2-Chloro-6-methylnicotinic Acid Propylamide (III). This was obtained similarly. Yield 44% mp 49-50°C (from hexane). Found, %: N 13.14; Cl 16.95. $C_{10}H_{13}ClN_2O$. Calculated, %: N 13.17; Cl 16.67.

2-Chloro-6-methylnicotinic Acid Butylamide (IV). This was obtained similarly. Yield 40%, mp 42-43°C (from hexane). Found, %: N 12.06; Cl 15.58. $C_{11}H_{15}ClN_2O$. Calculated, %: N 12.35; Cl 15.63.

2-Arylamino-6-methylnicotinic Acid Alkylamides (V-XIII). A solution of 0.01 mole of the 2-chloro-6-methylnicotinic acid alkylamide and 0.01 mole of the arylamine in 20 ml of 50% acetic acid was boiled for 6 h, cooled, and neutralized with a 10% solution of sodium hydroxide. The precipitate which separated was filtered off and recrystallized from a mixture of benzene and hexane (1:2). The hydrochlorides of V-XIII were obtained by passing dry hydrogen chloride through a solution of the base in anhydrous ether.

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SYNTHESIS AND STUDY OF THE NEUROTROPIC ACTION OF 2-SUBSTITUTED METHANOISOINDOLES

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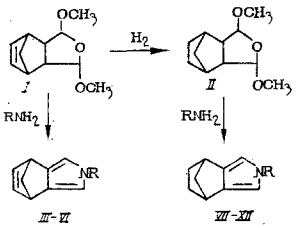
UDC 615.21:547.759.4

The biological properties of methanoisoindoles have almost not yet been studied. It is only known that their hexa- and octahydro analogs have hypotensive [1, 2], diuretic [3, 4], and antidiabetic activity [5].

We have already shown [6] that hydrogenated derivatives of isoindole act on the central nervous system and certain other functions of the vegetative nervous system. We therefore searched for new neurotropic agents in the series of "bridged" isoindoles.

In the present work we describe the results of the study of the neurotropic activity of 2-substituted methanoisoindoles. The starting reagents in the synthesis of these compounds were the adduct (I) of the diene condensation of 2,5-dimethoxy-2,5-dihydrofuran with cyclopentadiene and the hydrogenated analog of this adduct (II) [7]. 4,7-Dihydro- (III-VI) and 4,5,6,7-tetrahydro-4,7-methanoisoindoles (VII-XII) were obtained by heating I or II in an acid medium with a primary amine:



III, VII: R = C_6H_5; IV, VIII: R = p-$C_6H_4CH_3$;
V, IX: R = p-$C_6H_4SO_2NH_2$;
VI, X: R = CH_2CH_2OH;
XI: R = C_6H_2(o-OH) (o-Cl) (m-NO_2);
XII: R = tert-C_4H_9.

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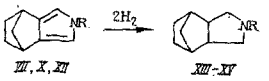
Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 15, No. 4, pp. 38-42, April, 1981. Original article submitted July 8, 1980.

0091-150X/81/1504-0252$07.50

2-Aryl-substituted methanoisoindoles III-V, VII-IX, XI are formed by the reaction of equimolecular amounts of the adduct and the amine in acetic acid for 1/2 and 1.5 h at 70-100°C. To prepare 2-hydroxyethyl (VI, X) and tert-butyl derivatives (XII), more rigid conditions are required: 100-120°C, 5-6 h of heating, ratio of reagents adduct–amine 1:2, and in this case the reaction is preferably carried out in propionic acid.

The octahydro-4,7-methanoisoindoles XIII-XV were synthesized by reducing VII, X, and XII in ethanol, under a hydrogen pressure of 100 atm, at 100°C, in the presence of 10% Ru/C:



III, X, XII XIII-XV

VII, XIII: R = C_6H_5; X, XIV; R = CH_2CH_2OH; XII, XV: R = tert-C_4H_9

According to TLC and GLC data, when 4,5,6,7-tetrahydro-4,7-methanoisoindole is hydrogenated under these conditions, only one isomer of octahydro-4,7-methanoisoindole is formed, and the reduction of VII proceeds selectively, with the retention of the benzene fragment. Due to the stereospecificity of this reaction, it was possible to assume a cis-position of the angular hydrogen atoms with respect to the ring.

