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SYNTHESIS OF 2-ALKYL(ARYL, HETARYL)-4-METHYL-1,2,3,4-TETRAHYDROQUINOLINES

V. V. Kuznetsov, A. É. Aliev, and N. S. Prostakov

We have developed a preparative, three stage of synthesis of substituted 1,2,3,4-tetrahydroquinolines. Treatment of N-aryl-imines with allylmagnesium bromide gave N-aryl-N-alkenylamines which were cyclized to the tetrahydroquinolines. The configurations and conformations of the 4-methyl-1,2,3,4-tetra-hydroquinolines containing different 2- substituents have been determined.

Di- and tetrahydroquinolines are used in medicine [1-3]. Compounds of this type are of interest for a study of their steric structure, the latter being important in the conformational analysis of condensed heterocyclic compounds.

This study continues our investigations into the use of imines in the synthesis of nitrogen containing rings [4-7]. We have developed a preparative, three stage synthesis of 4-methyl-1,2,3,4-tetrahydroquinolines with different substituents (alkyl, aryl, hetaryl) substituents at position 2.

The starting materials in these syntheses are the following available aldimines. N-butylidene- (I), benzylidene- (II), and m,p-dimethoxybenzylideneaniles (III), N-m, p-dimethoxybenzylidene-o-anisidine (IV) and the p-anisidine (V), N-α-furylidene- (VI), and 5-methyl-2-furylideneanilines (VII), and α-pyridine- (VIII), β-pyridine- (IX), and γ-pyridinealdehydeanils (X).

Treatment of these imines with alllylmagnesium bromide in ether of THF (depending on the starting material solubility) gave the previously unknown N-aryl-N-alkenylamines XI-XX.

TABLE 1. Physicochemical Properties of Compounds Synthesized

Compound	Empirical formula	Bp, °C/mm Hg	M^+	IR spectrum, ν_{NH}, cm^{-1}	Yield, %
XI	$C_{13}H_{19}N$	195...200/4	189	3400	46
XII	$C_{16}H_{17}N$	166...168/6	223	3396	78
XIII	$C_{18}H_{21}NO_2$	178...180/2	267	3390	55
XIV	$C_{19}H_{23}NO_3$	198...200/2	313	3415	53
XV	$C_{19}H_{23}NO_3$	240...242/5	313	3380	51
XVI	$C_{14}H_{15}NO$	146...149/6	213	3395	50
XVII	$C_{15}H_{17}NO$	106...110/10	227	3400	53
XVIII	$C_{15}H_{16}N_2$	155...156/2	224	3405	94
XIX	$C_{15}H_{16}N_2$	165...170/3	224	3240	64
XX	$C_{15}H_{16}N_2$	170...175/3	224	3340	62
XXI	$C_{13}H_{19}N$	215...220/4	189	3396	62
XXII	$C_{16}H_{17}N$	0,70*	223	3365	50
XXIII	$C_{15}H_{16}N_2$	0,39*[2]	224	3395	67
XXIV	$C_{15}H_{16}N_2$	0,31*[2]	224	3278	64
XXV	$C_{15}H_{16}N_2$	0,24*[2]	224	3300	87
XXVI	$C_{18}H_{21}NO_2$	0,51*[2]	283	3360	5
XXVII	$C_{19}H_{23}NO_3$	0,45*2	313	3348	2

*R_f: system hexane–ethyl acetate, 5:1.

*[2]R_f: system hexane–ethyl acetate, 1:1.

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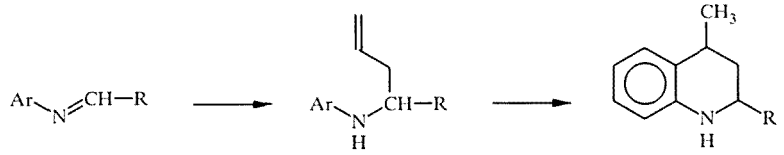
TABLE 2. PMR Spectra Data for Homoallylamines XI-XX ($CDCl_3$, TMS)

