Allylboration and cyclization of 3,4-dihydroisoquinoline derivatives. Synthesis of the benzopyrrocoline system

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A novel approach to hexahydropyrrolo[2,1-*a*]isoquinolines (hexahydrobenzo[*g*]pyrrocolines) based on the allylboration of 3,4-dihydroisoquinolines followed by closure of the pyrrolidine ring through the hydroboration — oxidation — intramolecular *N*-alkylation sequence was developed.

Key words: allylboration of azomethines, 3,4-dihydroisoquinolines, hydroboration, hexahydropyrrolo[2,1-*a*]isoquinolines.

Organoboranes of allylic type add to the C=N bond of imines,[1–7] quinolines, phenanthridine,[8–10] and isoquinoline,[8,9,11] forming (after deboration) 3-butenylamines,[1–7] amino derivatives of cyclopentane[6] and cyclohexane[6,7] with exocyclic double bonds or α-allylated heterocycles, respectively.[8–11] All these reactions proceed under mild conditions and are not accompanied by side processes. The compounds prepared by the allylboration of azomethines contain an N—H fragment and one or several double bonds and can be used as starting materials in the syntheses of pyrrolidine derivatives, simple and complex alkaloids, or their analogs.

In the present paper, the allylboration of two derivatives of 3,4-dihydroisoquinoline (**1** and **1a**) with triallylborane and the transformation of 1-allyl-3,3-dimethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**4**) into 8,9-dimethoxy-5,5-dimethyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (**6**) are described (Scheme 1).

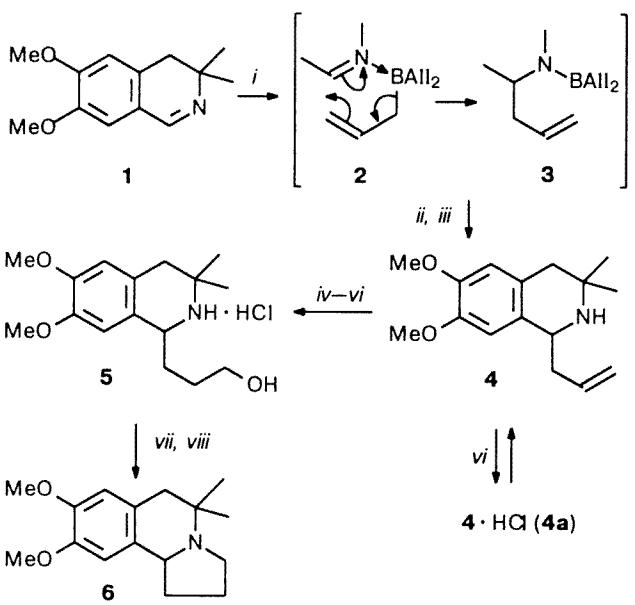
As expected, the reaction of azomethine **1** with triallylborane proceeded under mild conditions and affords aminoborane **3**, deboration of which by successive treatment with methanol and aqueous alkali gave amine **4** identified as hydrochloride **4a** (yield 74 %).

The addition of a B—allyl fragment to the C=N bond of azomethine **1** proceeds *via* allylic rearrangement (**2**).

The hydroboration—oxidation of 1-allylic derivative **4** afforded alcohol **5** in a yield of 70 %. Tetrapropyldiborane, $(Pr_2BH)_2$, generated *in situ* from Pr_2BOMe and $LiAlH_4$ in ether, was used as the hydroborating agent.

When heated with thionyl chloride in CH_2Cl_2 followed by treatment with K_2CO_3, aminoalcohol **5** underwent intramolecular cyclization forming tricyclic compound **6** in 67 % yield.

Scheme 1



Reagents and conditions:

i. $(\text{allyl})_3B$, Et_2O, 36 °C, 1 h;

ii. MeOH, 20 °C; *iii.* NaOH (5 mol L^{-1}); *iv.* $(Pr_2BH)_2$;
v. H_2O_2, NaOH (5 mol L^{-1}); *vi.* HCl;
vii. $SOCl_2$, CH_2Cl_2, reflux 3 h;
viii. K_2CO_3, EtOH, reflux 2 h.

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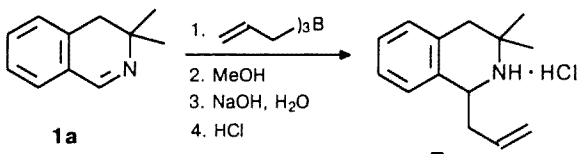
The transformation **1→4→6** is the first example of the construction of a benzopyrrocoline system from the isoquinoline system. It should be noted that the benzopyrrocoline fragment is a structural unit of a series of depressants.[12]

1-Allyl-3,3-dimethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (**7**, 62 %) is synthesized by the allylboration of azomethine **1a** with triallylborane (Scheme 2).

