SYNTHESIS AND PSYCHOTROPIC ACTIVITY OF 2-PHENOXY-PROPIONAMIDOXIMES AND THEIR ANALOGS

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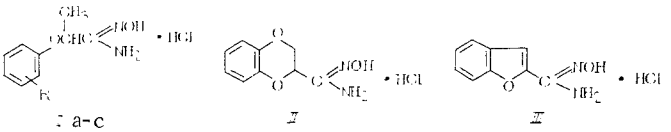
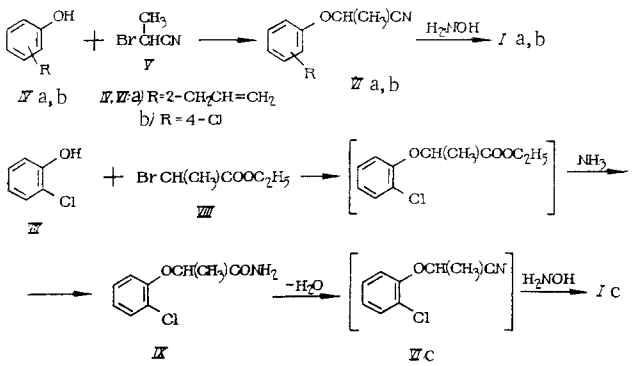
Compounds containing aryloxy groups, especially carboxamidoximes, have been found in recent years to have the properties of atypical antidepressants (naprodoxim, MG-18415, L-7526, trizoxim) [2, 3, 4, 7]. The majority of these were aryloxypropionamidoximes. In a search for new effective antidepressant substances, and in order to study the relationship between structure (character and position of substituents on the benzene ring) and psychotropic activity, the synthesis of 2-phenoxypropionamidoximes (Ia-c) containing such substituents as allyl and chlorine on the aromatic nucleus was undertaken. The amidoximes of 1,4-benzodioxane-2-carboxylic acid (II) and benzofuran-2-carboxylic acid (II) also were synthesized as cyclic analogs of compounds I in which one of the fragments of the molecule is fixed:



I a-c II III

I: a — R = 2-$CH_2CH=CH_2$, b — R = 4-Cl, c — R = 2-Cl.

Amidoximes Ia, b were synthesized by alkylation of the corresponding phenols (IVa, b) with 2-bromopropionitrile (V) in methylethyl ketone in the presence of potassium carbonate, and subsequent reaction of the resulting 2-phenoxypropionitriles (VIa, b) with hydroxylamine:



IV a, b I, IV: a) R = 2-$CH_2CH=CH_2$; b) R = 4-Cl V VI a, b

IV VIII IX IV c

Amidoxime Ic was obtained by reaction of 2-chlorophenol (VII) with ethyl 2-bromopropionate (VIII) with subsequent amination to the amide (IX), dehydration of the latter, and reaction of the resulting nitrile with hydroxylamine. The synthesis of amidoximes II and III involved the reaction of hydroxylamine with the nitriles of 1,4-benzodioxane-2- and benzofuran-2-carboxylic acids.

The structures of amidoximes Ia-c and II were confirmed by elemental analysis and IR and PMR spectral data. In the IR spectra of compounds Ia-c, II, and III and also naprodoxim [i.e., 2-(1-naphthoxypropionamidoxime (X)], obtained in chloroform solution (c = 0.01-0.1 M), showed absorption bands at a frequency of about 3590 cm^{-1} (ν_{OH}), and also bands at 3510 cm^{-1} ($\nu_{assym,\ NH_2}$) and 3400 cm^{-1} ($\nu_{sym,\ NH_2}$), which corresponded to values calculated by the Bellamy—Williams formula [1]. In the 3260-3330 cm^{-1} region were wide bands for bonded —OH, and the 1650-1670 cm^{-1} re-

