Preparative electroreduction of *trans*-2-allyl-6-methyl(phenyl)-1,2,3,6-tetrahydropyridine

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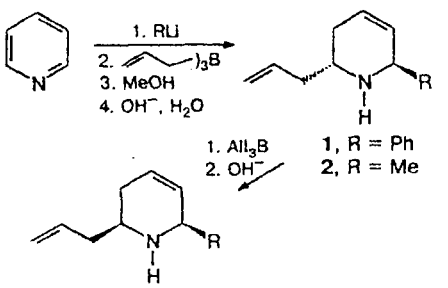
Electrocatalytic hydrogenation of *trans*-2-allyl-6-phenyl-1,2,3,6-tetrahydropyridine and *trans*-2-allyl-6-methyl-1,2,3,6-tetrahydropyridine in 40% aqueous DMF in the presence of AcOH on a nickel cathode gave *trans*-6-phenyl-2-propylpiperidine and *trans*-2-methyl-6-propylpiperidine ((±)-epidihydropinidine), respectively. Direct electroreduction of *trans*-2-allyl-6-phenyl-1,2,3,6-tetrahydropyridine in anhydrous DMF on a mercury cathode afforded a 7 : 5 mixture of *trans*- and *cis*-2-allyl-6-phenylpiperidine. The structure of the latter compound was confirmed by 2D NOESY spectroscopy. The possible mechanism of formation of the *cis*-isomer is discussed.

Key words: *trans*-2-allyl-6-methyl(phenyl)-1,2,3,6-tetrahydropyridine, (±)-epidihydropinidine, piperidines, electrocatalytic hydrogenation, electroreduction.

The pyridine ring is the major structural fragment of a large series of natural alkaloids.[1,2] Thus many species of conifers (pines and spruces) and some insects produce unsymmetrically 2,6-disubstituted piperidines, *cis*-isomers being formed more often than their *trans*-analogs. These alkaloids exhibit high teratogenic and embryotoxic activities.[1] Apparently, their biological function consists in protection against parasites and pests (species antagonists).

The key stage of one of the most convenient and promising procedures for the synthesis of these alkaloids and their analogs involves reductive *trans*-2,6-dialkylation of pyridine.[3,4] This multistage one-pot procedure is based on a combination of 1,2-addition of RLi to pyridine and *trans*-allylation with triallylborane (Scheme 1). The yields of *trans*-6-alkyl(aryl)-2-allyl-1,2,3,6-tetrahydropyridines exceed 90%.

Scheme 1



Previously,[4,5] it has been established that *trans*-amines were transformed into thermodynamically more stable *cis* isomers upon heating with triallylborane (160—190 °C) followed by alkaline deboronation of the aminoborane initially formed.

Hydrogenation of *trans*- (**2**) and *cis*-2-allyl-6-methyl-1,2,3,6-tetrahydropyridine over Raney nickel in AcOH (100 °C, 100 atm. H_2, 9 h) afforded the alkaloids (±)-epidihydropinidine (*trans*-2-methyl-6-propylpiperidine)[3,4] and (±)-dihydropinidine (*cis*-2-methyl-6-propylpiperidine),[4,5] respectively. In this work, *trans*-6-phenyl-2-propylpiperidine (**3**) was prepared from *trans*-2-allyl-6-phenyl-1,2,3,6-tetrahydropyridine (**1**) under analogous conditions in 70% yield. Thus, both double bonds in 2-allyl-6-R-1,2,3,6-tetrahydropyridines were hydrogenated over Raney nickel at 100 °C and at H_2 pressure of 100 atm.[4]

