STEREOCHEMISTRY OF ETHYNYLATION, NORMANT, AND GRIGNARD REACTIONS IN THE 1-ALKYLDECAHYDRO-4-QUINOLONE SERIES

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The different stereochemistries of the addition of acetylene and vinyl- or ethylmagnesium bromides to 1-alkyl- and 1,2,2-trimethyl-trans-decahydro-4-quinolones are shown. In the ethynylation of mixtures of cis- and trans-1-alkyldecahydro-4-quinolones, one acetylenic alcohol of the cis series was isolated in each case in addition to two epimeric (with respect to the 4 position) trans alcohols. The configurations of the synthesized alcohols were established by IR spectroscopy.

Continuing our study of the stereochemistry of nucleophilic reactions involving addition to the carbonyl group of γ-decahydroquinolones (for example, see [1-3]), in the present research we have studied the addition of sodium acetylide in liquid ammonia and of vinyl- and ethylmagnesium bromides to decahydro-4-quinolone and its 1-alkyl- and 1,2,2-trimethyl-substituted derivatives. The starting decahydro-4-quinolone and 1-alkyldecahydro-4-quinolones were obtained by the method in [4] by cyclization of β-diethylaminoethyl 1-cyclohexenyl ketone with the appropriate amines. The cyclization products were obtained as mixtures of cis and trans ketones, the ratio of which was determined by gas–liquid chromatography (GLC) (Table 1). The picrates of the individual cis- and trans-1-alkyldecahydro-4-quinolones were isolated by fractional crystallization of the mixture of picrates. We were unable to isolate the pure picrate of cis isomer III in the case of 1-methyldecahydro-4-quinolone. The individual 1-alkyl-trans-decahydro-4-quinolones II, IV, VI, and VIII were obtained by decomposition of the corresponding picrates with a column filled with Al_2O_3. We were unable to isolate free cis-decahydroquinolones III, V, VII, and IX because of their isomerization to the trans-ketones.

A mixture of two epimeric (with respect to the 4 position) acetylenic alcohols is formed in high yield as a result of the addition of sodium acetylide in liquid ammonia to trans-decahydroquinolones I, II, IV, VI, and VIII. The individual acetylenic alcohols were isolated by crystallization of the bases or hydrochlorides (Table 2). The ratios of the acetylenic alcohols with an axial ethynyl group to their epimers in the reaction products were 2 : 1 in all cases, according to the TLC data.

In order to determine the configurations of the synthesized acetylenic alcohols, we obtained their acetates (Table 3). The spatial orientation of the hydroxy group in the epimeric acetylenic alcohols was determined from the ν_{O-H} frequency and the form of the ν_{C-O} band of their acetates. It is known [5] that the axial OH group in alicyclic alcohols has a higher ν_{O-H} frequency than the equatorial OH group. One ν_{C-O} absorption band at 1200-1260 cm^{-1} was observed in the spectra of the acetates of the equatorial alcohols, whereas two or more bands in the same region were observed in the spectra of the acetates of the axial alcohols [3, 6, 7]. It is seen from Table 2 that acetylenic alcohols XIV, XVII, XX, and XXIII have higher ν_{O-H} frequencies than acetates XXVI, XXIX, XXXII, and XXXV – three or four ν_{C-O} bands. In contrast to this, acetylenic alcohols XIII, XVI, XIX and XXII have lower ν_{O-H} absorption frequencies, but their acetates XXV, XXVIII, XXXI, and XXXIV have a singlet ν_{C-O} band. On the basis of this, an axial orientation of the hydroxy group should be assigned to alcohols XIV, XVII, XX, and XXIII, and an equatorial orientation should be assigned to alcohols XIII, XVI, XIX, and XXII. The relative rates of esterification of the epimeric acetylenic alcohols confirm the IR spectral data: alcohols XIII, XVI, XIX, and XXII form esters faster by a factor of two than alcohols XIV, XVII, XX, and XXIII.

