SYNTHESIS OF TRICYCLIC ANALOGS OF INCASANE

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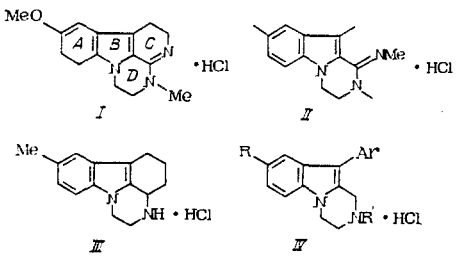
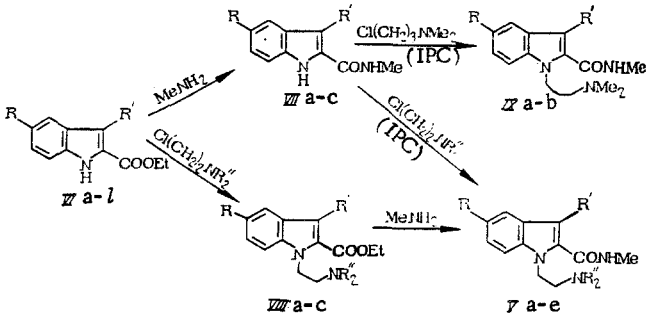
To clarify the influence of structural factors on the biological activity of the original Soviet-manufactured antidepressant incasane (I) [1], we considered modification of its molecule and synthesis of tricyclic compounds of the general formula (II) having the main fragments (the pyrazino[1,2-a]indole residue, the amidine group) that are present in the structure of I.



A distinguishing feature of II compared with I is the opening in II of ring C, and the absence of the β-carbonyl and tryptamine fragments related to it. Thus, by comparing the pharmacological action of I and II, we were able to clarify whether the presence in I of a tryptamine fragment plays a decisive role in preserving the biological activity. A further reason for carrying out such a modification was the fact that in the structure of another Soviet-manufactured antidepressant, pyrazidol (III) [3], ring C is alicyclic and not heterocyclic, and consequently, the tryptamine fragment is absent in the molecule of III. Moreover, data have been published in the literature [4] showing that tricyclic pyrazino-[1,2-a]indoles (IV), structurally related to II, also exhibit antidepressive action.

The starting materials for the preparation of II were aminoamides (V), synthesized by two process variants from substituted 2-ethoxycarbonylindoles (VI) according to the scheme:



R = H(Va — VIIIa), MeO (Vb—e, VIb—d, VIIb, c, VIIIb, c, IXa, b);
R′ = H (Va — c, VIa, b, VIIa, b, VIIIa, b), Me (Vd, VIc, VIIc, IXa), Ph (Ve, VId, VIIIc, IXb); R″ = Me (Va, c — e, VIIIa, c), CH_2Ph (Vb, VIIIb).

Of these two process variants, the optimal is the preparation of V by conversion of esters VI into amides (VII), followed by alkylation of VII by disubstituted aminoethyl chlorides under conditions of interphase catalysis (IPC). In another process variant, because of the instability of esters VI in an alkaline medium, their alkylation with aminoethyl chlorides had to be carried out in anhydrous DMFA in the presence of NaH, which makes this method very unsuitable from the preparative point of view. The dimethylaminopropyl derivatives (IX), homologous to V, were also synthesized by alkylation of amides VII with 3-dimethylaminopropyl chloride under IPC conditions.

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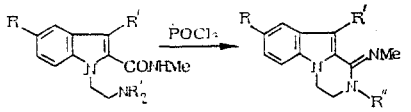
TABLE 1. Properties of Compounds II, V, VII-IX

