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SYNTHESIS OF HYDROGENATED 2,7-DIMETHYLPYRROLO[3,4-*b*]INDOLES – ANALOGS OF DIMEBON

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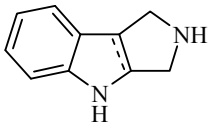
A schemes have been proposed for the synthesis of novel 4-substituted 2,7-dimethyl-3,4-dihydro-1H- and previously unknown 2,7-dimethyl-cis-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-b]indoles. In the case of the Dimebon structural analog 2,7-dimethyl-4-[2-(6-methylpyridin-3-yl)ethyl]-3,4-dihydro-1H-pyrrolo-[3,4-b]indole a broad spectrum of pharmacological activity was found in the hydrogenated pyrroloindoles suitable for the development of medicines via the "magic bullet" concept. A strong dependence of the antagonist relationship of the synthesized compounds towards histamine H_1 and serotonin 5-HT_6 receptors with the nature of the substituent in the 4 position and the degree of hydrogenation of the pyrrolo[3,4-b]indoles was demonstrated.

Keywords: antihistamine agents, Dimebon, pyrrolo[3,4-*b*]indoles.

Heterocyclic compounds containing a hydrogenated pyrrolo[3,4-*b*]indole fragment **1** can be considered as structural analogs of 2,3,4,5-tetrahydro-1H-pyrido[4,3-*b*]indoles **2** which have an exceptionally broad spectrum of pharmacological activity and are licensed materials within a medico-pharmaceutical understanding of this term. An excellent example of this series of compounds is Dimebon, i.e. 2,8-dimethyl-5-[2-(2-methylpyridin-5-yl)ethyl]-



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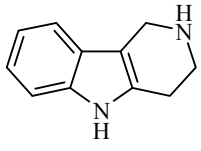

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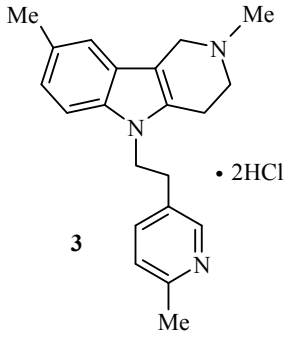

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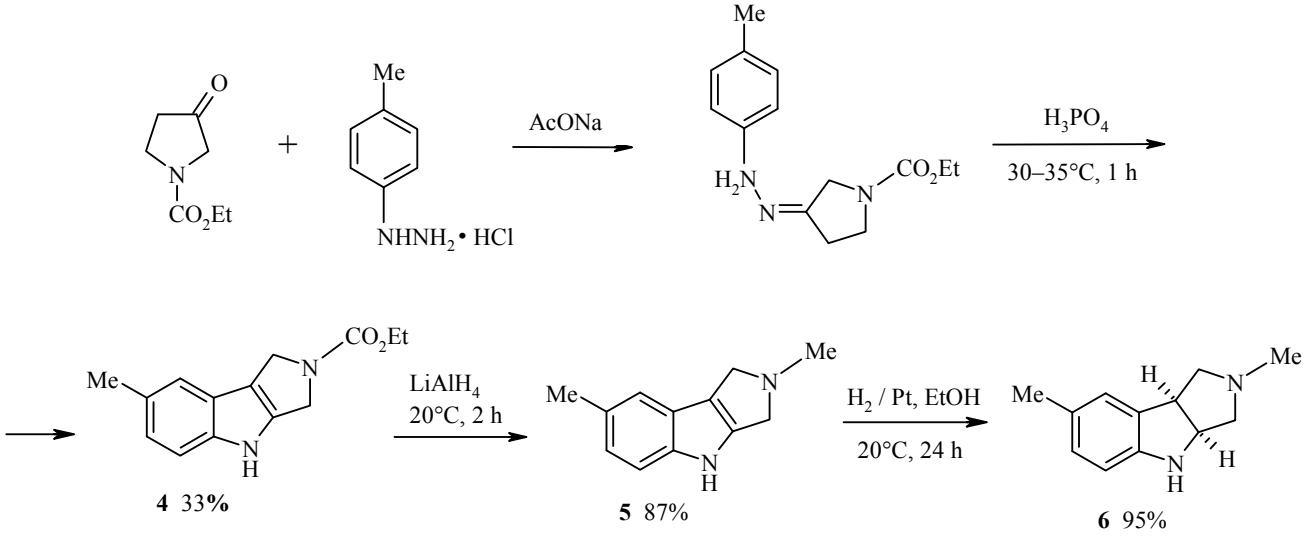
2,3,4,5-tetrahydro-1H-pyrido[4,3-*b*]indole dihydrochloride (**3**). Dimebon was first synthesized in 1961 [1, 2], used from 1983 in Russia as an antihistamine preparation [3, 4], and recently regarded as an effective agent in the therapy of neurodegenerative illnesses, e.g. in particular Alzheimer's and Huntington's diseases [5, 6].

