Intramolecular cyclization of *ortho*-(cyclohex-2-enyl)anilines. Modified synthesis of ellipticine

A. G. Mustafin, I. N. Khalilov, R. R. Ismagilov, Z. M. Baimetov, L. V. Spirikhin, I. B. Abdrakhmanov, and G. A. Tolstikov*

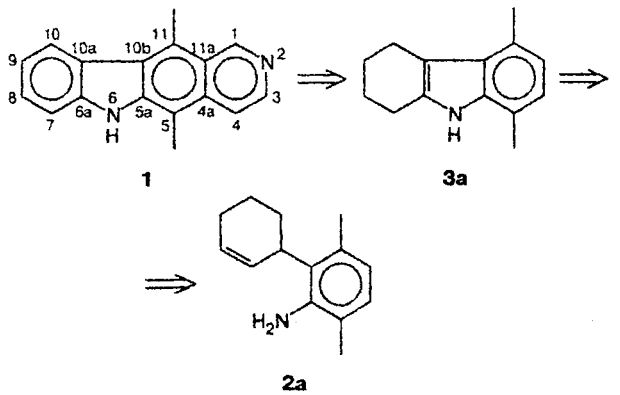
Institute of Organic Chemistry, Ufa Research Center of the Russian Academy of Sciences, 71 prosp. Oktyabrya, 450054 Ufa, Russian Federation. Fax: +7 (347 2) 35 6066

It was found that the reactions of arylamines with 3-bromocyclohexene afforded hydrocarbazole compounds in 64—78% yields. A modified procedure for the synthesis of antitumor alkaloid ellipticine was proposed.

Key words: arylamines, 2,5-xylidine, 3-bromo(chloro)cyclohexene, *ortho*-(cyclohex-2-enyl)-2,5-xylidine, 1,4-dimethylcarbazole, ellipticine.

Alkaloid ellipticine (**1**), which was isolated from leaves of the plant *Ochrosia elliptica* Labill (the Apocynaceae family),[1] and some of its synthetic analogs exhibit high antitumor activity.[2,3] In this connection, several preparative procedures for the synthesis of ellipticine and its derivatives were proposed based on traditional methods (see, for example, Refs. 4—8).

The Claisen rearrangement of *N*-alkenylarylamines and intramolecular cyclization of *N*- and *C*-alkenylarylamines, which we have studied over a period of years, serve as the basis for a promising procedure for the synthesis of quinoline and indole derivatives.[9—12] Our approach to ellipticine is based on the use of the original cyclization reaction of *ortho*-(cyclohex-2-enyl)-2,5-xylidine (**2a**) to form 5,8-dimethyltetrahydrocarbazole (**3a**), which is a known intermediate in the synthesis of ellipticine.[13,14]



1 **3a**

2a

The reaction of equimolar amounts of 2,5-xylidine (**4a**) and 3-chlorocyclohexene (**5a**) afforded *N*-(cyclohex-2-enyl)-2,5-xylidine (**6a**). The rearrangement of the latter in the presence of Lewis or Brønsted acids gave compound **2a** (Table 1) in a yield of up to 79%. The more promising variation of the rearrangement, which involves heating of a fourfold excess of arylamine **4a** with halide **5a** in the absence of acid at 140 °C, afforded product **2a** in 82% yield.

Intramolecular cyclization of compound **2a** was performed with the use of polyphosphoric acid (PPA), UV irradiation, and the $PdCl_2(PhNO_2)_n$ complex.[9] The maximum yield of hexahydrocarbazole **7a** (75%) was attained when the reaction was carried out in PPA (Scheme 1). In the case of catalysis with the Pd^{II} complex or photocyclization, which are often used in the synthesis of heterocycles from 2-alkenylarylamines,[15,16] products **3a** and **7a** were obtained in 30 and 15% yields, respectively. Later on, we succeeded in modifying the scheme of the synthesis of the key intermediates by developing the procedure for the preparation of these compounds in one preparative step. Thus, heating of a fourfold molar excess of arylamine **4a** with 3-bromocyclohexene (**5b**) at 150 °C for 5 h gave a mixture of products **3a** and **7a** in a molar ratio of 3 : 2 in a total yield of 78%. Apparently, *N*-alkenylamine **6a**

Table 1. Conditions of the rearrangement of compound **6a** and the yields of compound **2a**

Catalyst	Solvent	*T*/°C	τ/h	Yield of **2a** (%)
$AlCl_3$	Xylene	140	5	68
$ZnCl_2$	Xylene	140	4	75
$BF_3 \cdot Et_2O$	—*	170	6	51
HCl**	Xylene	140	3	79

