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STEREOSELECTIVE REDUCTION OF THE ACTIVE SUBSTANCE OF THE MEDICINAL PREPARATION DIMEBON TO THE CORRESPONDING *cis*- AND *trans*-1,2,3,4,4*a*,9*b*-HEXAHYDRO DERIVATIVES

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Convenient preparative methods have been developed for the reduction of the active substance of the medicinal preparation Dimebon (2,8-dimethyl-5-[2-(6-methylpyrid-3-yl)ethyl]-1,2,3,4-tetrahydro-γ-carboline) to the corresponding racemic cis- and trans-1,2,3,4,4a,9b-hexahydro derivatives, distinguished by a high degree of stereoselectivity. The structures of the obtained diastereomeric hexahydro-γ-carbolines were confirmed by various physicochemical methods, including X-ray structural analysis.

Keywords: Dimebon, 1,2,3,4-tetrahydro-γ-carbolines, 1,2,3,4,4*a*,9*b*-hexahydro-γ-carbolines, stereoselective reduction.

Chemical modification of lead-compounds is one of the methods of creating and searching for new biologically active compounds, on the basis of which medicinal agents may be created which possess larger effect in comparison with the precursors [1]. Very frequently lead-compounds become known drugs released onto the market [2]. One of such lead-compounds without doubt is the original domestic preparation Dimebon (2,8-dimethyl-5-[2-(6-methylpyrid-3-yl)ethyl]-2,3,4,5-tetrahydro-1H-pyrido[4,3-*b*]indole, **1**), which possesses a broad pharmacological profile [3]. At the present time it is used in medical practice as an antihistamine agent [4]. In addition Dimebon displays cardioprotective [5] and antiarrhythmic properties [6], it shows an effect on the transmission of nerve impulses and the metabolism of catecholamines in brain structures [7], protects neurons from the neurotoxic action of β-amyloid (EC_{50} = 25μM), displays the action of a calcium channel blocker (IC_{50} = 57 μM), it has inhibiting activity in relation to cholinesterases (IC_{50} = 7.9 μM and 42 μM for butyryl- and acetylcholinesterase respectively) [8], and demonstrates improvement of memory and cognitive ability. It is also a blocker of the NMDA subtype of glutamate receptors (ED_{50} = 42 mg/kg), activating the AMPA subtype at low concentrations [9]. At the present moment Dimebon is patented as a therapeutic agent intended for the treatment of neurodegenerative diseases, in particular Alzheimer's disease [10] and Huntington's

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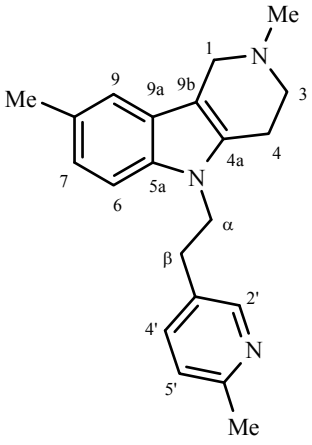
chorea [11]. With the aim of revealing new physiologically active derivatives in the γ-carboline series we have developed methods of reducing Dimebon to 1,2,3,4,4a,9b-hexahydro-γ-carboline derivatives distinguished by high stereoselectivity.



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Dimebon

A whole series of grounds served as the reason for selecting precisely this direction of chemical modification of the lead-compound. In the first place, hexahydro-γ-carbolines possess an extremely broad spectrum of biological activity. Principally, they show action on the CNS, emerging as psychotropic agents [3]. Secondly, compounds of this series with *cis* and *trans* linkage of the piperidine and pyrrole fragments possess, sometimes, a different physiological action [3 and literature cited therein]. Finally, the presence in the side chain of molecule **1** of a pyridine fragment capable of complex formation with complex metal hydrides may, to a significant extent, affect the stereochemical result of reduction in comparison with methods known in the literature for 5-unsubstituted 1,2,3,4-tetrahydro-γ-carbolines. In particular, on reducing tetrahydro-γ-carbolines containing an aminoalkyl substituent $(CH_2)_nNR_2$ at atom N(5), competition was observed between the two variants of the intramolecular reduction, which leads to the formation of a mixture with a different ratio of *cis* and *trans* isomers depending on the length of the alkyl chain (for more detail on the mechanisms of reduction see [12]). Consequently the development of methods, distinguished by highly stereoselective reduction of such compounds as Dimebon, seemed not only of applied but also of theoretical interest.

Reduction with hydrogen over PtO_2 [13], with borane complexes with THF [14], with pyridine [15] or trimethylamine [16] in strongly acidic medium, $NaBH_4$ in carboxylic acids (as a rule in CF_3CO_2H) [17], and also with metallic Na in liquid ammonia [18] or triethylsilane in CF_3CO_2H [19] lead to the formation of isomers of hexahydro-γ-carbolines with a *cis* junction of the pyrroline and piperidine rings. In addition, reduction with Zn or Sn in acidic medium is mainly accompanied by the formation of the corresponding *cis* isomer [20].

