SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF NEW INCAZAN ANALOGS

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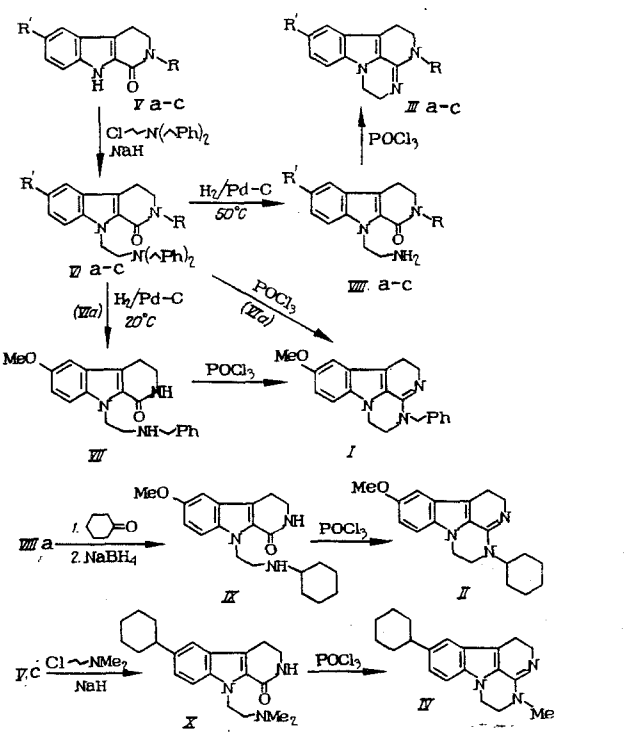
As a continuation of our studies [3] on the relationship between the biological activity, structural factors, and the nature of substituents in pyrazino [1,2,3-1,m]-β-carboline which is the base of the antidepressant incazan [1], we synthesized and studied the pharmacological activity of the following new analogs of that compound: 4-benzyl (I) and 4-cyclohexyl- (II) 10-methoxy-4H-1, 2,5,6-tetrahydropyrazino [1,2,3-1, m]-β-carbolines, 4-desmethylincazan (IIIa), the 3-methyl isomer of incazan (IIIb) as well as the 10-cyclohexyl derivatives (IIIc) and (IV).

The recognized method of synthesizing incazan [2] by alkylating 6-methoxy-1-oxo-1,2,3, 4-tetrahydro-β-carboline with dimethylaminoethyl chloride followed by cyclating the resultant 9-(2-dimethylaminoethyl)-6-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline in $POCl_3$ was found to be impractical for obtaining compounds II and III because of the low accessibility of dicyclohexylaminoethyl chloride and the unstable base form of aminoethyl chloride. We therefore devised a new version of this method which entails the alkylation of 2-R-6-R^1-oxo-1,2,3, 4-tetrahydro-β-carboline (Va-c) with easily available 2-dibenzylaminoethyl chloride [5]. This results in the formation of 2-R-6-R^1-9-(2-dibenzylaminoethyl)-1-oxo-1,2,3,4-tetrahydro-β-carboline (VIa-c). The presence of benzyl groups on the nitrogen atom in VI allows for significantly broader synthesis possibilities with this method.

In examining the destructive hydrogenation of VI at atmospheric pressure on 20% $Pd(OH)_2$ on charcoal, we found this reaction is strongly temperature-dependent. At 20°C the monobenzyl derivative (VII) is formed from VIa while at 50°C complete debenzylation occurs resulting in the formation of (VIIIa-c). The aminoethyl derivatives of VIIIa, c are the key com-



III, V, VI, VIII a: R=H, R'=MeO; b R=Me, R'=MeO; c R=H, R' = cyclohexyl

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TABLE 1

Compound	Dose, mg/kg (orally)	Decrease in reserpine-induced blepharoptosis in mice (blepharoptosis, %)	Increase in 5-OTP-induced head agitation in mice (number of mice with head tremors, %)	LD_{50}, oral administration, mg/kg (mice)
I	25	100 (n=36)	20 (n=30)	225
II	25	80 (n=12)	10 (n=20)	260
IIIa	25	50* (n=18)	50* (n=30)	400
IIIb	25	45* (n=18)	60* (n=30)	390
IIIc	10	20* (n=24)	50** (n=30)	>1000
IV	10	30* (n=24)	50* (n=30)	>1000
Incazan	25	55* (n=42)	50** (n=30)	445