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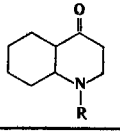
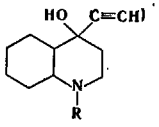
TABLE 1



Compound	Ring fusion	R	Percentage in mixture, %	Picrate								
				mp, °C	R_f	empirical formula	found, %			calc., %		
							C	H	N	C	H	N
II	trans	CH_3	91	191—192	0,29	$C_{10}H_{17}NO \cdot C_6H_3N_3O_7$	48,7	5,4	14,2	48,5	5,1	14,1
IV	trans	C_2H_5	78	190—191	0,30	$C_{11}H_{19}NO \cdot C_6H_3N_3O_7$	49,5	5,5	13,8	49,8	5,4	13,7
V	cis	C_2H_5	22	166—167	0,30		49,5	5,3	13,7			
VI	trans	n-C_3H_7	82	158—159	0,36	$C_{12}H_{21}NO \cdot C_6H_3N_3O_7$	51,0	5,8	13,3	50,9	5,7	13,2
VII	cis	n-C_3H_7	18	132—133	0,36		51,0	5,6	13,4			
VIII	trans	i-C_3H_7	82	182—183	0,36		50,8	5,9	13,4			
IX	cis	i-C_3H_7	18	181—182	0,36		50,9	5,5	13,2			

TABLE 2

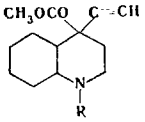


Compound	Ring fusion	R	O—H orientation	ν_{O-H}, cm^{-1}	R_f	mp, °C	Hydrochloride							
							mp, °C	empirical formula	found, %				calc., %			
									C	H	Cl	N	C	H	Cl	N
XI	trans	H	*e*	—	0,45	144—145	253—254	$C_{11}H_{17}NO$[a]	74,0	9,6		7,8	73,7	9,6		7,8
XII[b]	trans	H	*a*	—	0,60	180—181	272—273		74,0	9,6		7,8				
XIII[b]	trans	CH_3	*e*	3608	0,64	136—137	232—233									
XIV[b]	trans	CH_3	*a*	3610	0,82	134—135	279—280									
XV	cis	CH_3	*a*	3604	0,82	—	261—262	$C_{12}H_{19}NO \cdot HCl$	62,8	8,6	15,2	6,1	62,7	8,8	15,2	6,1
XVI	trans	C_2H_5	*e*	3608	0,66	127—128	200—201	$C_{13}H_{21}NO$[a]	75,4	10,4		6,6	75,3	10,2		6,8
XVII	trans	C_2H_5	*a*	3611	0,83	124—125	259—260		75,6	10,3		6,7				
XVIII	cis	C_2H_5	*a*	3605	0,83	—	239—240	$C_{13}H_{21}NO \cdot HCl$	64,3	8,9	14,7	5,7	64,1	9,1	14,5	5,7
XIX	trans	n-C_3H_7	*e*	3609	0,69	82—83	217—218	$C_{14}H_{23}NO$[a]	76,3	10,5		6,5	76,0	10,5		6,3
XX	trans	n-C_3H_7	*a*	3610	0,85	102—103	225—226		75,9	10,6		6,2				
XXI	cis	n-C_3H_7	*a*	3605	0,85	76—77	206—207	$C_{14}H_{23}NO \cdot HCl$	65,2	9,2	14,0	5,6	65,0	9,4	13,8	5,4
XXII	trans	i-C_3H_7	*e*	3608	0,65	118—119	276—277	$C_{14}H_{23}NO$[a]	76,1	10,5		6,1	76,0	10,5		6,3
XXIII	trans	i-C_3H_7	*a*	3610	0,85	137—138	273—274		76,1	10,4		6,3				
XXIV	cis	i-C_3H_7	*a*	3605	0,85	78—79	234—235	$C_{14}H_{23}NO \cdot HCl$	64,9	9,6	13,8	5,2	65,0	9,4	13,9	5,4

[a]These compounds have been previously synthesized (see [7, 9]).