This statement allows one reliably to propose that a synthesis and study of the properties of novel structural analogs of Dimebon in the little examined series of pyrrolo[3,4-*b*]indoles is undoubtedly of interest in a search for novel, pharmacologically active molecules.

The first pyrrolo[3,4-*b*]indoles were prepared by cyclization of substituted 3-(phenylhydrazono)-pyrrolidin-2-ones under Fischer reaction conditions and subsequent $LiAlH_4$ reduction of the 1,4-dihydro-2H-pyrrolo[3,4-*b*]indol-3-ones formed [7, 8]. A single stage synthesis was proposed later based on Fischer cyclization of 2-ethoxycarbonyl-3-(phenylhydrazono)pyrrolidines [9-13]. One further synthesis of 2,4-di-substituted tetrahydropyrrolo[3,4-*b*]indoles consists of the reaction of 2,3-di(bromomethyl)-1-phenyl-sulfonylindole with primary amines [14, 15].

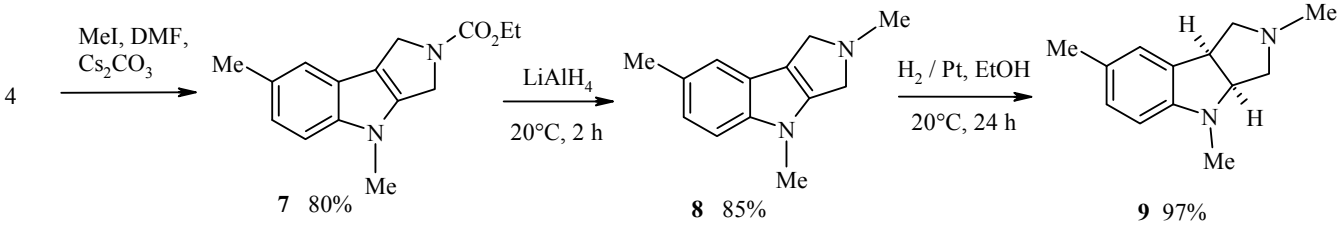
In continuation of our work [16-18] on the synthesis and study of the biological activity of structural analogs of Dimebon **3** it appeared appropriate to prepare some hydrogenated 2,7-dimethylpyrrolo[3,4-*b*]indoles and to study their pharmacological properties. For preparation of the needed pyrrolo[3,4-b]indoles we have used well known reactions. Our task involved just a choice of necessary structures and optimal schemes for their synthesis.

Starting from 1-ethoxycarbonylpyrrolidin-3-one and *p*-tolylhydrazine we have prepared 2-ethoxy-carbonyl-7-methyl-3,4-dihydro-1H-pyrrolo[3,4-*b*]indole (**4**), reduced it with $LiAlH_4$ to 2,7-dimethyl-3,4-dihydro-1H-pyrrolo- [3,4-*b*]indole (**5**), and hydrogenated the latter in almost quantitative yield to 2,7-dimethyl-*cis*-1,2,3,3a,4,8*b*-hexahydropyrrolo[3,4-*b*]indole (**6**) (the first representative of a novel heterocyclic system).

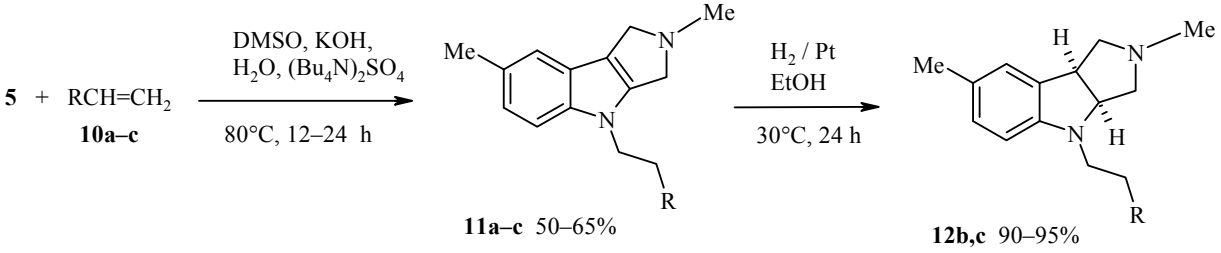


The 2,4,7-trimethyl-3,4-dihydro-1H-pyrrolo[3,4-*b*]indole (**8**) and its hydrogenated analog **9** were prepared by successive methylation of compound **4**, reduction of the 2-ethoxycarbony- 4,7-dimethyl derivative **7** formed to the trimethyl derivative **8**, and hydrogenation of the latter using hydrogen on platinum.

It is known that 2-alkyl-γ-carbolines unsubstituted in the 5 and 8 positions readily take part in a Michael reaction in the presence of metallic sodium and add 2- and 4-vinylpyridines to give 5-(pyridinylethyl)-γ-carbolines [19]. It was found later that the use of DMSO as solvent in this reaction leads to a powerful activation of the anions formed by the action of sodium or sodium hydride on 2-alkyl-γ-carbolines. As a result of this, reaction becomes possible with 3-vinylpyridines in which the vinyl bond is rather weakly polarized, none the less, forming Dimebon **3** under these conditions [20].



