SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF 1-IMINO-1,2,3,4-TETRAHYDROPYRAZINO[1,2-*a*]INDOLE DERIVATIVES

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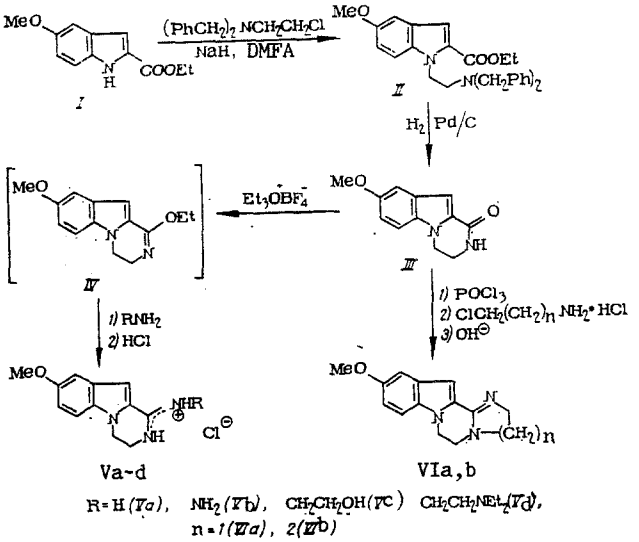
In continuation of the investigation [4] to discover the structural-biological activity relationship of compounds in the series of tetracyclic antidepressants, which include the original antidepressant incasan [2], in the present work we synthesized a group of tri- and tetracyclic compounds, which are derivatives of 1-imino-1,2,3,4-tetrahydropyrazino[1,2-*a*]= indole (Va-d, VIa, b). Compounds Va-d differ in their structure from incasan by the presence of an opened pyridine fragment of a β-carboline system, and also by the absence of a substituent at the piperazine nitrogen atom at the 2-position.



To prepare compound Va, the first representative of this group, we initially tried to remove the benzyl radicals by hydrogenation of N- and N'-benzyl derivatives of Va. However, these attempts did not lead to positive results. Therefore, for the preparation of V, we decided to use lactam III. A compound of this type – 1-oxo-10-phenyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole (VII) – was previously synthesized by cyanomethylation of 3-phenyl-2-ethoxycarbonylindole with chloroacetonitrile, reduction of the 1-cyanomethyl-3-phenyl-2-ethoxycarbonylindole formed to 1-(2-aminomethyl)-3-phenyl-2-ethoxycarbonylindole, and cyclization of the latter into VII [5]. However, this method is not very convenient preparatively, because of the lack of availability of chloroacetonitrile, its relatively high toxicity, and also the rigorous conditions of the reduction of the cyanomethyl derivative. We have developed a new approach to the synthesis of III consisting in alkylation of 5-methoxy-2-ethoxycarbonylindole (I) with N,N-dibenzylaminoethyl chloride, followed by hydrogenolysis of 1-(2-N,N-dibenzylaminoethyl)-5-methoxy-2-ethoxycarbonylindole (II) leading to the formation of III.

Treatment of III with triethyloxonium fluoroborate results in the formation of the lactim ether IV, which was reacted with primary amines to give compounds Va-d. Boiling of III in phosphorus oxychloride in the presence of chloroalkylamine hydrochlorides gave the tetracyclic compounds VIa, b, which form also by an intramolecular cyclization of compounds V [R = $CH_2(CH_2)_nCl$], when the reaction mixture is treated with alkali during the separation of the reaction product.