*Difference from control reliable at $p < 0.001$.
**The same at $p < 0.05$.

pounds for synthesizing unsubstituted pyrazino[1,2,3-1, m]-β-carbolines IIIa, c on the nitrogen atoms as well as for the synthesis of compounds containing various substituents in position 4, such as compound II. The only limitation of this method is the availability of the corresponding aldehyde or ketone. Compound VIIIb can be used to obtain IIIb, an isomer of incazan, and difficult to synthesize by other methods. When the dibenzyl and monobenzyl derivatives VIa and VII are treated with $POCl_3$ they yield the identical cyclization product I. The cyclohexyl analog of incazan, compound IV, was obtained from 1-oxo-6-cyclohexyl-1,2,3,4-tetrahydro-β-carboline and 2-dimethylaminoethyl chloride in the same manner as the synthesis of incazan [2].

EXPERIMENTAL (CHEMICAL)

1-Oxo-6-cyclohexyl-1,2,3,4-tetrahydro-β-carboline (Vc) was obtained from cyclohexylanaline sulfate and 3-ethoxycarbonyl-2-piperidone by the method employed for the synthesis of 6-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (Va) [4] with a 68% yield, mp 253-255°C (EtOH).

2-Methyl-6-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (Vb). A mixture of 30 g (0.14 mole) of Va and 300 ml of $POCl_3$ was boiled for 1.5 h. The mixture was cooled to 4°C. The precipitate was filtered off, washed with 250 ml of abs. ether and placed into 350 ml of MeOH at 6°C. The mixture was stirred for 1 h at room temperature, and for 1.5 h while boiling . The mixture was then cooled after which a solution of 40 g of K_2CO_3 in 500 ml of water was added, followed by extraction with 3 × 300 ml $CHCl_3$. The extract was dried over Na_2SO_4, the $CHCl_3$ was vacuum-distilled, and the residue was dissolved in 500 ml of benzene to which 14 ml (0.15 mole) of Me_2SO_4 was added. The mixture was then boiled for 10 h, cooled, and the precipitate was filtered off and washed with benzene. Yield was 16 g (50%) of Vb, mp 288-290°C (EtOH).

9-(2-Dibenzylaminoethyl)-6-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (VIa). A 1.17 g (0.044 mole) portion of NaH was added in small quantities to a suspension of 8.34 g (0.039 mole) of Va in 45 ml of dry DMFA at 25-30°C. The reaction mixture was stirred for 1 h at 30°C and for 4 h at 55-60°C. A 11.53 g (0.044 mole) portion of 2-dibenzylaminoethyl chloride was added to the mixture which was then left to stand for 5 h. The mixture was cooled and the precipitate was filtered off and washed on a filter (2 × 15 ml DMFA and 4 × 20 ml water). Yield was 11.83 g (70%) of VIa, mp 179-180°C (EtOH), mp of the hydrochloride 235-236°C (EtOH).

A similar method was employed to obtain 9-(2-dibenzylaminoethyl)-2-methyl-6-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (VIb) from Vb at a yield of 84%, mp 147-148°C (EtOH); 9-(2-dibenzylaminoethyl)-6-cyclohexyl-1-oxo-1,2,3,4-tetrahydro-β-carboline (VIc) was obtained from Vc at a yield of 58%, mp 175-177°C (EtOH); 9-(2-dimethylaminoethyl)-6-cyclohexyl-1-oxo-1,2,3,4-tetrahydro-β-carboline (X) was obtained from Vc at a yield of 62%, mp of the hydrochloride 260-262°C (EtOH).