The physicochemical properties of the synthesized compounds are listed in Table 1.

In the IR spectra of compounds III-XIII, in the 1490-1610 cm^{-1} absorption region, there are several intense bands corresponding to the stretching vibrations of multiple bonds of the aromatic and pyrrole rings. In the spectra of III, VII, and XIII, a strong band in the 750 cm^{-1} region has been noticed due to nonplanar deformational vibrations of the C–H groups of the monosubstituted benzene ring. For IV, V, VIII, and IX, an intense band in the 804-820 cm^{-1} region is characteristic (1,4-disubstituted benzene). In the spectra of compounds VI, X, XII with no aryl fragment in their structure, absorption is observed in the region of 740-760 cm^{-1}, corresponding to extraplanar vibrations of the C–H bonds of the pyrrole nucleus. The presence of the latter has been also confirmed by the absorption band in the 1565 cm^{-1} region (pyrrole) [8]. In the spectra of V and IX, strong bands in the 1150 and 1325 cm^{-1} region correspond to symmetrical and antisymmetrical stretching vibrations of the SO_2 group. The broad stretching vibrations band in the 3200-3550 cm^{-1} region indicates the presence of associated hydroxyl groups in isoindoles VI, X, XI, and XIV.

The PMR spectra of 4,7-dihydro- and 4,5,6,7-tetrahydromethanoisoindoles confirm their structure. The proton singlet of the pyrrole ring is observed in the weakest field (6.5 ppm). In the spectra of 2-aryl substituted derivatives III-V, VII-IX, XI, and XIII, the signals of the benzene ring appear in a weak field (6.15-7.20 ppm). In the spectrum of XII, the proton signal of the tert-butyl group (1.38 ppm) is shifted more to the weaker field from its usual position (1.05 ppm). This is possibly due to the magnetic anisotropy of the pyrrole ring. In the spectra of all the synthesized compounds there are strong-field signals (1.6-2.2 and 1.3-2.0 ppm) corresponding to the methylene and methine protons. The absence of proton signals of the pyrrole ring in XIII-XV confirms the completeness of hydrogenation of these compounds.

EXPERIMENTAL PHARMACOLOGICAL SECTION

The general action, toxicity, and neurotropic activity of the above 2-substituted methanoisoindoles have been studied.

The acute toxicity was studied in nonlinear white mice and rats at intraperitoneal administration of solutions of the compounds in oil. The LD_{50} was calculated by the method of probit analysis according to Litchfield and Wilkoxon [9]. We found that almost all the methanoisoindoles are relatively slightly toxic (at intraperitoneal administration of 500-1000 mg/kg). The most toxic is 2-(1-hydroxyethyl)-octahydro-4,7-methanoisoindole XIV (LD_{50} 100 mg/kg).

The neurotropic activity was studied on white mice weighing 20-22 g each. Doses were used corresponding to 0.1 LD_{50} for mice. The effect on the central nervous system function was studied by the following tests; behavioral reactions, residence time on "parallel walls," prolongation of narcotic action of hexenal (70 mg/kg subcutaneously), orientational reactions by the method described in [10], changes in the spontaneous motor activity, aggressiveness, rectal temperature, reaction with phenamine (10 mg/kg) and reserpine (2 mg/kg). The anti-

TABLE 1. 2-Substituted 4,7-Dihydro-, 4,5,6,7-Tetrahydro- and Octahydro-4,7-Methanoisoindoles

