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4,7-DIHYDRO-, 4,5,6,7-TETRAHYDRO-, AND OCTAHYDROISOINDOLES (AND METHANOISOINDOLES). (REVIEW)

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Data on the synthesis and biological characteristics of hydrogenated isoindoles and methanoisoindoles are reviewed and analyzed.

Keywords: isoindoles, biological activity, mechanism, synthesis.

4,7-Dihydro-, 4,5,6,7-tetrahydro-, and octahydroisoindoles (and methanoisoindoles) were first obtained half a century ago [1]. Since then a considerable amount of information has accumulated on the synthesis and characteristics of isoindoles with a hydrogenated carbocycle, but it has not, however, been included in any of the reviews on the chemistry of isoindoles [2-6]. Some uncoordinated data on the "bridged" analogs of isoindole have also not been classified.

In the mean time isoindoles and methanoisoindoles, well known as substances with clearly defined physiological activity [7-10], provide the basis for the creation of the modern highly effective hypertensive agent tripamide [11-13]. The 4,5,6,7-tetrahydroisoindole fragment is present in the molecules of LSD-25 [14] and cycloprodiogiosin [15, 16]. The only isoindole found in nature [17] has a 4,7-dihydro structure.

The aim of the present review was to gather and analyze data on the synthesis and biological characteristics of iso- and methanoisoindoles with a partly or completely hydrogenated carbocycle. Analysis of the biological activity of such compounds is of interest specifically for the synthesis of such substances with specific physiological characteristics.

1. SYNTHESIS OF 4,7-DIHYDRO- AND 4,5,6,7-TETRAHYDROISOINDOLES (AND METHANOISOINDOLES)

1.1. Intermolecular Cyclization of 1,2-Disubstituted Cyclohexenes and Cyclohexanes

The first representatives of isoindoles with a hydrogenated carbocycle **1** and **2** were obtained by the reaction of 1,2-bifunctional derivatives of cyclohexene and cyclohexane **3** with nitrogen reagents – ammonia [1] and *p*-nitroaniline [18, 19] – in an acidic medium.

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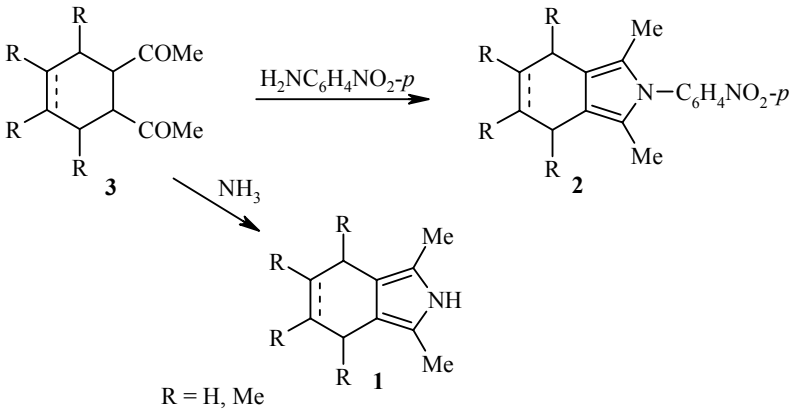
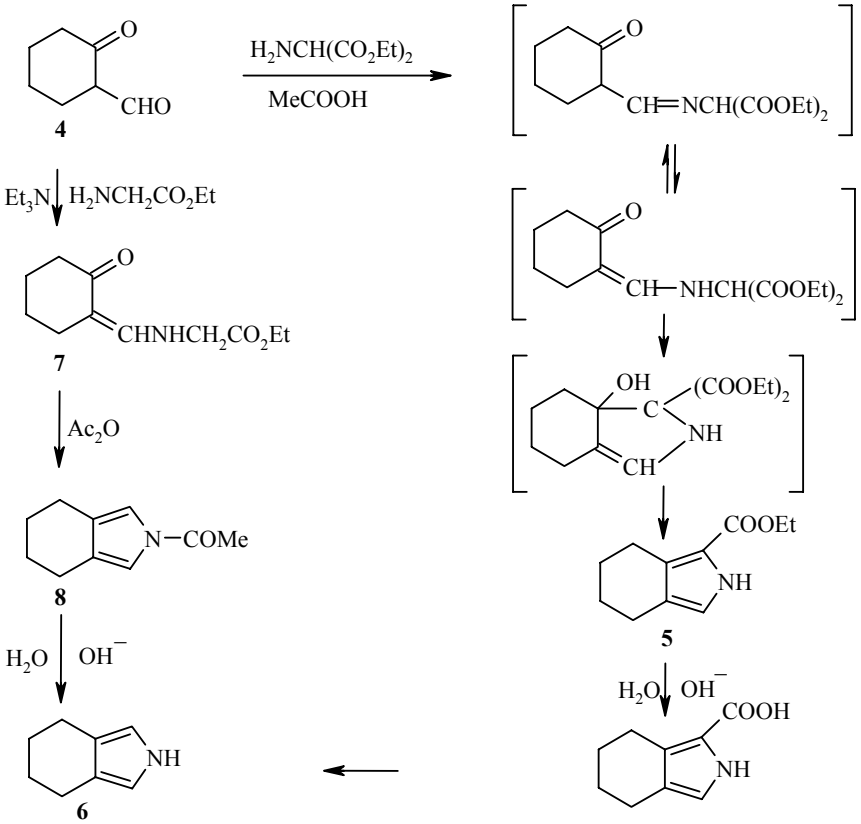