However, it should be emphasized that piperidines **1** and **2** contain two double bonds of different nature, namely, the terminal and endocyclic bonds. Their selective functionalization is important for further development of the chemistry of this class of compounds. Selective hydrogenation of the endocyclic double bond with retention of the terminal double bond is of particular interest. Apparently, this problem cannot be solved by chemical (using diimine NH=NH)[6] or homogeneous catalytic (for example, using $RuCl_2 \cdot (PPh_3)_3$) [7] hydrogenation, because under these conditions the rate of hydrogenation of terminal olefins substantially exceeds that of cyclohexene. Ionic hydrogenation[8] of compounds

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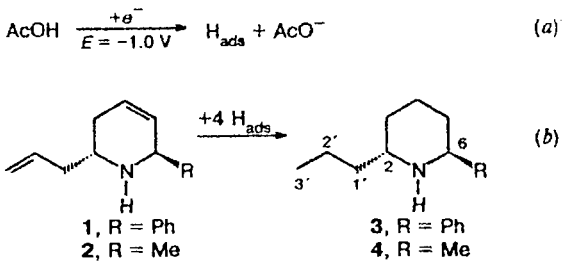
1 and 2 also cannot be used for structural reasons (there are no substituents at the endocyclic double bond).

However, a few examples of successful use of an electrochemical method for reduction of isolated double bonds on low-hydrogen-overpotential cathodes are documented.[9] These double bonds are generally not reduced on high-hydrogen-overpotential cathodes. The electrochemical behavior of allyltetrahydropyridines has not been studied previously.

It was of interest to examine the possibility of selective hydrogenation of one of the double bonds in allyltetrahydropyridines by the electrochemical method. In this work, we made use of a procedure developed previously for pretreatment of a nickel electrode[10] and conditions (the composition of the medium)[11] that appeared to be optimum for electrocatalytic hydrogenation of citral to citronellol.

Electrochemical hydrogenation of piperidines 1 and 2 was carried out on a nickel electrode, whose surface was covered with dispersed nickel, in an aqueous-organic solvent (40% DMF) in the presence of AcOH at $E = -1.0$ V. Electrolysis resulted in *trans*-6-phenyl-2-propylpiperidine (3) and *trans*-6-methyl-2-propylpiperidine (4) (alkaloid (±)-epidihydropinidine), respectively, in 90—95% yields (according to GLC). The ^{1}H and ^{13}C NMR spectra of the compounds obtained are identical with those of compounds 3 and 4 synthesized by catalytic hydrogenation over Raney nickel. Hence, the process proceeded with retention of the *trans*-configuration of the substituents with respect to the piperidine ring (Scheme 2).

Scheme 2

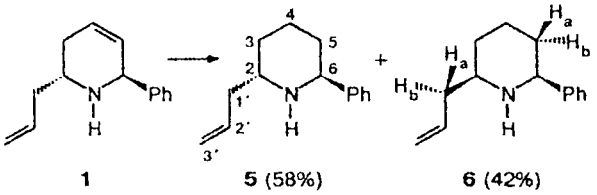


Apparently, in this case only the first stage (*a*), namely, generation of hydrogen on an activated nickel electrode from the acidic component of the solution at $E = -1.0$ V, was an electrochemical process, while hydrogenation occurred in the second stage (*b*) as a result of addition of atomic hydrogen that was adsorbed on a nickel surface to the double bonds of amines 1 or 2. Thus, the mechanism of electrocatalytic hydrogenation was realized.

It should be noted that electrocatalytic hydrogenation proceeded at room temperature and atmospheric pressure, *i.e.*, under milder conditions than those of the heterogeneous catalytic process. Preliminary activation of the cathode by electroprecipitation of nickel is a substantially simpler procedure than that used for the preparation of Raney nickel. It is also essential that the electrocatalytic method can be used for hydrogenation of small amounts of a compound, this being of importance in laboratory studies.