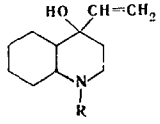
[b]The results of analysis for the bases are presented here.

TABLE 3



Compound	Ring fusion	R	$OCOCH_3$ orientation	$\nu_{C=O}$, cm^{-1}	R_f	mp, °C	Hydrochloride								
							mp, °C	empirical formula	found, %				calc., %			
									C	H	Cl	N	C	H	Cl	N
XXV	trans	CH_3	*e*	1234	0,80	82–83	157–158		61,8	8,2	13,0	5,2				
XXVI	trans	CH_3	*a*	1224, 1238, 1260	0,70	64–65	225–226	$C_{14}H_{21}NO_2 \cdot HCl$	61,8	8,1	13,0	5,2	61,9	8,2	13,0	5,2
XXVII	cis	CH_3	*a*	1233, 1253	0,86	—	208–209		62,2	8,5	12,7	5,2				
XXVIII	trans	C_2H_5	*e*	1237	0,82	65–66	234–235		63,2	8,5	12,6	4,7				
XXIX	trans	C_2H_5	*a*	1227, 1239, 1259	0,78	—	234–235	$C_{15}H_{23}NO_2 \cdot HCl$	63,3	8,6	12,5	4,7	63,0	8,5	12,4	4,9
XXX	cis	C_2H_5	*a*	1234, 1252	0,87	—	207–208		63,2	8,2	12,5	5,0				
XXXI	trans	*n*-C_3H_7	*e*	1236	0,83	75–76	224–225		63,9	8,8	11,6	4,8				
XXXII	trans	*n*-C_3H_7	*a*	1224, 1238, 1258	0,80	69–70	236–237		64,0	8,8	11,9	4,5				
XXXIII	cis	*n*-C_3H_7	*a*	1232, 1252	0,97	—	219–220	$C_{16}H_{25}NO_2 \cdot HCl$	64,3	8,6	11,9	4,8	64,1	8,7	11,8	4,7
XXXIV	trans	*i*-C_3H_7	*e*	1237	0,82	135–136	246–247		64,0	8,5	11,5	4,6				
XXXV	trans	*i*-C_3H_7	*a*	1220, 1227, 1238, 1260	0,76	98–99	225–226		64,3	9,0	12,0	4,8				
XXXVI	cis	*i*-C_3H_7	*a*	1233, 1253	0,88	—	234–235		64,1	8,7	11,8	4,6				

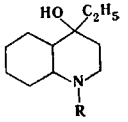
TABLE 4



Compound	Ring fusion	R	$CH=CH_2$ orientation	R_f	mp, °C	mp of hydrochloride, °C	Empirical formula	Found, %			Calculated, %		
								C	H	N	C	H	N
LI	trans	H	*a*	0,45	146–147	238–239	$C_{11}H_{19}NO$	73,2	10,6	7,7	72,9	10,6	7,7
LII	trans	H	*e*	0,60	119–120	216–217		73,2	10,6	7,7			
LIII	trans	CH_3	*a*	0,64	127–128	221–222	$C_{12}H_{21}NO$	73,6	10,6	7,2	73,8	10,8	7,2
LIV	trans	CH_3	*e*	0,82	117–118	204–205		74,1	11,0	7,2			
LV	cis	CH_3	*e*	0,82	—	126–127	$C_{12}H_{21}NO \cdot C_6H_3N_3O_7$	50,8	5,7	13,2	50,9	5,7	13,2
LVI	trans	C_2H_5	*a*	0,66	118–119	—	$C_{13}H_{23}NO$	74,8	11,0	6,7	74,6	11,1	6,8
LVII	trans	C_2H_5	*e*	0,83	109–110	164–165		74,4	11,0	6,7			
LVIII	cis	C_2H_5	*e*	0,83	—	206–207	$C_{13}H_{23}NO \cdot HCl$	63,8	9,7	5,7	63,5	9,8	5,7
LIX	trans	*n*-C_3H_7	*a*	0,69	—	180–181[a]	$C_{14}H_{25}NO \cdot C_6H_3N_3O_7$	52,9	6,4	12,6	53,1	6,2	12,4
LX	trans	*n*-C_3H_7	*e*	0,85	91–92	135–136	$C_{14}H_{25}NO$	75,3	11,3	6,3	75,3	11,3	6,3
LXI	cis	*n*-C_3H_7	*e*	0,85	—	205–206	$C_{14}H_{25}NO \cdot HCl$	65,0	10,1	5,1	64,7	10,1	5,4
LXII	trans	*i*-C_3H_7	*a*	0,65	52–53	215–216		64,9	10,4	5,3			
LXIII	trans	*i*-C_3H_7	*e*	0,85	90–91	206–207	$C_{14}H_{25}NO$	75,4	11,6	6,0	75,3	11,3	6,3
LXIV	cis	*i*-C_3H_7	*e*	0,85	—	140–141[a]	$C_{14}H_{25}NO \cdot C_6H_3N_3O_7$	53,0	6,3	12,5	53,1	6,2	12,4

