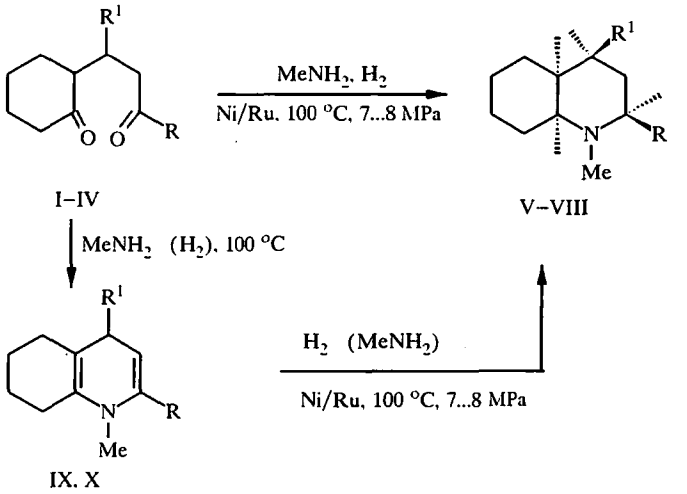
Chemistry of Heterocyclic Compounds, Vol.35, No. 7, 1999

SATURATED NITROGEN-CONTAINING HETEROCYCLES. 18.* CATALYTIC SYNTHESIS AND FORMATION MECHANISM OF SUBSTITUTED *cis*-DECAHYDRO-QUINOLINES AND THEIR ISOLOGUES

T. G. Nikolaeva, N. V. Petrova, and A. P. Kriven'ko

Hydromethylamination of 1,3-diaryl-3-(2-oxocyclohexyl)propan-1-ones produces N-methyl-2,4-diaryldecahydroquinolines with cis-fused hetero- and carbocycles that are stabilized in the A conformation. The reaction involves $\Delta^{2,3,9,10}$-hexahydroquinoline intermediates and their subsequent reduction.

A large group of alkaloids that selectively affect various functions of nerve-cell membranes is derived from *cis*-decahydroquinoline [2]. We studied the catalytic hydroamination of available δ-diketones derived from *n*-propylcyclohexane in order to develop a stereospecific synthesis of substituted decahydroquinolines that are structurally similar to the natural alkaloids. However, as we reported previously, the desired results are not obtained if ammonia and ethanolamine are used as the aminating agents. The reaction products are tetrahydroquinolines for hydroamination [3] and oxazolohydroquinolines for hydroethanolamination [4].



I, V, IX R = R^1 = Ph; II, VI R = Ph, R^1 = C_6H_4-OMe-*p*; III, VII R = C_6H_4-OMe-*p*, R^1 = Ph; IV, VIII, X R = Ph, R^1 = C_6H_4-Cl-*p*

* For No. 17, see [1].

N. G. Chernyshevskii Saratov State University, Saratov 410026, Russia; e-mail: sorokin.ch.sgu@oda.ssu.runnet.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 929-933, July, 1999. Original article submitted May 12, 1998.