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TABLE 1. PMR Spectra of Compounds II, V, VI

Compound	Chemical shift, δ, ppm								SSCC, Hz					
	3	4	6	7	MeO	9	10	others	3—4	6—7	6—9	6—10	7—9	other
III	3,62	4,22	7,44	6,94	3,77	7,14	6,94	8.07 NH	6	9	0,6	0,8	2,5	—
Va	3,88	4,38	7,46	7,11	3,84	7,17	7,48	—	5	9	0,6	0,8	2,4	—
Vb	3,89	4,36	7,45	7,07	3,83	7,15	7,34	—	6	9	0,6	0,8	2,4	—
Vc	3,89	4,36	7,44	7,07	3,83	7,16	7,48	3,61; 3,86 CH_2CH_2	6	9	0,6	0,9	2,4	5 CH_2CH_2
Vd	3,95	4,37	7,44	7,08	3,83	7,16	7,66	3,60; 3,80 CH_2CH_2 3,38; 1,40 CH_2CH_3	6	9	0,6	0,8	2,4	6,5 CH_2CH_2 7,5 CH_2CH_3
VIa·HCl	3,93	4,49	7,50	7,14	3,84	7,19	7,38	4,06; 4,09 CH_2CH_2	6	9	0,7	0,9	2,2	—
VIb·HCl	3,94	4,38	7,42	7,06	3,83	7,15	7,36	3,58; 3,73 2,21 $(CH_2)_3$	6	9	—	—	2,4	5,7 $(CH_2)_3$

Note. The spectrum of III was run in $(CD_3)_2SO$; the spectrum of V and VI was run in CD_3OD.

EXPERIMENTAL (CHEMICAL)

The PMR spectra were run on an XL-200 spectrometer (Varian, Switzerland) and the mass spectra on a MAT-112 spectrometer (Varian, FRG). The results of the elemental analyses corresponded to the calculated values.

1-(2-Dibenzylaminoethyl)-5-methoxy-2-ethoxycarbonylindole (II). A 5.9-g portion (0.24 mole) of NaH was added to 44.7 g (0.2 mole) of I in 250 ml of absolute DMFA at a temperature not exceeding 30°C. The mixture was stirred for 30 min, heated to 60°C, stirred for another hour, and 63.6 g (0.24 mole) of dibenzylaminoethyl chloride [7] was added. Heating was continued for another 4 h, and DMFA was distilled under vacuum. A 250-ml portion of water was added, and the mixture was extracted with 2 × 150 ml of ether. The extract was dried over Na_2SO_4, filtered, and evaporated. Yield 82.1 g (90%) of II in the form of an oil, which crystallized on prolonged standing in a refrigerator. mp 65-67°C (MeOH). $M^{+\cdot}$ 442, $C_{28}H_{30}N_2O_3$.

8-Methoxy-1-oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole (III). A solution of 50 g (0.11) mole of II in 500 ml of ethanol was hydrogenated at atmospheric pressure and at a temperature of 50°C in the presence of 3 g of 20% $Pd(OH)_2$ on activated carbon until the absorption of hydrogen ceased (~5 liters of H_2, about 4 h). The solvent was distilled under vacuum, 350 ml of DMFA, and then 1 g of p-$CH_3C_6H_4SO_3H$ was added, and the mixture was boiled for 2 h. The hydrogenation catalyst was filtered off from the hot solution. The filtrate was cooled, and the product was filtered off. Yield 14.7 g (60%) of III. Evaporation of the mother liquor to 75 ml gave a further 3.4 g of III. Overall yield 74%, mp 287-290°C (DMFA). $M^{+\cdot}$ 216, $C_{12}H_{12}N_2O_2$.

8-Methoxy-1-ethoxy-3,4-dihydropyrazino[1,2-*a*]indole (IV). A 13.6 g portion (0.07 mole) of triethyloxonium fluoroborate was added at the boiling point to a suspension of 11.3 g (0.05 mole) of III in 200 ml of dry $CHCl_3$. The precipitate dissolved rapidly, and began to reprecipitate again immediately. The mixture was boiled for 5 h, then cooled to 10°C, and after adding 200 ml of $CHCl_3$, a solution of 15 g of K_2CO_3 in 200 ml of water, cooled to 5°C, was added. The mixture was stirred for 10 min, the organic layer was separated, dried over Na_2SO_4, and evaporated under vacuum. Yield 11.8 g (92%) of IV, $M^{+\cdot}$ 244. The product was subsequently used without purification.