[a]The data for the picrate are presented.

TABLE 5



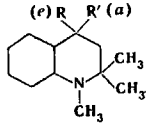
Compound	Ring fusion	R	4-C_2H_5 orientation	R_f	mp, °C	mp of hydrochloride, °C	Empirical formula	Found, %			Calculated, %		
								C	H	N	C	H	N
XXXVII	trans	H	*a*	0,45	177—178	254—255	$C_{11}H_{21}NO$	72,4	11,4	7,6	72,1	11,5	7,6
XXXVIII	trans	H	*e*	0,60	96—97	245—246		72,2	11,7	7,7			
XXXIX	trans	CH_3	*a*	0,64	145—146	208—209	$C_{12}H_{23}NO$	73,8	11,6	7,2	73,0	11,8	7,1
XL[a]	trans	CH_3	*e*	0,82	100—101			73,1	11,6	7,1			
XLI	cis	CH_3	*e*	0,82	49—51	130—131[b]	$C_{12}H_{23}NO \cdot C_6H_3N_3O_7$	50,7	6,0	13,1	50,7	6,1	13,1
XLII	trans	C_2H_5	*a*	0,66	119—120	212—213	$C_{13}H_{25}NO$	74,0	11,8	6,6	73,9	12,0	6,6
XLIII	trans	C_2H_5	*e*	0,83	94—95	130—131		74,1	11,9	6,6			
XLIV	cis	C_2H_5	*e*	0,83	—	189—190[b]	$C_{13}H_{25}NO \cdot HCl$[c]	62,9	10,8	5,8	63,0	10,6	5,7
XLV	trans	n-C_3H_7	*a*	0,69	—	174—175[b]	$C_{14}H_{27}NO \cdot C_6H_3N_3O_7$	52,8	6,6	12,4	52,9	6,7	12,3
XLVI	trans	n-C_3H_7	*e*	0,85	67—68	105—106[b]	$C_{14}H_{27}NO$	74,4	12,0	6,2	74,6	12,1	6,2
XLVII	cis	n-C_3H_7	*e*	0,85	—	119—120[b]	$C_{14}H_{27}NO \cdot C_6H_3N_3O_7$	53,1	6,5	12,5	52,6	6,7	12,3
XLVIII	trans	i-C_3H_7	*a*	0,65	62—63	222—223	$C_{14}H_{27}NO$	74,8	12,1	6,2	74,6	12,1	6,2
XLIX	trans	i-C_3H_7	*e*	0,85	70—71	214—215		74,7	12,2	6,2			
L	cis	i-C_3H_7	*e*	0,85	—	114—115[b]	$C_{14}H_{27}NO \cdot C_6H_3N_3O_7$	53,2	7,0	12,5	52,9	6,7	12,3

[a]Previously synthesized in [9].

[b]The data for the picrate are presented.

[c]Found: Cl 14.2%. Calculated: Cl 14.2%.