0009-3122/99/3507-0813$22.00©1999 KluwerAcademic/Plenum Publishers

TABLE 1. Characteristics and IR Spectra of Compounds IV-X

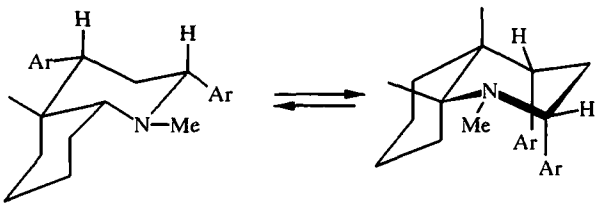
Compound	Empirical formula	Found, % / Calculated, %				mp, °C	IR Spectrum, ν, cm^{-1}	Yield, %
		C	H	N	Cl			
IV	$C_{21}H_{21}ClO_2$	71.69 / 71.89	6.17 / 6.00	—	10.29 / 10.13	117-118	1680 (C=O conj.), 1720 (C=O unconj.), 3020-3080 (Ph)	75
V*	$C_{22}H_{27}N$	86.47 / 86.56	8.87 / 8.85	4.69 / 4.59	—	120-121	2785 (N–CH_3), 3020-3060 (Ph)	78
VI	$C_{23}H_{29}NO$	81.55 / 81.39	8.67 / 8.65	4.58 / 4.48	—	108-109	2770 (N–CH_3), 2840 (OCH_3), 3015-3080 (Ph)	60
VII	$C_{23}H_{29}NO$	81.61 / 81.39	8.40 / 8.65	4.48 / 4.18	—	87-89	2775 (N–CH_3), 2830 (OCH_3), 3010-3075 (Ph)	74
VIII	$C_{22}H_{26}ClN$	77.48 / 77.76	7.71 / 7.65	4.26 / 4.12	10.20 / 10.40	109-110	2785 (N–CH_3), 2850 (OCH_3), 3020-3080 (Ph)	75
IX	$C_{22}H_{23}N$	87.69 / 87.71	8.09 / 7.64	4.92 / 4.65	—	77-78	1620, 1680 (C=C), 2780 (N–CH_3), 3030-3080 (Ph)	62
X	$C_{22}H_{22}ClN$	78.63 / 78.69	6.64 / 6.56	4.42 / 4.17	10.70 / 10.58	82-84	1630, 1680 (C=C), 2780 (N–CH_3), 3010-3080 (Ph)	53

* Yield 48% [4].

In continuation of these studies, we performed catalytic hydromethylamination of 1,3-diaryl-3-(2-oxocyclohexyl)propan-1-ones I-IV, of which the 1,5-diketone IV is first reported. The reaction was carried out in alcoholic medium containing a five-fold molar excess of methylamine at 100°C at 7-8 MPa of H_2 pressure in the presence of Raney Ni modified with Ru. The N-methyl-2,4-diaryldecahydroquinolines V-VIII, including some containing electron-donating or electron-withdrawing substituents in the aryl rings, were obtained in high yields.

The characteristics and IR spectra of decahydroquinolines V-VIII are listed in Table 1.

The PMR spectra (Table 2) of V-VIII contain signals of the substituent protons: at 1.95-1.97 ppm (singlet) for N-methyl, at 6.81-7.37 ppm (multiplet) for aryls, and at 3.76-3.80 ppm (singlet) for methoxy. The signals of the protons at $C_{(2)}$ and $C_{(9)}$ overlap and appear as a weakly resolved multiplet at 2.74-3.16 ppm. The ^{13}C NMR spectra of V-VII (Table 3) contain nine resonances for the decahydroquinoline framework. One feature of *cis*-fused carbo- and heterocycles in decahydroquinolines is the presence of a strong-field signal at 20 ppm and less [6]. This arises from a γ-*gauche*-interaction of the substituents. The spectra of V-VII contain the resonance of the carbon atom $C_{(7)}$ namely in this region (20.16-20.19 ppm). The weak-field position of the signals of the N-methyl groups at the atoms $C_{(2)}$ and $C_{(4)}$ is consistent with the substituents occupying equatorial positions. A characteristic of the *cis*-decahydroquinolines is the conformational flexibility and the capability to exist in two conformers A and B that differ in the position of the axial C–C bond relative to the nitrogen atom:



A B

The resonance of the atom $C_{(8)}$ at 30.80-30.87 ppm indicates that the isolated *cis*-decahydroquinolines are stabilized in the A conformation (in conformation B this signal occurs at 15.65 ppm) [5, 6].

The results demonstrate that the studied reaction gives stereospecifically the *cis*-isomers of 1,2,4-substituted decahydroquinolines.

We carried out the stepwise hydromethylamination of diketones I-IV in order to elucidate the formation mechanism of the decahydroquinolines. The methylamination was performed with strict control of the hydroamination conditions but without catalyst. The N-methyl-2,4-diaryl-$\Delta^{2,3,9,10}$-hexahydroquinolines IX and X were isolated in 55-58% yields (Table 1).