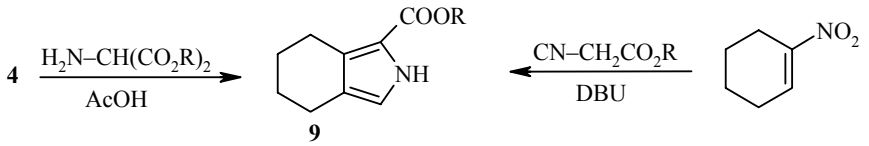
Compounds **1** proved unstable, but compounds **2** were isolated with yields of 80-90%.

In [20] the Knorre reaction was examined as applied to the synthesis of 4,5,6,7-tetrahydroisoindoles. The reaction of 2-formylcyclohexanone (**4**) with aminomalonic ester in acetic acid resulted in the formation of 2-ethoxycarbonyl-4,5,6,7-tetrahydroisoindole (**5**). In addition to spectral methods its structure was demonstrated by chemical transformations, i.e., by saponification followed by decarboxylation to unsubstituted tetrahydroisoindole **6**. The condensation of compound **4** with glycine ethyl ester hydrochloride in alcohol in the presence of triethylamine gave the enamine **7**, which underwent cyclization by the action of acetic anhydride into 2-acetyl-4,5,6,7-tetrahydroisoindole (**8**). In an alkaline medium the latter was converted into compound **6** with a yield of 6%.



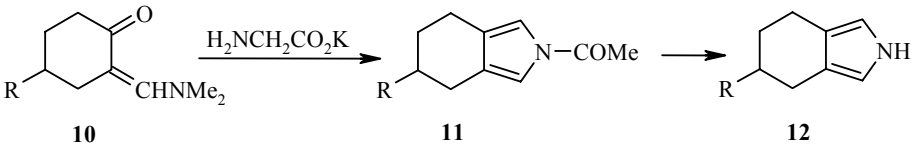
The synthesis of tetrahydroisoindoles **9** unsubstituted at the nitrogen atom by the reaction of compound **4** with aminomalonates has been used for the production of symmetrical porphyrins [21].

The tetrahydroisoindoles **9** are also produced by the reaction of 1-nitrocyclohexene with isocyanoacetates in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [21].



R = Me, Et, *t*-Bu

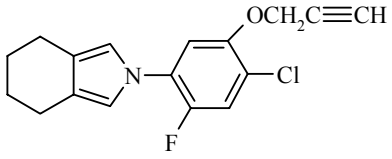
The synthesis of the tetrahydroisoindoles **11** and **12** from aminomethylene derivatives of 2-formylcyclohexanone **10** was realized successfully in the presence of glycine salts [22].



R = NEt_2, NH_2, NHCOMe

With tetramethylammonium glycinate it was possible to obtain high yields of the N-acetyl derivatives of isoindoles **11**, which were easily transformed by saponification into the analogs **12** unsubstituted at the nitrogen atom [23].

The production of the tetrahydroisoindole **13** by the reaction of 1,2-diformylcyclohexane with 4-chloro-2-fluoro-5-propargyloxyaniline was described in [24]. Compound **13** is distinguished by high herbicidal activity against weeds in rice.