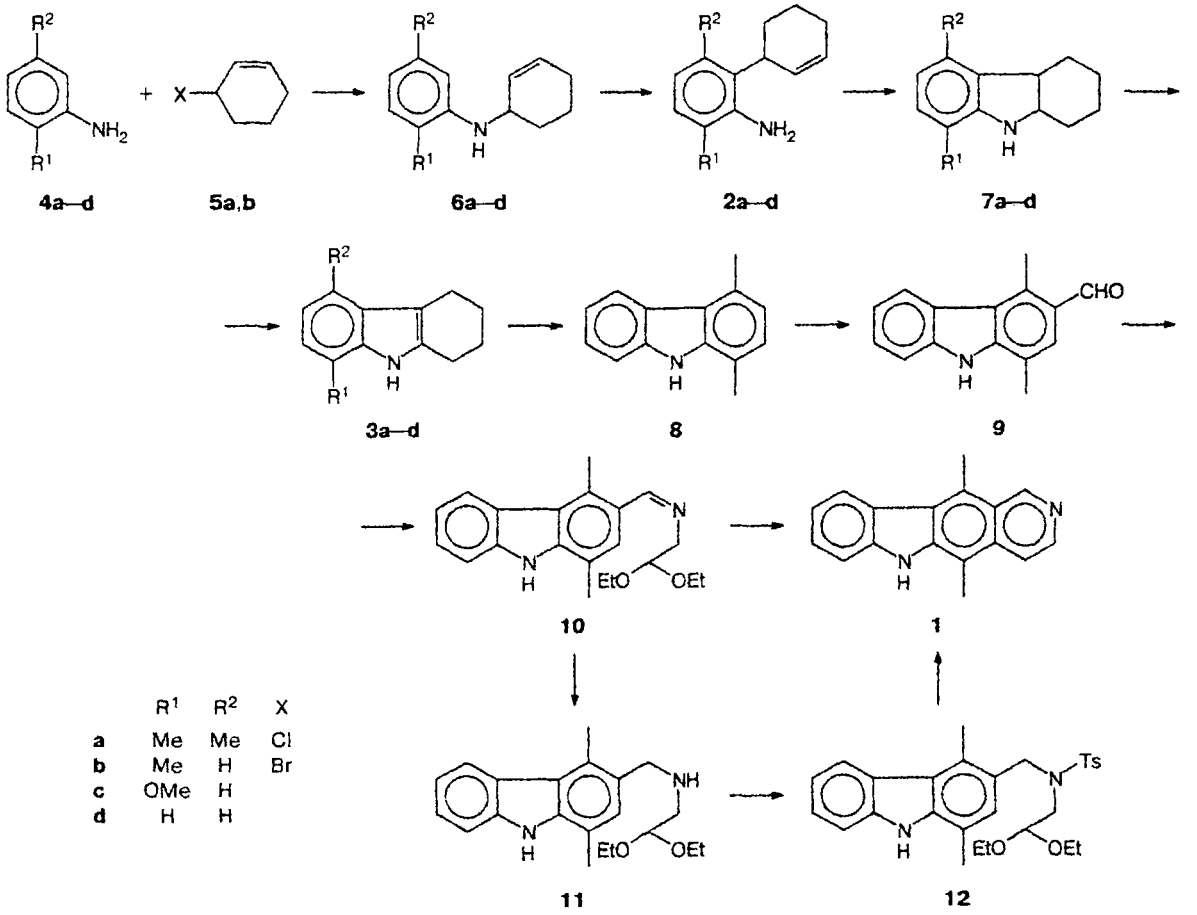
* Without a solvent.

** Hydrochloride of amine **6a** was used (see the Experimental section).

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 11, pp. 2144—2149, November, 1999.

1066-5285/99/4811-2121 $22.00

Scheme 1



	R^1	R^2	X
a	Me	Me	Cl
b	Me	H	Br
c	OMe	H	
d	H	H	

underwent the Claisen rearrangement followed by intramolecular cyclization of *ortho*-alkenylamine **2a** to heterocycle **7a** under the action of HBr.