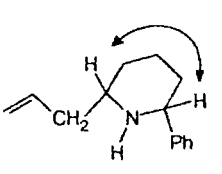
Electroreduction of *trans*-2-allyl-6-phenyl-1,2,3,6-tetrahydropyridine (1) in anhydrous DMF on a high-hydrogen-overpotential cathode (Hg) (a 0.1 *M* Bu_4NClO_4 solution as the background) gave different results. At a potential close to the background discharge ($E = -2.8$ V), the double bond of the heterocycle was reduced with retention of the allyl fragment (Scheme 3). The product obtained was a 7 : 5 mixture of *trans*- (5) and *cis*-2-allyl-6-phenylpiperidine (6) (according to the data of ^{13}C NMR spectroscopy and GLC analysis). Their total yield was ~90% (according to the data of GLC analysis).

Scheme 3



cis-Isomer 6 was isolated in pure form by chromatography on a column with Al_2O_3. Its structure was confirmed by physicochemical methods (^{1}H and ^{13}C spectroscopy and mass spectrometry). The assignment of the signals in the ^{1}H NMR spectra was made based on the ^{1}H—^{1}H COSY spectral data. The *cis*-configuration of amine 6 was confirmed by two-dimensional phase-sensitive 2D NOESY spectroscopy. The presence of H-2→H-6 nuclear Overhauser effects unambiguously indicates that the substituents are in the *cis*-orientations with respect to the heterocyclic ring of amine 6.

We failed to isolate *trans*-amine 5 in pure form. However, the results of studies of its mixture with *cis*-amine 6 by ^{13}C NMR spectroscopy, GLC, and TLC confirm the structure of compound 5. Thus the ^{13}C NMR spectra of the mixture have two sets of peaks, one of which corresponds to the signals of *cis*-isomer 6. The second set contains characteristic signals of the C atoms of the allyl group (CH_2=CH) at δ 117 and 136 and does not contain signals in the region of 126—127.5 ppm (C-4=C-5 in the ring). The signals from the C-2 (δ 51.33)



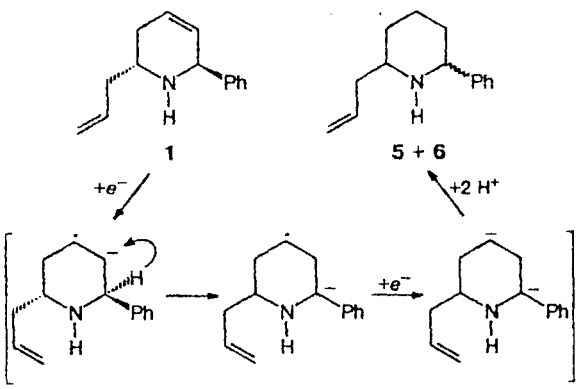
6

and C-6 (δ 54.0) atoms, whose upfield shifts relative to the corresponding signals of *cis*-isomer **6** are 5—8 ppm (for *cis*-amine **6**: at δ 56.67 and 62.32 for C-2 and C-6, respectively), are indicative of the presence of *trans*-amine **5** in the mixture.

It should also be noted that the chromatographic characteristics of *cis*- and *trans*-piperidines (**6** and **5**), like those of the corresponding *cis*- and *trans*-2-allyl-6-phenyl-1,2,3,6-tetrahydropyridines, differ substantially. Thus when the GLC analysis was carried out in the isothermal mode, the retention time of the *cis*-isomer is ~3 min shorter than that of the *trans*-isomer. Under the same conditions, the difference in the retention time of the initial piperidine **1** and the *trans*-isomer **5** is only ~0.5 min. The R_f values of the *cis*- and *trans*-isomers of piperidines **6** and **5** (TLC on Alufol, 1 : 1 hexane—ether) are 0.46 and 0.19, respectively. This allowed us to detect the *cis*-isomer in the mixture, to estimate the ratio between **5** and **6**, and to separate the *cis*-isomer of **6** on a column with Al_2O_3.