Reaction of IV with Amines

A. A 6.8-g portion of IV in 45 ml of a 14% solution of NH_3 in MeOH was heated at 100°C for 10 h in an autoclave. The mixture was cooled and crystallized from 2% HCl. Yield 4 g (57%) of 1-amino-8-methoxy-3,4-dihydropyrazino[1,2-*a*]indole hydrochloride (Va), mp 259-261°C (water). M^+ 215, $C_{12}H_{13}N_3O \cdot HCl$.

B. A mixture of 4.9 g (0.02 mole) of IV and 13 ml (0.4 mole) of hydrazine in 50 ml of ethanol was boiled for 5 h. The mixture was cooled, the precipitate was filtered off and

crystallized from 2% HCl. Yield 3.7 g (61%) of 1-hydrazino-8-methoxy-3,4-dihydropyrazino-[1,2-*a*]indole hydrochloride (Vb), mp 232-234°C (water), M^+ 230. $C_{12}H_{14}N_4O \cdot HCl \cdot 2H_2O$.

C. A mixture of 4.9 g (0.02 mole) of IV and 2.5 ml (0.04 mole) of monoethanolamine in 25 ml of ethanol was boiled for 12 h. The solvent was evaporated under vacuum, the residue was dissolved in a minimal amount of acetonitrile, and the product was precipitated by an alcoholic solution of HCl. Yield 4.2 g (71%) of 1-(2-hydroxyethylamino)-8-methoxy-3,4-dihydropyrazino[1,2-*a*]indole hydrochloride (Vc), mp 212-214°C (water). M^+ 259, $C_{14}H_{17}N_3O_2 \cdot HCl$.

In a similar way, from IV and diethylaminoethylamine, 8-methoxy-1-(2-dihydroethylamino-ethylamino)-3,4-dihydropyrazino[1,2-*a*]indole dihydrochloride (Vd) was obtained in a 75% yield, mp 231-234°C (MeCN). M^+ 314, $C_{18}H_{26}N_4O \cdot 2HCl$.

10-Methoxy-2,3,5,6-tetrahydroimidazolo[2',1':3,4]pyrazino[1,2-*a*]indole (VIa). A mixture of 8.64 g (0.04 mole) of III in 60 ml of $POCl_3$ was boiled for 2 h. A 6.96-g portion (0.06 mole) of 2-chloroethylamine hydrochloride was added, and the mixture was boiled for a further 3 h. Phosphorus oxychloride was evaporated under vacuum, the residue was hydrolyzed with ice water and an NH_3 solution was added to pH 10-11. The precipitate was filtered off, dried and crystallized from toluene with activated carbon. Yield 5.7 g (60%) of VIa, mp 190-193°C (toluene). M^+ 241. $C_{14}H_{15}N_3O$. mp of hydrochloride of VIa 285-288°C (EtOH-water). $C_{14}H_{15}N_3O \cdot HCl$. In a similar way, from III and 3-chloropropylamine hydrochloride, the hydrochloride of 11-methoxy-2H-3,4,6,7-tetrahydropyrimido[2',1':3,4]pyrazino[1,2-]indole (VIb) was obtained in 60% yield. mp 253-256°C (MeOH). M^+ 255, $C_{15}H_{17}N_3O \cdot HCl$. The PMR spectral data of III and the hydrochlorides of Va-d and VIa, b are given in Table 1.

EXPERIMENTAL (PHARMACOLOGICAL)

The pharmacological investigation of the synthesized[a] compounds was carried out with respect to several parameters, characteristic for the antidepressant action of incasan [1]. The effect was studied on the behavior of "release" from water in an emotional-stressor swimming test, on the depressant action of reserpine, on the activating effects of 5-OTP and L-DOPA, on the hypothermal effects of apomorphine and tremorine. From these tests it is possible to judge the influence on the seretonino-, adreno-, dopamino-, and cholinoreactive systems of the brain. The tests were carried out on mice of both sexes, weighing 18-20 g each.