It is known that intramolecular cyclization of 2-alkenylanilines under the action of Pd^{II} complexes in a nitrobenzene solution yields quinolines and indoles, while a portion of the solvent is reduced to aniline.[10] Hence, we used nitrobenzene instead of an excess of 2,5-xylidine as the solvent and dehydrogenating agent. Heating of equimolar amounts of compounds **4a** and **5b** in a nitrobenzene solution at 140 °C for 4—5 h afforded exclusively tetrahydrocarbazole **3a** in 61% yield.[14] Apparently, hexahydrocarbazole **7a**, which was formed in the course of the reaction, was converted into compound **3a**. It should be noted that the procedure developed for the synthesis of carbazole derivatives is a rather general method because the reactions of substituted anilines **4b—d** with halide **5b** also afforded heterocycles **3b—d** and **7b—d** in total yields of 64—78%. At the subsequent stage, a mixture of compounds **3a** and **7a** was dehydrogenated under the action of Pd/C to form 1,4-dimethylcarbazole (**8**)[17] in 87% yield. Formylation of carbazole **8** by the reaction of the resulting aldehyde **9** with 2,2-diethoxyethylamine to form imine **10** proceeded rather smoothly.[18] Direct cyclization of imine **10** in polyphosphoric acid gave ellipticine[2,18] (**1**) in 15% yield. Reduction of imine **10** on Raney nickel to form compound **11** followed by cyclization of *N*-tosylate of the latter (**12**) in a dioxane solution appeared to be the preferential procedure for the synthesis of the target product.[19] In this case, the yield of ellipticine reached 80% (or 55% with respect to imine **10**).

Experimental

The IR spectra were obtained on a UR-20 instrument. The ^1H and ^{13}C NMR spectra were recorded on Tesla BS-567 B (100 MHz) and Bruker AM-300 (75 MHz) instruments (Me_4Si as the internal standard; $CDCl_3$ or DMSO-d_6 as the solvents). The mass spectra (EI) were measured on an MKh-13-06 instrument (the energy of ionizing electrons was 70 eV; the temperature of the ionization chamber was 200 °C). The GLC analysis was carried out on an LKhM-8 MD chromatograph (a 2700×3-mm column with 5% SE-30 on Chromaton N-AW-DMCS, the flow rate of helium was 30 mL min^{-1}).

The physicochemical constants of the compounds synthesized are given in Tables 2 and 3. The spectral characteristics of compounds **2** and **6a—d** correspond to those reported previously.[13,20]

Table 2. Boiling (melting) points and the spectral characteristics of compounds **1**, **2a—d**, **3a—d**, **6a—d**, **7a—d**, and **8—12**