Reduction of tetrahydro-γ-carbolines to the corresponding *trans* hexahydro derivatives is carried out, as a rule, using borane or its complexes with subsequent treatment with strong acid [21]. The key stage in this process is the formation of a borane–tetrahydro-γ-carboline complex at the N(2) atom.

With the aim of searching for an efficient method of reducing Dimebon to the corresponding *cis* derivative **2** we tried a series of known literature methods: solution of the BH_3–THF complex in CF_3CO_2H [14] and in 15% HCl solution, $NaBH_4$ in CF_3CO_2H [17], metallic Na in liquid ammonia [18], and amalgamated Zn in hydrochloric acid [20]. The results of the reduction are given in Table 1.

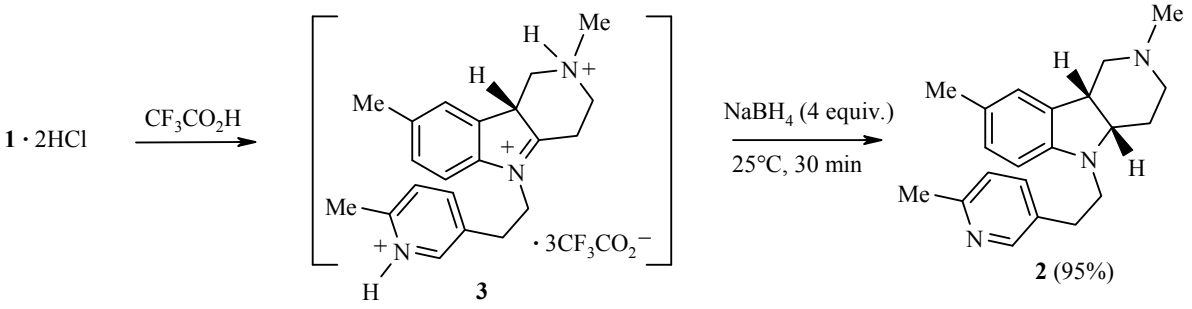
It is worth mentioning that the best results were obtained using 4 equiv. $NaBH_4$ in trifluoroacetic acid (complete conversion), while the use of 2 equiv. $NaBH_4$ [17] was accompanied by incomplete reduction of the initial compound **1** (conversion 85-90%). A further virtue of the proposed method is the possibility to reduce

TABLE 1. Results of *cis* Reduction of Dimebon

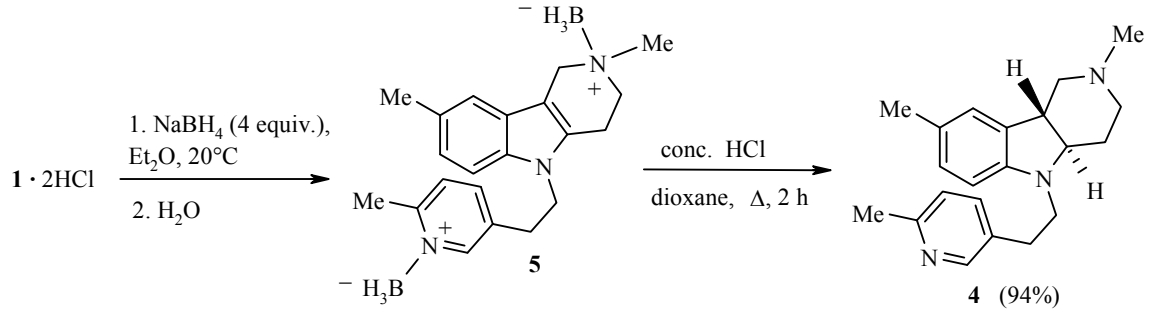
Method	Reducing system	Reaction conditions	Conversion, %*
A	Zn (10 equiv.)–$HgCl_2$ (0.1 equiv.)–conc. HCl	Boiling, 10 h	~30–35
B	Na–NH_3 (liq.)–THF (abs.)	-35– (-40) °C, 15 min	~60
C	1 mol/l BH_3–THF (4.0 equiv.)–15% HCl–dioxane	Boiling, 1 h	~20
D	1 mol/l BH_3–THF (2.5 equiv.)–CF_3CO_2H	Boiling, 1 h	~10
E	$NaBH_4$ (1–2 equiv.)–CF_3CO_2H	20°C, 0.5–3 h	~85–90
F	$NaBH_4$ (4 equiv.)–CF_3CO_2H	20°C, 0.5 h	~100

*Conversion was calculated from data of ^{1}H NMR spectra.