We have used this reaction for preparing the 2,7-dimethyl-4-(pyridinylethyl)-3,4-dihydro-1H-pyrrolo[3,4-*b*]indoles (**11a-c**). Reaction of the pyrrolo[3,4-*b*]indole **5** with the vinylazines **10a-c** occurs more smoothly to form the least amount of side and tarry products if it is carried out in the biphasic system of DMSO and 60% KOH in the presence of $(Bu_4N)_2SO_4$ as phase-transfer catalyst. It should be noted that reaction with 4-vinylpyridine (**10c**) occurs more readily (4-8 h, 40ºC) under these conditions than with 2-vinylpyridine (**10a**) and, especially, with 6-methyl-3-vinylpyridine (**10b**), completion of which demands a higher temperature (80ºC) and longer reaction time (12-24 h). The 4-pyridinylethyl derivatives **11b** and **11c** obtained were hydrogenated on platinum in 90-95% yield to the hexahydro derivatives **12b,c**.



10, 11 a R = 2-Py; **10–12 b** R = 6-Me-3-Py, **c** R = 4-Py

From the 2,7-dimethyl-*cis*-1,2,3,3a,4,8*b*-hexahydropyrrolo[3,4-*b*]indole (**6**) under standard reaction conditions we have prepared the corresponding 4-pyridin-3-ylmethyl, 4-benzoyl, 4-benzenesulfonyl, and 4-phenylamido derivatives **13-16** respectively.

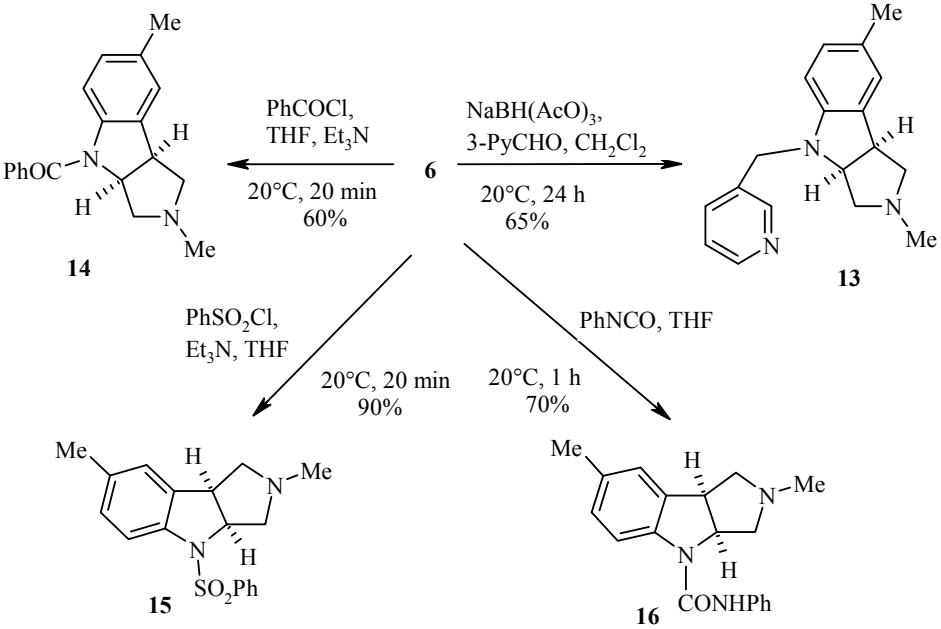


TABLE 1. Physicochemical Characteristics and Mass Spectra of Compounds **4-9**, **11-16**

Compound	Empirical formula	Found, % / Calculated, %			LC-MS, *m/z* (M+H)
		C	H	N	
4	$C_{14}H_{16}N_2O_2$	68.63 / 68.83	6.42 / 6.60	11.57 / 11.47	246
5•HCl	$C_{12}H_{14}N_2$•HCl	64.55 / 64.72	6.58 / 6.79	12.36 / 12.58	187
6•2HCl	$C_{12}H_{16}N_2$•2HCl	55.37 / 55.18	6.75 / 6.95	10.93 / 10.73	189
7	$C_{15}H_{19}N_2O_2$	69.27 / 69.47	7.22 / 7.38	10.96 / 10.80	259
8•HCl	$C_{13}H_{16}N_2$•HCl	65.68 / 65.95	7.08 / 7.24	11.72 / 11.83	201
9•2HCl	$C_{13}H_{18}N_2$•2HCl	56.48 / 56.73	7.17 / 7.32	10.42 / 10.18	203
11a•2HCl	$C_{19}H_{21}N_3$•2HCl	62.44 / 62.64	6.27 / 6.36	11.66 / 11.53	292
11b•2HCl	$C_{20}H_{23}N_3$•2HCl	63.27 / 63.49	6.28 / 6.66	18.77 / 18.74	306
11c•2HCl	$C_{19}H_{21}N_3$•2HCl	62.42 / 62.64	6.18 / 6.36	11.39 / 11.53	292
12b•3HCl	$C_{20}H_{25}N_3$•3HCl	57.37 / 57.63	6.56 / 6.77	10.27 / 10.08	308
12c•3HCl	$C_{19}H_{23}N_3$•3HCl	56.72 / 56.66	6.65 / 6.51	10.28 / 10.43	294
13•**2**HCl	$C_{18}H_{21}N_3$•HCl	61.09 / 61.37	6.37 / 6.58	12.07 / 11.93	280
14•HCl	$C_{19}H_{20}N_2O$•HCl	69.19 / 69.40	6.68 / 6.44	8.73 / 8.52	293
15•HCl	$C_{18}H_{20}N_2O_2S$•HCl	59.45 / 59.25	5.99 / 5.80	7.73 / 7.68	329
16•HCl	$C_{19}H_{21}N_3O$•HCl	66.58 / 66.37	6.23 / 6.45	12.47 / 12.22	308