Compound	B.p./°C (*p*/Torr), M.p./°C*	MS, *m/z* $[M]^+$	IR, ν/cm^{-1}	^{1}H NMR ($CDCl_3$, δ, *J*/Hz)*
1	314—315 [315—317][2]	—	—	2.88 (s, 3 H, C(5)H_3); 3.32 (s, 3 H, C(11)H_3); 7.66 (d, 1 H, C(4)H, *J* = 7.8); 7.20—7.75 (m, 4 H, Ar); 8.15 (br.s, 1 H, NH); 8.52 (d, 1 H, C(3)H); [2.77 (s, 3 H, C(5)H_3); 3.23 (s, 3 H, C(11)H_3); 7.87 (d, 1 H, C(4)H, *J* = 7.0); 7.10—7.70 (m, 3 H, Ar, C(7)H, C(8)H, C(9)H); 8.30—8.60 (m, 2 H, C(3)H, C(10)H); 11.32 (br.s, 1 H, NH)][2]
2a	160—162 (1)	201	735, 1620, 3380, 3470	1.73 (m, 6 H, 3 CH_2); 1.98 (s, 3 H, C(2)H_3); 2.18 (s, 3 H, C(5)H_3); 3.58 (s, 2 H, NH_2); 3.76 (m, 1 H, CH); 5.73 (m, 2 H, HC=CH); 6.28 (d, 1 H, Ar, *J* = 7.5); 6.63 (d, 1 H, Ar, *J* = 7.5)
2b	132 (2)	187	750, 904, 1620, 3400, 3480	1.55 (br.s, 4 H, 2 CH_2); 1.85 (br.s, 2 H, CH_2); 2.09 (s, 3 H, Me); 3.76 (m, 1 H, CH); 3.28 (s, 2 H, NH_2); 5.60 (m, 2 H, HC=CH); 6.30—6.80 (m, 3 H, Ar)
2c	126—129 (2)	203	750, 1460, 1600, 2900, 3380, 3470	1.67 (m, 6 H, 3 CH_2); 3.13 (m, 1 H, CH); 3.65 (s, 2 H, NH_2); 3.68 (s, 3 H, OMe); 3.73 (m, 1 H, CH); 5.67 (m, 2 H, HC=CH); 6.30—6.77 (m, 3 H, Ar)
2d	118—120 (2)	173	760, 1620, 3370, 3450	1.55—1.87 (m, 6 H, C(3)H_2); 3.14 (m, 1 H, CH); 3.34 (s, 2 H, NH_2); 5.62 (m, 2 H, HC=CH); 6.36—6.85 (m, 4 H, Ar)
3a	140—142 (1)	199	760, 1250, 1470, 1520, 2860, 2900, 3100, 3420	1.92 (m, 4 H, C(2)H_2, C(3)H_2); 2.31 (s, 3 H, Me); 2.52 (s, 3 H, Me); 2.65 (m, 2 H, C(4)H_2); 2.95 (m, 2 H, C(1)H_2); 6.65 (d, 1 H, *J* = 7.3); 6.71 (d, 1 H, *J* = 7.3); 7.6 (s, 1 H, NH)
3b	139—142 (1)	185	780, 1260, 1520, 1600, 2860, 2800, 3420	1.88 (m, 4 H, C(2)H_2, C(3)H_2); 2.41 (s, 3 H, Me); 2.69 (m, 4 H, C(1)H_2, C(4)H_2); 6.94—7.35 (m, 3 H, Ar); 7.60 (s, 1 H, NH)
3c	142—145 (1)	201	770, 1260, 1510, 1620, 2870, 2940, 3400	1.45 (m, 4 H, C(2)H_2, C(3)H_2); 1.82 (m, 4 H, C(1)H_2, C(4)H_2); 3.80 (s, 3 H, OMe); 4.20 (s, 1 H, NH); 6.70 (s, 3 H, Ar)
3d	135—138 (1)	171	760, 1260, 1500, 1600, 2860, 2950, 3340	1.85 (m, 4 H, C(2)H_2, C(3)H_2); 2.03 (m, 4 H, C(1)H_2, C(4)H_2); 6.00 (s, 1 H, NH); 7.00—7.65 (m, 4 H, Ar)
6a	140 (2)	201	720, 1580, 1610, 3350	1.62 (m, 6 H, C(3)H_2); 1.98 (s, 3 H, C(2)H_3); 2.22 (3 H, C(5)H_3); 3.23 (s 1 H, NH); 3.92 (s, 1 H, CH); 5.70 (m, 2 H, HC=CH); 6.16 (s, 1 H, Ar); 6.28 (d, 1 H, Ar, *J* = 7.5); 6.75 (d, 1 H, Ar, *J* = 7.5)
6b	112 (2)	187	760, 910, 1620, 3400	1.68 (m, 6 H, 3 CH_2); 2.18 (s, 3 H, CH_3); 3.14 (s, 1 H, NH); 3.76 (m, 1 H, CH); 5.66 (m, 2 H, HC=CH); 6.20—6.77 (m, 4 H, Ar)
6c	118 (2)	203	760, 1450, 1600, 2910, 3400	1.56 (m, 6 H, 3 CH_2); 3.20 (s, 1 H, NH); 3.62 (s, 3 H, CH_3); 3.83 (m, 1 H, CH); 5.90—6.63 (4 H, Ar)
6d	108 (2)	173	740, 1279, 1480, 1515, 1600, 3410	1.50—1.80 (m, 6 H, CH_2); 3.16 (s, 1 H, NH); 3.77 (s, 1 H, CH); 5.63 (m, 2 H, HC=CH); 6.35—7.12 (m, 5 H, Ar)
7a	130—134 (1)	201	800, 1270, 1600, 2860, 2930, 3360	1.51 (m, 4 H, C(2)H_2, C(3)H_2); 1.70 (m, 4 H, C(1)H_2, C(4)H_2); 1.98 (s, 3 H, Me); 2.11 (s, 3 H, Me); 2.82 (m, 1 H, C(4a)H); 3.70 (m, 1 H, C(8b)H); 6.34 (d, 1 H, Ar, *J* = 7.7); 6.65 (d, 1 H, Ar, *J* = 7.7); 8.15 (s, 1 H, NH)
7b	128—130 (1)	187	780, 1280, 1520, 1600, 2860, 2920, 3370	1.66—1.83 (m, 6 H, C(2)H_2, C(3)H_2, C(4)H_2); 1.95 (s, 3 H, Me); 2.05 (m, 2 H, C(1)H_2); 2.70 (m, 1 H, C(4a)H); 3.58 (m, 1 H, C(8b)H); 6.40—6.73 (m, 3 H, Ar); 7.2 (s, 1 H, NH)

(to be continued)