According to the range of their action and activity in tests with reserpine, 5-OTP, L-DOPA, the compounds studied are close to incasan. In a dose of 25 mg/kg (enterally), compounds Va-d decrease blepharoptosis in mice, caused by reserpine (2.5 mg/kg, intraperitoneally) by 50-40%, compounds VIa, b by 25-20%; incasan in the same dose decreases the reserpine effect by 50% ($P < 0.05$). The compounds studied enhance the spasmodic activity of 5-OTP according to intensification of head shaking by 40-60%, compared with incasan – by 50% ($P < 0.05$). Compounds V and VI intensify the action of L-DOPA, increasing its hyperthermal effect by 1.2-1.8°C ($P < 0.05$), incasan – by 2.5°C ($P < 0.02$). In contrast to incasan these compounds do not display a substantial effect on the behavior of the animals in the swimming test. The compounds studied practically do not influence the hypothermal action of apomorphine, while incasan decreases it by 1.3°C ($P < 0.05$). Only Vc, d decreased hypothermia due to tremorine, which is possibly explained by a certain anticholinergic effect of these compounds. After enteral administration of compounds Va-d and VIa, b the LD_{50} in white mice is equal to 550, 600, 780, 800, 325, and 300 mg/kg, respectively, and that of incasan 445 mg/kg.

Thus, in the antagonism to reserpine and intensification of the action of 5-OTP, the analogs of incasan studied are similar to incasan, but with regard to the remaining tests carried out, they are inferior to it in their activity. Compounds Va-d are less toxic, while VIa, b are more toxic than incasan. With respect to the sum of activity and toxicity parameters, the compounds possess no advantage over incasan.

It should be noted that opening of the pyridine fragment of the incasan molecule affects the activity of the compound less than the opening of the pyrazine ring [3, 6]. The presence in compounds VIa, b of an additional condensed ring makes them more toxic in comparison with Va-d.

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2,3,4a,9,10,10a-HEXAHYDRO-4H-NAPHTHO[2,1-b]-1,4-OXAZINES

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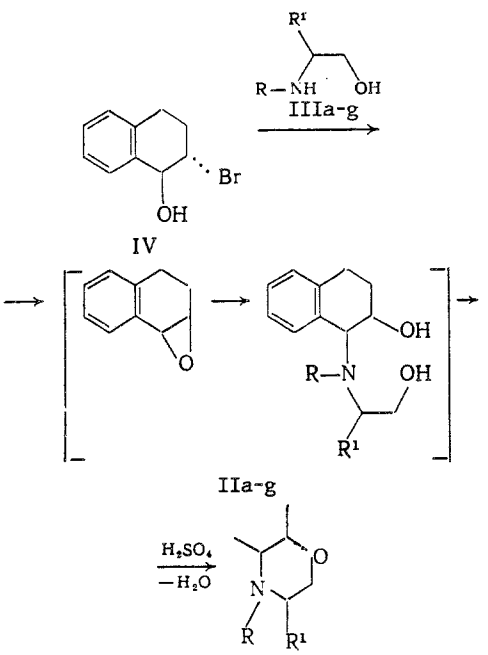
As a continuation of our search for biologically active substances in the series of tricyclic systems containing amorpholine fragment [2-4], we employed the following pattern to synthesize derivatives of naphtho[2,1-b]oxazines (Ia-c, e, f):



Ia-c, e, f

R = H (Ia, f – IIa, f), Me (Ib-IIIb).
Et (Ic-IIIc), Bu (Ie-IIIe),
i = Pr (IId, IIId) C_6H_{11} (IIg, IIIg),
R^1 = H Ia-c, e-IIIa-c, e; IId, g; IIId, g)
Et (If-IIIf)

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