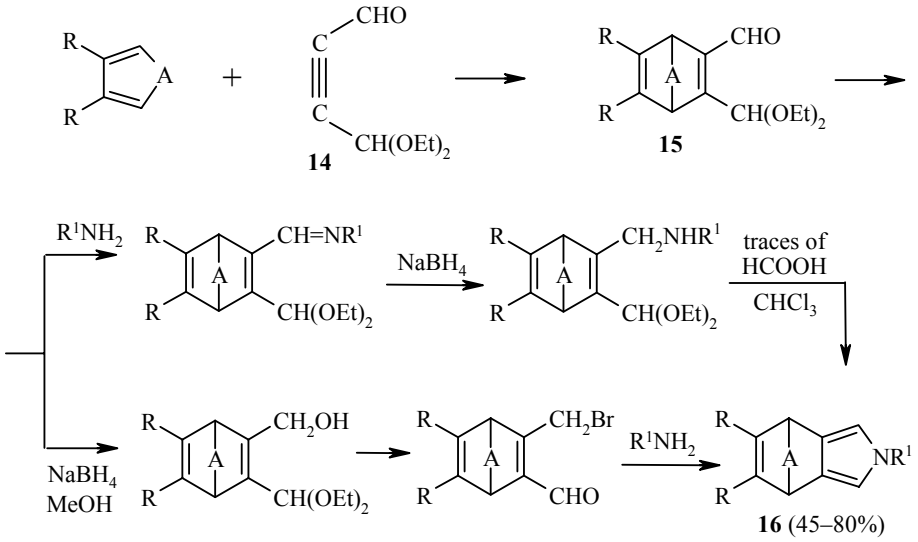


13

One type of intermolecular cyclization in the 1,2-bifunctional derivatives of cyclohexene with primary amines provides a method for the synthesis of 4,7-dihydroisoindoles, including "bridged" compounds **14**. This method is based on transformations of adducts **15** from the diene condensation of 2,3-dimethyl-1,3-butadiene and 1,3-cyclohexadiene with the monoacetal of acetylenedicarbaldehyde **16** (Scheme 1) [25].

The methods for the synthesis of hydrogenated isoindoles described above have many stages and involve poorly available reagents.

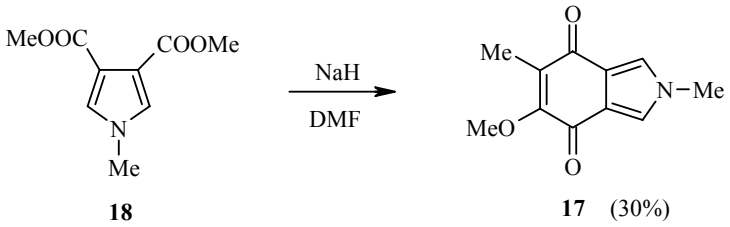
Scheme 1



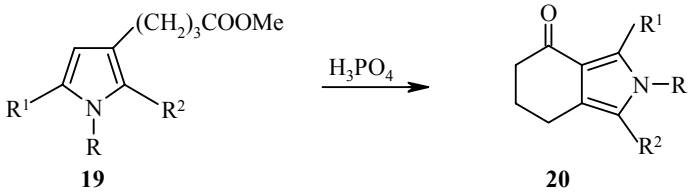
R = H, Me; R^1 = H, Me, Ph; A = CH_2–CH_2, 2H

1.2. Intramolecular Cyclization of Pyrroles

One method for the construction of the carbocycle in isoindoles is intramolecular cyclization of 3-substituted and 3,4-disubstituted pyrroles. This is the easiest method of obtaining synthetic analogs of the natural 6-methoxy-2,5-dimethyl-4,7-dihydroisoindole-4,7-dione (**17**), which was isolated from a fungus of the *Reniera* species in 1982 [17]. The structure of **17** was confirmed by independent syntheses from 3,4-dimethoxy-1-methylcarbonylpyrrole. The latter was converted into the diketone **18**, which underwent cyclization to compound **17** in the presence of sodium hydride.

