SYNTHESIS AND ORIENTATIONAL PHARMACOLOGICAL STUDY OF HYDROGENATED ISOINDOLES

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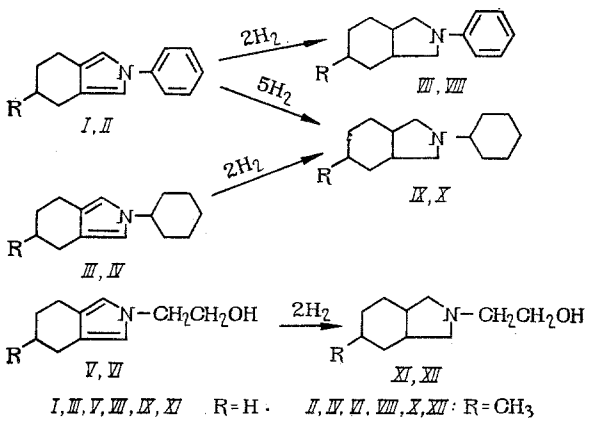
The synthesis and antimicrobial activity of 4,7-dihydro- and 4,5,6,7-tetrahydroisoindoles have been reported earlier [1]. In a continuation of the investigation of the biological properties of this new class of compounds, we have hydrogenated a series of 4,5,6,7-tetrahydroisoindoles and studied the pharmacological activity of several of the hydrogenated isoindole derivatives with respect to their structure. The octahydroisoindoles are the reduction products from 4,5,6,7-tetrahydroisoindoles and contain the same structural fragments as preparations used in the treatment of cardiovascular [2] and psychological [3] illnesses.

The hydrogenation occurs according to the following scheme:



I, III, V, VII, IX, XI R=H · II, IV, VI, VIII, X, XII: R=CH3

We studied the influence of temperature, catalyst type, solvent nature, and type of N-substituent on the product yield. The catalysts used were Raney nickel, ruthenium dioxide, rhodium, activated aluminum oxide, and platinum dioxide. The hydrogenation was conducted in acetic acid, ethanol, or isopropanol at initial hydrogen pressure of 100 atm.

The most effective catalysts in the reduction of tetrahydroisoindolines were the ruthenium and rhodium catalysts, which permitted a smooth hydrogenation of the pyrrole ring at 60°C; in compounds I and II simultaneous hydrogenation of the benzene ring also occurred (Table 1). In the presence of Raney nickel, the same reaction occurs at a higher temperature (100°C). The hydrogenation with Raney nickel at 60°C is impeded, as is indicated from the significant amount of unreacted tetrahydroisoindoline obtained along with the octahydro reaction products.

TABLE 1. Yield of Octahydroisoindoles (in %) with Respect to Reaction Conditions (solvent — acetic acid)

Catalyst	Reaction temperature, °C	Starting 4,5,6,7-tetrahydroisoindole					
		I	II	III	IV	V	VI
NiR	60	41	43	23	29	17	21
NiR	100	76	77	69	71	57	63
RuO_2	60	73	75	65	60	62	66
Rh/Al_2O_3	60	82	85	78	75	65	68

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TABLE 2. Octahydroisoindoles VII-XII

Compound	Yield, %	bp, °C/mm	d_4^{20}	n_D^{20}	MR_D		Found, %			Formula	Calc., %		
					found	calc.	C	H	N		C	H	N
VII	84	57—8*	—	—	—	—	83,40	9,48	7,06	$C_{14}H_{19}N$	83,65	9,53	6,97
VIII	86	95—6*	—	—	—	—	83,53	9,49	6,63	$C_{15}H_{21}N$	83,79	9,85	6,52
IX	82	106—9/1	0,9536	1,5030	64,16	64,19	81,36	12,46	6,75	$C_{14}H_{25}N$	81,23	12,17	6,77
X	85	102—4/1	0,9634	1,4987	68,72	68,81	81,72	12,43	5,94	$C_{15}H_{27}N$	81,52	12,31	6,34
XI	82	112—5/2†	1,021	1,5200	49,68	49,44	70,71	11,00	8,43	$C_{10}H_{19}NO$	70,96	11,32	8,28
XII	86	119—22/2	1,025	1,5175	54,12	54,06	71,82	11,43	7,80	$C_{11}H_{21}NO$	71,91	11,55	7,64

*mp; substance was purified by recrystallization from 96% ethanol.
†Literature data [4]: bp 78-82°C/0.75 mm.

Platinum dioxide exhibits a high selectivity in the hydrogenation of compounds I and II. In the presence of this catalyst at room temperature, only reduction of the pyrrole ring occurs. The octahydroisoindole VII and VIII having N-phenyl substituents are obtained in 84-86% yields (Table 2). The selectivity of the process decreased on increasing the temperature. Hydrogenation products obtained at 100°C were almost exclusively 2-cyclohexyloctahydroisoindoles IX and X (yield 76 and 80%).