TABLE 6



Compound	R	R′	ν_{O-H} or ν_{C-O}, cm^{-1}	R_f	mp, °C	mp of hydrochloride, °C	Empirical formula	Found, %			Calculated, %		
								C	H	N	C	H	N
LXV	C≡CH	OH	3611	0,68	129—130	262—263	$C_{14}H_{23}NO$	76,1	10,3	6,4	76,0	10,5	6,3
LXVI	C≡CH	$OCOCH_3$	1232, 1254	0,70	89—90	248—249	$C_{16}H_{25}NO_2 \cdot HCl$[a]	64,2	9,0	4,8	64,1	8,7	4,7
LXVII	C_2H_5	OH	—	0,68	122—123	237—238	$C_{14}H_{27}NO$	74,8	12,3	6,2	74,6	12,1	6,2
LXVIII	$CH=CH_2$	OH	—	0,68	100—101	247—248	$C_{14}H_{25}NO$	75,3	11,3	6,4	75,3	11,3	6,3

[a]Found: Cl 11.8%. Calculated: Cl 11.8%.

The established orientation of the hydroxy group of the epimeric acetylenic alcohols is in conformity with their chromatographic mobilities.

The configuration of secondary bases XI and XII was established by their conversion to tertiary bases XIII and XIV by methylation of the nitrogen atom.

In order to obtain the cis isomers of the acetylenic alcohols we also subjected the mixture of cis-trans-ketones to ethynylation. As a result of this, in addition to the epimeric (with respect to the 4 position) acetylenic alcohols of the trans series, we also isolated acetylenic alcohols of the cis series XV, XXI, and XXIV. Analysis of the reaction products by GLC reveals ~10% of the cis isomer of the acetylenic alcohol in the mixture in each case. An axial orientation of the hydroxy group was assigned, from the form of the band in the IR spectra of acetates XXVII, XXX, XXXIII, and XXXVI, to alcohols XV, XVIII, XXI, and XXIV (Table 3).

Mainly (65-85%) 4-vinyl- (LII, LIV, LVII, LX, and LXIII, Table 4) and 4-ethyl-substituted (XXXVIII, XL, XLIII, and XLIX, Table 5) alcohols with equatorial vinyl or ethyl groups, identical to the alcohols obtained by selective and exhaustive hydrogenation of acetylenic alcohols XII, XIV, XVII, XX, and XXIII, are formed in the reaction of the individual trans-ketones I, II, IV, VI, and VIII with vinyl- and ethylmagnesium bromides. Their epimers with respect to the 4 position, which are present in small amounts in the resulting mixtures, were identified by thin-layer chromatography (TLC) with vinyl (LI, LIII, LVI, LIX, and LXII) and saturated (XXXVII, XXXIX, XLII, XLV, and XLVIII) alcohols, which have axial alkenyl or alkyl substituents and are obtained by hydrogenation of acetylenic alcohols XI, XIII, XVI, XIX, and XXII. We were able to isolate alcohol XXXIX, which has an axial C_2H_5 group, only in one case by crystallization of the mixture of epimeric 1-methyl-4-ethyl-trans-decahydro-4-quinolones.

4-Vinyl- (LV, LVIII, LXI, and LXIV) and 4-ethyl-substituted (XLI, XLIV, and XLVII) alcohols of the cis series were obtained by means of selective and exhaustive hydrogenation of the corresponding acetylenic alcohols XV, XVIII, XXI, and XXIV.

The data obtained in this research indicate that the addition of sodium acetylide in liquid ammonia to trans-decahydro-4-quinolone and 1-alkyl-trans-decahydro-4-quinolones takes place by preferred axial attack of the reagent with a three-dimensional specificity that is the reverse of that in the addition of organomagnesium compounds.