The free bases were purified by crystallization, column chromatography, or HPLC. Most of the hydrogenated pyrrolo[3,4-*b*]indoles prepared in this study are unstable as the base or the hydrochlorides containing water and rapidly tar upon storage. On the other hand, the anhydrous hydrochlorides are crystalline, white or cream powders which are stable with prolonged storage under normal conditions.

The structure of the pyrrolo[3,4-*b*]indoles obtained was confirmed by ^{1}H NMR spectroscopic and LC-MS data. The values of the molecular ions correspond to their molecular weights and the proton chemical shifts in the ^{1}H NMR spectra unambiguously characterize the structure of the products and are identical to literature data and the authors opinion (Tables 1 and 2). Elemental analytical data (Table 1) is also in agreement.

We have studied the ability of the synthesized hydrogenated pyrrolo[3,4-*b*]indoles **8, 9, 11a-c, 12b,c** to block calcium currents induced by the H_1 histamine receptor in SK-N-SH cells and also the ability of these compounds, depending on concentration, to block the functional response to serotonin stimulation of HEK293 cells, stably expressed the recombinant human 5-HT_6 receptor (Table 3).

In order to evaluate the effects of the synthesized γ-carboline derivatives on calcium currents induced by the H_1 histamine receptors we carried out two variants of the experiments. In a) the investigated compounds were added to the mixture before addition of histamine and the intensity measured as stage 1 and in b) the compound was introduced after addition of histamine and the rate of lowering of cytosolic calcium measured as stage 2. Data for the compounds activity, expressed as the concentration of half effect (IC_{50}), is summarized in Table 3.

