molecule is therefore stable in the lowest π,π^*-triplet state and is reduced only by strong H-donors.

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INTRAMOLECULAR CYCLIZATION OF ortho-(CYCLOHEX-2-ENYL)ANILINES

SYNTHESIS OF ELLIPTICINE

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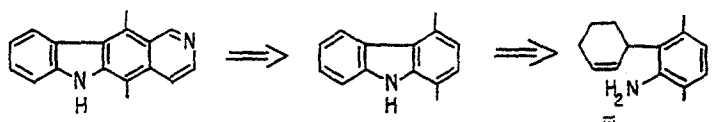
A convenient method is proposed for the synthesis of the alkaloid ellipticine, which possesses a pronounced antitumoral activity. The interaction of 3-bromocyclohexene (1 equiv.) and 2,5-xylylidine (4 equiv., 150°C, 5 h) gave a mixture of hexa- and tetrahydrocarbazoles which was dehydrogenated in the presence of Pd/C to the key synthon 1,4-dimethylcarbazole. The formylation of the carbazole by the Vilsmeier-Haack reaction, interaction with 2,2-diethoxyethylamine, and reduction of the imine formed over Raney nickel led to 3-(2,2-diethoxyethylaminomethyl)-1,4-dimethylcarbazole, the boiling of the N-tosylate of which gave ellipticine in high yield.

The alkaloid ellipticine (I), isolated from the leaves of the plant Ochrosia elliptica Gabil (fam. Apocynaceae) [1], and some of its synthetic analogues possess a high antitumoral activity [2, 3]. In view of this, several methods for synthesizing ellipticine and its derivatives based on traditional methods have been developed [4, 5].

A retrosynthetic analysis of the structure of ellipticine (I) has enabled a convenient approach to the synthesis of the alkaloid to be discovered. We have previously realized a fairly simple route using ortho-(cyclohex-2-enyl)-2,5-xylidine (III), the cyclization of which, followed by dehydrogenation, led to 1,4-dimethylcarbazole (II) — the key compound in the synthesis of ellipticine (I) [6].



I II III

The Claisen rearrangement of N-alkenylarylamines that has been developed over a number of years and the intramolecular cyclization of N- and C-alkenylarylamines form a promising

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TABLE 1. Reaction Conditions and Yields of Compound (IIIa)

Catalyst, Solvent	Reaction Temperature and Time	Yield, %
$AlCl_3$, xylene	140°, 5 h	68
$ZnCl_2$, xylene	140°, 4 h	87
$BF_3(OEt_2)_2$*	170°, 6 h	50
HCl, xylene	140°, 3 h	90

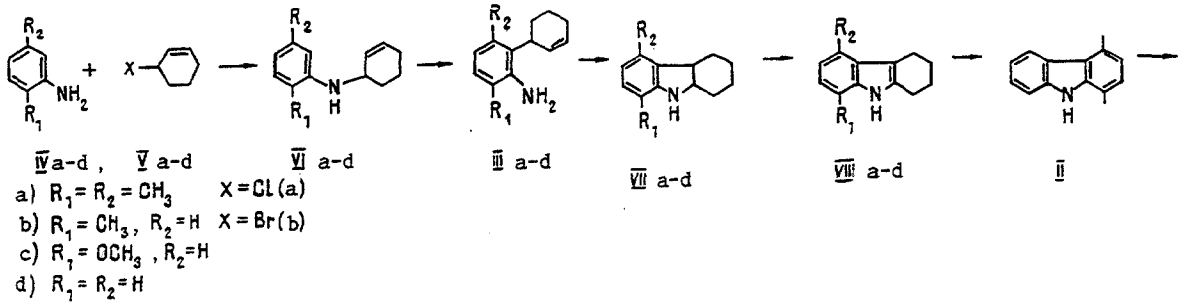
*Without a solvent.