The hydrogenation of 4,5,6,7-tetrahydroisoindoles in acetic acid, ethanol, or isopropanol gave approximately the same product yields. The nature of the N-substituents has a significant influence on reaction time. Under similar conditions, compounds having a hydroxyethyl group were hydrogenated more slowly than the cyclohexyl and phenyl derivatives (12 and 6 h, respectively).

The purity of the synthesized compounds was determined using gas–liquid chromatography (GLC). The chromatographic data indicated that only one isomer of octahydroisoindole is formed in the reduction of the pyrrole ring. The stereoselectivity of the hydrogenation permits proposal of cis hydrogen atoms with respect to the octahydroisoindole ring.

In IR spectra for compounds VII and VIII, the presence of a phenyl ring is indicated by characteristic absorption bands at 3100-3000, 1600-1470, and 760-690 cm^{-1} [5]. These bands are absent in spectra for compounds IX and X which confirms complete hydrogenation. The presence of associated hydroxyl groups in compounds XI and XII is indicated by a broad band of valence vibrations in the region 3400-3200 cm^{-1}. Stretching vibrations for C–O–H in the hydroxyl group are confirmed by an intensive absorption at 1130 cm^{-1} [5].

EXPERIMENTAL

Pharmacological

An orientational study of the activity of compounds VIII, X, and XII as well as previously prepared [1, 6] 2-phenyl-4,7-dihydroisoindole (XII), its 5-methyl homolog (XIV), I, and II was conducted using white mice. The compounds were injected intraperitoneally as oily solutions 30-60 minutes before testing. The activity was studied using the following tests: potentiation of hexenal-induced sleep (70 mg/kg intraperitoneally introduced), influence on orientational reaction, change in the spontaneous locomotory motions, change in body temperature, and influence on general state and behavior of laboratory animals. The LD_{50} was calculated by the method of Lichfield and Wilcoxon (observation period – 7 days).

The studied compounds do not cause catalepsy and have no analgesic or antispasmodic (Corazole, 76.5 mg/kg, subcutaneous; strychnine, 1.2 mg/kg, subcutaneous) activity. Preparations I, II, X, and XII cause a decrease in motor activity and orientational reaction; II and XII decrease the body temperature, and XII potentiates the narcotic activity of Hexenal.

The pharmacological activity test results are presented in Table 3.

The majority of the compounds studied show a depressive influence on the central nervous system, although preparations XIII and XIV have a clearly stimulative effect. This is probably caused by the presence of double bonds in the six-membered ring of the isoindole system.

An analysis of the toxic doses of the isoindoles shows a definite trend in increasing toxicity in the order XIV < XIII < II < I < VIII < XII < X. This trend is associated with the degree of saturation of the compounds. Phenyl groups on the nitrogen atom also increase the toxicity. It is increased sharply on substituting the phenyl group by a hydroxyethyl or cyclohexyl group in the octahydroisoindoles. A methyl group in position 5 generally lowers the toxicity.

Chemical

The IR spectra were recorded on a UR-20 instrument using KBr tablets, petrolatum, or hexachlorobutadiene. Product purity was determined by GLC on a Tsvet-101 instrument with column length 1 m, 15% nonstationary phase, Carbowax 20 M on Chromaton N, and carrier gas (helium) rate 60 ml/min.

TABLE 3. Effect of Isoindolesin 0.1 LD_{50} Doses on the Central Nervous System

Compound	Lethal dose LD_{50}, mg/kg	Nature of action at toxic doses	Influence on spontaneous motor activity, passes/h	Influence on body temperature, °C	Change in orientational reaction	Duration of Hexenal-induced sleep, min
I	1000	Sleep, dyspnea, cyanosis, death in side position	1010±59 801±48 $P<0,05$	36,8±0,58 36,7±0,5 $P>0,05$	34±1,7 25±2,8 $P<0,001$	50±3 53±5 $P>0,05$
II	1750	Ataxia, clonic convulsions, death in side position	982±73 638±67 $P<0,05$	38,1±0,4 36,6±0,45 $P<0,05$	35±1,5 25±2 $P<0,001$	51±1 59±9 $P>0,05$
VIII	750	Sleep, dyspnea, cyanosis, death in stomach position	935±53 804±50 $P>0,05$	36,5±0,48 36,8±0,47 $P>0,05$	33±2,5 33±2,5 $P>0,05$	58±2 62±3 $P>0,05$
X	56	Ataxia, clonic convulsions, dyspnea, death in side position	960±42 499±35 $P<0,001$	37,1±0,5 37,1±0,57 $P>0,05$	35±1,7 20±2,2 $P<0,001$	50±6 62±7 $P>0,05$
XII	250	Sleep, dyspnea, cyanosis, death in stomach position	973±48 467±31 $P<0,001$	37,5±0,48 35,5±0,49 $P<0,05$	35±1,7 23±1,9 $P<0,001$	59±3 94±8 $P<0,05$
XIII	2000	Ataxia, diminished breathing, twitching of extremities, death in side position	921±7 1890±28 $P<0,001$	37,3±0,2 38,3±0,3 $P<0,05$	25±2 150±5 $P<0,001$	52,0±5 43,0±3 $P>0,05$
XIV	2500	Ataxia, weak twitching of extremities, death in side position	968±12 2545±18 $P<0,001$	37,1±0,2 40,0±0,3 $P<0,05$	23±2 190±3 $P<0,001$	49±4 41±3 $P>0,05$