Compound	Yield, %	mp, °C	Found, %			Empirical formula	Calculated, %			R_f‡
			C	H	N		C	H	N	
III	60	274—7	86,71	5,92	6,92	$C_{15}H_{13}N$	86,91	6,32	6,75	0,32
IV	68	211—3	86,61	6,34	6,26	$C_{16}H_{15}N$	86,84	6,83	6,33	0,31
V	63	243—5	63,32	5,28	10,00	$C_{15}H_{14}N_2O_2S$	62,93	4,93	9,79	0,35
VI	62	95—7	75,98	7,59	7,51	$C_{11}H_{13}NO$	75,41	7,48	7,99	0,57
VII	54	228—30	80,99	7,26	6,50	$C_{15}H_{15}N$	80,69	6,91	6,69	0,40
VIII	87	238—40	86,22	7,51	6,32	$C_{16}H_{17}N$	86,06	7,67	6,27	0,48
IX	78	275—7	62,60	5,43	10,00	$C_{15}H_{16}N_2O_2S$	62,48	5,59	9,72	0,39
X	95	106—8	74,42	8,39	7,69	$C_{11}H_{15}NO$	74,54	8,53	7,90	0,52
XI	75	223—5	59,21	4,38	9,33	$C_{15}H_{13}N_2O_3Cl$	59,12	4,30	9,19	0,33
XII	64	103—4 (1)*	82,68	9,95	7,29	$C_{13}H_{19}N$	82,48	10,12	7,39	0,52
XIII	48	103—5	79,55	8,96	12,49	$C_{15}H_{19}N$	79,26	8,43	12,33	0,55
XIV	44	104—6 (1)*	73,05	10,16	7,62	$C_{11}H_{19}NO$	72,88	10,57	7,70	0,65
XV	51	50—1†	80,52	11,67	7,49	$C_{13}H_{23}N$	80,76	11,99	7,25	0,62

*Bp, °C (mm Hg).

†Bp 81-3°C (5 mm Hg).

‡Al_2O_3 activity grade II. Heptane—benzene (19:1) system. Developing agent — iodine.

spasmodic action was estimated by the test of the reaction with corazole. The influence on the conditioned reflexes and rate of their production was studied on white rats weighing 180-200 g each.

All the methanoisoindoles tested have different degrees of neurotropic activity. Compounds with an aryl radical attached to the nitrogen atom give a similar pharmacological effect. They lower the body temperature of the animals, decrease aggressiveness, increase the residence time of the mice on "parallel walls" (without appearances of virtual catalepsy), and increase the duration of hexenal-induced sleep, characteristic of tranquilizers [11-13]. Compounds IV, IX, and XI do not influence the spasmodic action of corazole, the orientational reaction, the motor activity, and conditioned reflex activity.

Methanoisoindole III differs from the other compounds in the degree of expression of its action on the central nervous system function: not only does it cause a decrease of 2° in the body temperature, but it also prevents the development of phenamine hyperthermia, which may indicate the antiadrenergic properties of this compound. Compound III also inhibits the development of phenamine induced hyperactivity in mice and decreases the spontaneous motor activity (from 279.1 ± 24.3 to 104.2 ± 17.1 runs in 10 min) and reliably doubles the duration of the latent period of combat of mice (from 55.7 ± 7.7 to 102.3 ± 12.1 sec; $P < 0.01$). Compound III has a pronounced antispasmodic action: It prevents the development of strychnine-induced spasms in 87.4% of mice. The compound prolongs the latent period of conditional avoidance reflex in rats by a factor of 2.1. The duration of hexenal-induced sleep is increased by the action of III by a factor of 2.8 (IX — by a factor of 2.4; IV — 2.3; XI — by a factor of 1.9). Because of the antiphenamine action of methanoisoindole III, we can assume the presence of adrenolytic properties in it [14].

Compounds with a hydroxyethyl group attached to the nitrogen atom occupy an intermediate position with respect to the degree of expression of the depressant action on the central nervous system function, with octahydromethanoisoindole XIV acting most strongly and in the largest number of tests. It lowers the aggressiveness by a factor of 2, the motor activity by a factor of 1.5, the orientational reaction by a factor of 1.5, prolongs the hexenal-induced sleep by a factor of 1.5, and increases the latent period of spasmodic attack induced by the administration of corazole (from 12.4 ± 0.4 to 18.8 ± 2 min; $P < 0.001$).

In contrast to XIV, tetrahydromethanoisoindole X does not influence the orientational reaction and motive activity, and while it prolongs the hexenal-induced sleep by a factor of not more than 1.3, it increases the latent period of conditional avoidance reflex by a factor of 2.9, and at the same time inhibits the rate of production of a conditional defensive reflex by a factor of 1.5.