TABLE 2. Conditions for the Cyclization of 6-(Cyclohex-2-enyl)-2,5-xylidine (IIIa) and Yields of the Products (VIIa) and (VIIIa)

Reaction Conditions	Reaction temperature and time	Yields of Compounds, %	
		VIIa	VIIIa
$PdCl_2$, nitrobenzene	140°, 1 h	–	30
UV irradiation, benzene or hexane	20°, 2 h	15	5–7
Polyphosphoric acid	130–140°, 5 h	75	–

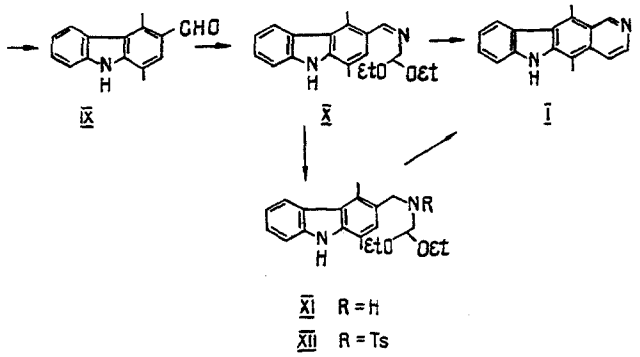
route to the synthesis of quinoline and indole derivatives [7-10]. To choose the most convenient methods for obtaining the hydrocarbazoles (VIIa-d) and (VIIIa-d) we have synthesized the ortho-(cyclohex-2-enyl)anilines (IIIa-d). These compounds were obtained both by the direct method – i.e., by heating 2-chlorocyclohexene (Va) with 3-4 equiv. of the arylamines (IVa-d) – and also from the compounds (VIa-d) obtained beforehand. The N-alkenylarylamine (VIa) was rearranged into the ortho- compound (IIIa) under the action of Lewis and Bronsted acids (Table 1). In the methods studied, the best results were obtained on catalysis by $ZnCl_2$ and HCl, when the yield of product (IIIa) reached 90%.

For the intramolecular cyclization of substance (IIa) we used polyphosphoric acid (PPA), UV irradiation, and the complex $PdCl_2 \cdot (PhNO_2)_n$. The maximum yield of the hexahydrocarbazole (VIIa) amounted to 75% and was achieved by the use of PPA (Table 2). On photocyclization and catalysis by Pd(II), which are frequently used for the heterocyclization of 2-alkenylarylamines [11, 12], the yields of the products (VIIa) and (VIIIa) amounted to 15 and 30%, respectively. The dehydrogenation of the hydrocarbazoles (VIIa) and (VIIIa) with the formation of 1,4-dimethycarbazole (II) was carried out in accordance with [13].



IVa-d, Va-d; VIa-d; IIIa-d; VIIa-d; VIIIa-d; II

a) $R_1 = R_2 = CH_3$ X = Cl(a)
b) $R_1 = CH_3$, $R_2 = H$ X = Br(b)
c) $R_1 = OCH_3$, $R_2 = H$
d) $R_1 = R_2 = H$



IX; X; I

XI R = H
XII R = Ts

Subsequent experiments unexpectedly showed that on the interaction of 3-bromocyclohexene (Vb) with an excess of the arylamine (IVa) a mixture of hexahydro- and tetrahydrocarbazoles (VIIa) and (VIIIa) was formed with high yields. For example, by heating compounds (IVa) (4 equiv.) and (Vb) (1 equiv.) at 150°C for 5 h a mixture of the products (VIIa) and (VIIIa) in a ratio of 2:3 was obtained with a yield of 78%. It had been established previously that on the intramolecular cyclization of 2-(1-methylbut-2-enyl)anilines under the action of $PdCl_2 \cdot (PhCN)_2$ in nitrobenzene solution quinoline and indole derivatives were formed and part of the solvent was reduced to aniline [8]. In this case, therefore, in place of an excess of 2,5-xylidine we used nitrobenzene as solvent and dehydrogenating agent.