Note: Numerator) control data; demoninator) test data. P) Significance of differences in comparison to control group of mice.

TABLE 4. 4,5,6,7-Tetrahydroisoindoles

Compound	Yield, %	bp, °C/mm	n_D^{20}	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
III	38,7	138—40/2	1,5390	82,75	10,39	7,24	$C_{14}H_{21}N$	82,70	10,41	6,90
IV	44	135—6/3	1,5280	83,46	10,93	6,40	$C_{15}H_{23}N$	83,02	10,66	6,45
V	67	137—8/4	1,5370	72,34	9,39	7,94	$C_{10}H_{15}NO$	72,69	9,15	8,48
VI	70	149—52/6	1,5320	73,93	10,01	8,14	$C_{11}H_{17}NO$	73,70	9,56	7,81

4,5,6,7-Tetrahydroisoindoles I and II were obtained according to [1, 6].

2-Cyclohexyl-4,5,6,7-tetrahydroisoindole (III). A mixture of 3.0 g (0.016) isohexahydrobenzo-1,3,-dimethoxytetrahydrofuran, prepared according to [7], 1.6 g (0.016 mole) cyclohexylamine, and 5 ml glacial acetic acid were heated on a boiling water bath for 1.5 h. The product was treated in the cold with a saturated solution of sodium bicarbonate. The oil which separated was extracted with ether, and the ether extracts were washed with water and dried with magnesium sulfate. After solvent removal the substance was vacuum distilled and the fraction with bp 138-140°C/2mm was collected. Yield 1.2 g (38.7%).

Compound IV was obtained analogously (see Table 4).

2-(1'-Hydroxyethyl)-4,5,6,7-tetrahydroisoindole (V). A mixture of 5.6 g (0.03 mole) 1,3-dimethoxyoctahydrobenzofuran, 3.6 g (0.06 mole) freshly distilled monoethanolamine, and 15 ml propionoic acid were heated at 120-125°C for 6 h on a glycerin bath. The methanol formed in the reaction is driven off during the heating. On cooling, the contents of the flask were decanted in crushed ice and sodium hydroxide was added until attainment of a strongly basic reaction. The oil which separated was extracted with ether. After removal of the ether, the product was heated to boiling with 5 ml methanol and 0.5 g potassium hydroxide for 4 h. The ester impurities are saponified in this manner. The methanol was further driven off and the residue was treated with water (20 ml). A yellow oil separated and was extracted with ether. The ether extracts were dried with calcined magnesium sulfate. After removal of the ether, the product was vacuum distilled and the fraction with bp 137-138°C/2mm was collected. Yield 3.4 g (67%).

Compound VI was prepared analogously (see Table 4).

Hydrogenation Method. A rotary autoclave with a capacity of 150 ml was charged with 0.015-0.03 mole tetrahydroisoindole, 50-80 ml solvent, and an appropriate amount of catalyst (1-2% PtO_2, RuO_2, and Rh/Al_2O_3 or 10-15% Raney nickel, based on quantity to be hydrogenated). The hydrogenation was conducted at initial hydrogen pressure of 100 atm and at temperature necessary for saturation. At the end of saturation the hydrogen of the autoclave was discharged and the catalyst was filtered off. After solvent removal at reduced pressure, the liquid products were vacuum distilled; the crystalline products were recrystallized from ethanol.

Compounds VII-XII were obtained in this manner (see Table 2).

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF N-ARYL FURAN-SUBSTITUTED AMINES AND THEIR DERIVATIVES

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Many aryl-substituted furanoamines possess biological activity [1-2]. In addition, amines containing functional groups three carbons from the furan ring are of interest as intermediates in the synthesis of heterocyclic bases such as pyrrolidylalkanols [3]. Finally, they can be used in the synthesis of possible neurotropic preparations [4].

Simple methods for the preparation of aryl substituted furanoamines are not available in the literature.

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