The electrochemical process on a mercury cathode occurred as direct electroreduction of the double bond of the heterocycle. The quantity of electricity passed was 2 F mol^{-1}. The formation of the *cis*-isomer of **6** in the course of reduction unambiguously indicates that the carbon atom adjacent to the reaction center, *viz.*, the C-6 atom containing the phenyl substituent, is involved in the reaction (Scheme 4).

Scheme 4



After the transfer of the first electron to the substrate molecule, the radical anion is formed in an aprotic medium. This radical anion is stabilized through the transfer of the H-6 atom to position 5 of the heterocycle. The coplanarity of the intermediate structure formed is a prerequisite for such stabilization. The rapid transfer of the second electron excludes radical processes (dimerization or resinification) and subsequent protonation of the dianion affords a mixture of the *trans*- and *cis*-isomers of piperidines **5** and **6**. In this case, the mechanism of isomerization differs fundamentally from that of isomerization of *trans*-allylpiperideines into the corresponding *cis*-derivatives upon heating with triallylborane.[4,5]

Therefore, using *trans*-allyl-6-phenyl-1,2,3,6-tetrahydropyridine as an example, it was demonstrated that the endocyclic double bond of the ring can, in principle, be reduced with retention of the allyl fragment by the electrochemical method on a high-hydrogen-overpotential cathode. However, this process was accompanied by isomerization. On the contrary, electrocatalytic hydrogenation of allyltetrahydropyridines on a Ni_{disp}/Ni cathode (40% aqueous DMF, an excess of AcOH) gave the same results as the catalytic hydrogenation on Raney nickel, which is commonly used for reduction of isolated double bonds, and can successfully compete with the latter method.

Experimental

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200P spectrometer in $CDCl_3$. The ^{1}H—^{1}H COSY and 2D NOESY spectra were measured on a Bruker AMX-400 instrument with $SiMe_4$ as the internal standard. The IR spectra were obtained on a UR-20 spectrophotometer. The mass spectra (EI, 70 eV) were measured on a Kratos MS-30 spectrometer. The GLC analysis was carried out on an LKhM-80 instrument (a 3 m × 3-mm column with 5% XE-60, Chromaton N-AW-DMCS as the stationary phase).

Preparative electrolysis at a controlled potential was performed with the use of a P-5848 potentiostat in a porous glass diaphragm cell (V = 50 mL) under argon. Cylindrical Ni-plate (S_{work} ≈ 0.9 dm^2) and mercury pool (S_{work} ≈ 0.45 dm^2) electrodes were used as the cathode. A Pt-gauze electrode was used as the anode. A saturated calomel electrode was used as the reference electrode. Before distillation, DMF was kept over K_2CO_3 and dried over 4 Å molecular sieves. After distillation, the DMF contained 0.2—0.3% of H_2O determined by Fischer's method.

The initial compounds **1** and **2** were prepared according to a procedure reported previously.[4]