It was established that heating equimolar amounts of compounds (IVa) and (Vb) gave only the tetrahydrocarbazole (VIIIa), with a yield of 59%. Consequently, the hexahydrocarbazole (VIIa) formed in the course of the reaction had been converted into compound (VIIIa). But it must be mentioned that the use of the preceding method for obtaining the key synthon in the synthesis of ellipticine is more justified, since in the following stage the mixture of compounds (VIIa) and (VIIIa) was dehydrogenated to 1,4-dimethylcarbazole (II) under the action of Pd/C with a yield of 87%. The formylation of the carbazole (II) and the interaction of substance (IX) with 2,2-diethoxyethylamine to form the imine (X) took place fairly smoothly [14]. The direct cyclization of the imine (X) in polyphosphoric acid led to ellipticine (I) with a yield of 15%. The optimum variant proved to be the reduction of imine (X) over Raney nickel to compound (XI) followed by the cyclization of its N-tosylate in dioxane solution [5]. In this case, the yield of ellipticine amounted to 80%.

EXPERIMENTAL

IR spectra were taken on a UR-20 instrument, PMR spectra on a Tesla BS-567 B instrument (100 MHz, internal standard TMS, solvents $CDCl_3$ and DMSO-d_6), and mass spectra on a MKh-13-06 instrument with an energy of the ionizing electrons of 70 eV and a temperature of the ionization chamber of 200°C. GLC analysis was conducted on a LKhM-8 MD chromatograph with a 3 × 2700 mm column containing 5 of SE-30 on Chromaton N-AW-DMCS at a rate of flow of helium of 30 ml/min. The physicochemical constants of the compounds obtained are given in Table 3.

Synthesis of N-(Cyclohex-2-enyl)arylamines (VIa-d). 3-Chlorocyclohexene (11.6 g; 0.1 mole) was added to a solution of 12 g (0.1 mole) of arylamine (IV) in 50 ml of triethylamine, and the mixture was heated at 80-90°C for 2 h. Then it was treated with water (3 × 20 ml) and with 30% KOH solution, and was dried over $MgSO_4$. The solvent was driven off under reduced pressure, and the residue was rectified in vacuum. The yields of the products amounted to 75-86%.

Catalytic Rearrangement of the N-Alkenylarylamine (VIa). a) A solution of 7 g (35 mmole) of compound (VIa) in 20 ml of xylene was treated with 7 mole of catalyst (see Table 1) and was boiled for 3 h. The reaction mixture was washed with an aqueous solution (15%) of KOH, and the organic layer was separated off, dried over KOH, and distilled in vacuum. The yield of compound (IIIa) was 68-90%. b) A mixture of 1.7 g of compound (VIa) and 2.6 ml of $BF_3 \cdot (Et_2O)_2$ was heated at 170°C for 6 h. Then it was treated with Na_2CO_3 solution and was extracted with ether (3 × 30 ml). The organic layer was dried over KOH, and the ether was evaporated off. The product, compound (IIIa), was purified by column chromatograph on Al_2O_3 with benzene–hexane (1:1) as eluent. The yield of compound (IIIa) was 50%.

1,4-Dimethyl-5,6,7,8,12,13-hexahydrocarbazole (VIIa). Compound (IIIa) (10 g) was heated in polyphosphoric acid (60 g; 50 g of H_3PO_4 + 10 g of P_2O_5) at 140°C for 5 h. Then the mixture was treated with concentrated KOH solution and was extracted with benzene (5 × 50 ml). The extract was dried over $MgSO_4$, the solvent was driven off under reduced pressure, and the residue was rectified in vacuum. This gave 7.5 g (75%) of substance (VIIa).

Photochemical Cyclization of (IIIa). In a quartz reactor with an atmosphere of argon, 1 g of compound (IIIa) in 800 ml of benzene or hexane was irradiated with a DRT-375 lamp for 45 min. The solvent was evaporated off under reduced pressure, and the residue was chromatographed on Al_2O_3 with benzene–hexane (1:4) as eluent. This gave 15% of compound (VIIa). 5.7 % of (VIIIa), and 25% of (IIIa).

Cyclization under the Action of $PdCl_2$. A solution of 0.5 g of substance (IIIa) in 10 ml of nitrobenzene was treated with 0.25 mmole of $PdCl_2$ and was heated in an autoclave at 140°C for 2 h. The solvent was driven off in vacuum, and the product was isolated by chromatography on Al_2O_3, with benzene as eluent. The yield of compound (VIIIa) was 30%.