Scheme 2



1a **7**

It should be noted here that our attempts to realize the allylation with 1-methyl- (**1b**) and 1-methylthio-3,3-dimethyl-3,4-dihydroisoquinoline (**1c**) failed. These azomethines do not react with triallylborane even at 90—130 °C (3 h) and are recovered unchanged. Apparently, this is associated with steric hindrances. The structures of the compounds obtained were confirmed by elemental analysis (Table 1) and physicochemical methods (IR, ^1H and ^{13}C NMR spectroscopy and mass spectrometry).

Thus, in the IR spectra of isoquinoline bases and their hydrochlorides (**4**, **4a**, and **7**), the absorption bands characteristic of the terminal double bond (CH_2=CH, 1645 cm^{-1}) and the NH group (3300 cm^{-1}) are observed, and in the spectrum of the base prepared from salt **5**, the bands at 3310 cm^{-1} (NH) and 3625 cm^{-1} (OH) are present.

In the EI-MS of tricyclic compound **6**, the peak of the molecular ion (*m/z* 261) and peaks corresponding to the losses of H, Me, and MeO are observed. In the ^{13}C NMR spectrum of **6** (in $CDCl_3$) fifteen (not sixteen) signals are present: 10 aliphatic and 5 aromatic carbon atoms; the C-8 and C-9 atoms have the same chemical shift (147.3 ppm). However, in the spectrum of its picrate in $(CD_3)_2SO$, the chemical shifts of C-8 and C-9 are different (148.2 and 148.4 ppm), and twenty signals are observed: sixteen of them correspond to the heterocyclic system and four belong to the picrate fragment.

Experimental

All the operations with organoboron compounds were carried out under dry argon.

The IR spectra of the compounds synthesized were recorded with a Specord M-80 spectrometer in a film (bases) or in KBr (hydrochlorides), and the ^1H and ^{13}C NMR spectra were recorded with Bruker AC-200P and Bruker AMX-400 instruments. Mass spectra were recorded with an MAT-311 spectrometer (70 eV). Isoquinoline bases were obtained from the corresponding salts by treatment with 10 % NaOH followed by extraction with ether. Azomethines **1a,b** were synthesized by the known procedure (Ref. 13).

1-Allyl-6,7-dimethoxy-3,3-dimethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (4a). A solution of azomethine **1** (2.19 g, 10 mmol) in ether (10 mL) was added with stirring to a solution of triallylborane (1.47 g, 11 mmol) in ether (5 mL), and the mixture was refluxed for 1 h. Then methanol (1 mL) and a 5 *M* solution of NaOH (2.9 mL) were added successively at *ca.* 20 °C and the mixture was stirred for 30 min. The ethereal layer was separated and the aqueous layer was extracted with ether (2 × 5 mL). The combined ethereal extracts were washed with water and brine and dried over K_2CO_3. The solution was concentrated to 10 mL and HCl was passed to obtain hydrochloride **4a**, which was recrystallized from 2-propanol and dried *in vacuo*. Yield 2.2 g. ^1H NMR (CD_3OD), δ: 1.3 and 1.6 (both s, 6 H, 2 Me); AB spin system: δ_A 2.75 and δ_B 3.15 ($H_2C(4)$, J = 17.1 Hz); 3.83 (s, 6 H, 2 MeO); 4.5 (dd, HC(1), ^3J = 8.4 Hz, ^3J = 4.6 Hz); 5.30 (m, 2 H, CH_2=C); 5.95 (m, 1 H, C=CH); 6.77 and 6.95 (both s, 2 H, HC(5) and HC(8)). ^{13}C NMR (CD_3OD), δ: 21.6 and 27.3 (2 Me); 39.5 and 39.8 (C(4) and C—C=); 53.7 (C(1)); 56.2 (C(3)); 56.4 and 56.7 (2 MeO); 110.3 and 113.3 (C(5) and C(8)); 120.9 (H_2C=); 123.9 and 124.9 (C(4a) and C(8a)); 133.9 (=CH—); 149.8 and 150.5 (C(6) and C(7)).

