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trans-cis-Isomerization of *trans*-2-Allyl-6-alkyl(aryl)-1,2,3,6-tetrahydropyridines on Heating with Triallylborane. Synthesis of (±)-Dihydropinidine.

Yuri N. Bubnov,*[a] Elena V. Klimkina,[a] Anatoly V. Ignatenko,[a] and Ilya D. Gridnev[b]

[a]N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky Prospect 47, Moscow, Russia

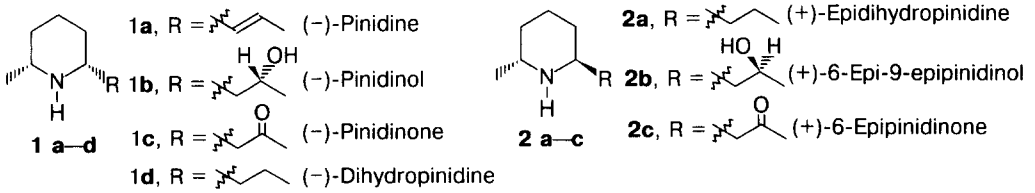
[b]A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, Moscow, Russia

Dedicated to Professor Walter Siebert on the occasion of his 60th birthday

Abstract: *A convenient method for isomerization of trans-2-allyl-6-alkyl(aryl)-1,2,3,6-tetrahydropyridines into the corresponding cis-isomers is presented.* © 1997 Elsevier Science Ltd.

2,6-Disubstituted piperidine alkaloids are abundant in nature and have been isolated from several *Pinus* (pine) and *Picea* (spruce) species, e.g. **1a–c** and **2a–c**. The pines appear to contain only *cis*-disubstituted piperidines, while the spruces contain both *cis*- and *trans*-isomers.[1] (–)-Pinidinone **1c** was also isolated from coccinellid ladybird beetles (*Cryptolaemus montrouzieri*)[2] and Mexican bean beetles (*Epilachna varivestis*).[3] The latter coccinellid contains also dihydropinidine **1d**. Many of the alkaloids (**1**—**2**) were found to be highly teratogenic and embriotoxic.[1]

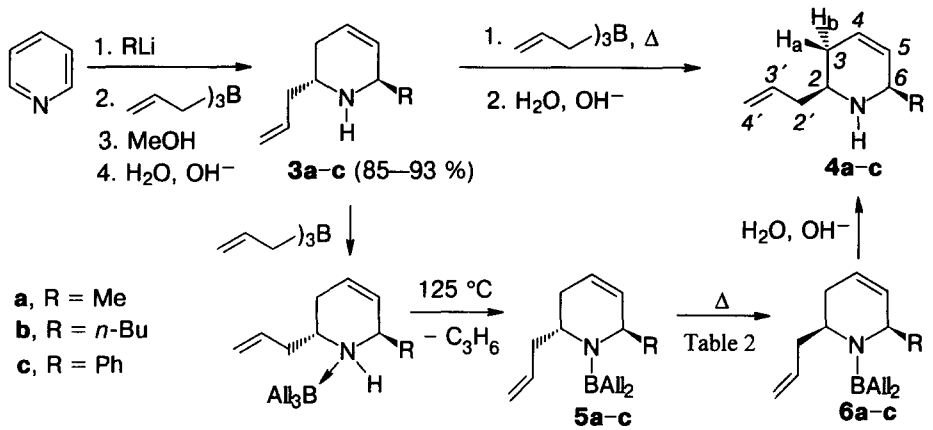
Several syntheses of the alkaloids **1** and **2**[1,3,4] including chiral ones[5] have been described previously.



Recently, we have found a convenient approach to *trans*-2,6-diallyl- **3** (R = Allyl)[6] and *trans*-2-allyl-6-alkyl(aryl)-1,2,3,6-tetrahydropyridines **3a–c**.[7] The synthesis of **3a–c** is based on the combination of the 1,2-addition reaction of RLi to pyridine and *trans*-allylboration of the intermediate imine that is formed on the treatment of the adduct with triallylborane and alcohol.[7] The alkaloid (±)-epidihydropinidine was synthesized by hydrogenation of **3a**.

As it is underlined above, nature (pines, spruces, ants and ladybird beetles) produces more *cis*-2,6-disubstituted piperidine alkaloids than their *trans*-analogues. Therefore, the use of "boron" methodology would be attractive for an output not only to *trans*-, but also to *cis*-isomers.