Compound	Yield, %	mp*, °C	Found, %				Empirical formula	Calculated, %			
			C	H	Cl	N		C	H	Cl	N
IIa·HCl	48	264—6	62,33	6,09	14,45	16,59	$C_{13}H_{16}ClN_3$	62,52	6,46	14,20	16,83
IIb·HCl	58	240—2**	67,85	6,39	9,66	11,76	$C_{20}H_{22}ClN_3O$	67,50	6,23	9,96	11,81
IIc·HCl	50	285—7***	60,19	6,80	12,34	14,98	$C_{14}H_{16}ClN_3O$	60,10	6,49	12,67	15,02
IId·HCl	45	223—5	61,23	6,90	11,81	14,57	$C_{15}H_{20}ClN_3O$	61,32	6,86	14,30	12,07
IIe·HCl	42	289—91	67,60	6,16	10,07	11,73	$C_{20}H_{22}ClN_3O$	67,50	6,23	9,96	11,81
Va·HCl	60 (A), 50 (B)	210—2	59,27	7,22	12,62	14,70	$C_{14}H_{20}ClN_3O$	59,67	7,15	12,58	14,91
Vb·HCl	50 (A), 0 (B)	177—9	70,25	6,46	7,30	8,98	$C_{27}H_{30}ClN_3O_2$	69,89	6,52	7,64	9,06
Vc·HCl	55 (A)	223—6	58,10	7,40	13,55	11,61	$C_{15}H_{22}ClN_3O_2$	57,78	7,11	11,37	13,48
Vd·HCl	50 (A)	235—7	59,06	7,35	10,84	12,98	$C_{16}H_{24}ClN_3O_2$	58,98	7,42	10,88	12,90
Ve·HCl	63 (B)	213—5	64,63	6,77	9,19	10,58	$C_{21}H_{26}ClN_3O_2$	65,02	6,76	9,14	10,83
VIIa	93	210—2	68,76	5,92	—	16,01	$C_{10}H_{10}N_2O$	68,95	5,76	—	16,08
VIIb	95	230—2	64,77	6,04	—	13,72	$C_{11}H_{12}N_2O_2$	64,69	5,92	—	13,71
VIIc	92	228—30	66,15	6,49	—	12,72	$C_{12}H_{14}N_2O_2$	66,04	6,47	—	12,84
VIIIa·HCl	56	188—91	60,52	7,20	12,10	9,35	$C_{15}H_{21}ClN_2O_2$	60,70	7,13	11,95	9,44
VIIIb·HCl	86	150—3	70,51	6,45	7,32	5,98	$C_{28}H_{31}ClN_2O_3$	70,21	6,52	7,40	5,85
VIIIc·HCl	87	177—80	65,15	6,95	8,64	6,84	$C_{22}H_{27}ClN_2O_3$	65,58	6,75	8,80	6,95
IXa·HCl	57	215—7	59,95	7,57	10,61	12,13	$C_{17}H_{26}ClN_3O_2$	60,08	7,71	10,43	12,36
IXb·HCl	63	210—3	65,61	7,25	8,97	10,81	$C_{22}H_{28}ClN_3O_2$	65,74	7,02	8,82	10,45

*II, VII – recrystallized from alcohol, V, VIII, IX – from acetonitrile.
**mp of the base 102-3°C.
***mp of the base 195-7°C.

To prepare pyrazinoindoles II, we used a method developed by us earlier for the synthesis of I [2], consisting in the cyclization by phosphorus oxychloride of compounds containing a substituted amide and β-dialkylaminoethyl fragments in their structure, which involves the formation of pyrazine ring.

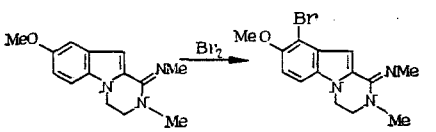


Va-e IIa-e

R = H (IIa), MeO (II b—e); R′ = H (IIa — c), Me (IId), Ph (IId);
R″ = Me (IIa, c—e), CH_2Ph (IIb).

The study of the transformations of V into II showed that this cyclization proceeds most readily in the case of the dibenzylaminoethyl derivative Vb, which is probably due to the fairly high polarization of the N—C bond in the dibenzylamino group. It should be noted that an attempt to cyclize the 3-dimethylaminopropyl derivative IX was accompanied by extensive resinification of the reaction mixture, so that the corresponding diazepino[1,2-a]indole could not be isolated.

The study of the reactivity of this group of compounds carried out using IIc as an example showed that they are more inert compared with indoles to electrophilic reagents, and in particular, they do not enter into the Vilsmeier reaction and do not undergo aminomethylation. The reaction proceeds only with strong electrophilic agents, such as bromine, but in the aromatic ring and not at the 3-position of the indole fragment, with the formation of IIf.



IIc IIf

The position of the bromine atom in IIf was confirmed by the PMR spectral data. In the spectrum of IIf, the proton signal is not split at the 7-position with a coupling constant of the order of magnitude of 2.5 Hz (the meta-constant), while for the spectra of compounds IIb-e this splitting of the signal is characteristic. In the IR spectra of II, an absorption band with a frequency of 1610 cm^{-1} ($\nu_{C=N}$) is observed. In the hydrochlorides of II this band is shifted to 1640-1650 cm^{-1} and bands appear at 3400 cm^{-1} (ν_{NH}) and 1550 cm^{-1} (δ_{NH}). The structure of the compounds obtained was also confirmed by mass spectral data.

In the pharmacological investigation of the derivatives of this group it was found that compounds IIa, c, d exhibit a moderately expressed antireserpinic action and intensify the hyperthermal action of l-dopa to some extent, but they are less active than incasane with respect to the same factors. At the same time, they are 1.5-2 times less toxic than incasane. Compound IIf does not have these effects. All the compounds are ineffective according to the "water saving" swimming test, which is one of the prime experimental indices of antidepressive action.