Table 2 (*continued*)

Compound	B.p./°C (*p*/Torr), M.p./°C*	MS, *m/z* $[M]^+$	IR, ν/cm^{-1}	^1H NMR ($CDCl_3$, δ, *J*/Hz)*
7c	134—137 (1)	203	780, 1260, 1530, 1620, 2870, 2910, 3400	1.48 (m, 2 H, C(3)H_2); 1.75 (m, 4 H, C(4)H_2, C(2)H_2); 2.25 (m, 2 H, C(1)H_2); 3.05 (m, 1 H, C(4a)H); 3.76 (m, 1 H, C(8b)H); 3.82 (s, 3 H, OMe); 5.87 (s, 1 H, NH); 6.75 (m, 3 H, Ar)
7d	130—133 (1)	173	770, 1300, 1500, 1620, 2860, 2040, 3380	1.76 (m, 6 H, C(2)H_2, C(3)H_2, C(4)H_2); 2.02 (m, 2 H, C(1)H_2); 2.65 (m, 1 H, C(4a)H); 3.50 (m, 1 H, C(8b)H); 5.90 (s, 1 H, NH); 6.60—6.95 (m, 2 H, Ar); 7.00—7.27 (m, 2 H, Ar)
8	94	195	750, 760, 815, 1270, 1385, 1600, 2870, 2930, 3415	2.49 (s, 3 H, Me); 2.79 (s, 3 H, Me); 6.78 (d, 1 H, Ar, *J* = 7.2); 6.96 (d, 1 H, Ar, *J* = 7.2); 7.08—7.34 (m, 3 H, Ar); 7.41 (d, 1 H, C(8)H, *J* = 7.0); 8.10 (s, 1 H, NH)
9	213 [215—216][18]	223	735, 880, 1270, 1640, 2920, 3340	2.57 (s, 3 H, Me); 3.18 (s, 3 H, Me); 7.28—7.57 (m, 3 H, Ar); 7.71 (s, 1 H, C(2)H); 8.20 (d, 1 H, C(8)H, *J* = 7.6); 10.42 (s, 2 H, NH, CHO)
10	130 [130][18]	338	760, 890, 1100, 1460, 1510, 1600, 2920, 2980, 3470	1.22 (t, 6 H, 2 C$\underline{H}_3$CH$_2$, *J* = 7.0); 2.38 (s, 3 H, Me); 2.75 (s, 3 H, Me); 3.62—3.87 (m, 6 H, 3 CH_2); 4.69 (t, 1 H, OCHO, *J* = 6.0); 6.81—7.15 (m, 3 H, Ar); 7.45 (s, 1 H, C(2)H); 7.70 (d, 1 H, C(8)H, *J* = 7.1); 8.30 (s, 1 H, HC=N); 8.60 (s, 1 H, NH)
11	105	340	750, 880, 1060, 1100, 1460, 1500, 1600, 2900, 2970, 3380, 3470	1.20 (t, 6 H, 2 C$\underline{H}_3$CH$_2$, *J* = 6.9); 2.48 (s, 3 H, Me); 2.85 (s, 3 H, Me); 3.64 (q, 4 H, 2 CH_2, *J* = 6.9); 3.68 (d, 2 H, CH_2N, *J* = 6.0); 3.97 (s, 2 H, ArCH_2N); 4.72 (t, 1 H, OCHO, *J* = 6.0); 7.25 (s, 1 H, C(2)H); 7.16—7.44 (m, 3 H, Ar); 8.20 (d, 1 H, C(8)H, *J* = 7.6); 8.44 (s, 2 H, 2 NH)
12	184	—	—	1.16 (t, 6 H, 2 C$\underline{H}_3$CH$_2$, *J* = 7.2); 2.42 (s, 3 H, Me); 2.46 (s, 3 H, Me); 2.82 (s, 3 H, Me); 3.25 (d, 2 H, CH_2N, *J* = 6.0); 3.48 (q, 4 H, 2 CH_2, *J* = 7.2); 4.42 (t, 1 H, CH, *J* = 6.0); 4.69 (s, 2 H, ArCH_2N); 7.00 (s, 1 H, C(2)H); 7.25—7.52 (m, 3 H, C(5)H, C(6)H, C(7)H; 2 H, Ts); 7.76 (d, 2 H, Ts, *J* = 7.6); 8.12 (d, 1 H, C(8)H, *J* = 7.3); 7.44 (s, 1 H, NH)

* Literature data are given in brackets.