We have found that *trans*-amines **3a–c** (like **3** (R = Allyl)[6]) are transformed into the corresponding *cis*-isomers **4a–c** on heating with triallylborane at 140—190 °C (Table 1) followed by deboronation with alkali.



The reaction of **3a–c** with triallylborane gives the corresponding N→B complex, the B—C bond in which is cleaved at 120—130 °C leading to the evolution of 1 mole of propene and the formation of the aminoborane **5** (Table 1).

Table 1. Physical Properties and ^{11}B NMR Spectral Data of Compounds **5** and **6**.

R	5				6		
	B.p.°C (Torr)	n_D^{19}	Yield (%)	δ(^{11}B)	n_D^{19}	δ(^{11}B)	Content of **5**[a] (%)
Me	90—92(1)	1.5091	92	44.7	1.4998	43.1	~1
n-Bu	100—102(1)	1.5056	93	49.9	1.4983	48.9	~3
Ph	134—136(1)	1.5295	85	45.4	—	—	~20

[a]Determined by ^{13}C NMR.

Under the following heating (Table 2), *trans*-aminoboranes **5** are isomerized into the corresponding *cis*-isomers **6** (Table 1), deboronation of which by methanol (0—20 °C) and NaOH solution (10 %) leads to **4a–c** with 60—70 % isolated yields. Amines **4a,b** thus obtained contained 1—3 % of *trans*-isomers (Table 1,2), which were separated by distillation or column chromatography on Al_2O_3 (eluent hexane—ether, 10:1).

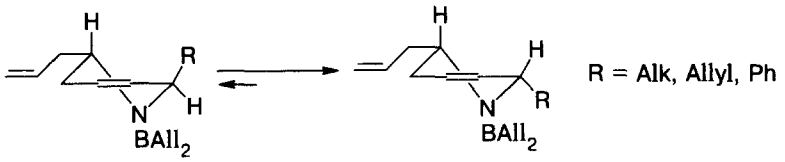
Table 2. Conditions of Isomerization of *trans*-Isomers **5** to *cis*-Products **6** by Heating with Triallylborane.

R	Temp. (°C)	Time of heating, (h)	**5**:**6** Ratio
Me	130—135	1	70:30[a]
	140—145	+3	20:80[a]
	160—165	6.5	1:99[b]
n-Bu	135—140	1	80:20[a]
	160—165	+3	5:95[a]
	200	6	3:97[b]
Ph	135—140	1	100:0[a]
	160—165	3	75:25[a]
	195	+2	20:80[a,b]
	195	12	20:80[a,b]

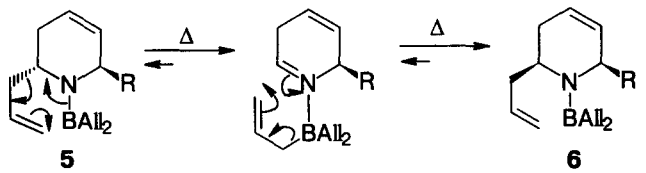
[a]Determined by ^{13}C NMR of the crude mixture of **5** and **6**. [b]Determined by gas chromatography of deboronated product.

In the case of aminoborane **5c**, isomerization was not complete even after prolonged heating at 195 °C (12 hours); the ratio **5c**:**6c** = 20:80 seems to be an equilibrium one. Amine **4c** was isolated in pure state by chromatography on Al_2O_3 (eluent hexane—ether, 20:1).

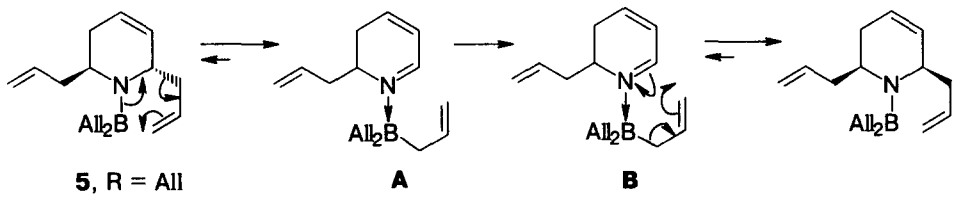
The driving force for isomerization **5**→**6** is the greater thermodynamic stability of *cis*-isomers (two pseudoequatorial groups) compared to the corresponding *trans*-isomers.