1-Allyl-3,3-dimethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (7) was prepared similarly from azomethine **1a** (1.59 g, 10 mmol) and triallylborane (1.47 g, 11 mmol). Yield 1.47 g. ^1H NMR (CD_3OD), δ: 1.25 and 1.54 (both s, 6 H, 2 Me);

Table 1. Characteristics of compounds **4a**, **5**—**7**

Compound	Yield (%)	M.p./°C (Pr^iOH)	IR, ν/cm^{-1}	Found / Calculated (%)				Molecular formula
				C	H	N	Cl	
4a	74	210—212	1645, 3300	64.27 / 64.52	8.34 / 8.12	4.93 / 4.70	12.10 / 11.96	$C_{16}H_{24}ClNO_2$
5	70	188—189	3310 (NH); 3625 (OH)	60.88 / 60.84	8.59 / 8.30	4.61 / 4.43	11.40 / 11.23	$C_{16}H_{26}ClNO_3$
6 (picrate)	67	177—178	—	52.20 / 53.87	5.64 / 5.34	11.63 / 11.42	—	$C_{22}H_{26}N_4O_9$
7	62	161—163	1645, 3300	70.96 / 70.72	8.58 / 8.48	6.04 / 5.89	14.57 / 14.91	$C_{14}H_{20}ClN$

AB spin system: δ_A 2.79 and δ_B 3.18 (2 H, $H_2C(4)$, J_{AB} = 17.0 Hz); 2.70 and 3.10 (both m, 2 H, CH_2—C=); 4.58 (dd, 1 H, HC(1), ^3J = 8.5 Hz, ^3J = 4.5 Hz); 5.2 (m, 2 H, CH_2=C); 5.94 (m, 1 H, C=CH); 7.3 (m, 4 H, CH arom.). ^{13}C NMR (CD_3OD), δ: 21.6 and 27.3 (2 Me); 39.6 and 39.9 (C(4) and $CHCH_2$); 54.0 (C(1)); 56.2 (C(3)); 121.1 (CH_2=C); 127.0; 126.5; 129.3 and 130.7 (C(5), C(6), C(7), C(8)); 132.0 and 132.4 (C(4a) and C(8a)); 133.6 (C=CH_2).

1-(3-Hydroxypropyl)-6,7-dimethoxy-3,3-dimethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (5). A solution of methoxy(dipropyl)borane (3.20 g, 25 mmol) in ether (10 mL) was added at 20 °C to a suspension of lithium aluminum hydride (0.27 g, 7 mmol) in ether (10 mL) and the mixture was stirred for 1 h. A solution of base **4** (2.60 g, 10 mmol) in ether (7 mL) was added and the mixture was refluxed for 1 h. Then methanol (0.5 mL), a 5 *M* NaOH solution (6.5 mL), and 25 % H_2O_2 (10.6 mL) were added successively at 5 °C, and the mixture was refluxed for 1 h. The ethereal layer was separated, and the aqueous layer was extracted with ether (7×5 mL). The combined ethereal extracts were dried over K_2CO_3 and concentrated to 10 mL, and hydrochloride **5** (2.21 g) was prepared as described above. ^1H NMR (CD_3OD), δ: 1.25 and 1.52 (both s, 6 H, 2 Me); 1.65, 2.22, 3.60 (all m, $(CH_2)_2CH_2O$); 3.76 and 3.78 (both s, 6 H, 2 Me); 4.46 (t, 1 H, NCH, J = 5.5 Hz); AB spin system: δ_A 2.70 and δ_B 3.02 (2 H, $H_2C(4)$, J_{AB} = 16.8 Hz); 6.72 and 6.84 (both s, 2 H, HC(5) and HC(8)). ^{13}C NMR (CD_3OD), δ: 21.6 and 27.6 (2 Me); 28.4 ($CH_2CH_2CH_2$); 32.2 ($CHCH_2$); 39.5 (C(4)); 54.0 (C(1)); 55.7 (C(3)); 56.5 and 56.7 (2 MeO); 62.3 (CH_2OH); 110.2 and 113.3 (C(5) and C(8)); 124.0 and 125.2 (C(4a) and C(8a)); 149.9 and 150.3 (C(6) and C(7)).

8,9-Dimethoxy-5,5-dimethyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline picrate (6). Thionyl chloride (3.6 mL, 30 mmol) was added to a solution of hydrochloride **5** (3.16 g, 10 mmol) in CH_2Cl_2 (10 mL), and the mixture was refluxed for 3 h. The solvent and excess of $SOCl_2$ were removed *in vacuo*. Ethanol (5 mL) and K_2CO_3 (4.14 g) were added to the residue and the mixture was refluxed for 2 h. Then ether (10 mL) was added at 20 °C and a precipitate was filtered off and washed with ether (3 × 5 mL). To the combined ethereal-alcoholic solution, an ethereal solution of picric acid (2.29 g, 10 mmol) was added. The picrate of compound **6** obtained was recrystallized from 2-propanol. Yield 3.28 g. ^{13}C NMR (DMSO-d_6), δ: 21.3 and 31.4 (2 Me); 24.2 and 25.2 (C(1) and C(2)); 33.9 (C(6)); 47.1 (C(3)); 55.4 and 55.6 (2 MeO); 57.7 and 59.7 (C(5) and C(10b)); 108.8 and 111.6 (C(7) and C(10)); 148.2 and 148.4 (C(8) and C(9)); 122.5, 125.2, 141.8 and 160.9 (picric acid carbons).