***trans*-6-Phenyl-2-propylpiperidine (3).** *trans*-2-Allyl-6-phenyl-1,2,3,6-tetrahydropyridine **1** (0.86 g, 4.3 mmol) was hydrogenated in glacial AcOH (4 mL) in the presence of Raney nickel (0.02 g) in an autoclave at the H_2 pressure of 100 atm. (9 h, 100 °C). After separation of the catalyst, a 20% NaOH solution was added until the acid was completely neutralized. Then the mixture was extracted with ether. The extract was dried with K_2CO_3. Distillation afforded compound **3** in a yield of 0.61 g (70%), b.p. 100—101 °C (1 Torr), n_D^{19} 1.5239. MS, m/z (I_{rel} (%)): 203 $[M]^+$ (18), 188 $[M - Me]^+$ (2), 174 $[M - Et]^+$ (4), 161 $[M - C_3H_6]^+$ (35), 160 $[M - Pr]^+$ (100), 132 $[M - (Pr + C_2H_4)]^+$ (12), 118 $[M - (C_3H_6 + Pr)]^+$ (17), 117 $[M - 2\,Pr]^+$ (93), 105 $[M - (C_3H_6 + C_4H_8)]^+$ (13), 104 $[M - (Pr + C_4H_8)]^+$ (37), 91 $[C_7H_7]^+$ (30). IR (neat), ν/cm^{-1}: 3280 (br), 3060, 3020, 2920, 2860, 2800, 1600, 1490, 1455, 1440, 1365, 1330, 1305, 1265, 1210, 1175, 1140, 1120, 1085, 1050, 1030, 985, 915, 875, 850, 755, 730, 700, 650. ^{1}H NMR (200 MHz), δ: 0.85—1.05 (t, 3 H, Me); 1.2—1.9 (m, 11 H, CH_2 and NH); 2.95—3.1 (m, 1 H, H-2); 3.87—4.02 (m, 1 H, H-6); 7.1—7.4 (m, 5 H, Ph). ^{13}C NMR, δ: 14.00 (Me); 19.51 and 20.08 (C-4, C-2′); 29.58, 33.39, 34.50 (C-1′, C-3, C-5); 51.61 (C-2); 54.02 (C-6); 126.48 (C_p); 126.53, 128.10 ($C_{o,m}$); 145.09 (C_i).

***trans*-6-Phenyl-2-propylpiperidine hydrochloride (3 · HCl).** Hydrochloride 3 · HCl was prepared from amine **3** (0.18 g, 0.9 mmol) and an ethereal solution of HCl in a yield of 0.19 g (90%), m.p. 197—198 °C (from ether—MeOH). Found (%): C, 69.75; H, 9.20; N, 5.72; Cl, 14.86. $C_{14}H_{22}ClN$. Calculated (%): C, 70.13; H, 9.25; N, 5.84; Cl, 14.78. IR (KBr pellets), ν/cm^{-1}: 3420 (br), 3190, 2930, 2730, 2700, 2540, 2520, 1590, 1500, 1460, 1430, 1420, 1385, 1340, 1325, 1295, 1270, 1240, 1210, 1170, 1155, 1115, 1080, 1050, 1040, 1010, 940, 925, 895, 760, 705, 655, 535. ^{1}H NMR (200 MHz), δ: 0.8—2.5 (m, 13 H, CH_2 and Me); 3.1—3.5 (m, 1 H, H-2); 4.0—4.4 (m, 1 H, H-6); 7.15—7.95 (m, 5 H, Ph); 9.7 (br.s, 2 H, NH). ^{13}C NMR, δ: 13.64 (Me); 18.01 and 19.06 (C-4, C-2′); 24.77, 28.17, 31.10 (C-1′, C-3, C-5); 53.0 (C-2); 54.75 (C-6); 127.77, 128.43, 128.74 ($C_{o,m,p}$); 135.47 (C_i).

Electrocatalytic hydrogenation of *trans*-2-allyl-6-phenyl-1,2,3,6-tetrahydropyridine (1) on a nickel cathode. Before electrolysis, the nickel electrode was activated by electroprecipitation of dispersed nickel on the smoothed surface from an 0.5 *M* $NiCl_2 \cdot 6H_2O$ solution for 1 h at a cathode current density of 0.1 A · dm^{-2}. Then the electrode was washed with water. Electrolysis of an 0.015 *M* solution of piperidine **1** was carried out in the presence of 0.15 *M* AcOH in an 0.1 *M* KCl solution (40% aqueous DMF) (the volume of the catholyte was 50 mL) for 4 h at $E = -1.0$ V. After completion of electrolysis, the solution was alkalized to pH 12 and extracted with ether. The extract was washed with water and dried with K_2CO_3. Amine **3** was obtained in 90—95% yield (GLC). The ^{1}H and ^{13}C NMR spectra of the resulting product coincide with those of compound **3** described above.