The transformation **5**→**6** seems to proceed as a deallylboronation—allylboronation process (elimination—addition of the fragment B—Allyl)



It should be mentioned that isomerization **5**→**6** proceeds under more drastic conditions (135—200 °C, Table 2) than that of 2,6-diallylcompound **5** (R = All) (130—135 °C, 2h).[6b] This discrepancy could be explain as following:



In the case of **5** (R = All), elimination of 6-allylic group (not 2-All) takes place mainly leading to the complex **A** with a system of conjugated double bonds which can not form in the course of isomerization of **5a–c**. Subsequent allylboration of the C=N bond (**B**) leads to *cis*-aminoborane.

The structures of the compounds **4a–c** are corroborated with the data of IR, MS, ^1H and ^{13}C NMR.[8] The assignment of signals in ^1H NMR spectra was confirmed by ^1H—^1H COSY spectra. The *cis*-configuration of amines **4a–c** was established by 2D NOESY experiments.

Hydrogenation of **4a** over Raney Ni in acetic acid (100 atm H_2, 95—100 °C) led (71 %) to the alkaloid (±)-dihydropinidine **1d** ((±)-*cis*-2-methyl-6-propylpiperidine), b.p. 46 °C/6 Torr, n_D^{19} 1.4467; **1d** · HCl, m.p. 210—211 °C (lit. data: 207—210 °C,[4a] 212—213 °C,[4b]); ^1H and ^{13}C NMR spectra of **1d** and **1d** · HCl are in accordance with spectra described previously.[4b,4a]

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8. **4a:** B.p. 46—47/6 Torr, n_D^{19} 1.4755. IR (neat, cm^{-1}) 3280 (br), 3070, 3020, 2960, 2910, 2830, 2790, 1640, 1465, 1430, 1370, 1310, 1125, 995, 920, 790, 725, 685. ^1H NMR (400 MHz, $CDCl_3$): δ 1.08 (d, 3H, CH_3, ^3J = 6.8 Hz), 1.42 (br.s, 1H, NH), 1.80 (dm, 1H, H-3b, ^2J = 17.2 Hz), 1.94 (dm, 1H, H-3a, ^2J = 17.2 Hz), 2.18 (m, 2H, H-2′), 2.79 (m, 1H, H-2), 3.46 (m, 1H, H-6), 5.05 (dd, 1H, H-4′a, ^3J = 11.3 Hz, ^2J = 1.0 Hz), 5.09 (dd, 1H, H-4′b, ^3J = 17.1 Hz, ^2J = 1.0 Hz), 5.50 (dm, 1H, H-5, ^3J = 10.0 Hz), 5.64 (dm, 1H, H-4, ^3J = 10.0 Hz), 5.78 (m, 1H, H-3′). ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.84 (CH_3), 30.76 (C-3), 39.91 (C-2′), 49.14 and 51.16 (C-2 and C-6), 115.92 (C-4′), 123.23 (C-4), 130.76 (C-5), 133.87 (C-3′). EIMS: 96 [M–C_3H_5]$^+$. Anal. calc. for $C_9H_{15}N$: C 78.77, H 11.02, N 10.21. Found: C 78.89, H 11.14, N 9.87.

   4a • HCl: M.p. 199—200 °C (from ether:methanol). ^1H NMR (200 MHz, $CDCl_3$): δ 1.65 (d, 3H, CH_3, J = 6.71 Hz), 2.2—2.85 (m, 3H, H-2′ and H-3a), 2.9—3.4 (m, 2H, H-3b and H-2), 3.85—4.1 (m, 1H, H-6), 5.0—5.35 (m, 2H, H-4′), 5.45—6.05 (m, 3H, —CH=), 9.25—9.8 (br.s, 1H, NH), 9.8—10.4 (br.s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.61 (CH_3), 27.58 (C-3), 37.21 (C-2′), 51.39 and 54.04 (C-2 and C-6), 119.25 (C-4′), 125.30 (C-4), 125.94 (C-5), 131.66 (C-3′).