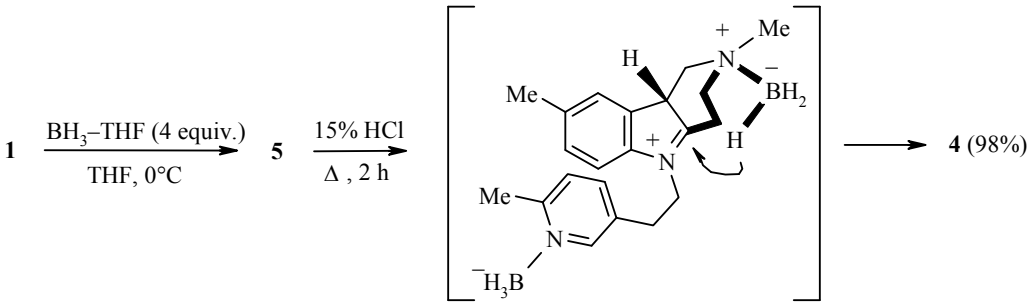
the initial compound both as the base and as the dihydrochloride. The use of a commercial solution of the BH_3–THF complex (1 M) proved to be ineffective as also was reduction using metals. It is important to note that on using boron hydrides the formation of the *cis* derivative was effected as a result of intermolecular hydride transfer to the indoleninium cation **3**, formed on protonation of tetrahydro-γ-carboline in strongly acidic medium.



Reduction of Dimebon (**1**·2HCl) to the corresponding *trans* derivative **4** was effected by the procedure known from the literature [15], implying the initial formation of a borane–tetrahydro-γ-carboline complex **5** on interacting the carboline hydrochloride with $NaBH_4$ and its subsequent treatment with strong acid.



A change in the order of adding BH_3–THF complex and acid may lead to a change in the stereochemistry of the reduction process. In the case of *cis* reduction by method C (Table 1) the BH_3–THF complex is added to a solution of Dimebon in 15% HCl, but treatment of compound **1** as the base with BH_3–THF complex, and then with 15% HCl leads to the product of *trans* reduction **4**. The reason for the observed phenomenon may be that on treatment of base **1** with a solution of BH_3 in THF an irreversible bonding of borane with the tertiary N(2) atom and the nitrogen atom of the pyridine ring occurs accompanied by the formation of complex **5**, which in acidic medium undergoes reduction into *trans* derivative **4** as a result of intramolecular hydride transfer, proceeding through a six-membered transition state.



The *trans* derivatives **4**, obtained by the two methods given above, possesses identical ^{1}H and ^{13}C NMR spectra, and the trihydrobromide gave no depression of melting point (mp 234-235°C), while a mixture of compounds **2** and **4** melted at 220-221°C.

TABLE 2. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			m/z $[M]^+$	mp, °C	Yield, %
		C	H	N			
1	$C_{21}H_{25}N_3$				319	120-121	39
	$C_{21}H_{25}N_3 \cdot 2HBr$	52.53 / 52.41	5.51 / 5.65	8.72 / 8.73		270-271	
2	$C_{21}H_{27}N_3$				321	—	95
	$C_{21}H_{27}N_3 \cdot 3HBr$	44.79 / 44.71	5.39 / 5.36	7.30 / 7.45		213-215	
4	$C_{21}H_{27}N_3$				321	—	92 (98)
	$C_{21}H_{27}N_3 \cdot 3HBr$	44.65 / 44.71	5.29 / 5.36	7.39 / 7.45		234-235	

TABLE 3. ^{1}H NMR Spectra of Compounds **2** and **4***

Group of atoms	Chemical shifts, δ, ppm (*J*, Hz)	
	cis isomer **2**	*trans* isomer **4**
H*a*-4		1.71 (1H, ddd, J_1 = 12.6, J_2 = 11.9, J_3 = 4.3)
H*e*-4		1.94 (1H, m)
H*a*-3	1.89-2.02 (4H, m)	2.10 (1H, ddd, J_1 = 11.9, J_2 = 11.7, J_3 = 2.7)
H*a*-1		2.18 (1H, dd, J_1 = 10.8, J_2 = 10.6)
8-CH_3	2.27 (3H, s)	2.30 (3H, s)
2-CH_3	**2.24 (3H, s)**	**2.43 (3H, s)**
6'-CH_3	2.51 (3H, s)	2.55 (3H, s)
H-4a	**3.48 (1H, m)**	**2.65 (1H, ddd, J_1=12.6, J_2 = 11.9, J_3 = 3.1)**
β-H	2.82 (2H, t, J = 7.4)	2.82 (2H, t, J = 7.4)
H-9b	**3.17 (1H,** ddd, J_1 = 10.1, J_2 = 6.6, J_2 = 6.1)	**2.86 (1H, m)**
H*e*-3	2.45 (1H, m)	3.02 (1H, m)
α-H	3.24-3.33 (2H, m)	3.24-3.35 (2H, m)
H*e*-1	2.70 (1H, dd, J_1 = 11.4, J_2 = 6.1)	3.44 (1H, dd, J_1 = 10.6, J_2 = 2.7)
H-6	6.45 (1H, t, J = 8.2)	6.54 (1H, t, J = 8.0)
H-9	6.92-6.94 (2H, m)	6.89 (1H, s)
H-7		6.96 (1H, t, J = 8.0)
H-5'	7.10 (1H, t, J = 7.9)	7.09 (1H, t, J = 7.8)
H-4'	7.45 (1H, dd, J_1 = 7.9, J_2 = 2.1)	7.46 (1H, dd, J_1 = 7.8, J_2 = 2.0)
H-2'	8.38 (1H, t, J = 2.1)	8.38 (1H, t, J = 2.0)

* In Tables 3 and 4 characteristic signals are distinguished in bold type.