Our investigations thus indicate that the combination of the tryptamine fragment and the amidine function in the structure of I appears to be an important condition for the manifestation of the antidepressant activity characteristic of incasane.

EXPERIMENTAL

The IR spectra were run in a mineral oil on a UR-20 spectrophotometer (GDR), the PMR spectra on a XL-200 spectrometer ("Varian" Switzerland) in a CD_3OD solution, using TMS as standard; and the mass spectra on a MAT-112 spectrometer ("Varian," GFR). The data on the synthesized compounds are given in Table 1.

Methylamides of Indole-2-carboxylic Acid (VII). A mixture of 0.04 mole of indole-2-carboxylic acid ethyl ester (VI), 0.04 mole of $MeNH_2 \cdot HCl$ and 60 ml (0.4 mole) of a 25% solution of $MeNH_2$ in MeOH is heated in an autoclave at 110-120°C for 3 h. After cooling, the mixture is poured into 250 ml of water, the precipitate is filtered, washed with water, and dried.

Ethyl Esters of 1-(2-Dialkylaminoethyl)indole-2-carboxylic Acid (VIII). Sodium hydride (0.037 mole) is added in small portions, at a temperature not exceeding 30°C to a solution of 0.034 mole of VI in 30 ml of dry DMFA. After 30 min, the mixture is heated to 60°C, 0.037 mole of 2-dialkylaminoethyl chloride is added, and the mixture is stirred at the same temperature for 4 h. After distilling off DMFA in vacuo, the residue is diluted with 50 ml of water, and the mixture is extracted with three 25 ml portions of ether. The extract is dried over Na_2SO_4, filtered, and the product is precipitated as the hydrochloride by an alcoholic solution of HCl.

Methylamides of 1-(2-Dialkylaminoethyl)indole-2-carboxylic Acid (V). A. A mixture of 0.045 mole of VII, 0.045 mole of dialkylaminoethyl chloride hydrochloride, 0.0045 mole of benzyltriethylammonium chloride in 200 ml of benzene and 20 ml of 45% NaOH is boiled with vigorous stirring for 6 h. The hot organic layer is separated, and benzene is distilled off. The residue is dissolved in 50 ml of acetonitrile, filtered, and the product is precipitated as the hydrochloride by an alcoholic solution of HCl.

B. A 0.025 mole portion of VIII as the hydrochloride and 40 ml of a 25% MeOH solution of $MeNH_2$ is heated for 5 h in an autoclave at 110-120°C for 5 h. After cooling, the mixture is poured into 250 ml of water and extracted with three 50 ml portions of ether. The extract is dried in vacuo over Na_2SO_4, evaporated in vacuo, and the residue is dissolved in 35 ml of acetonitrile, and the product is precipitated as the hydrochloric by an alcoholic solution of HCl.

Methylamides of 1-(3-Dimethylaminopropyl)indole-2-carboxylic Acid (IX) are obtained from VII and dimethylaminopropyl chloride hydrochloride in a similar way as compound V by method A.

1-Methylimino-1,2,3,4-tetrahydropyrazino[1,2-a]indoles (IIa-e). A 0.01 mole portion of hydrochloride V is boiled in 30 ml of $POCl_3$ for 5 h. The mixture is evaporated in vacuo, the residue is cautiously hydrolyzed with cold water, the mixture is made alkaline to pH 10.0 with an ammonia solution, and the product is filtered. The product is sometimes obtained in the form of oil. In such case, it is extracted with three 50 ml portions of ether, the extract is dried over Na_2SO_4, and evaporated in vacuo. The product is dissolved in 20 ml of acetonitrile, filtered, and precipitated as the hydrochloride by an alcoholic solution of HCl.

9-Bromo-2-methyl-1-methylimino-8-methoxy-1,2,3,4-tetrahydropyrazino[1,2-a]indole (IIf). A solution of 0.44 ml (8.4 mmoles) of bromine in 15 ml of dioxane is added at 75°C to a solution of 1.78 g (7.7 mmoles) of IIc in 20 ml of dioxane, and the mixture is stirred at this temperature for 2 h. The mixture is cooled, the precipitate is filtered, suspended in 75 ml of water, and a solution of ammonia is added with stirring to pH 10.0. The precipitate is filtered, washed with water, and dried. Yield 2 g (61%) of IIf, mp 165-167°C (benzene). Found, %: C 51.72, H 4.98, Br 24.46, N 12.91. $C_{14}H_{16}BrN_3O$. Calculated, %: C 52.18, H 5.01, Br 24.80, N 13.04. mp of the hydrochloride 255-7°C (alcohol).

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