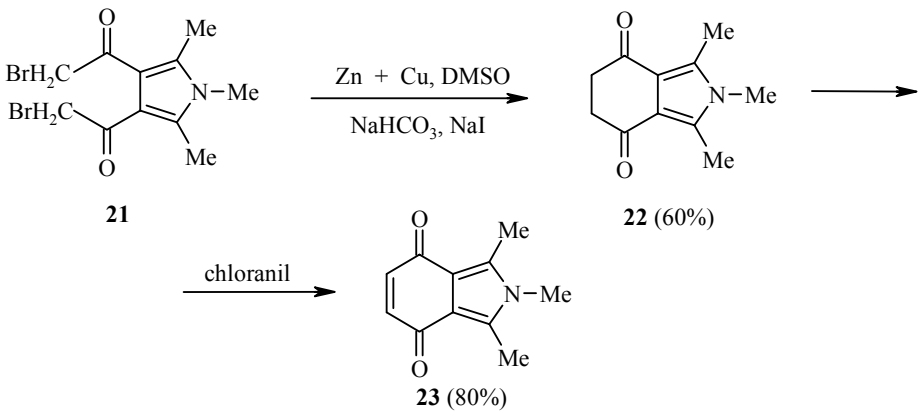


The 4-oxo-4,5,6,7-tetrahydroisoindoles **20** were formed when 3-pyrrolepropanecarboxylic acids **19** were heated in the presence of phosphoric acid [26].



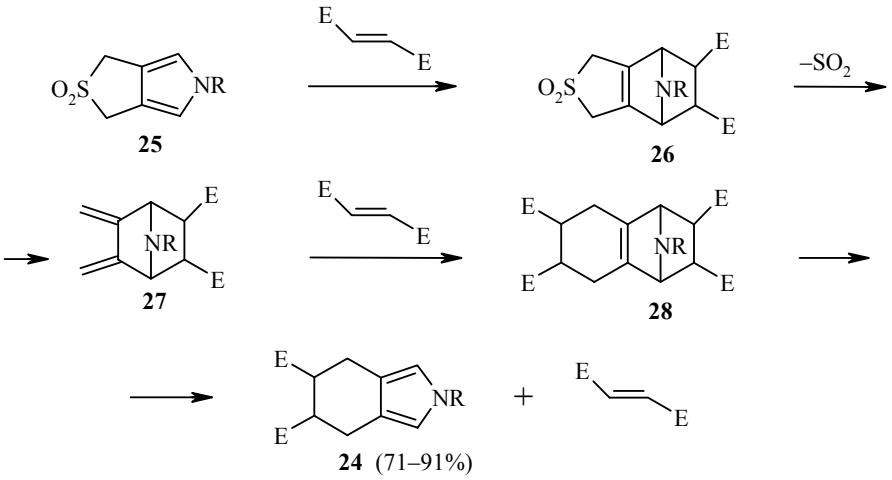
R, R^1, R^2 = H, Me, Ph

The cyclization of 3,4-di(bromoacetyl)-1,2,5-trimethylpyrrole (**21**) in DMSO at 50°C leads to 4,7-dioxo-4,5,6,7-tetrahydroisoindole **22**, which is converted by the action of chloranil into 4,7-dioxo-4,7-dihydroisoindole **23** [47].



21 **22** (60%) **23** (80%)

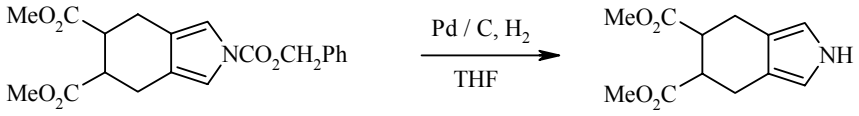
A method for the synthesis of 4,5,6,7-tetrahydroisoindoles **24** through the diene condensation of thienopyrrole oxide **25** with dimethyl fumarate, dimethyl maleate,and *trans*-1,2-bis(phenylsulfonyl)ethylene was described in [28]. The adduct **26** is converted by the elimination of SO_2 into the diene **27**, which enters into diene condensation with another molecule of the dienophile. Retrodiene rearrangement of the formed adduct **28** leads to the separation of the dienophile and the formation of compounds **24**:



25 **26** **27** **28** **24** (71–91%)

R = Me, CH_2Ph, COPh, CO_2CH_2Ph, Ts; E = CO_2Me; SO_2Ph

With heating in a sealed tube at 170-240°C the reaction takes 10-38 h. By debenzyloxycarbonylation in the case where R = CO_2CH_2Ph and E = SO_2Ph the isoindole **29** was obtained.