The stereochemical results of reduction for the *cis* and *trans* isomers **2** and **4** were confirmed by a combination of physicochemical methods.

In the ^{1}H and ^{13}C NMR spectra (Tables 3 and 4) of compounds **2** and **4** differences were observed which are characteristic of diastereomers. In the ^{1}H NMR spectra of compounds **2** and **4** the values of the chemical shifts and multiplicity of practically all the aliphatic protons of the piperidine ring differed significantly. The values of the chemical shifts of the H-4*a* and H-9*b* protons, which are 3.48 and 3.17 ppm for the *cis* isomer **2**

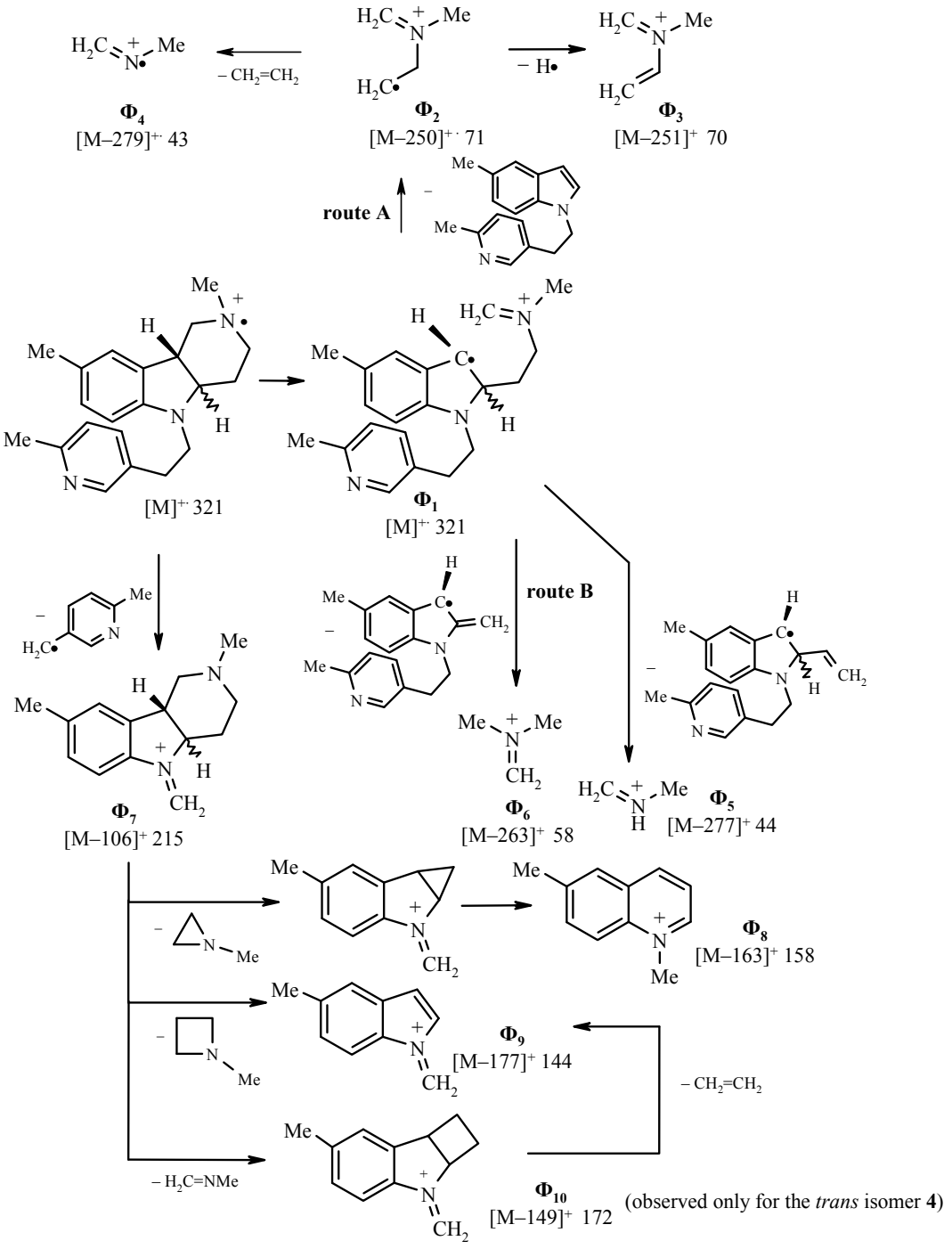
TABLE 4. ^{13}C NMR Spectra of Compounds **2** and **4**