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gion showed weak $\nu_{C=N}$ bands. The IR spectra of II and III, obtained in CCl_4 ($c \leqslant 0.002$ M), showed bands at 3630 cm^{-1} ($\nu_{free\ OH}$), 3420 and 3520 cm^{-1} (ν_{NH_2}) and 3300-3320 cm^{-1} ($\nu_{bonded\ OH}$). The IR data confirmed that the amidoximes I-III in $CHCl_3$ and CCl_4 solution exist in the form of the amidoxime tautomers. The bands in the 3260-3330 cm^{-1} region of the IR spectra of compounds II and III do not disappear at high dilution, indicating the presence of intramolecular hydrogen bonds (IHB) between the hydroxyl group and, in all probability, the heterocyclic oxygen atom; IHB in the case of amidoxime III participates in the formation of a six-membered ring, and in the case of amidoxime II (in accordance with Dreiding models), the most advantageous is the formation of a seven-membered ring between the hydroxyl group and O_4 in a semi-chair or semi-boat conformation of 1,4-benzodioxane. As for compounds Ia-c and naprodoxim X, the IR spectra, obtained in CCl_4 at high dilution ($c = 0.001$ M) did not show bands in the 3260-3330 cm^{-1} region, which indicates the absence of IHB in these compounds. Consequently, independently of the presence of absence of IHB, compounds I-III in $CHCl_3$ or CCl_4 solution retain the tautomeric form in which amidoximes of more simple structures are found [8]. The PMR spectra of compounds Ib, c (in $CDCl_3$) are characterized by proton signals δ, ppm: CH_3 groups at 1.50 and 1.55 (d, 3H, J = 7 Hz); amino groups, 4.74 and 4.76 (s, 2H); methine group, 4.69 and 4.71 (q, 1H, J = 7 Hz); and the hydroxyl groups, 7.9 and 8.69. The PMR spectrum of naprodoxime in $CDCl_3$ shows analogous collection of signals: δ, ppm: 1.72 (d, 3H, J = 7 Hz); 4.70 (s, 2H, NH_2); 4.90 (q, 1H, CH, J = 7 Hz); 8.60 (s, 1H, OH).

EXPERIMENTAL CHEMISTRY

IR spectra were obtained on a Perkin-Elmer 580 instrument, and PMR spectra were recorded on an HA-100 spectrometer. Ionization constants were determined potentiometrically by titration in 50% alcohol (20°).

2-Phenoxypropionitriles (VIa, b). A mixture of 2.68 g (0.02 mole) of the corresponding phenol and 2.76 g (0.02 mole) of anhydrous potassium carbonate in 15 ml of methylethyl ketone was boiled for 30 min, cooled, and treated with stirring with 3 g (0.022 mole) of 2-bromopropionitrile and boiled for 10 h. The reaction mixture was filtered, the filtrate was concentrated under vacuum, and the residue was distilled to give nitriles VIa, b.

2-(2-Chlorophenoxy)propionamide (IX). A mixture of 17.4 g (0.135 mole) of 2-chlorophenol VII, 18.7 g (0.135 mole) of anhydrous potassium carbonate, and 27 g (0.15 mole) of ethyl 2-bromopropionate was boiled for 15 h, filtered, and the residue after concentration was dissolved in ethyl acetate, washed with 2 N NaOH, concentrated under vacuum, and the residue was vacuum-distilled to give ethyl 2-(2-chlorophenoxy)propionate, bp 125-127°C (6 mm Hg). A mixture of the latter with 200 ml of 16% NH_3 in methanol was stirred for 10 h at about 20°C in an autoclave and concentrated to give 15.8 g of amide IX.

2-(2-Chlorophenoxy)propionitrile (IVc). To a suspension of 12 g (0.06 mole) of amide IX in 35 ml of anhydrous pyridine and 0.3 ml of dimethylformamide under ice cooling was added dropwise 8 ml of $POCl_3$. The mixture was stirred 1 h at about 20°C and heated 0.5 h at 60°C. The reaction mixture was diluted with water, extracted with benzene, and the extract was concentrated under vacuum to give the nitrile VIc, bp 128-129°C (6 mm), which was used for the preparation of amidoxime Ic.

2-Phenoxypropionamidoxime Hydrochlorides (Ia-c). To a mixture of 0.05 mole of the corresponding nitrile VI and 0.05 mole of hydroxylamine hydrochloride in 70 ml of absolute alcohol was added dropwise with stirring a solution of sodium ethoxide (from 0.05 mole of Na and 30 ml of absolute alcohol). The reaction mixture was boiled for 2.5 h, filtered, the filtrate was evaporated under vacuum, and the residue was dissolved in ether. An ethereal solution of hydrogen chloride was added to give the hydrochlorides Ia-c. Constants and analytical data for Ia-c, VIa-c, and IV are given in Table 1.