Synthesis of *N*-(cyclohex-2-enyl)-2,5-xylidine (6a). 3-Chlorocyclohexene (**5a**) (11.6 g, 0.1 mol) was added to a solution of arylamine **4a** (12.1 g, 0.1 mol) in Et_3N (50 mL). The reaction mixture was heated at 80—90 °C for 2 h and then treated with water (3×20 mL). The product was extracted with EtOAc and the organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure, the residue was distilled *in vacuo*, and product **6a** was obtained in a yield of 15 g (75%).

Catalytic rearrangement of *N*-(cyclohex-2-enyl)-2,5-xylidine (6a). ***A.*** A catalyst (7 mmol) (see Table 1) was added to a solution of compound **6a** (7 g, 35 mmol) in xylene (20 mL). The reaction mixture was refluxed for 4—5 h and then washed with a 15% KOH solution. The organic phase was dried over $MgSO_4$ and concentrated and the residue was distilled *in vacuo*. Product **2a** was obtained in 68—75% yield.

B. $BF_3 \cdot Et_2O$ (2.6 mL) was added to compound **6a** (1.7 g, 14 mmol). The reaction mixture was heated at 170 °C for 6 h, treated with Na_2CO_3, and extracted with ether (3×30 mL). The organic layer was dried over KOH and the ether was evaporated. Column chromatography on Al_2O_3 (a 1 : 1 benzene—hexane mixture as the eluent) afforded compound **2a** in a yield of 0.87 g (51%).

C. Gaseous HCl was bubbled through a solution of compound **6a** (5 g, 25 mmol) in ether (100 mL) until the formation of the precipitate ceased. The precipitate of *N*-alkenylamine hydrochloride that formed was filtered off, washed with ether (3×30 mL), and dried under reduced pressure. Hydrochloride of compound **6a** that formed was dissolved in xylene (20 mL) and heated at 140 °C for 3 h. The workup was performed according to procedure ***A***. Product **2a** was obtained in a yield of 3.95 g (79%).

D. 3-Chlorocyclohexene (11.6 g, 0.1 mol) was added to arylamine **4a** (47.6 g, 0.4 mol) and the reaction mixture was heated at 140—150 °C for 5 h. The consumption of compounds **4a** and **5a** and accumulation of compound **2a** were monitored by GLC. After completion of the reaction, the mixture was treated with a 30% KOH solution (3×100 mL),

Table 3. ^{13}C NMR spectrum of ellipticine (**1**) (DMSO-d_6)

Atom	δ	Atom	δ	Atom	δ
C(1)	148.1	C(9)	119.4	C(10b)	129.2
C(3)	127.3	C(10)	125.5	C(10a)	108.4
C(4)	123.8	C(11)	141.3	C(6a)	137.3
C(5)	122.8	C(11a)	129.2	C(5')H_3	11.8
C(7)	110.8	C(4a)	157.9	C(11')H_3	14.4
C(8)	125.6	C(5a)	132.6		

the organic phase was dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. Compound **2a** was obtained in a yield of 16.5 g (82%).

5,8-Dimethyl-1,2,3,4,4a,8b-hexahydrocarbazole (7a). Amine **2a** (10 g, 55 mmol) in polyphosphoric acid (60 g, *i.e.*, 50 g of H_3PO_4 (85%) + 10 g of P_2O_5) was heated at 140 °C for 5 h. The reaction mixture was treated with a 30% KOH solution and extracted with benzene (5×50 mL). The extract was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was rectified *in vacuo* and compound **7a** was obtained in a yield of 7.5 g (75%).

Photochemical cyclization of compound 2a. A solution of compound **2a** (1 g, 5 mmol) in benzene or hexane (800 mL) was irradiated with the use of a DRT-375 lamp in a quartz reactor under an argon atmosphere for 45 min. Then the solvent was evaporated under reduced pressure and the residue was chromatographed on a column with Al_2O_3 using a 1 : 4 benzene—hexane mixture as the eluent. Compounds **2a**, **3a**, and **7a** were obtained in yields of 0.25 g (25%), 0.07 g (7%), and 0.15 g (15%), respectively.

Cyclization of compound 2a under the action of $PdCl_2$. $PdCl_2$ (0.25 mmol) was added to a solution of compound **2a** (0.5 g, 2.5 mmol) in nitrobenzene (10 mL) and the reaction mixture was heated in an autoclave at 140 °C for 2 h. The solvent was removed *in vacuo* and the residue was chromatographed on a column with Al_2O_3 (benzene as the eluent). Compound **3a** was obtained in a yield of 0.15 g (30%).