The PMR spectra of IX and X (Table 2) contain signals of the substituents and two well resolved one-proton doublets at 4.81 and 4.88 ppm (J^3_{34} = 5.36-5.37 Hz) and at 3.95-3.99 and 3.89-3.90 ppm (J^4_{34} = 4.72-4.80 Hz) for the protons at $C_{(3)}$ and $C_{(4)}$. This is consistent with the 1,4-dihydropyridine structure. The presence of two weak-field signals at 138.60 ($C_{(2)}$) and 134.23 ppm ($C_{(9)}$) in the ^{13}C NMR spectrum of IX (Table 3) is further evidence of this.

TABLE 2. PMR Spectra of Decahydro- and Hexahydroquinolines V-X ($CDCl_3$, δ, ppm)

Compound	$C_{(3)}$–H (d)	$C_{(4)}$–H (d)	$C_{(2)}$–H, $C_{(9)}$–H (m)	N–CH_3 (s)	OCH_3 (s)	Ar (m)
V	—	—	2.77-3.16	1.97	—	7.19-7.31
VI	—	—	2.74-3.16	1.96	3.76	6.73-7.40
VII	—	—	2.80-3.15	1.95	3.80	6.81-7.37
VIII	—	—	2.78-3.16	1.96	—	6.89-7.32
IX	4.81-4.88	3.90-3.98	—	2.76	—	7.21-7.29
X	4.81-4.88	3.89-3.95	—	2.73	—	6.30-7.26

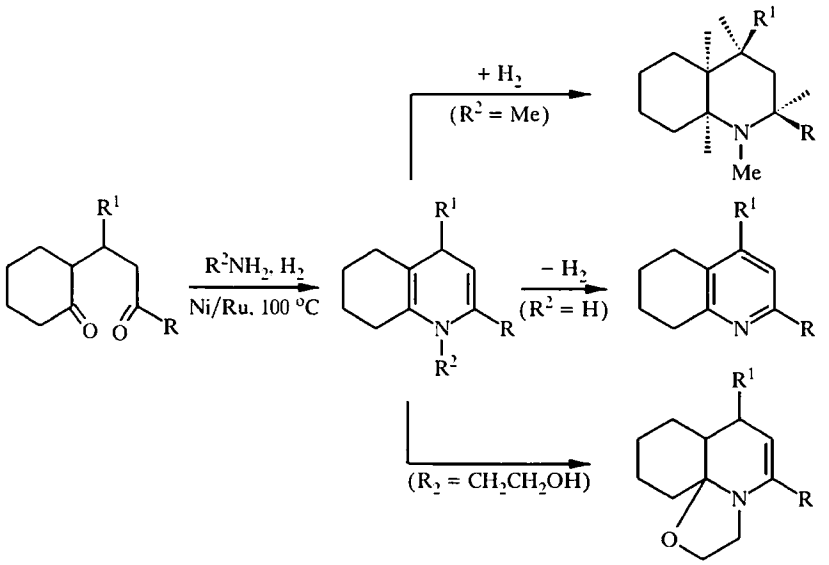
TABLE 3. ^{13}C NMR Spectra of N-Methyl-2,4-diaryldecahydro- and -$\Delta^{2,3,9,10}$-hexahydroquinolines V-VII and IX ($CDCl_3$, δ, ppm)

Compound	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	$C_{(9)}$	$C_{(10)}$	N–CH_3
V*	71.15	35.82	45.76	21.05	26.82	20.18	30.84	64.53	44.50	39.50
VI	71.10	36.08	44.91	20.99	26.82	20.19	30.80	64.42	44.31	39.60
VII	70.32	35.79	45.70	21.03	26.80	20.16	30.87	64.56	44.26	39.43
IX	138.60	106.23	46.37	21.66	23.23	26.50	28.06	134.23	112.23	35.93

* Described previously [5].