1,4-Benzodioxane-2-carboxamidoxime Hydrochloride (II). To a suspension of 12 g (0.075 mole) of 2-cyano-1,4-benzodioxane and 5.2 g (0.075 mole) of hydroxylamine hydrochloride in 50 ml of absolute alcohol was added dropwise a solution of sodium ethoxide (from 0.075 mole of Na and 25 ml of absolute alcohol). The reaction mixture was stirred for 2 h at 20°C, filtered, the precipitate was washed with boiling alcohol, and the alcohol solutions were concentrated under vacuum to give 13.5 g (95%) of the free base of amidoxime II, mp 136-137°C (from isopropanol). pK_a^1 = 3.50 (associated proton), pK_a^2 = 11.50 (exchangeable proton). Found, %: C 55.65; H 5.22; N 14.48. $C_9H_{10}N_2O_3$. Calculated, %: C 55.66; H 5.19; N 14.43.

TABLE 1. Derivatives of 2-Phenoxypropionic Acid

Compound	mp (°C) or bp (°C) (mm Hg)	Found, %				Elemental formula	Calculated, %				Yield, %
		C	H	Cl	N		C	H	Cl	N	
Ia	106—107	56,17	6,71	14,16	11,0	$C_{12}H_{16}N_2O_2 \cdot HCl$	56,14	6,67	13,81	10,91	66
Ib	151—152	42,98	5,05	28,22	11,29	$C_9H_{11}ClN_2O_2 \cdot HCl$	43,04	4,82	28,24	11,16	72
Ic	116 (dec.)	. . .	. . .	28,51	. . .	$C_9H_{11}ClN_2O_2 \cdot HCl$			28,24		40
VIa	123 (6)	76,84	7,15	—	7,74	$C_{12}H_{13}N$ (O)	76,97	7,00	—	7,48	77,5
VIb	123—4 (5)	59,59	4,44	19,51	7,64	C_9H_8ClNO	59,51	4,44	19,52	7,71	75
IX	99—100	54,24	5,06	—	17,61	$C_9H_{10}ClNO_2$	54,14	5,05	17,76	—	69

Note. Recrystallization solvents: Ia, b, isopropanol—absolute ethanol; Ic, isopropanol—petroleum ether; IX, 50% alcohol.

Hydrochloride II. mp 142°C (dec). Found, %: Cl 15.26. $C_9H_{10}N_2O_3 \cdot HCl$. Calculated, %: Cl 15.37.

Benzofuran-2-carboxamidoxime (III). This was prepared analogously to II; mp 186°C (dec), Lit. [5] mp 188-189°C.

EXPERIMENTAL PHARMACOLOGY

The antidepressant activity of the amidoxime hydrochlorides Ia, b, II, and III was studied in experiments on mice (body weight = 18-22 g) through their ability to potentiate the effects of phenamine (phenocol) and 5-hydroxytryptamine (serotonin), and their antagonism to the action of reserpine. In addition, we studied myorelaxant activity. Experiments were carried out in the first half of the day. Immediately after the test, mice were placed in self-contained cages situated in the experimental room. Each dose was studied on 6-10 animals. The compounds were introduced intraperitoneally 40 min before evaluating the effect. For comparison, the known antidepressants imipramine and naprodoxim were used. The results of the study were worked up statistically with the calculation of ED_{50} by the method of [6].

The phenamine potentiation effect was measured by the ability of the substances to increase the number of animals (mice) showing the phenamine symptomology upon intraperitoneal, one-time injection of the substance with a minimal dose of phenamine (ED_{50} = 12 mg/kg). A positive effect was considered a symptomology prolongation of 4 min.

Antagonism to reserpine was tested by hypothermia in mice kept in a thermostatted chamber. Reserpine was injected in a dose of 2.5 mg/kg intraperitoneally, and the test material was injected 30 min after the reserpine. Rectal temperatures were measured 2, 3, and 4 h after introduction of the preparation.

Potentiation of the action of 5-hydroxytryptamine (5-HT) in mice was determined by means of the "head twitch" test. The substance was injected intraperitoneally 30-40 min after the injection of 5-HT (200 mg/kg, intraperitoneally). We recorded the number of twitches occurring during a 2-min interval of each 10-min period for 1 h.

The influence on muscle tonus and motor coordination was studied by the rotating rod method (rotation speed = 5 rpm, diameter = 2 cm). Animals failing under the influence of the test chemicals were restrained on the rod for 2 min to examine any manifestation of a break in motor coordination.