Compound	Chemical shift, δ, ppm (multiplicity, J, Hz)						
	-CH-	$-CH_2$	$CH_2=$ (2H, m)	=CH (1H, m)	Ar	R	Other
XI	3,52...3,72 (m)*	2,22...2,50 (m)	4,90...5,17	5,52...6,07	6,52...7,27	1,00...1,67 (7H, m)	—
XII	4,35 (t, 7,0)	2,50 (t, 7,0)	5,00...5,25	5.52...5,92	6,41...7,35		4,08 (1H, br.s ,NH)
XIII	4,22...4,42 (m)*	2,42...2,62 (m)	5,00...5,27	5.55...5,95	6,45...7,17		3,85 (6H, s, OCH_3)
XIV	4,20...4,37 (m)	2,55 (t, 8,0)	5,00...5,27	5.55...5,97	6,30...6,94		3,80 (3H, s, OCH_3); 3,82 (6H, s, OCH_3)
XV	4,15...4,35 (m)	2,40...2,50 (m)	5,00...5,27	5.52...5,95	6,30...6,68		3,64 (3H, s, OCH_3); 3,80 (6H, s, OCH_3)
XVI	4,52 (t, 7,0)	2,60 (t, 7,0)	5,00...5,25	5.52...5,91	6,52...7,08 (5H, m); 6,20 (2H, m, β-$H_{fur.}$); 7,24 (1H, m, α-$H_{fur.}$)		3,90 (1H, br.s ,NH)
XVII	4,44 (t, 7,0)	2,59 (t, 7,5)	4,99...5,32	5.65...5,96	6,50...7,14 (5H, m); 6,24 (2H, m, β-$H_{fur.}$)		2,22 (3H, s, CH_3); 3,60 (1H, br.s ,NH)
XVIII	4,40...4,62 (m)*	2,52...2,75 (m)	5,00...5,25	5,52...6,02	6,45...7,65 (8H, m); 8,56 (1H, m, 2-$H_{pyrid.}$)		—
XIX	4,36...4,55 (m)	2,45...2,65 (m)	5,02...5,30	5,52...6,01	6,30...7,30 (6H, m); 7,76 (1H, m, 3-$H_{pyrid.}$); 8,50 (2H, m, 2-H, 6-$H_{pyrid.}$)		4,15 (1H, br.s ,NH)
XX	4,15...4,66 (m)*	2,42...2,65 (m)	5,02...5,27	5,47...5,96	6,40...7,15 (5H,m); 7,30 (2H,m, 3-$H_{pyrid.}$); 8,53 (2H, m, 2-H, 6-$H_{pyrid.}$)		—

*Overlaps NH proton signal.

TABLE 3. Overall PMR Spectra of 2-Allyl(aryl)-1,2,3,4-tetrahydroquinolines XXI-XXVII (80 MHz, $CDCl_3$, TMS)

Compound	Chemical shift, δ, ppm						
	4-CH_3 d	4-H m	NH br.s	2-H m	2-R	5-H, 8-H m	Others
XXI	1,30	2,90	3,60	4,23	1,43...1,65 (4H, m); 0,94 (3H, q)	6,44...7,22	—
XXII	1,30	3,05	3,79	4,41	6,37...7,42		—
XXIII	1,35	3,10	4,20	4,62	7,35...8,60	6,52...7,20	—
XXIV	1,35	3,14	4,49	3,96	7,30...8,62	6,54...7,19	—
XXV	1,34	3,12	4,46	4,01	7,34...8,56	6,56...7,17	—
XXVI	1,40	2,82	3,27	3,75	6,60...7,15		3,80; 3,87 (3H, s, OCH_3)
XXVII	1,35	3,13	4,47	4,30	6,59...7,03		3,77; 3,90 (3 and 6H, s, OCH_3)



I–X XI–XX XXI–XXVII

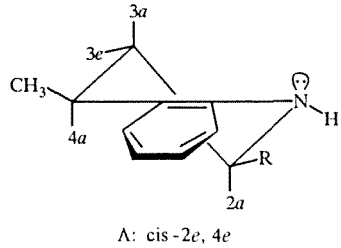
I—III, VI—XIII, XVI—XX Ar = C_6H_5; IV, XIV Ar = $C_6H_4OCH_3$-*o*; V, XV Ar = $C_6H_4OCH_3$-*p*;
I, XI, XXI R = C_3H_7; II, XII, XIII, XXII R = C_6H_5; III—V, XIII—XV, XXVI
R = $C_6H_3(OCH_3)$-*m,p*; VI, XVI R = pyrid-2; VII, XVII R = 5-methylpyrid-2; VIII, XVIII, XXIII
R = α-C_5H_4N; IX, XIX, XXIV R = β-C_5H_4N; X, XX, XXV R = γ-C_5H_4N

