10,3	6,7	$C_{13}H_{21}NO$	75,3	10,2	6,7
XVI	133—134	0,47	3611	—	—	2800	—	*e*	*a*	74,0	12,0	6,7	$C_{13}H_{25}NO$	73,9	11,9	6,6
XVII	126—127	0,41	3478	—	—	2800	—	*a*	*e*							
XVIII	90—91	0,38	3478, 3611	—	—	2800	—	*e*	*a*	69,3	10,3	6,2	$C_{13}H_{23}NO_2$	69,3	10,2	6,2
VIII	118—119	0,56	3613	3318	1225, 1245	2800	9,68	*a*	*e*							
IX	112—113	0,40	3609	3316	1230	2800	9,36	*e*	*a*	75,7	10,4	6,3	$C_{14}H_{23}NO$	75,9	10,5	6,3
XIX	86—87	0,38	3609	—	—	2800	—	*e*	*a*	74,5	11,8	6,2	$C_{14}H_{27}NO$	74,6	12,0	6,2
XX	80—81	0,31	3480	—	1225, 1240, 1255	2800		*a*	*e*							
XXI	111—112	0,22	3480, 3609	—	1245	2800	—	*e*	*a*	70,4	10,4	5,8	$C_{14}H_{25}NO_2$	70,2	10,5	5,8
X	99—100	0,60	3614	3318	1220, 1232	2800	9,80	*a*	*e*							
XI	95—96	0,50	3611	3318	1245	2800	9,50	*e*	*a*	77,6	11,1	5,3	$C_{17}H_{29}NO$	77,5	11,1	5,3
XII	140,5—141	0,24	3615	3310	—	—	9,78	*a*	*e*							
XIII	138—139	0,20	3612	3311	—	—	9,38	*e*	*a*	75,3	10,2	6,6	$C_{13}H_{21}NO$	75,3	10,2	6,7
XXII	151—152	0,20	3612	—	—	—	—	*e*	*a*	73,9	11,9	6,6	$C_{13}H_{25}NO$	73,9	11,9	6,6
XXIII	126—127	0,42	3614, 3480	—	—	—	—	*e*	*a*	69,3	10,3	6,2	$C_{13}H_{23}NO_2$	69,3	10,2	6,2
XXIV	170—171	0,32	3480	—	—	—	—	*a*	*e*							
XIV	126—127	0,41	3615	3318	1225, 1235	—	9,73	*a*	*e*							
XV	122—123	0,28	3610	3318	1245	—	9,48	*e*	*a*	76,1	10,6	6,3	$C_{14}H_{23}NO$	76,0	10,5	6,3
XXV	107—108	0,27	3610	—	—	—	—	*e*	*a*	74,6	12,0	6,2	$C_{14}H_{27}NO$	74,6	12,1	6,2
XXVI	117—118	0,18	3480	—	1220, 1235	—	—	*a*	*e*							
XXVII	114—115	0,16	3480, 3611	—	—	—	—	*e*	*a*	70,1	10,2	5,9	$C_{14}H_{25}NO_2$	70,2	10,5	5,8

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*Data for the α-hydroxy ether.

were determined by potentiometric titration of 0.01 N solutions of their hydrochlorides with a 0.5 N solution of NaOH at 25°C. The accuracy in the measurements was ±0.05.

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