TABLE 3. Boiling (melting) Points and Spectral Characteristics of Compounds (VII)-(XII)

Compound	bp, °C mp, °C	M+	IR spectrum, ν, cm^{-1}	PMR spectrum (δ, ppm, J, Hz)
1	2	3	4	5
VIIb	128—130/1 mm	187	780; 1280; 1520; 160; 2860; 2920; 3370	1,66—1.83 (m, 8H, $4CH_2$) 1,95 (s, 3H, CH_3); 2, 30 (m, CH); 3,26 (s, NH); 3.58 (m, HC—N) 6,30—6,93(m, ArH)
VIIc	134—137/1 mm	203	780; 126?; 1530; 1620; 2870; 2910; 3400	1,43—2.21 (m, 8H, $4CH_2$); 2,94—3,06 (m, 1H, CH); 3,79—3,81 (m, 1H, HC—N); 3.82 (s, OCH_3); 3,85(s, H, NH); 6,58—6.76(m, 3H, ArH)
VIId	130—133,1 mm	173	770; 1300; 1500; 1620; 2860; 2930; 3040; 3380	1,57—2,08(m, 8H, $4CH_2$) 2,57—2,68 (m, 1H, CH); 3,57(m, 1H, HC—N); 4,65(s, 1H, NH); 6,53—7.16(m, 4H, ArH)
VIIIa	140—142/1 mm	199	760; 1250; 1470; 1520; 2860; 2900 3100; 3420	2,31(s, 3H, CH_3; 2,52 (s, 3H, CH_3) 2,65(m, 4H, $2CH_2$), 2,95(m, 4H, $2CH_2$); 6,65(d, 1H, ArH, J=7,3 Hz); 6,71(d, 1H, ArH, J=7,3 Hz); 7,6(s. 1H, NH)
VIII b	139—142,1 mm	185	780; 1260; 1520; 1600; 2860; 2800; 342	1,86—1,91 (m, 4H, $2CH_2$); 2,92(s, 3H, CH_3); 2.64—2,75(m, 4H, $2CH_2$); 6,88—7,35(m, ArH) 7,47 (s, 1H, NH)
VIII c	142—145/1 mm	201	770; 1260; 1510; 1620; 2870; 2940; 3400	1,42—2,06 (m, 8H, $4CH_2$); 3,64 (s, NH); 3,80 (s, 3H, OCH_3); 6,70—6,83 (m, 3H, ArH)
VIII d	135—138/1 mm	171	760; 1260; 1500; 1600; 2860; 2950; 3340	1,73—2,29(m, 8H, $4CH_2$): 5,80 (s, 1H, NH); 7,19—7,63(m, 4H, ArH)
IX	213	223	735:880; 1270; 1640; 2920; 3340;	2,61 (s,3H, CH_3); 2,70(s, 3H, CH_3); 7,08(s,1H, ArH); 7.15—8,01 (m, 3H); 8,15 (dd,, 1H, ArH, J_1=2Hz, J_2= 8 Hz); 10,39 (s, CHO)
X	130	338	760; 890; 1100; 1460; 1510; 1600; 2920; 2980; 3470	1,22(t, 6H, $2CH_3$, J=7Hz), 2,38 (s, 3H, CH_3); 2,75 (s, 3H, CH_3); 3,62—3,87 (m, 6H, $3CH_2$); 4,90 (t, 1H, O—CH—O, J=5 Hz); 7,01—7,41 (m, 3H, ArH); 7,78 s, 1H, ArH), 8,20 (d, 1H, ArH, J=8 Hz); 8,72 (s, HC=N—); 8,88 (s, 1H, NH)
XI	105	340	750; 880; 1060; 1100; 1460;1500; 1600; 2900; 2970; 3380; 3470	1,20 (t, 6H, $2CH_3$, J=7Hz), 2,72(s, 2H, CH_2); 2,48 (s, 3H, CH_3); 2,85 (s, 3H, CH_3); 3,64(q, 6H, $3CH_2$, J=8Hz), 3,97(s, 1H, NH); 4,72 (t, 1H, CH, J= =8Hz; 7,16—7,44 (m, 4H, ArH); 8,22 (d 1H, ArH, J=8Hz); 8,44(s, 1H, NH)
XII	184	—	—	1,16 (t, 6H, $2CH_3$, J=7Hz), 2,42(s, 3H, CH_3); 2,46(s, 3H, CH_3); 2,82(s, 3H, CH_3); 3,48(d, 2H, CH_2 J=7Hz); 3,62(q, 4H, $2CH_2$, J=8Hz); 4,72 (t, 1H, CH, J = 8Hz); 4,92 (s. 2H, CH_2—Ar); 7,16—8,18 (m, 9H, ArH); 8,32 (s, 1H, NH)