TABLE 2. ^{1}H NMR Spectra of the Pyrrolo[3,4-*b*]indoles

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
4	
5•HCl	2.35 (3H, s, 7-CH_3); 2.57 (3H, s, 2-CH_3); 3.82-3.86 (3H, m, 1-CH_2, 3-CH_2); 3.90 (1H, m, 1-CH_2); 6.89 (1H, m, H-6); 7.10 (1H, s, H-8); 7.26 (1H, m, H-5); 10.87 (1H, br. s, 4-NH)
6•2HCl	2.14 (3H, s, 7-CH_3); 2.16 (3H, s, 2-CH_3); 2.30 (1H, m, H-3); 2.46 (1H, m, 3-CH_2); 2.67 (2H, m, H-1); 3.71 (1H, m, H-8*b*); 4.21 (1H, m, H-3*a*); 5.42 (1H, br. s, 4-NH); 6.25 (1H, d, *J* = 7.8, H-5); 6.68 (1H, d, *J* = 7.8, H-6); 6.75 (1H, s, H-8)
7	
8•HCl	2.40 (3H, s, 7-CH_3); 2.63 (3H, s, 2-CH_3); 3.67 (3H, s, 4-CH_3); 3.90 (2H, br. s, 3-CH_2); 3.96 (2H, br. s, 1-CH_2); 6.93-6.97 (1H, m, H-6); 7.16 (1H, s, H-8); 7.28-7.31 (1H, m, H-5)
11a•2HCl	2.30 (3H, s, 7-CH_3); 2.45 (3H, s, 2-CH_3); 3.07 (2H, m, Py$C\underline{H}_2CH_2$); 3.58 (2H, br. s, Py$CH_2C\underline{H}_2$); 3.74 (2H, br. s, 3-CH_2); 4.36 (2H, m, 1-CH_2); 6.82 (1H, m, H-6); 7.01 (1H, s, H-8); 7.05 (1H, m, H-5 Py); 7.18 (1H, m, H-5); 7.22 (1H, m, H-3 Py); 7.57 (1H, m, H-4 Py); 8.48 (1H, m, H-6 Py)
11b•2HCl	2.40 (3H, s, 7-CH_3); 2.44 (3H, s, 6-CH_3Py); 2.51 (3H, s, 2-CH_3); 2.98 (2H, m, Py$C\underline{H}_2CH_2$); 3.59 (2H, m, Py$CH_2C\underline{H}_2$); 3.81 (2H, m, 3-CH_2); 4.28 (2H, m, 1-CH_2); 6.93 (1H, m, H-6); 7.15 (2H, m, H-5,8); 7.37 (2H, m, H-4 Py, H-5 Py); 8.16 (1H, m, H-2 Py)
11c•2HCl	2.39 (3H, s, 7-CH_3); 2.54 (3H, s, 2-CH_3); 3.04 (2H, m, Py$C\underline{H}_2CH_2$); 3.67 (2H, br. s, Py$CH_2C\underline{H}_2$); 3.84 (2H, br. s, 3-CH_2); 4.35 (2H, m, 1-CH_2); 6.93 (1H, m, H-6); 7.15 (3H, m, H-8, H-3 Py, H-5 Py); 7.38 (1H, m, H-5); 8.45 (2H, m, H-2 Py, H-6 Py)
12b•3HCl	2.14 (3H, s, 7-CH_3); 2.17 (3H, s, 6-CH_3Py); 2.28 (1H, m, 1-CH_2); 2.42 (3H, s, 2-CH_3); 2.64-2.80 (4H, m, Py$C\underline{H}_2C\underline{H}_2$); 3.32-3.21 (3H, m, 1-$CH_2$, 3-$CH_2$); 3.74 (1H, m, 8*b*-CH); 4.14 (1H, m, 3*a*-CH); 6.24 (1H, m, H-6); 6.74 (2H, m, H-5, H-5 Py); 7.16 (1H, s, 8-H); 7.58 (1H, m, H-4 Py); 8.33 (1H, m, H-2 Py)
13•2HCl	2.13 (3H, s, 7-CH_3); 2.17 (3H, s, 2-CH_3); 2.45 (2H, m, 1-CH_2); 2.72 (2H, m, 3-CH_2); 3.77 (1H, m, 8*b*-CH); 4.17 (1H, m, 3*a*-CH); 4.40 (2H, m, PyCH_2); 6.18 (1H, d, *J* = 8.0, H-5); 6.71 (1H, d, *J* = 8.0, H-6); 6.79 (1H, s, H-8); 7.33 (1H, m, H-5 Py); 7.67 (1H, d, *J* = 7.7, H-4 Py); 8.45 (1H, d, *J* = 4.1, H-6 Py); 8.51 (1H, s, H-2 Py)
14•HCl	2.25 (3H, s, 7-CH_3); 2.76 (3H, s, 2-CH_3); 3.25-3.51 (3H, br. m, 1-CH_2, 3-CH_2, 8*b*-CH); 3.77 (1H, br. s, 1-CH_2); 4.25 (1H, br. s, 3-CH_2); 5.19 (1H, br. s, 3*a*-CH); 6.94 (1H, br. m, H-6); 7.20 (1H, s, H-8); 7.54 (6H, br. m, H-5, Ph); 10.05 (1H, br. s, NH)
15•HCl	2.24 (3H, s, 7-CH_3); 2.82 (3H, s, 2-CH_3); 3.45 (4H, br. m, 1-CH_2, 3-CH_2); 4.07 (1H, br. s, 8*b*-CH); 4.97 (1H, br. s, 3*a*-CH); 7.04 (1H, s, H-8); 7.07 (1H, d, *J* = 8.6, H-6); 7.36 (1H, d, *J* = 8.6, H-5); 7.58 (2H, t, *J* = 7.9, H-3 Ph, H-5 Ph); 7.70 (1H, t, *J* = 7.5, H-4 Ph); 7.84 (2H, d, *J* = 7.9, H-2 Ph, H-6 Ph); 10.15 (1H, br. s, NH)
16•HCl	2.19 (3H, s, 7-CH_3); 2.24 (3H, s, 2-CH_3); 2.58 (2H, m, 1-CH_2, 3-CH_2); 2.82 (1H, d, *J* = 8.8, 3-CH_2); 2.91 (1H, d, *J* = 10.0, 1-CH_2); 3.93 (1H, m, 8*b*-CH); 5.07 (1H, m, 3*a*-CH); 6.92 (1H, d, *J* = 8.0, H-6); 6.99 (1H, s, H-8); 7.01 (1H, m, H-4 Ph); 7.28 (2H, m, H-3,5 Ph); 7.52 (2H, m, H-2 Ph, H-6 Ph); 7.70 (1H, d, *J* = 8.0, H-5); 8.38 (1H, s, CONH)

As is evident in Table 3 the nature of the substituent in position 4 of the heterocycle and the degree of hydrogenation strongly influence its ability of the compound to block calcium currents induced by histamine receptors in stage 1. Hence the 4-methyl derivatives **8**·HCl and **9**·HCl are 30-50 times less active than Dimebon. Within the series of 2,7-dimethyl-4-(2-pyridinylethyl)-3,4-dihydro-1H-pyrrolo[3,4-*b*]indoles **11a-c** a transition from the 4-[2-(pyridin-2-yl)ethyl] derivative **11a** to 4-[6-methyl-2-(pyridin-3-yl)ethyl]- and to 4-[2-(pyridin-4-yl)ethyl] derivatives **11b** and **11c** respectively is accompanied by an increase in activity from IC_{50} = 0.32 in compound **11a** to 0.20 in **11b** and to 0.08 μmol/l for **11c** and the activity of the latter is more than twice that of Dimebon (for which IC_{50} = 0.16 μmol/l). The change from tetrahydro derivatives **11b,c** to the corresponding