The IR spectra of XI-XX (Table 1) show NH absorption bands in the region 3240-3415 cm^{-1}, the characteristic starting imine $\nu_{C=N}$ bands at 1640-1680 cm^{-1} were absent. PMR spectra proved most informative in confirming the structures of these allylamines (Table 2). The allyl proton signals for XI-XX showed a typical shift and multiplicity and were readily assigned. The presence of two multiplets at 4.90-5.32 (2H) and 5.47-6.07 (1H) as well as the triplet signal (2H) at 2.20-2.65 ppm in all of the synthesized compounds were diagnostic of the $-CH_2-CH=CH_2$ fragment.

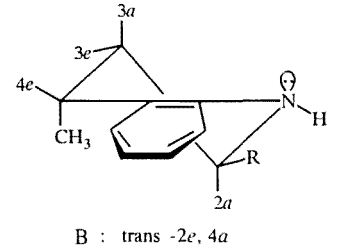
Brief heating with conc. H_2SO_4 causes intramolecular electrophilic cyclization of allylamines XI-XX (Tables 1, 3).

According to PMR spectral data, the compounds obtained were formed as a mixture of two geometric isomers whose ratio was 1:1 for the tetrahydroquinoline XXI and 4:1 for XXII-XXV.

The configuration and conformation of these isomers were determined by a detailed analysis of their high resolution PMR spectra (Table 4). Nuclear Overhauser (NOE) difference (NOEDIFF) spectroscopy [8] was used to determine the mutual configuration of protons 2a-H and 3a-H in the predominant isomers and thus the substituents at positions 2 and 4. Saturation of the 2a-H signal caused no NOE in 3a-H. The value of the NOE for 2a-H and 4a-H was around 10%. This unambiguously points to a trans disposition of protons 2a-H and 3a-H and cis for 2a-H and 4a-H. It thus supports the existence of the predominant isomer of XXII-XXVa as a half chair conformer with a cis relationship for the substituents at positions 2 and 4. A more detailed rationale for the structure of one of the tetrahydroquinolines (XXIII) has previously been reported by us [9]. The vicinal spin–spin coupling $^3J_{3a4a}$ (Table 4) confirms the pseudo equatorial orientation of the 4-methyl group. According to the values of $^3J_{2a3a}$ and $^3J_{3e4e}$ (Table 4), the minor isomer B of XXII-XXV also exists in the half chair conformation but with trans oriented substituents. The minor isomer B has an equatorial substitutent at positions 2 and an axial methyl at 4.



A: cis-2*e*, 4*e*



B : trans-2*e*, 4*a*

TABLE 4. ^1H NMR Spectral Data for 4-Methyl-1,2,3,4-tetrahydro-2-phenyl(pyridyl)quinolines XXII-XXV (400 MHz, $CDCl_3$, TMS)

Compound	Chemical shift, δ, ppm										
	Isomer	2-H	3a-H	3e-H	4-H	4-CH_3	5-H	6-H	7-H	8-H	NH	2-R
XXII	cis	4,49	1,78	2,12	3,15	1,37	7,20	6,72	7,03	6,54	3,98	7,44 (*o*); 7,38 (*m*); 7,32 (*p*)
	trans	4,49	2,06	1,86	2,94	1,38	7,10	6,70	7,04	6,57	4,06	7,43 (*o*); 7,37 (*m*); 7,32 (*p*)
XXIII	cis	4,63	1,70	2,31	3,17	1,36	7,18	6,72	7,03	6,62	*	7,20...8,57
	trans	4,62	2,06	2,02	2,90	1,37	7,08	6,69	7,04	6,64	*	7,20...8,74
XXIV	cis	4,51	1,78	2,11	3,16	1,37	7,20	6,75	7,03	6,56	3,98	7,30...8,64
	trans	4,52	2,05	1,86	2,94	1,37	7,10	6,70	7,04	6,58	4,12	7,28...8,64
XXV	cis	4,46	1,70	2,11	3,13	1,34	7,18	6,74	7,03	6,57	4,03	7,35...8,57
	trans	4,48	1,99	1,86	2,85	1,34	7,08	6,71	7,04	6,59	4,18	7,32...8,55