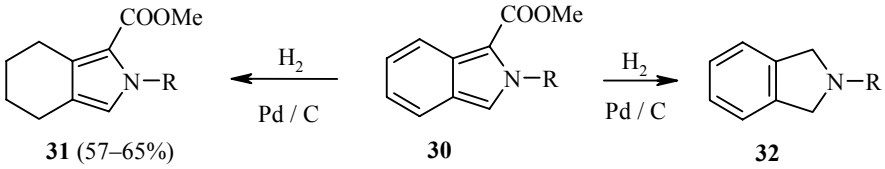


29 (80%)

1.3 Transformations of the Isoindole Ring

Isoindoles with a partly or fully saturated carbocycle are produced during the reduction of aromatic isoindoles or during the dehydrogenation or oxidation of the octahydro derivatives of isoindole.

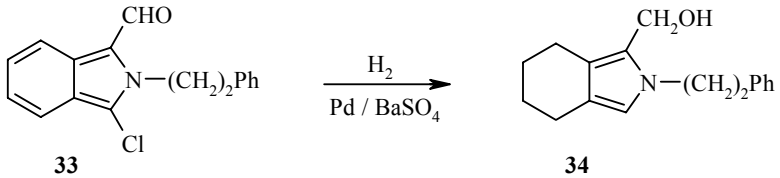
Depending on the substituent at the nitrogen atom, the reduction of 1-methoxycarbonylisoindoles **30** in the presence of 10% Pd/C at increased hydrogen pressure and at 50°C takes place either at the carbocyclic fragment leading to compounds **31** or in the pyrrole ring with the formation of the isoindoline **32** [29].



31 (57–65%) **30** **32**

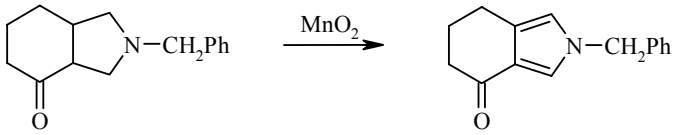
31 R = H, Me, CH_2Ph; **32** R = Ph

During the hydrogenation of 1-chloro-3-formyl-2-(β-phenylethyl)isoindole (**33**) at $Pd/BaSO_4$ 4,5,6,7-tetrahydroisoindole **34** is formed through reduction of the carbonyl group to alcohol and the elimination of chlorine [30].



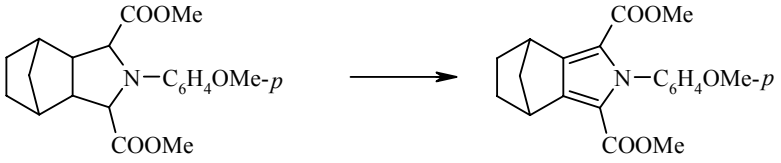
33 **34**

4-Oxo-4,5,6,7-tetrahydroisoindole **36** was obtained by the dehydrogenation of 4-oxooctahydroisoindole **35** with manganese dioxide in boiling THF [31].



35 **36** (50%)

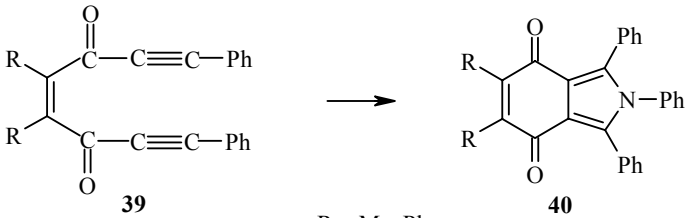
4,7-Methano-4,5,6,7-tetrahydroisoindole **38** was isolated with a yield of 67% by the oxidation of substituted octahydro-4,7-methanoisoindole **37**, which had been previously obtained by the reaction of norbornene with an aziridine derivative, by chloranil in *p*-cymene [32]:



37 **38**

1.4. Other Syntheses

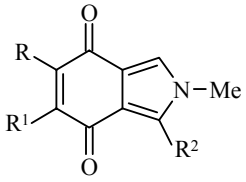
Analogs of natural 4,7-dihydroisoindole **17** were obtained by azacyclization of the dialkynes **39** with nitrosobenzene in boiling benzene. The yields of compounds **40** amounted to 5-15% [33]:



39 **40**

R = Me, Ph

A different approach to the syntheses of such compounds was proposed in [34-36]. Azomethine ylides were produced by heating α-amino acids with carbonyl compounds, and they formed the 4,7-dioxo-4,7-dihydroisoindoles **41** as a result of cycloaddition to quinones.