It was shown that compound Ia in a dose of 5 mg/kg was a similar antidepressant to the tricyclic structures and naprodoxim, and also is capable of potentiating the effect of phenamine. However, in contrast to these, the effect of Ia did not depend upon dose, and an increase in the test substance did not strengthen the effect. Compound III was not capable of potentiating the action of phenamine. Compound II, in doses of 5 and 10 mg/kg, weakened the hypothermic effect of reserpine; this effect was observed in the highest degree 2 h after the introduction of compound II.

The majority of the studied derivatives of 2-phenoxypropionamidoxime (compounds Ia, II, and III), like naprodoxim, did not show a stable persistent influence on the main manifestation of the activity of 5-HT. In a range of doses from 0.25 to 10 mg/kg, the action of the studied compounds was not dependent upon dose. It should be noted that with low doses of these compounds, a potentiation of a 5-HT-induced hyperkinesis was observed. The chlorosubstituted compounds Ib, c showed serotonin potentiation activity in doses of 5-10 mg/kg; in the case of the 2-chlorosubstituted Ic, the serotonin-potentiating effect was more expressed at the indicated doses, but increasing the dose to 20 mg/kg resulted in a lowering of the activity.

None of the studied analogs of naprodoxime in a range of doses of from 0.25 to 10 mg/kg produced a change in motor coordination in the experimental animals.

Thus, a study of the pharmacological properties of the 2-phenoxypropionamidoximes and their analogs showed that a majority exhibited psychotropic properties characteristic of substances with antidepressant activity. However, all of the studied compounds are less effective than the activity prototype, naprodoxim, which, according to our data, possesses expressed psychotropic properties, particularly in its antagonism to reserpine hypothermia, significantly exceeding those of the most active (ED_{50} = 0.1-1 mg/kg) of the known antidepressants (imipramine, amitryptyline, maprotiline, etc.).

The introduction of a chlorine atom in either the ortho or para positions of the benzene ring (compounds Ib, c) leads to an essential change in the spectra of pharmacological activities by comparison with other amidoximes studied. The indicated change in the spectrum of activity is characterized by central serotonin-positive action with weak effectiveness with respect to potentiation of phenamine and antagonism to reserpine.

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NITROGEN-CONTAINING ORGANOSILICON COMPOUNDS. CXXII. SYNTHESIS AND PHARMACOLOGICAL STUDIES OF TRIALKYLSILYLALKYLAMINOETHYL DICARBOXYLATE METHIODIDES

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In the course of studying the biological activity of organosilicon derivatives of aminoalcohols [1-5], we synthesized the methiodides of esters of organosilicon choline derivatives and dicarboxylic acids.

The organosilicon aminoalcohols Ia-g were synthesized from trialkyl(chloroalkyl)silanes and N-methylaminoethanol in the presence of triethylamine in a butanol medium. The products of reaction of trialkyl(2-hydroxyethylaminoalkyl)silanes with succinic, adipic, suberic, azelaic, and sebacic chlorides were treated with methyl iodide to obtain the methiodides III-VII.

$$RR'_2Si(CH_2)_nN(CH_3)CH_2CH_2OH \xrightarrow{(CH_2)_m[COCl]_2} \underset{I\ a\text{-}g}{} \longrightarrow \underset{II}{\left[RR'_2Si(CH_2)_nN(CH_3)CH_2CH_2OCO\right]_2(CH_2)_m} \xrightarrow{CH_3I} \left[RR'_2Si(CH_2)_n\overset{+}{N}(CH_3)_2CH_2CH_2OCO\right]_2(CH_2)_m \cdot 2I^-$$

IIIa-g–VIIa-g

a: $n = 1$, $R = R' = CH_3$; b: $n = 1$, $R = R' = C_2H_5$; c: $n = 3$, $R = C_2H_5$, $R' = CH_3$; d: $n = 3$, $R = CH_3$, $R' = C_2H_5$; e: $n = 3$, $R = CH_3$, $R' = C_3H_7$; f: $n = 3$, $R = CH_3$, $R' = C_4H_9$; g: $n = 3$, $R = R' = C_2H_5$.

III: $m = 2$; IV: $m = 4$; V: $m = 6$; VI: $m = 7$; VII: $m = 8$.

Hydrocarbon analogs of the succinic acid derivatives, containing 7- or 10-carbon chain substituents at the N atom, were also synthesized. Dimethiodides of di[2-(N-methyl-N-alkyl)-aminoethyl] succinates were obtained according to the same scheme as for the organosilicon derivatives:

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