Electrocatalytic hydrogenation of *trans*-2-allyl-6-methyl-1,2,3,6-tetrahydropyridine (2) on a nickel cathode. The process was carried out analogously to that described above for *trans*-2-allyl-6-phenyl-1,2,3,6-tetrahydropyridine (**1**). The product was obtained in 90—95% yield (GLC). The ^{1}H and ^{13}C NMR spectra of the product obtained are analogous to those of *trans*-2-methyl-6-propylpiperidine **4** described previously.[3,4]

Electroreduction of *trans*-2-allyl-6-phenyl-1,2,3,6-tetrahydropyridine (1) on a mercury cathode. Electrolysis of an 0.015 *M* solution of piperidine **1** was performed in an 0.1 *M* solution of Bu_4NClO_4 in anhydrous DMF (the volume of the catholyte was 50 mL) for 2 h at $E = -2.8$ V ($Q = 2$ *F* · mol^{-1}). After completion of electroreduction, water (40 mL) was added to the electrolysis solution. The mixture was extracted with ether. The extract was washed with water and dried with K_2CO_3. Volatile components were distilled off *in vacuo*. The mixture of compounds obtained (~0.15 g) contained *trans*-2-allyl-6-phenylpiperidine **5** (58%) and *cis*-2-allyl-6-phenylpiperidine **6** (42%) (according to GLC and ^{13}C NMR spectroscopic data). Amine **6** was isolated on a column with Al_2O_3 (5 : 1 hexane—ether as the eluent). R_f 0.46 (*cis*-isomer), R_f 0.19 (*trans*-isomer, Alufol, ether—hexane, 1 : 1).

***cis*-2-Allyl-6-phenylpiperidine (6).** MS, *m/z* (I_{rel} (%)): 160 $[M - C_3H_5]^+$ (20), 118 $[M - (C_3H_5 + C_3H_6)]^+$ (5), 117 $[M - (C_3H_5 + Pr)]^+$ (17), 104 $[M - (C_3H_5 + C_4H_8)]^+$ (7), 91 $[C_7H_7]^+$ (4), 77 $[C_6H_5]^+$ (9), 69 $[M - (C_3H_5 + C_7H_7)]^+$ (5), 58 $[C_3H_8N]$ (100). ^{1}H NMR (400 MHz), δ: 1.23 (m, 2 H, H-3); 1.5 (m, 2 H, NH, H_b-5); 1.65—2.0 (m, 3 H, H-4, H_a-5); 2.13 (m, 1 H, H_b-1′); 2.26 (m, 1 H, H_a-1′); 2.70 (m, 1 H, H-2); 3.62 (dd, 1 H, H-6, ^2J = 10.2 Hz, ^3J = 2 Hz); 5.1 (m, 2 H, CH_2=); 5.76 (m, 1 H, H-2′); 7.2—7.4 (m, 5 H, Ph). ^{13}C NMR, δ: 25.28 (C-4); 31.99 (C-3); 34.72 (C-5); 41.70 (C-1′); 56.67 (C-2); 62.32 (C-6); 117.22 (CH_2=); 126.64, 126.90, 128.25 ($C_{m,p,o}$); 135.61 (C-2′); 145.50 (C_i).

A mixture of *trans*- (5) and *cis*-2-allyl-6-phenylpiperidine (6). ^{13}C NMR, δ: 19.69 (**5**: C-4); 24.98 (**6**: C-4); 28.45 (**5**: C-3); 31.45 (**6**: C-3); 32.26 (**5**: C-5); 34.13 (**6**: C-5); 36.3 (**5**: C-1′); 41.19 (**6**: C-1′); 51.23 (**5**: C-2); 53.94 (**5**: C-6); 56.78 (**6**: C-2); 62.13 (**6**: C-6); 117.17, 117.32 (CH_2=); 126.21, 126.59, 126.64, 128.13, 128.23 ($C_{o,m,p}$); 135.27, 135.42 (C-2′); 143.54, 144.73 (C_i).

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