Carbon atom	Chemical shifts, δ, ppm		Carbon atom	Chemical shifts, δ, ppm	
	cis isomer **2**	*trans* isomer **4**		*cis* isomer **2**	*trans* isomer **4**
1-CH_2	58.00	56.94	C(9a)	132.31	131.04
2-CH_3N	46.46	45.89	**C(9b)**	**40.67**	**46.76**
3-CH_2	54.69	54.38	2'-CH	149.37	149.29
4-CH_2	25.30	29.51	C(3')	132.33	132.35
C(4a)	**61.13**	**72.06**	4'-CH	136.80	136.89
C(5a)	156.15	156.13	5'-CH	122.96	122.84
6-CH	107.63	107.77	C(6')	149.29	150.48
7-CH	128.01	127.60	6'-$\underline{C}H_3C$	23.98	24.01
C(8)	127.42	127.77	α-CH_2	48.05	49.24
8-CH_3	20.77	20.84	β-CH_2	30.22	30.38
9-CH	124.29	122.73			

TABLE 5. Results of COSY ^{1}H-^{1}H and ^{1}H-^{13}C experiments

Group of atoms	δ, ppm		
	^{1}H NMR spectrum	Chemical shifts of protons with which to be correlated	Cross-peaks in measuring ^{13}C
Compound **2**			
H*a*-1, H*a*-3, H*a*-4, H*e*-4	1.89–2.02	2.45, 2.70, 3.17	25.30, 54.69, 58.00
2-CH_3	2.24	—	46.46
8-CH_3	2.27	—	20.77
H*e*-3	2.45	1.89-2.02	54.69
6'-CH_3	2.51	—	23.98
H*e*-1	2.70	1.89-2.02, 3.17	58.00
β-H	2.82	3.24-3.33	30.22
H-9*b*	3.17	1.89-2.02, 2.70, 3.48	40.67
α-H	3.24–3.33	2.82	48.05
H-4*a*	3.48	1.89-2.02, 3.17	61.13
Compound **4**			
H*a*-4	1.71	1.94, 2.10, 2.65, 3.02	29.51
H*e*-4	1.94	1.72, 2.10, 2.65, 3.02	29.51
H*a*-3	2.10	1.71, 1.94, 3.02	54.38
H*a*-1	2.18	2.86, 3.44	56.94
8-CH_3	2.30	—	20.84
2-CH_3	2.43	—	45.89
6'-CH_3	2.55	—	24.01
H-4*a*	2.65	1.71, 1.94, 2.86	72.06
β-H	2.82	3.24–3.35	30.38
H-9*b*	2.86	2.18, 2.65	46.76
H*e*-3	3.02	1.71, 1.94, 2.10	54.38
α-H	3.24–3.35	2.82	49.24
H*e*-1	3.44	2.18, 2.86	56.94

and 2.65 and 2.86 ppm for the *trans* isomer respectively, differed especially strongly. There was one further significant difference, the signals of the protons of the CH_3 group on the N(2) atom in the ^1H NMR spectrum of compounds **2** and **4** were found at 2.24 and 2.43 ppm. Analogous differences were also observed in the ^{13}C NMR spectra of compounds **2** and **4**, where for the asymmetric atoms C(4*a*) and C(9*b*) the chemical shifts were 61.13 and 40.67 ppm for the *cis* and 72.06 and 46.76 ppm for the *trans* isomers respectively. Close values for the chemical shifts of the C(4*a*) and C(9*b*) atoms given in [22], which are 58.8 and 40.7 ppm for N(5)-acyl-*cis*-hexahydro-γ-carboline, 69.3 and 47.4 ppm for the isomeric *trans* derivative. For a precise assignment of the proton and carbon atom signals of the aliphatic region additional experiments were carried out by homo- (COSY ^1H-^1H) and heteronuclear (^1H-^{13}C) two-dimensional NMR spectroscopy (Table 5).



NMR double resonance experiments carried out for the *cis* derivative **2** showed that on irradiating the H-4 protons the multiplicity of the H-4a proton degenerates into a doublet with J = 6.6 Hz, corresponding to interaction with the vicinal H-9b proton. The value of this constant indicates a *cis* disposition of the H-4a and H-9b atoms and is in agreement with the value of the analogous constant (J = 6.6 Hz) for the *cis*-hexahydro-γ-carboline derivative given in the literature [22]. This fact indicates the *cis* configuration of compound **2**.