41

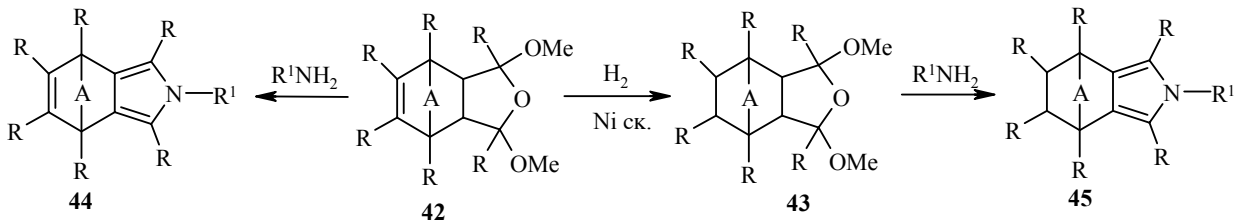
R = H, Me; R^1 = OMe, N(Me)Ph, SPh; R^2 = Ph, CH=CHPh

1-Acetyl-3-iodo-4,5,6,7-tetrahydroisoindole [37] and 1,3-diphenyl-4,5-dihydro-4,7-methanoisoindole were used as intermediates for the synthesis of more complicated molecules [38]. 1,3-Di(cyanomethyl)-2-phenyl-4,5,6,7-tetrahydroisoindole [39] was obtained with a yield of up to 0.5% from 2-phenylhexahydrophthalimide and Ph_3P=CHCN.

Thus, most of the methods for the synthesis of isoindoles with a partly or fully hydrogenated carbocycle described above were carried out on a small number of examples and do not have preparative significance.

1.5. Recyclization of Diene Synthesis Adducts Based on Methoxydihydrofurans with Primary Amines

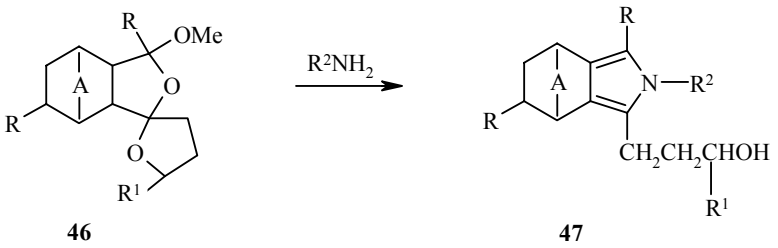
One of us in conjunction with coauthors developed a convenient method for the synthesis of 4,7-dihydro- and 4,5,6,7-tetrahydroisoindoles (and methanoisoindoles). The Diels–Alder adducts **42** obtained on the basis of 2,5-dimethoxy-2,5-dihydrofurans and also their hydrogenated analogs **43** are transformed when heated with primary amines under the conditions of acid catalysis into compounds of the isoindole series **44** and **45** [40-42]:



44 **42** **43** **45**

A = 2H, CH_2; R = H, Me; R^1 = Alk, *cyclo*-Hex, CH_2CH_2OH, Ar

The use of adducts with a spiroacetal structure **46** in the reaction leads to the formation of alcohols of the isoindole series **47** [43, 44].



46 **47**

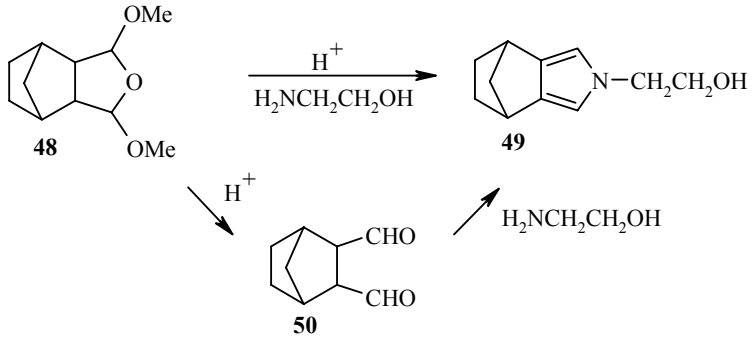
A = 2H, Me; R = H, Me; R^1 = H, Alk, Ar; R^2 = *cyclo*-Hex, CH_2CH_2OH, Ph, 4-MeC_6H_4

The method is simple to use, is based on fairly accessible reagents (the products of the electrolytic methoxylation of furan compounds [45-51]), and in most cases leads to high yields of the hydrogenated isoindoles (up to 97%). The reaction with amines is conducted in acetic or propionic acid at 70-120°C for 0.5-6 h. Synthesis in an inert atmosphere is preferred for adducts with the spiroacetal structure.