9-(2-Aminoethyl)-6-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (VIIIa). A 10 g (0.023 mole) portion of VIa was hydrogenated in 100 ml of EtOH in the presence of 0.5 g of 20% $Pd(OH)_2$ on charcoal at atmospheric pressure and a temperature of 50°C until the completion of hydrogen absorption. The solution was filtered while hot, and an alcohol solution of HCl was added to bring the pH to 3-4 after which the solution was evaporated to a volume of 25 ml and then cooled. The resultant precipitate was filtered off and washed with a small quantity of MeOH. The yield of 4.7 g (90%) of VIIIa hydrochloride, mp 277-279°C (EtOH—H_2O).

In a similar manner 9-(2-aminoethyl)-2-methyl-6-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline HCl (VIIIb) was obtained from VIc at a yield of 93%, mp 236-238°C (i-PrOH); 9-(2-aminoethyl)-6-cyclohexyl-1-oxo-1,2,3,4-tetrahydro-β-carboline HCl (VIIIc) was obtained from VIc at a yield of 77%, mp 270°C (DMFA); 9-(2-benzylaminoethyl)-6-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline HCl (VII) was obtained from VIa at a yield of 70%, mp 234-236°C (i-PrOH).

9-(2-Cyclohexylaminoethyl)-6-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (IX). A mixture containing 10.7 g (0.04 mole) of the VIIIa base, 8 ml (0.08 mole) of cyclohexanone, and 0.3 g of TsOH was boiled in 100 ml EtOH for 12 h. The mixture was cooled to room temperature, and after 1.57 g (0.04 mole) of $NaBH_4$ was added, it was stirred for 3 h, then boiled for 2 h. The solvent was vacuum-distilled, the residue was diluted with 30 ml of water and extracted by 2 × 25 ml of benzene. The extract was dried with K_2CO_3, and the product was precipitated as the hydrochloride by an alcohol solution of HCl. Yield was 8.2 g (53%) of the hydrochloride IX, mp 239-241°C (EtOH).

10-Methoxy-1H-2,3,5,6-tetrahydropyrazino [1,2,3-ℓ, m]-β-carboline (IIIa). A mixture of 10.9 g (0.04 mole) of the hydrochloride VIIIa in 70 ml of $POCl_3$ was boiled for 4 h. The mixture was vacuum-evaporated to dryness and the residue was boiled for 1 h in 100 ml of water with activated charcoal, then filtered, cooled, and made alkaline to pH 10-11. The precipitate was filtered off and recrystallized from 2% HCl. Yield was 5.2 g (51%) of the hydrochloride IIIa, mp 272-273°C.

In a similar manner 3-methyl-10-methoxy-1H-2,3,5,6-tetrahydropyrazino [1,2,3-ℓ, m]-β-carboline HCl (IIIb) was obtained from VIIIb at a yield of 77%, mp 305°C (decomp.); 10 cyclohexyl-1H-2,3,5,6-tetrahydropyrazino[1,2,3-1, m]-β-carboline HCl (IIIc) was obtained from VIIIc at a yield of 40%, mp 265°C (decomp.); 4-benzyl-10-methoxy-4H-1,2,5,6-tetrahydropyrazino[1,2,3-ℓ, m]-β-carboline HCl (I) was obtained from VII or VIa at a yield of 82 or 77%, mp 268-270°C; 10-methoxy-4-cyclohexyl-4H-1,2,5,6-tetrahydropyrazino [1,2,3-ℓ, m]-β-carboline HCl (II) was obtained from IX at a yield of 57%, mp 277-279°C; 4-methyl-10-cyclohexyl-4H-1,2,5,6-tetrahydropyrazino [1,2,3,-ℓ, m]-β-carboline HCl (IV) was obtained from X at a yield of 60%, mp 330-332°C.

The structures of the synthesized compounds were confirmed by mass-, IR, and PMR-spectral data, and element analysis.