   4b: B.p. 94—95/6 Torr, n_D^{19} 1.4757. IR (neat, cm^{-1}) 3300 (br), 3070, 3020, 2960, 2930, 2860, 1640, 1455, 1430, 1320, 1125, 995, 920, 825, 730. ^1H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, 3H, CH_3), 1.31 (m, 6H, CH_2 in Bu), 1.60 (br.s, 1H, NH), 1.83 (dm, 1H, H-3b, ^2J = 16.9 Hz), 1.94 (dm, 1H, H-3a, ^2J = 16.9 Hz), 2.17 (m, 2H, H-2′), 2.78 (dddd, 1H, H-2), 3.31 (m, 1H, H-6), 5.08 (m, 2H, H-4′), 5.54 (dm, 1H, H-5, ^3J = 10.0 Hz), 5.67 (dm, 1H, H-4, ^3J = 10.0 Hz), 5.77 (m, 1H, H-3′). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.16 (CH_3), 21.99 (C-1 in Bu), 27.1 (C-2 in Bu), 31.68 (C-3), 35.5 (C-3 in Bu), 40.35 (C-2′), 51.50 and 54.25 (C-2 and C-6), 116.43 (C-4′), 123.96 (C-4), 130.07 (C-5), 134.35 (C-3′). EIMS: 179 [M]$^+$, 138 [M–C_3H_5]$^+$, 122 [M–C_4H_9]$^+$, 80 [M–(C_4H_9 + CH_2=CH—CH_3)]$^+$. Anal. calc. for $C_{12}H_{21}N$: C 80.38, H 11.81, N 7.81. Found: C 80.15, H 11.71, N 7.82.

   4b • HCl: M.p. 193—194 °C (from ethyl acetate:methanol). ^1H NMR (200 MHz, $CDCl_3$): δ 0.7—1.1 (m, 3H, CH_3), 1.1—1.6 (m, 4H, H-1 and H-2 in Bu), 1.6—2.8 (m, 5H, H-3 in Bu, H-2′ and H-3a), 2.85—3.35 (m, 2H, H-2 and H-3b), 3.6—3.9 (m, 1H, H-6), 4.9—5.3 (m, 2H, H-4′), 5.5—6.0 (m, 3H, —CH=), 9.1—9.5 (br.s, 1H, NH), 9.65—10.1 (br.s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.60 (CH_3), 22.05 (C-1 in Bu), 27.13 (C-2 in Bu), 27.58 (C-3), 31.64 (C-3 in Bu), 37.03 (C-2′), 53.88 and 55.17 (C-2 and C-6), 118.86 (C-4′), 123.52 (C-4), 125.35 (C-5), 131.55 (C-3′).

   4c: B.p. 90—92/1 Torr, n_D^{19} 1.5492. IR (neat, cm^{-1}) 3200 (br), 3060, 3030, 2910, 2820, 1640, 1490, 1450, 1290, 995, 920, 855, 760, 705. ^1H NMR (200 MHz, $CDCl_3$): δ 1.6—1.85 (br.s, 1H, NH), 1.85—2.4 (m, 4H, —CH_2—), 2.85—3.1 (m, 1H, H-2), 4.35—4.6 (m, 1H, H-6), 4.9—5.25 (m, 2H, H-4′), 5.55—5.95 (m, 3H, —CH=), 7.1—7.5 (m, 5H, Ph). ^{13}C NMR (50 MHz, $CDCl_3$): δ 32.00 (C-3), 40.94 (C-2′), 52.63 (C-2), 60.21 (C-6), 117.40 (C-4′), 125.45 (C-4), 127.1 (C_p), 127.45 and 128.32 (C_o and C_m), 130.34 (C-5), 135.07 (C-3′), 143.92 (C_i). EIMS: 199 [M]$^+$, 158 [M–C_3H_5]$^+$.

   4c • HCl: M.p. 176—178 °C (from ether:methanol). ^1H NMR (400 MHz, $CDCl_3$): δ 1.82 (dd, 1H, H-2′a), 2.33 (m, 2H, H-2′b and H-3a), 2.45 (m, 1H, H-3b), 3.16 (m, 1H, H-2), 4.81 (br.s, 1H, H-6), 4.97 (d, 1H, H-4′a, ^3J = 17.0 Hz), 5.08 (d, 1H, H-4′b, ^3J = 10.1 Hz), 5.45 (m, 1H, H-3′), 5.61 (d, 1H, H-4, ^3J = 10.2 Hz), 6.0 (m, 1H, H-5), 7.23 (m, 3H, Ph), 7.59 (m, 2H, Ph), 9.25 (br.s, 2H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.15 (C-3), 35.29 (C-2′), 55.05 (C-2), 59.32 (C-6), 119.10 (C-4′), 124.6 (C-4), 126.56 (C_p), 128.42 (C_o), 129.90 (C-5 and C_m), 132.33 (C-3′), 139.79 (C_i). Anal. calc. for $C_{14}H_{18}NCl$: C 71.33, H 7.69, N 5.94, Cl 15.04. Found: C 71.63, H 7.76, N 5.77, Cl 15.01.

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