TABLE 3. Ability of Dimebon and Hydrogenated Pyrrolo[3,4-*b*]indoles to Block H_1 Histamine and Serotonin 5-HT_6 Receptors in Cell Function Experimental Conditions

Compound	IC_{50}, μmol/l		
	H_1		5-HT_6
	Stage 1	Stage 2	
Dimebon	0.16	1.58	2.14
8·HCl	3.16	1.26	>50
9·2HCl	5.01	3.16	>50
11a·2HCl	0.32	1.00	12.7
11b·2HCl	0.20	0.63	26.1
11c·2HCl	0.08	0.79	16.1
12b·3HCl	5.01	3.16	>50
12c·3HCl	0.79	1.58	>50
15·HCl			7.0

hexahydropyrrolo[3,4-*b*]indoles **12b,c** causes a 10-25-fold lowering of antihistamine activity. However, the 4-[2-(pyridin-4-yl)ethyl] derivative **12c** is 7 times more active than the 4-[2-(6-methylpyridin-3-yl)ethyl analog **12b**. It should be noted that changing from stage 1 to stage 2 for the pyrrolo[3,4-*b*]indoles **11a-c** and **12c** is accompanied, as in the case of Dimebon, by a 2-10-fold lowering of the IC_{50} value while compounds **8, 9** and **12b** show a 1.5-3-fold increase in activity.

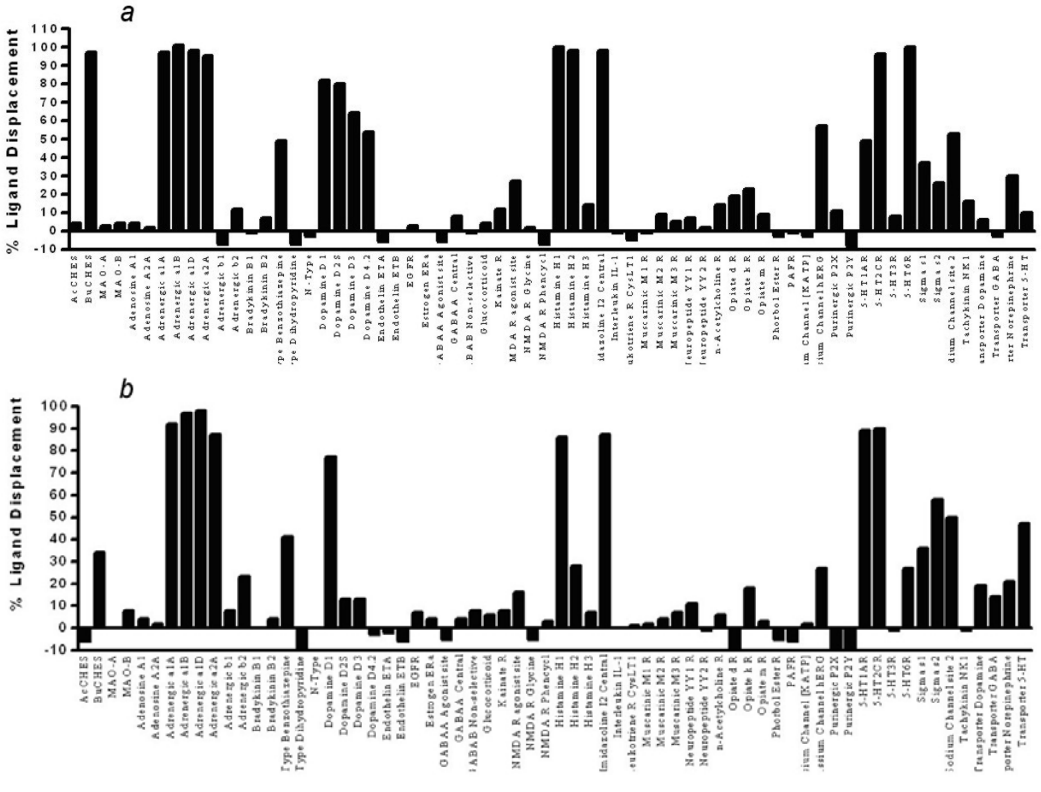


Fig. 1. Profile of the interactions of compounds **3** (*a*) and **11b** (*b*) with different receptors and ion channels. The interactions were calculated from the displacement of radiolabelled ligands from their complex with the corresponding receptors. Dimebon **3** and the pyrrolo[3,4-*b*]indole **11b** were at a concentration of 10 μM.