Investigation of the mass spectra of compounds **2** and **4** (see EXPERIMENTAL), which are diastereoisomers, showed that dissociative ionization of the N(5)-substituted isomers with *cis* and *trans* structures under the action of electron impact generally proceeds in a similar manner (the main fragmentation ions **Φ$_2$-Φ$_6$** are analogous forming molecules of N-methylpiperidine [23] on electron impact), however there are also extremely significant differences. For the *trans* isomer **4**, route **B** is effected preferentially, in the course of which, as the result of a McLafferty rearrangement, the ion **Φ$_6$** with *m/z* 58 (100%) is formed, while for the *cis* isomer route **A** dominates with the formation of ion **Φ$_3$** with *m/z* 70 (100%).

Evidently the McLafferty rearrangement proceeds significantly more readily for compound **4** as a result of the features of the spatial structure of the fragmentation ion *trans*-**Φ$_1$**. In this case proton H-4a proved to be spatially contiguous to fragment $H_2C{=}N^+$, which aids the formation of the six-membered transition state necessary for this rearrangement. In the case of the *cis*-**Φ$_1$** ion the H-4a proton proved to be on the opposite side of the $H_2C{=}N^+$ group, which reduces the probability of undergoing dissociative ionization by route **B**, consequently β-elimination of the cation-radical **Φ$_2$** is effected far more easily for compound **2**, being transformed into the fragment ions **Φ$_3$** and **Φ$_4$**.

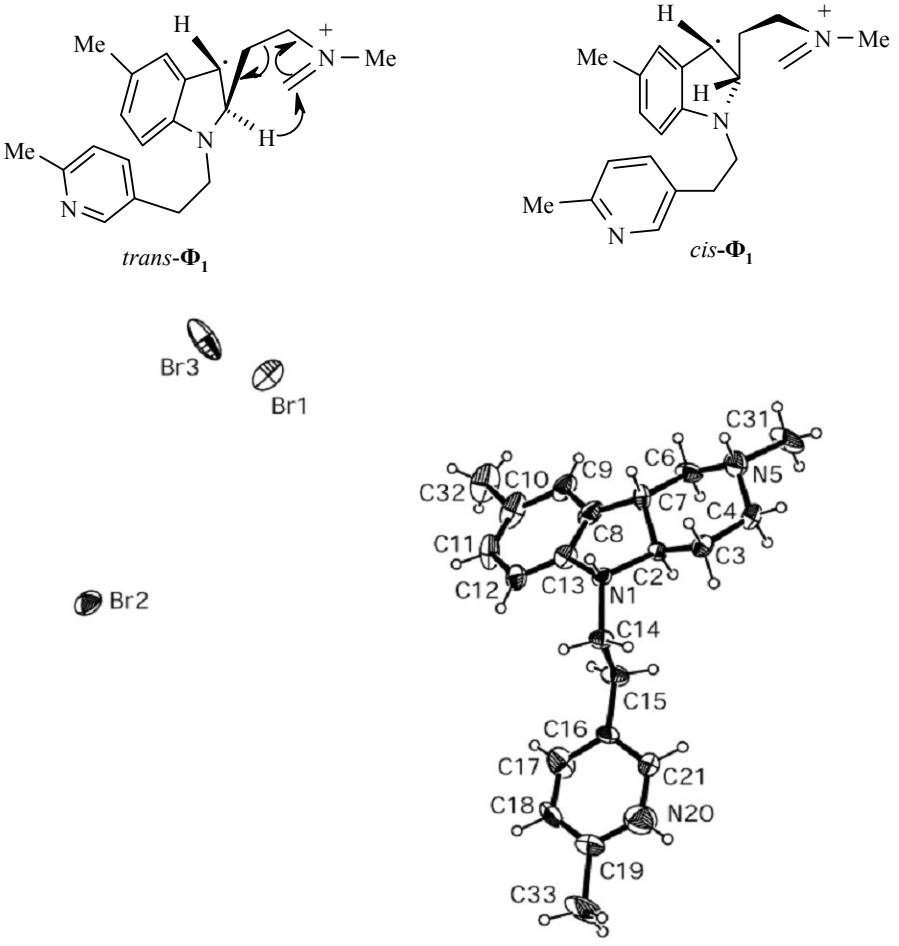


Fig. 1. Molecular structure of *trans* isomer **4**.

In addition a peak for the ion Φ_{10}, which was absent from the spectrum of *cis* derivative **2**, was observed in the mass spectrum of *trans* isomer **4**.

The structure of the trihydrobromide of *trans* isomer **4** was established by X-ray structural analysis (Fig. 1).

Repeated attempts to grow a monocrystal of *cis* isomer **2** trihydrobromide proved to be unsuccessful. Crystals formed from the mother liquor left in the air in the course of time proved to be the dihydrobromide of Dimebon (**1**) (Fig. 2), which is evidently formed on oxidation of compound **2** by oxygen of the air in alcoholic solution.

The complete crystallographic information on structures **1** and **4** have been deposited in the Cambridge Bank of Structural Data (deposit No. CCDC 736428 and CCDC 721100 respectively) and will be published in the journal of *Kristallografiya*.