The reactions described above were also studied in the case of 1,2,2-trimethyl-trans-decahydro-4-quinolone (X), obtained by the method in [7]. Analysis of decahydroquinolone X by GLC did not reveal the presence of the cis form in it. Ketone X, being hindered because of the presence of two geminal methyl groups in the meta position relative to the carbonyl group, reacts with sodium acetylide in liquid ammonia strictly selectively to give only one isomer of acetylenic alcohol LXV in high yield (94%) (Table 6). The relatively high ν_{O-H} frequency of the hydroxy group of alcohol LXV and the doublet form of the ν_{C-O} band of its acetate LXVI make it possible to assign an axial orientation to the hydroxy group. Thus in this case one observes unusual (for ethynylation) stereospecificity with exclusive equatorial incorporation of the ethynyl group.

Vinyl and saturated alcohols LXVII and LXVIII, which were found to be identical to the alcohols obtained by hydrogenation of acetylenic alcohol LXV, were obtained by reaction of ketone X with vinyl- and ethyl-magnesium bromides. The latter confirms the equatorial orientation of the ethynyl group in alcohol LXV.

EXPERIMENTAL

Starting decahydroquinolones I-IX (Table 1) were obtained by cycylization of β-diethylaminoethyl 1-cyclohexenyl ketone [4] with 40% aqueous amines (1 : 1.5) in methanol at 70-80° for 6 h; decahydroquinolone X was obtained by cyclization of isobutenyl 1-cyclohexenyl ketone with methylamine [8]. Thin-layer chromatography (TLC) of the ketones was accomplished on plates (70 by 25 mm) with Woelm Al_2O_3 in a chloroform–hexane system (4 : 1). The picrates of the ketones were obtained and crystallized from ethanol. The trans-ketone bases were isolated by decomposition of the corresponding picrates in a column filled with Al_2O_3 by elution with chloroform. Analysis of the ketones by GLC was accomplished with a Khrom-31 chromatograph with a glass capillary column (100 m by 0.5 mm) on an Apiezon K stationary phase at 160° and a helium pressure at the inlet of 1.1 atm.

Acetylenic alcohols XI-XXIV and LXV (Tables 2 and 6) were prepared by ethynylation of the corresponding decahydroquinolones with sodium acetylide in liquid ammonia under the conditions previously described in [1]. Acetylenic alcohols XI and XII were extracted with ethyl acetate, and the remaining alcohols were extracted with diethyl ether. Thin-layer chromatography of the acetylenic alcohols was accomplished in a chloroform–

ethanol system (30 : 1). The trans-alcohols were isolated from the mixture of cis-trans-acetylenic alcohols obtained from the mixture of cis-trans-ketones by crystallization of the bases from hexane ethyl acetate (4 : 1); the uncrystallizable residue was vacuum fractionated and converted to a mixture of the hydrochlorides; fractional reprecipitation of the latter yielded the individual hydrochloride of the cis-alcohol. The ratios of the isomers in the primary mixtures were determined by GLC with a glass capillary column (100 m by 0.5 mm) on a stationary phase consisting of Apiezon K and 10% Carbowax 20 M at 180° and a helium pressure at the inlet of 1.1 atm. Quantitative analysis was accomplished from the areas of the peaks.

Acetates XXV-XXXVI and LXVI (Tables 3 and 6) were obtained by acetylation of alcohols XI-XXIV and LXV with a mixture of acetic anhydride and acetyl chloride at 70-80°.

Acetylenic alcohols XI and XII were methylated to alcohols XIII and XIV with a mixture of 40% aqueous formalin and 85% formic acid at 100°.

The vinyl (LI-LXIV and LXVIII) and 4-ethyl-substituted (XXXVII-L and LXVII) amino alcohols (Tables 4 and 6) were synthesized from the corresponding ketones by means of the Normant and Grignard reactions under the conditions described in [2] and also by catalytic reduction of the acetylenic alcohols in the presence of the Lindlar catalyst and $Pd/CaCO_3$ at room temperature, respectively.

The IR spectra of $3 \cdot 10^{-3}$ M CCl_4 solutions of the compounds were recorded with a UR-20 spectrometer.

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