Preparation of mixtures of tetrahydrocarbazoles (3a—d) and hexahydrocarbazoles (7a—d). 3-Bromocyclohexene (**5b**) (30 mmol) was gradually added to arylamine **4a—d** (120 mmol) and the reaction mixture was heated at 150 °C for 5 h. The cooled reaction mixture was treated with a 30% KOH solution (3×100 mL) and extracted with benzene. The organic layer was dried over $MgSO_4$ and distilled *in vacuo*. The yields of the products were 2.8 g (47%) (**3a**) and 1.8 g (31%) (**7a**); 2.5 g (45%) (**3b**) and 1.7 g (30%) (**7b**); 2.8 g (46%) (**3c**) and 1.8 g (30%) (**7c**); and 1.9 g (38%) (**3d**) and 1.3 g (26%) (**7d**). In all the cases, compounds **3** and **7** were obtained in a molar ratio of 3 : 2.

1,4-Dimethylcarbazole (8). Pd/C catalyst (1.5 g, 5%) was added to a solution of a mixture of compounds **3a** and **7a** (5 g) taken in a molar ratio of 3 : 2 in trimethylbenzene (20 mL). The reaction mixture was refluxed for 3 h and filtered. Petroleum ether (50 mL, b.p. 40—70 °C) was added to the filtrate. Compound **8** was obtained as a white powder in a yield of 4.2 g (87%).

3-Formyl-1,4-dimethylcarbazole (9). 1,4-Dimethylcarbazole (**8**) (2.3 g, 12 mmol) was added to a mixture of *N*-methylformanilide (2.1 g, 16 mmol) and $POCl_3$ (2.2 g, 14 mmol) in dichlorobenzene (6 mL) and the reaction mixture was heated on a water bath for 5 h. The workup of the reaction mixture was carried out according to a procedure reported previously.[14] Product **9** was obtained in a yield of 1.2 g (46%).

Table 4. Data of elemental analysis of compounds **3a—d**, **7a—d**, and **8—12**

Compound	Found / Calculated (%)			Molecular formula
	C	H	N	
3a	84.23 84.42	8.41 8.54	7.02 7.04	$C_{14}H_{17}N$
3b	83.95 84.32	7.99 8.11	7.52 7.57	$C_{13}H_{15}N$
3c	77.48 77.61	7.26 7.46	6.76 6.97	$C_{13}H_{15}NO$
3d	84.09 84.21	7.59 7.60	7.48 8.19	$C_{12}H_{13}N$
7a	83.31 83.58	9.34 9.45	6.84 6.97	$C_{14}H_{19}N$
7b	83.55 83.42	9.29 9.09	7.66 7.49	$C_{13}H_{17}N$
7c	76.63 76.85	8.17 8.37	6.81 6.90	$C_{13}H_{17}NO$
7d	82.74 83.24	8.65 8.67	7.84 8.09	$C_{12}H_{15}N$
8	86.39 86.15	6.91 6.67	7.22 7.18	$C_{14}H_{13}N$
9	80.85 80.72	6.01 5.83	6.17 6.28	$C_{15}H_{13}NO$
10	74.46 74.56	7.32 7.69	8.49 8.28	$C_{21}H_{26}N_2O_2$
11	74.19 74.12	8.25 8.23	8.29 8.21	$C_{21}H_{28}N_2O_2$
12*	67.39 67.50	6.48 6.67	5.50 5.83	$C_{27}H_{32}N_2O_4S$

* For S, found/calculated (%): 6.21/6.67.

3-(2,2-Diethoxyethyliminomethyl)-1,4-dimethylcarbazole (10). A mixture of compound **9** (1 g, 4.5 mmol) and 2,2-diethoxyethylamine (0.6 g, 4.5 mmol) was heated at 100 °C for 2 h. After cooling, the reaction mixture was fractionated by column chromatography on silica gel ($CHCl_3$ as the eluent) and compound **10** was obtained in a yield of 1.25 g (82.7%).

3-(2,2-Diethoxyethylaminomethyl)-1,4-dimethylcarbazole (11). A solution of imine **9** (2 g, 9 mmol) in anhydrous EtOH (50 mL) in the presence of catalyst (Raney nickel) (0.4 g) was hydrogenated in an autoclave at ~20 °C and 8 atm. for 24 h. After purification by chromatography on silica gel ($CHCl_3$ as the eluent), product **11** was obtained in a yield of 1.5 g (74.6%).