As noted above, Dimebon **3** efficiently binds to 5-HT_6 receptors which are potential targets for the development of medicines against illnesses connected with memory disorders. In this connection we have studied the ability of the hydrogenated pyrrolo[3,4-*b*]indoles **8, 9, 11a-c, 12b,c, 15** to interact with serotonin 5-HT_6 receptors (Table 3). We studied the concentration dependent ability of these compounds to block the functional response to serotonin stimulation of HEK293 cells stably expressed the recombinant human 5-HT_6 receptor. With serotonin stimulation of these cells there was observed an increased synthesis of intracellular cyclic AMP as calculated using LANCE technology [21].

Studies have shown that, by contrast with Dimebon, the synthesized pyrrolo[3,4-*b*]indoles either weakly block 5-HT_6 receptors (**11a-c**, IC_{50} from 12.7 to 26.1 μmol/l) or are overall inactive (IC_{50} greater than 50 μmol/l for **8, 9, 12b,c**) and this agrees with data for the displacement of radiolabelled ligands from their complex with 5-HT_6 receptors by the pyrrolo[3,4-*b*]indole **11b** (Figure 1). An exception is the 2,7-dimethyl-4-phenylsulfonyl-*cis*-1,2,3,3a,4,8*b*-hexahydropyrrolo[3,4-*b*]indole (**15**) with a marked antagonist activity towards 5-HT_6 receptors (IC_{50} = 7.0 μmol/l) and this is a general characteristic of heterocyclic compounds containing a phenylsulfonyl substituent [22-24].

Studies of the pharmacological activity of the synthesized compounds are continuing and the results will be published in a specific report.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian-400 (400 MHz, 27ºC) spectrometer using DMSO-d_6 with TMS as internal standard. Chromato-mass spectra were obtained on a Shimadzu HPLC chromatograph fitted with a Waters XBridge C_{18} column (4.6×150 mm), PE SCIEX API 150 (chemical ionization) mass detector, and Shimadzu spectrophotometric detector (λ_{max} 220 and 254 nm). According to the chromato-mass spectrometric data the purity of all of the synthesized compounds was greater than 98.0%. Preparative HPLC used a Shimadzu LC-8A system with a Dr Masch Reprosil-Pur C_{18}-AQ chromatographic column (20×250 mm) with a flow rate of 25 ml/min in gradient mode with a MeCN–water +0.05% CF_3COOH eluent.

Reagents were used from the companies Acros, Sigma-Aldrich, Lancaster, and ChemDiv, solvents were imported or native products of "chemically pure" or "pure" grade. Just before use, all of the reagents used were purified by crystallization from a suitable solvent or fractionally distilled. Solvents were purified and dried by reported methods.

In all cases monitoring of the reaction course and conversion of the substrate was carried out using chromato-mass spectrometry. The concentration of solutions and drying of solid materials were only carried out *in vacuo* with the exception of specified examples.

Ethyl 7-Methylpyrrolo[3,4-*b*]indole-2(1H,3H,4H)carboxylate (4). A solution of 1-ethoxycarbonyl-pyrrolidin-3-one (5.50 g, 35 mmol) was added with vigorous stirring to a solution of *p*-tolylhydrazine hydrochloride (5.56 g, 35 mmol) and AcONa (2.87 g, 35 mmol) in water (200 ml) and stirred for a further 15-30 min. The hydrazone precipitate formed was filtered off, washed three times with water, dried, ground up, washed with ether (2×100 ml), and dried in air. The hydrazone (11.3 g) was mixed with H_3PO_4 (85%, 40 ml), stirred for 1 h at 25-30ºC to full homogenization and solidification. A mixture of ice and water (350 ml) was added and the precipitate formed was filtered off, washed with water to pH 7 of the water washings, drained, dried, and crystallized from a mixture of acetonitrile and water (1:1) to give the pyrrolo[3,4-*b*]indole **4** (3.3 g, 33%).

2,7-Dimethyl-3,4-dihydro-1H-pyrrolo[3,4-*b*]indole (5). Compound **4** (2.44 g, 10 mmol) was stirred over 2 h at 20ºC with $LiAlH_4$ (50 mg, 13 mmol) in dry ether (15 ml) under an argon atmosphere. An aqueous solution of NaOH (10%, 50 μl) was added and the product was stirred until hydrogen evolution ceases. The reaction mixture was filtered off and the organic layer was separated, dried over K_2CO_3, and evaporated to dryness to give the pyrrolo[3,4-*b*]indole **5** (1.64 g, 87%).

2,7-Dimethyl-*cis*-1,2,3,3a,4,8*b*-hexahydropyrrolo[3,4-*b*]indole (6). A mixture of the pyrrolo[3,4-*b*]indole **5** (0.5 g, 2.7 mmol) and PtO_2 (150 mg) in ethanol (20 ml) was stirred under a hydrogen atmosphere for 24 h at 20ºC. The reaction product was filtered off, evaporated, and chromatographed on silica gel impregnated with Et_3N using hexane–$CHCl_3$–Et_3N (4:2:1) as eluent. The yield of compound **6** was 0.48 g (95%).