EXPERIMENTAL (BIOLOGICAL)

The pharmacological study of incazan analogs tested their antidepressant activity. We examined the compounds' activity in the "water-avoidance" emotional behavior test ([6] by the increase in the number of water wheel rotations during active attempts by mice to get out of the water), in testing reaction of reserpine (2.5 mg/kg ip; by the diminution of blepharoptosis and hypothermia), in tests with 5-oxytryptamine (5-OTP, 50 mg/kg ip; by the increase in head agitation), L-dopa (200 mg/kg ip; by the increase in hyperthermia), in tests with apomorphine and tremorine (25 and 20 mg/kg respectively subcutaneously; by the decrease in hypothermia). The experiments were conducted on white mice of both sexes weighing 18-22 g. The compounds were administered orally. The LD_{50} of the compounds was also tested upon oral administration to mice.

Characteristic activity aspects of this group of substances were their antagonism to reserpine and potentiation of 5-OTP and L-dopa activity. This activity was indicative of their active antidepressant properties.

The most active compounds were the 10-cyclohexyl derivatives which exceeded the activity of incazan and were less toxic (see Table 1). As can be seen from the Table, compounds I and II, i.e., the 4-benzyl- and 4-cyclohexyl derivatives are significantly less active and more toxic than incazan. Compound IIIa, the 4-desmethyl derivative, like compound IIIb, the 3-methyl isomer of incazan, closely resemble incazan's activity and toxicity, whereas the 10-cyclohexyl derivatives IIIc and IV are markedly more active and less toxic than incazan.

All of the examined compounds also potentiated the hyperthermic effect of L-dopa by 2-3°C. Moreover, the potentiating effect of the 10-cyclohexyl derivatives was manifested at lower doses. These two compounds (IIIc and IV) at a dose of 10 and 25 mg/kg administered orally also heightened the activity of the mice in the behavioral swimming test whereas the rest of the compounds (administered orally at 10 and 25 mg/kg) did not exhibit this effect.

None of the tested compounds significantly affected the action of apomorphine and tremorine.

Thus, the synthesis of incazan analogs with lipophilic substituents in position 10 holds promise with respect to the possible synthesis of substances that have greater antidepressant activity and are less toxic. On the other hand, the introduction of similar substituents in position 4 lowers the compounds' activity with respect to the examined indices.

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SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF CERTAIN 3,4-DIHYDROXYPIPERIDINES

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Several secondary-tertiary and tertiary-tertiary aryl-substituted 6-aryl-1-R-3 methyl-3, 4-piperidinediols were synthesized in our search for new pharmacological agents in the 3,4-dihydroxypiperidine series [5, 10]. The original 6-aryl-3-hydroxy-3-methylpiperidine-4-ones (X-XIV) were synthesized for the first time by reacting β-arylacryliloxyranes (III-VII) and methylamine. The synthesis of compounds VIII, IX, and XV is described in [6, 8].

The reduction of 6-aryl-3-hydroxypiperidine-4-ones X-XIV by sodium borohydride in isopropyl alcohol primarily results in the formation of 6-aryl-3e,4e-dihydroxy-1e,3a-dimethylpiperidines (XVI-XX). Furthermore, the stereochemistry of the process is the same as in the case of the 6-phenyl analog [7].

In order to synthesize the stereoisomer 6e-aryl-3e,4a-dihydroxy-1e,3a-dimethylpiperidines (XXI and XXII) we took advantage of an early devised method of reducing 3e-hydroxy-1e, 3a-dimethyl-6e-phenylpiperidine-4-one [3] by the use of tert-butylmagnesium chloride in a solution of tetrahydrofuran.

We synthesized bi-tertiary 3,4-piperidinediols (XXIII-XXIX) by reacting the corresponding 3-hydroxypiperidine-4-ones with organic magnesium reagents. Thus, 1e-benzyl-3a-hydroxy-3e-methyl-6e-phenylpiperidine-4-one (XV) condenses with methylmagnesium bromide or methyl magnesium iodide to form primarily (80%) 1e-benzyl-3a,4e-dihydroxy-3e,4a-dimethyl-6e-phenylpiperidine (XXIII). Its methyl analog 3a,4e-dihydroxy-1e,3e,4a-trimethyl-6e-phenylpiperidine (XXIV) was synthesized by catalytic debenzylation of XXIII followed by methylation with methyl iodide. When piperidine-4-one VIII reacts with methyl-, ethyl-, or phenylmagnesium

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