Spin–spin coupling constants, J, Hz 1)

Compound	Isomer	2, 3a	2, 3e	3a, 3e	3a, 4	3e, 4	4,4-CH_3	4, 5	4, 7	5, 6	5, 7	6, 7	6, 8	7, 8
XXII	cis	11,4	2,9	-12,8	11,8	5,3	6,9	1,3	0,8	7,6	1,5	7,2	1,2	7,9
	trans	10,1	3,0	-12,8	5,3	4,0	7,2	*	*	7,5	1,5	7,2	1,5	7,9
XXIII	cis	11,3	2,9	-12,7	11,8	5,2	6,8	1,2	0,8	7,3	1,6	7,2	1,2	7,9
	trans	9,1	4,5	-12,9	5,3	4,2	7,2	*	*	7,3	1,6	7,3	1,1	7,9
XXIV	cis	11,5	2,8	-12,9	11,8	5,4	6,8	1,2	0,8	7,7	1,6	7,2	1,3	7,9
	trans	10,1	3,4	-13,1	5,3	3,6	7,1	0,7	*	7,7	1,6	7,3	1,2	7,9
XXV	cis	11,3	2,9	-12,9	11,8	5,3	6,8	1,2	0,8	7,8	1,6	7,3	1,2	7,9
	trans	9,1	3,6	-13,0	5,1	4,7	7,1	*	*	7,6	1,6	7,3	1,2	7,9

The cis-trans ratio of isomers A and B for the tetrahydroquinolines XXII-XXV is 4:1, i.e. the intramolecular cyclization of the corresponding N-aryl-N-alkenylamines occurs with a high degree of stereoselectivity.

Under similar conditions we were not able to cyclize the 4-amino-1-butenes XIII-XVII due to strong tarring of the reaction mass. Under milder conditions (addition of conc. H_2SO_4 to a chloroform solution of allylamines XIII, XIV at 0°C) it was possible to separate the corresponding heterocyles XXVI, XXVII in low yields (2-5%). Along with singlet signals for the CH_3O groups at 3.80 and 3.87 ppm in the PMR spectrum of XXVI there is present a doublet at 1.40 ppm for the 4-CH_3 group protons, characteristic for XXI-XXV described above.

EXPERIMENTAL

PMR spectra for the synthesized compounds were recorded on Bruker WP-80 and WM-400 spectrometers using $CDCl_3$ solvent. IR spectra were taken on a Specord IR-75 instrument as thin layers between KBr plates. Alufol plates were used for TLC.

Elemental analytical data for C, H, and N agreed with that calculated.

N-Aryl-N-alkenylamines XI-XX. The corresponding imine I-X (0.03 mole) in absolute ether or THF (50 ml) was added in stages to a solution of allylmagnesium bromide which had been prepared from magnesium (0.15 mole) and allyl bromide (0.05 mole) in absolute ether (150 ml). The product has heated for 2-4 h and decomposed using a saturated solution of ammonium chloride. The ether layer was separated and the aqueous layer extracted with ether (3 × 50 ml), and dried with $MgSO_4$. The ether was evaporated and the product distilled *in vacuo*. The parameters for XI-XX are given in Tables 1 and 2.

4-Methyl-1,2,3,4-tetrahydroquinolines XXI-XXVII. A mixture of the corresponding phenylamino compound XI-XVI, XVIII-XX (0.005 mole) and H_2SO_4 monohydrate (5 ml) was heated at 60°C for 2-4 h. The product was poured onto ice and basified with aqueous ammonia solution (25%) to pH 8-9. After extraction with ether (3 × 30 ml) and evaporation of solvent, the residue was purified on an Al_2O_3 column (h = 10 cm, d = 2 cm, eluent ethyl acetate–pentane, 1:1). The parameters for XXI-XXVII are given in Tables 1, 3, and 4.

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