The basicity of the amine is important in this reaction. Aliphatic amines that readily form salts in an acidic medium are partially passivated under the reaction conditions and only react with the adducts at elevated temperature and with prolonged heating (3-5 h, 100-120°C). The 2-aryl-substituted dihydro- and tetrahydroisoindoles (and methanoisoindoles) are formed most readily and with high yields; aromatic amines react with the adducts at 70-100°C in 0.5-1 h. It was established by a potentiometric method that a weakly acidic medium (pH 6.8) is an important condition for the addition of amines to the adducts [52].

A series of investigations were carried out in order to establish the mechanism of the supposed recyclization of the adducts of dimethoxydihydrofurans or methoxyspirononenes to dihydro- and tetrahydroisoindoles (and methanoisoindoles) [53-55].

In the case of the synthesis of 2-(2-hydroxyethyl)-4,5,6,7-tetrahydro-4,7-methanoisoindole (**49**) it was shown by means of data from GLC and TLC that the reaction of the adduct **48** and the amine begins with cleavage of the tetrahydrofuran ring in the acidic medium with the formation of the 1,4-dicarbonyl compound **50** [53].



48 **49** **50**

In order to confirm the reaction scheme the bicycloheptane-1,2-dial **50** was synthesized, and it was shown by PMR spectroscopy that it had the *cis* configuration [56]. It was established by GLC that it was the main intermediate of the reaction. Thus, in accordance with the generally accepted scheme for such processes [57] the proposed recyclization is based on initial cleavage of the tetrahydrofuran ring to the dialdehyde followed by nucleophilic attack at one carbonyl group with the formation of an aminal and subsequent intramolecular azacyclization and dehydration stages. The nature of the medium plays an important role; it is not possible to synthesize the isoindoles in an aprotic medium [53].

The method we developed for the synthesis of hydrogenated isoindoles has a wide range of application and can be extended to various compounds with acetal structures, including those with spiro atoms [48-51]. This makes it possible to obtain isoindoles with functional groups in the side chain at the α-position of the pyrrole ring.

The 4,7-dihydro- and 4,5,6,7-tetrahydroisoindoles exhibit all the typical characteristics of 3,4-disubstituted pyrroles, including the ability to undergo electrophilic substitution at the α-position of the pyrrole ring. The formylation of 2-phenyl-4,7-dihydro- and 4,5,6,7-tetrahydroisoindoles **51** by the Vilsmeier–Haack method was described in [58, 59].

51 **51a**

R = H, Me

The aldehydes **51a** were obtained with yields of 52-75%, and their functional derivatives (semicarbazones and 2,4-dinitrophenylhydrazones) were obtained with quantitative yields.

The recyclization of diene condensation adducts based on methoxydihydrofurans with primary amines has found use in the synthesis of biologically active compounds having specific characteristics [43, 59-69] and also in the production of the 4,5,6,7-tetrahydroisoindole fragments of porphyrins [70].

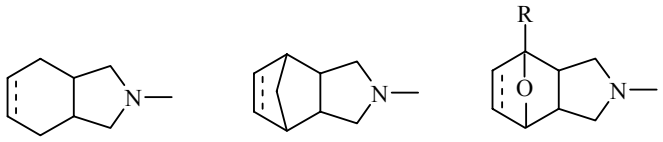
2. METHODS FOR THE PRODUCTION OF HEXA- AND OCTAHYDROISOINDOLES (AND METHANOINDOLES)

Many derivatives of octahydroisoindole and octahydromethanoisoindole have been synthesized as analogs of reserpine [71-73], dopamine [74], and substance P antagonists [75-77]. Preparative methods have been described for the synthesis of octahydroisoindoles by reduction of the carbonyl groups of phthalimides and phthalimidines, by intra- and intermolecular heterocyclization of acyclic systems in a diene condensation scheme, by catalytic hydroamination of 1,2-derivatives of cyclohexane, and by catalytic hydrogenation of unsaturated isoindoles.

2.1. Reduction of Carbonyl Groups in Phthalimides and Phthalimidines

Phthalimides and phthalimidines are similar in structure to isoindoles, are easily obtainable, and are therefore often used in the synthesis of isoindoles [2, 3, 5] and their isologs [7-10, 78-86].