3-[*N*-(2,2-Diethoxyethyl)-*N*-tosylaminomethyl]-1,4-dimethylcarbazole (12). A mixture of amine **11** (1.5 g, 4.8 mmol) and TsCl (0.92 g, 4.8 mmol) in dry pyridine (8 mL) was kept at ~20 °C for 72 h. The precipitate of the salt of pyridine hydrochloride was filtered off, water (30 mL) was added to the filtrate, and the product was extracted with $CHCl_3$ (5×20 mL). The extract was dried over $MgSO_4$, the solvent was removed under reduced pressure, and tosylate **12** was obtained in a yield of 2.03 g (92%).

Ellipticine (1). A mixture of tosylate **12** (0.4 g, 2.1 mmol), dioxane (12 mL), and a 21% HCl solution (0.8 mL) was refluxed for 6.5 h. The workup of the reaction mixture was

carried out according to a procedure reported previously.[15] Product **1** was obtained in a yield of 0.16 g (80%). The physicochemical characteristics of the synthesized alkaloid correspond to the published data[18,19] (see Table 2).

References

1. S. Goodwill, A. F. Smith, and E. C. Horning, *J. Am. Chem. Soc.*, 1959, **81**, 1903.
2. L. K. Dalton, S. Demerac, B. S. Elmes, J. W. Loder, J. M. Swan, and T. Tetei, *Aust. J. Chem.*, 1967, **20**, 2715.
3. G. H. Svoboda, G. A. Poore, and M. L. Montfort, *J. Pharm. Scien.*, 1968, **57**, 1720.
4. V. K. Kansal and P. Petier, *Tetrahedron*, 1986, **42**, 2389.
5. M. J. Hewlins, A. M. Oliveira-Campos, and P. V. R. Shannon, *Synthesis*, 1984, 284.
6. G. Alunni-Bistocchi, P. Orvietani, O. Mauffret, S. El Antri, A. Deroussent, P. C. Jacquignon, S. Fermandjian, A. Ricci, and E. Lescot, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2935.
7. A. K. Mohanakrishnan and P. C. Srinivasan, *J. Org. Chem.*, 1995, **60**, 1939.
8. N. Haider, K. Mereiter, and R. Wanko, *Heterocycles*, 1995, **41**, 1445.
9. I. B. Abdrakhmanov, A. G. Mustafin, G. A. Tolstikov, R. N. Fakhretdinov, and U. M. Dzhemilev, *Khim. Geterotsikl. Soedin.*, 1986, 325 [*Chem. Heterocycl. Compd.*, 1986, **3** (Engl. Transl.)].
10. I. B. Abdrakhmanov, A. G. Mustafin, G. A. Tolstikov, R. N. Fakhretdinov, and U. M. Dzhemilev, *Khim. Geterotsikl. Soedin.*, 1987, 505 [*Chem. Heterocycl. Compd.*, 1987, **4** (Engl. Transl.)].
11. I. B. Abdrakhmanov, A. G. Mustafin, V. M. Sharafutdinov, A. S. Taichinova, and G. A. Tolstikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1985, 839 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1985, **34**, 760 (Engl. Transl.)].
12. I. B. Abdrakhmanov, A. G. Mustafin, and G. A. Tolstikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1988, 1852 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1988, **37**, 1657 (Engl. Transl.)].
13. A. G. Mustafin, I. N. Khalilov, I. B. Abdrakhmanov, and G. A. Tolstikov, *Khim. Prirod. Soedin.*, 1989, 816 [*Chem. Nat. Comp.*, 1989 (Engl. Transl.)].
14. A G. Mustafin, I. N. Khalilov, V. M. Sharafutdinov, D. I. D'yachenko, I. B. Abdrakhmanov, and G. A. Tolstikov, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 630 [*Russ. Chem. Bull.*, 1997, **46**, 609 (Engl. Transl.)].
15. S. L. Hegedus, *Tetrahedron*, 1984, **40**, 2415.
16. B. Scholl and H.-J. Hansen, *Helv. Chim. Acta*, 1980, Bd. **63**, 1823.
17. E. C. Horning, M.-G. Horning, and G. N. Walker, *J. Am. Chem. Soc.*, 1948, **70**, 3935.
18. P. A. Cranwell and J. E. Saxton, *J. Chem. Soc.*, 1962, 3482.
19. A. H. Jackson, P. R. Jenkins, and P. V. R. Shannon, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1698.
20. I. B. Abdrakhmanov, V. M. Sharafutdinov, and G. A. Tolstikov, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 1982, 2160 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1985, **32** (Engl. Transl.)].

Received May 18, 1998;
in revised form April 29, 1999