Base **6** was obtained as an oil by the action of a solution of alkali on the picrate followed by extraction with ether. EI-MS, m/z: 261 $[M]^+$, 260 $[M-H]^+$, 246 $[M-CH_3]^+$, 230 $[M-CH_3O]^+$. ^1H NMR (400 MHz, $CDCl_3$), δ: 1.03 and 1.28 (both s, 6 H, 2 Me); 1.80 (m, $H_2C(1)$, $H_2C(2)$); AB spin system: δ_A 2.38 and δ_B 2.88 ($H_2C(6)$, J_{AB} = 16.1 Hz); 2.4 and 2.72 (both m, 2 H, $H_2C(3)$); 2.81 (t, 1 H, HC(10b), J = 6.4 Hz); 3.83 and 3.84 (both s, 6 H, 2 MeO); 6.51 and 6.58 (both s, 2 H, HC(7) and HC(10)). ^{13}C NMR ($CDCl_3$), δ: 20.5 and 29.4 (2 Me); 21.9 and 31.0 (C(1) and C(2)); 38.8 (C(6)); 45.1 (C(3)); 51.3 (C(5)); 55.7 and 55.9 (2 MeO); 57.6 (C(10b)); 108.8 and 111.5 (C(7) and C(10)); 126.2 and 130.0 (C(6a) and C(10a)); 147.3 (C(8) and C(9)).

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References

1. Yu. N. Bubnov and B. M. Mikhailov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1967, 472 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1967, 467 (Engl. Transl.)].
2. Yu. N. Bubnov, V. S. Bogdanov, and B. M. Mikhailov, *Zh. Obshch. Khim.*, 1968, **38**, 260 [*J. Gen. Chem. USSR*, 1968, **38** (Engl. Transl.)].
3. Y. Yamamoto, S. Nishii, K. Maruyama, T. Kamatsu, and W. Itoh, *J. Am. Chem. Soc.*, 1986, **108**, 7778.
4. R. W. Hoffmann, G. Eichler, and A. Endesfelder, *Liebigs Ann. Chem.*, 1983, 2000.
5. Yu. N. Bubnov, V. I. Zheludeva, T. Yu. Rudashevskaya, and T. K. Kuznetsova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1989, 1179 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1989, **38**, 1073 (Engl. Transl.)].
6. L. I. Lavrinovich, A. V. Ignatenko, and Yu. N. Bubnov, *Izv. Akad. Nauk, Ser. Khim.*, 1992, 2597 [*Bull. Russ. Acad. Sci., Div. Chem. Sci.*, 1992, **41**, 2051 (Engl. Transl.)].
7. M. E. Gurskii, S. B. Golovin, A. V. Ignatenko, and Yu. N. Bubnov, *Izv. Akad. Nauk, Ser. Khim.*, 1992, 2198 [*Bull. Russ. Acad. Sci., Div. Chem. Sci.*, 1992, **41**, 1724 (Engl. Transl.)].
8. Yu. N. Bubnov, *Pure Appl. Chem.*, 1994, **66**, 235.
9. Yu. N. Bubnov, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 1203 [*Russ. Chem. Bull.*, 1995, **44**, 1156 (Engl. Transl.)].
10. Yu. N. Bubnov, S. V. Evchenko, and A. V. Ignatenko, *Izv. Akad. Nauk, Ser. Khim.*, 1992, 2815 [*Bull. Russ. Acad. Sci., Div. Chem. Sci.*, 1992, **41**, 2239 (Engl. Transl.)].
11. Yu. N. Bubnov, S. V. Evchenko, and A. V. Ignatenko, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 1325 [*Russ. Chem. Bull.*, 1993, **42**, 1268 (Engl. Transl.)].
12. B. E. Maryanoff, D. F. McComsey, J. F. Gardocki, R. P. Shank, M. J. Constanzo, S. O. Nortey, C. R. Schneider, and P. E. Setler, *J. Med. Chem.*, 1987, **30**, 1433.
13. A. G. Mikhailovskii, B. B. Aleksandrov, and M. I. Vakhrin, *Khim. Geterotsikl. Soedin.*, 1992, 1144 [*Chem. Heterocycl. Comp.*, 1992 (Engl. Transl)].

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