Hydrogenation of IX and X (alcoholic solution of methylamine, 100°C, 7-8 MPa, Ni/Ru) produces N-methyl-2,4-diaryl-*cis*-decahydroquinolines V and VIII (48-53% yields) that are identical to those obtained via direct hydromethylamination of diketones I and IV.

Previous [3, 4] and new results summed up suggest that the hydroamination of δ-diketones I-IV involves intermediates like IX and X with the 1,4-dihydropyridine moiety. Depending on the aminating agent, the intermediates are then transformed into *cis*-decahydroquinolines *via* *cis*-addition of H_2 (under hydromethylamination conditions), dehydrogenated into 5,6,7,8-tetrahydroquinolines (on hydroamination [3]), or affected by "double" N,O-cyclization (on hydroethanolamination [4]):



Thus, the study of catalytic hydromethylamination of 1,3-diaryl-3-(2-oxocyclohexyl)propan-1-ones led to the development of a method for preparation of N-methyl-2,4-diaryl-*cis*-decahydroquinolones.

EXPERIMENTAL

IR spectra were recorded on a Specord M-80 instrument as vaseline oil mulls. NMR (^1H and ^{13}C) spectra were taken on Varian FT-80A and Bruker AC-200 instruments in $CDCl_3$ with TMS internal standard.

Starting 1,5-diketones I-IV were prepared according to the method [7]. 3-(4-Chlorophenyl)-3-(2-oxocyclohexyl)-1-phenylpropan-1-one (IV) was synthesized for the first time. Its characteristics are given in Table 1.

Hydromethylamination of Diketones I-IV (General Method). An autoclave (250 ml) is charged with diketone (0.03 mol), alcohol (70 ml) saturated with methylamine (0.15 mol), and Raney Ni (~1 g) modified with Ru.

The reaction is carried out at 100°C and 7-8 MPa of H_2 pressure for 10-12 h. The mixture is evaporated to 2/3 the volume and cooled. The crystalline precipitate of compounds V-VIII is filtered off and recrystallized from ethanol–isopropanol (1:1).

Methylamination of Diketones I and IV was performed by the above method but without the catalyst. Hexahydroquinoline IX is recrystallized from ethanol; the compound X, from isopropanol.

N-Methyl-2,4-diphenyl-*cis*-decahydroquinoline (V). An autoclave (150 ml) is charged with hexahydroquinoline IX (3.01 g, 0.01 mol), alcohol (50 ml) containing methylamine (1.24 g, 0.04 mol), and Ni/Ru catalyst (~0.5 g). The reaction is carried out at 100°C and 7.5 MPa of H_2 pressure for 5 h. Decahydroquinoline V (1.62 g, 53%) is isolated by the above method.

Decahydroquinoline VIII is prepared analogously from X in 48% yield. The melting points of the compounds V and VIII prepared by direct hydromethylamination of I and IV and by catalytic reduction of the hexahydroquinolines IX and X are identical. The melting points of mixed samples are not depressed.

REFERENCES

1. T. G. Nikolaeva, I. C. Poddubnyi, and A. P. Kriven'ko, *Khim. Geterotsikl. Soedin.*, No. 7, 945 (1995).
2. G. V. Grishina and V. M. Potapov, *Khim. Geterotsikl. Soedin.*, No. 5, 579 (1987).
3. V. G. Kharchenko, A. P. Kriven'ko, O. V. Fedotova, and T. G. Nikolaeva, *Khim. Geterotsikl. Soedin.*, No. 7, 944 (1982).
4. T. G. Nikolaeva, P. V. Reshetov, A. P. Kriven'ko, and V. G. Kharchenko, *Khim. Geterotsikl. Soedin.*, No. 10, 1370 (1983).
5. P. V. Reshetov, O. V. Fedotova, A. P. Kriven'ko, and V. G. Kharchenko, *Khim. Geterotsikl. Soedin.*, No. 5, 608 (1990).
6. F. W. Vierhapper and E. L. Eliel, *J. Org. Chem.*, **42**, 51 (1977).
7. C. F. Allen and H. R. Sallans, *Can. J. Res.*, **9**, 574 (1933).