Production of Mixtures of the Hexa- and Tetrahydrocarbazoles (VII a-d) and (VIIIa-d). 3-Bromocyclohexene (5 g; 0.31 mole) was gradually added to 20 g (0.17 mole) of one of the arylamines (IVa-d), and the mixture was heated at 150°C for 5 h. The cooled reaction mixture was treated with a 30% solution of KOH (3 × 100 ml), dried over $MgSO_4$, and distilled in vacuum. The total yields of the products amounted to: 78% for (IIIa), 75% for (IIIb), 76% for (IIIc), and 64% for (IIId).

1,4-Dimethylcarbazole (II). A solution of 5 g of the mixture of compounds (VIIa) and (VIIIa) in 20 ml of trimethylbenzene was treated with 1.5 g of 5% Pd/C and was boiled for

3 h. Then the reaction mixture was filtered and was washed with hot ethyl acetate. The solution was concentrated and was treated with 50 ml of petroleum ether (40-70°C). The product precipitated in the form of a white powder. Yield 4.2 g (87%).

3-Formyl-1,4-dimethylcarbazole (IX). 1,4-Dimethylcarbazole (2.3 g) was added to a mixture of 2.1 g of N-methylformanilide and 2.2 g of $POCl_3$ in 6 ml of dichlorobenzene, and the resulting reaction mixture was heated in the water bath for 5 h. Then it was worked up as described in [14]. The yield of compound (IX) was 1.2 g (46%).

3-(2,2-Diethoxyethyliminomethyl)-1,4-dimethylcarbazole (XI). A mixture of 1 g of compound (IX) and 0.66 ml of 2,2-diethoxyethylamine was heated at 100°C for 2 h. The product was purified by column chromatography on silica gel with chloroform as eluent. Yield 1.25 g (82.7%).

3-(2,2-Diethoxyethylaminomethyl)-1,4-dimethylcarbazole (X). The imidazole (X) (2 g) in 50 ml of absolute ethanol was hydrogenated in the presence of 0.4 g of catalyst (Raney nickel) in an autoclave under a pressure of 8 atm. at room temperature for 24 h. After purification on silica gel (eluent—chloroform) 1.5 g (74.6%) of compound (XI) was obtained.

3-[N-(2,2-diethoxyethyl)-N-tosylaminomethyl]-1,4-dimethylcarbazole (XII). A mixture of 1.5 g of the amine (XI) and 0.94 g of p-toluenesulfonyl chloride in 8 ml of dry pyridine was left at room temperature for 72 h. The pyridine hydrochloride that had deposited was filtered off and, after the addition of 30 ml of water to the reaction mixture, the product was extracted with chloroform (5 × 20 ml). The extract was dried with $MgSO_4$ and the solvent was driven off under reduced pressure, to give 2.03 g (92%) of the tosylate (XII).

Ellipticine (I). A mixture of 0.4 g of the tosylate (XII), 12 ml of dioxane, and 0.8 ml of 6 M hydrochloric acid was boiled for 6.5 h. The reaction mixture was worked up as in [15]. The yield of product was 0.16 g (80%). The physicochemical characteristics of the alkaloid obtained agreed with those given in the literature [14, 15].

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