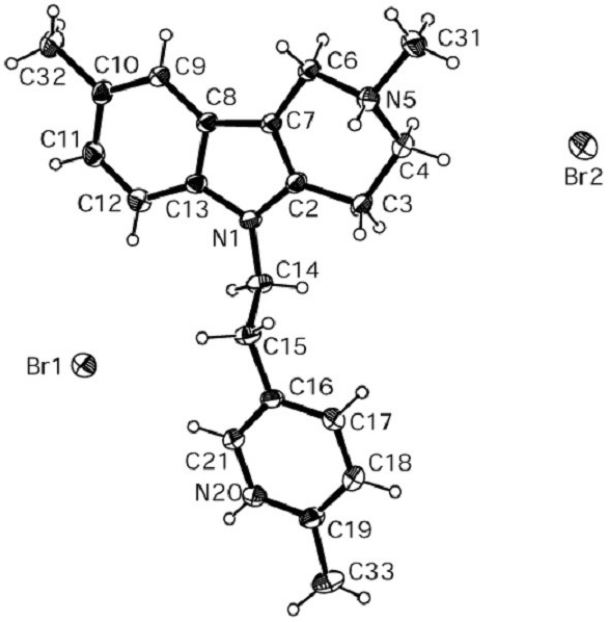


Fig. 2. Molecular structure of Dimebon **1**, formed on growing crystals of *cis* isomer **2**.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra using double resonance $\{^{1}H\text{-}^{1}H\}$, APT, two-dimensional spectroscopy COSY $^{1}H\text{-}^{1}H$ and $^{1}H\text{-}^{13}C$, were recorded on a Bruker Avance-400 instrument. Chemical shifts were measured relative to the signal of the residual protons of the solvent $CDCl_3$ (δ 7.25 ppm). The mass spectra were obtained on an ITD-700 instrument (Finnigan MAT), electron impact (EU), 70 eV, mass range *m/z* 45-400. A check on the progress of reactions and the purity of the isolated compounds was obtained by TLC on Silufol UV-254 plates in the system chloroform–methanol, 10:1.

The initial Dimebon (**1**) was obtained by the known procedure of [24]. Commercial $NaBH_4$ (Fischer Scientific) and trifluoroacetic acid (Lancaster) were used in the reductions.

(4a*R′*,9b*S′*)-2,8-Dimethyl-5-[2-(6-methylpyrid-3-yl)ethyl]-2,3,4,4*a*,9*b*-hexahydro-1H-pyrido[4,3-*b*]-indole (*cis* isomer) (2). A. Zinc dust (0.60 g, 9.2 mmol) was added portionwise to a solution of Dimebon (0.145 g, 0.45 mmol) in ethanol (0.5 ml) in the presence of mercuric chloride (2 mg). Conc. HCl (2.5 ml) was

added dropwise at the same time, and the mixture was boiled for 10 h. After cooling, the reaction mixture was made strongly alkaline with 40% sodium hydroxide solution with stirring. The oil formed on the surface was extracted with ether (3×10 ml), the extract was dried with sodium sulfate and evaporated to dryness. A mixture (0.118 g) of compound **2** and the initial Dimebon **1** in a ratio 1:3 (according to data of ^{1}H NMR spectra) was obtained as a light-yellow oil, crystallizing on extended storage.

B Liquid ammonia (2 ml) was added to a solution of Dimebon (0.166 g, 0.52 mmol) in absolute THF (1 ml) at -40°C, after which metallic sodium was added in portions (3×0.04 g). An intense blue color was observed, which gradually changed to yellow. After adding all of the sodium the reaction mixture acquired a stable blue color. After 15 min the reaction mixture was decomposed by adding ammonium chloride, diluted with water, made alkaline with 10% sodium hydroxide solution, and extracted with methylene chloride (5×20 ml). The extract was dried with sodium sulfate and evaporated to constant mass. A yellow oil (0.153 g) was obtained, on chromatographic purification of which on silica gel with chloroform–methanol, 20:1, the final product **2** (0.09 g, 54%) was obtained as a light-yellow oil, acquiring a dark-brown color on standing in the air.

C. A commercial 1 M solution of BH_3–THF complex (1.05 ml, 1.05 mmol) and 15% HCl (1 ml) were added dropwise with stirring to a suspension of Dimebon dihydrochloride (0.10 g, 0.255 mmol) in dioxane (0.5 ml). The reaction mixture was boiled for 1 h, after cooling, water (10 ml) was added, and the dioxane distilled. The residue was made alkaline with 10% sodium hydroxide solution to pH 10-10.5, and extracted with methylene chloride (5×10 ml). The extract was dried with sodium sulfate, and evaporated to dryness. A mixture (0.079 g) of compound **2** and initial **1** in a 1:4 ratio (according to ^{1}H NMR spectral data) was obtained as a light-yellow oil.