The above results indicate that the methanoisoindoles studied, although they have a depressant action on the central nervous system functions, they have the properties of tranquilizers, and this effect is most strongly marked in the case of 2-phenyl-4,7-dihydro-4,7-methanoisoindole.

EXPERIMENTAL CHEMICAL SECTION

The IR spectra were run on the UR-20 apparatus. The liquid compounds were studied in a capillary-thin layer, and the crystals in mineral oil and hexachlorobutadiene. The PMR spectra were recorded on the Tesla apparatus (CSSR) (working frequency 80 MHz) in solutions of CCl_4 and $(CD_3)_2CO$. Hexamethylsiloxane served as the internal standard. GLC: Tsvet-101 apparatus, gas-carrier (helium) flow rate 60 ml/min, column 1 m long, 3 mm in diameter (15% Carbowax 20 M on Chromaton N). Temperature of column thermostat 220°C.

The synthesis of compounds I, II is described in [7], III, IV, and VIII in [15].

2-(p-Sulfonamidophenyl)-4,7-dihydro-4,7-methanoisoindole (V). A mixture of 1.96 g (0.01 mole) of I, 1.72 g (0.01 mole) of p-aminobenzenesulfonamide and 5 ml of glacial acetic acid is heated with stirring in a flask with a reflux condenser on a boiling water bath for 1.5 h. The reaction mixture is then poured into ice (10 g), and neutralized with potassium hydroxide. The crystals which precipitate are filtered, purified by reprecipitation with water from an acetone solution, and dried *in vacuo*.

Compounds IX and XI are obtained similarly.

2-Phenyl-4,5,6,7-tetrahydro-4,7-methanoisoindole (VII). This is prepared from II and aniline, similarly to V, but the mixture is heated at 70°C for 30 min.

2-(1-Hydroethyl)-4,7-dihydro-4,7-methanoisoindole (VI). A 5.88 g (0.03 mole) portion of I, 3.66 g (0.06 mole) of freshly distilled monoethanolamine and 15 ml of propionic acid are placed in a three-necked flask fitted with a mechanical stirrer, thermometer, and condenser set for downward distillation. The mixture is heated on a glycerol bath for 6 h at 120°C. The methanol formed in the preparation of methanoisoindole is distilled off. When cool, the reaction mixture is poured onto ice (30 g), and sodium hydroxide is gradually added to a strongly alkaline reaction. The crystals which precipitate are separated, and the mixture is boiled for 4 h with 15 ml of methanol and 1.5 g of potassium hydroxide to saponify the ester impurities. Methanol is then distilled off, the residue is washed from alkali, and reprecipitated with water from an acetone solution. The crystals are dried *in vacuo*.

Compound X is obtained similarly.

2-(tert-Butyl)-4,5,6,7-tetrahydro-4,7-methanoisoindole (XII). A solution of 5.94 g (0.03 mole) of II in 20 ml of propionic acid is placed in a three-necked flask fitted with a mechanical stirrer, reflux condenser, and dropping funnel. Then, 4.38 g (0.06 mole) of tert-butylamine are added dropwise in the course of 10 min. The flask contents are heated for 5 h on a glycerol bath at 120°C. The reaction mixture is then poured onto ice (50 g), and potassium hydroxide is added to pH 7.0. The oil which separates is extracted with ether. The ether extracts are washed with water, and dried over anhydrous magnesium sulfate. After the ether has been removed, the residue is distilled *in vacuo*.

2-Phenyloctahydro-4,7-methanoisoindole (XIII). A 6.3 g (0.03 mole) portion of VII, 60 ml of ethanol and 0.1 g of ruthenium on carbon are placed in a 150 ml rotatory autoclave. The mixture is hydrogenated at an initial hydrogen pressure of 100 atm at 100°C. At the end of the hydrogen absorption, the autoclave is discharged, and the catalyst filtered. The alcoholic solution is poured into water (100 ml). The precipitate which separates is filtered and dried *in vacuo*.

Compounds XIV and XV are obtained similarly, but after removal of ethanol under reduced pressure, the residue is distilled *in vacuo*.

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