Ethyl 4,7-Dimethylpyrrolo[3,4-*b*]indole-2(1H,3H,4H)carboxylate (7). A mixture of the indole **4** (0.37 g, 2.0 mmol), MeI (0.36 g, 2.5 mmol), and Cs_2CO_3 (750 mg) in N-methylpyrrolidone (10 ml) was stirred for 6 h at 50ºC. The reaction product was diluted with water and extracted with CH_2Cl_2 and the organic layer was dried (Na_2SO_4), filtered through a thin layer of silica gel, and evaporated to dryness to give the pyrrolo-[3,4-*b*]indole **7** (0.41 g, 80%).

2,4,7-Trimethyl-3,4-dihydro-1H-pyrrolo[3,4-*b*]indole (8) was prepared in 85% yield by the method reported before for compound **5**.

2,4,7-Trimethyl-*cis*-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-*b*]indole (9) was prepared in 97% yield by analogy with the method for compound **6**.

2,7-Dimethyl-4-(2-pyridinylethyl)-3,4-dihydro-1H-pyrrolo[3,4-*b*]indoles 11a-c (General Method). An 50% aqueous solution of $Bu_4N)_2SO_4$ (100 μl), the vinylpyridine **10a-c** (3-4 mmol) and a 60% aqueous solution of KOH (8-12 ml) were added to a solution of the pyrrolo[3,4-*b*]indole **5** (0.372 g, 2.0 mmol) in DMSO (2 ml). The reaction mixture was purged with argon and stirred for 12-24 h at 80ºC, treated with CH_2Cl_2, washed with water, and the organic layer was dried over K_2CO_3. Solvent was evaporated to dryness and the residue was chromatographed on silica gel impregnated with Et_3N using hexane–$CHCl_3$–Et_3N (5:4:1) as eluent.

2,7-Dimethyl-4-(2-pyridinylethyl)-*cis*-1,2,3,3a,4,8*b*-hexahydropyrrolo[3,4-*b*]indoles 12b,c were prepared in 90-95% yield using the method reported for compound **6**.

2,7-Dimethyl-4-(pyridin-3-ylmethyl)-*cis*-1,2,3,3a,4,8*b*-hexahydropyrrolo[3,4-*b*]indole (13). A solution of indole **6** (98 mg, 0.52 mmol) in CH_2Cl_2 (2 ml), pyridine-3-carbaldehyde (60 μl, 0.60 mmol), and $NaBH(AcO)_3$ (120 mg, 0.60 mmol) was stirred at room temperature for 2 h. Solvent was evaporated to dryness and the residue was separated using column chromatography as reported for compounds **10a-c** using hexane–$CHCl_3$–Et_3N (5:3:2) as eluent to give the pyrrolo[3,4-*b*]indole **13** (94 mg, 65%).

4-Benzoyl-2,7-dimethyl-*cis*-1,2,3,3a,4,8*b*-hexahydropyrrolo[3,4-*b*]indole (14). Benzoyl chloride (28 mg, 0.20 mmol) was added with stirring to a solution of the indole **6** (30 mg, 0.16 mmol) and Et_3N (20 mg, 0.20 mmol) in THF (3 ml) and stirred for a further 20 min at 20ºC. The precipitate was filtered off, washed with THF (10 ml), solvent evaporated, and the compound was separated column chromatographically as reported for compounds **10a-c** to give the pyrrolo[3,4-*b*]indole **14** (28 mg, 60%).

4-Benzenesulfonyl-2,7-dimethyl-*cis*-1,2,3,3a,4,8*b*-hexahydropyrrolo[3,4-*b*]indole (15). Benzene-sulfonyl chloride (35 mg, 0.20 mmol) was added to a stirred solution of indole **6** (30 mg, 0.16 mmol) and Et_3N (20 mg, 0.20 mmol) in THF (3 ml) and stirred for 20 min at 20ºC. Separation by the method for compound **14** gave the pyrrolo[3,4-*b*]indole **15** (59 mg, 90%).

N-Phenyl-2,7-dimethyl-1,2,3,3*a*-tetrahydropyrrolo[3,4-*b*]indole-4(8*b*H)-carboxamide (16). Phenyl-isocyanate (24 mg, 0.20 mmol) was added with stirring to a solution of the indole **6** (30 mg, 0.16 mmol) in THF (3 ml) and stirred for 4 h at 20ºC. Separation by the method reported for compound **14** gave the pyrrolo-[3,4-*b*]indole **16** (43 mg, 70%).

Hydrochlorides of the Pyrrolo[3,4-*b*]indoles 5, 6, 8, 9, 11a-c, 12b,c, 13-16. A test tube containing a solution of the pyrrolo[3,4-*b*]indole (2 mmol) in a mixture of dry ether–THF (9:1) was centrifuged, the solution of the indole carefully decanted off, and anhydrous HCl (6-8 mmol) in dry ether was added to it. The tube was held for 10 min at 20ºC in an ultrasonic bath, centrifuged, solvent poured off, and the procedure was repeated. The precipitate was dried *in vacuo* to give the pyrrolo[3,4-*b*]indole hydrochloride (white or cream colored crystals) in 93-97% yield. Analytical results are given in Table 1.

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