D. A commercial 1 M solution of the BH_3–THF complex (0.64 ml, 0.64 mmol) was slowly added dropwise to a solution of Dimebon dihydrochloride (0.10 g, 0.255 mmol) in trifluoroacetic acid (1.0 ml). The reaction mixture was boiled for 1 h, diluted with water (~1 ml) and the THF distilled. Further treatment of the reaction mixture was carried out analogously to procedure C. A mixture (0.080 g) of compound **2** and the initial Dimebon **1** in a ratio of 1:9 (according to ^{1}H NMR spectral data) was obtained as a light-yellow oil.

E. $NaBH_4$ (0.029 g, 0.75 mmol) was added in portions to a solution of Dimebon (as base) (0.10 g, 0.3 mmol) in trifluoroacetic acid (3.0 ml) at 20°C and the mixture stirred for 3 h. Further treatment of the reaction mixture was carried out analogously to procedure C. A mixture (0.092 g) of compound **2** and the initial Dimebon **1** in a ratio of 9:1 (according to data of ^{1}H NMR spectra) was obtained as a light yellow oil. The initial compound **1** was present according to TLC.

F. $NaBH_4$ (0.040 g, 1.02 mmol) was added in portions to a solution of Dimebon dihydrochloride (0.10 g, 0.255 mmol) in trifluoroacetic acid (2.5 ml) at 20°C and the mixture stirred for 30 min. Further treatment of the reaction mixture was carried out analogously to procedure C. A light-yellow oil (0.078 g, 95%) was obtained. The compound was homogeneous according to TLC. The obtained oil was dissolved in ethanol (3 ml), to which was added conc. HBr (0.2 ml), and the mixture left for 30 min. The solution was evaporated to dryness, and evaporated three times with toluene (5 ml). After recrystallization from ethanol a hygroscopic finely crystalline substance (0.105 g, 73%) of a light-yellow color was obtained. Mass spectrum *m/z* (I_{rel}, %): 321 (12.2) $[M]^+$, 277 (0.8), 215 (10.4), 170 (3.4), 158 (5.8), 157 (4.0), 144 (8.7), 120 (3.2), 82 (19.4), 80 (19.1), 71 (14.9), 70 (100), 58 (16.5), 44 (7.7), 43 (20.8), 42 (12.1).

(4*aR*',9*bR*')-2,8-Dimethyl-5-[2-(6-methylpyrid-3-yl)ethyl]-2,3,4,4*a*,9*b*-hexahydro-1H-pyrido[4,3-*b*]-indole (*trans* isomer) (4). A. $NaBH_4$ (0.12 g, 3.2 mmol) was added in portions with vigorous stirring to a suspension of Dimebon dihydrochloride (0.31 g, 0.79 mmol) in ether (8 ml), and the mixture was maintained for 2 h at 20°C. Water (15 ml) was then added, and the mixture stirred until complete cessation of the evolution of hydrogen (a white solid was precipitated). The solution was decanted, the residue dissolved in dioxane (10 ml), conc. HCl (7 ml) was added, and the mixture boiled for 2 h. After cooling, the reaction mixture was made alkaline with 10% sodium hydroxide solution to pH 10-10.5, and extracted with methylene chloride (4×20 ml).

The extract was dried over sodium sulfate, and evaporated to dryness. A light-yellow oil (0.234 g, 92%) was obtained. The compound was homogeneous by TLC. The obtained oil was dissolved in ethanol (5 ml), conc. HBr (0.5 ml) was added, and the solution left for 30 min. The solution was evaporated to dryness, and evaporated three times with toluene (10 ml). After recrystallization from ethanol a finely crystalline colorless substance (0.385 g, 86%) was obtained. Mass spectrum *m/z* (I_{rel}, %): 321 (8.4) $[M]^+$, 277 (2.9), 215 (26.8), 172 (21.2), 170 (5.6), 158 (9.0), 157 (7.6), 144 (9.9), 120 (9.8), 82 (25.1), 80 (26.1), 71 (2.8), 70 (27.9), 58 (100), 44 (13.7), 43 (6.8), 42 (9.2).

B. A commercial 1 M solution of BH_3–THF complex (2.60 ml, 2.60 mmol) was added dropwise to a solution of Dimebon (base) (0.205 g, 0.64 mmol) in absolute THF (5 ml) at 20°C, after which 15% HCl (10 ml) was added carefully, and the mixture boiled for 2 h. After cooling, the reaction mixture was made alkaline with 10% sodium hydroxide solution to pH 10-10.5, and was extracted with methylene chloride (5×20 ml). The extract was dried with sodium sulfate and evaporated to constant mass. A light-yellow oil (0.202 g, 98%) was obtained from which the trihydrobromide was obtained in 82% yield (0.290 g) by the procedure described above. The ^{1}H NMR spectrum of this compound was analogous to the spectrum of compound **4** obtained by method A. The trihydrobromide gave no depression of melting point on mixing with a sample of trihydrobromide **4**, synthesized by method A.

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