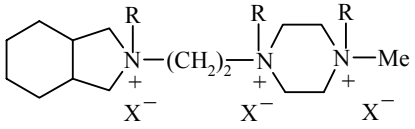
Reduction of the carbonyl groups in hydrogenated phthalimides and phthalimidines with lithium aluminum hydride is most often used. Rice and coauthors [7, 8, 78-80] obtained series of hexa- and octahydroisoindoles and their "bridged" derivatives **52** with various substituents at the nitrogen.



52

R = H, Me

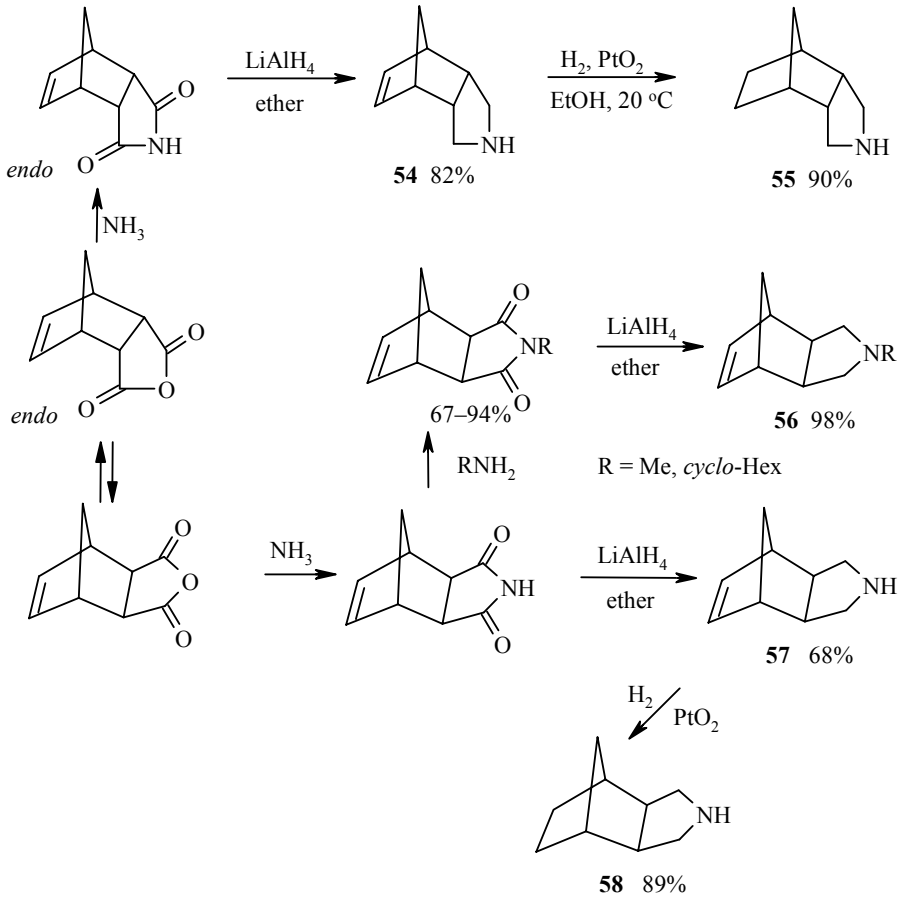
On the basis of these compounds quaternary salts **53** with clearly defined biological activity were obtained, e.g., see [7].



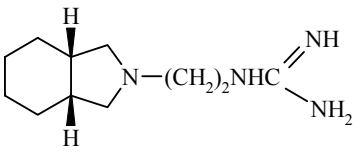
53

R = Alk; X = Cl, Br, I

In [81, 82] the Rice approach was applied to bridged hexa- and octahydroisoindoles, and special attention was paid to the stereochemical structure of methanoisoindoles **54-58** not substituted at the nitrogen atom.



Stereospecific syntheses of hydrogenated isoindoles and methanoisoindoles have played an enormous role in the development of methods for the preparation of highly active medicinal products, like some already used in medicine. Their syntheses are based on reduction of the C=O groups in the imides and imidines of tetra- and hexahydrophthalic acids and their "bridged" analogs with lithium aluminum hydride. Guanisoline **59** [83] and preparation "865-123" **60** [9, 84, 85], which are analogs of guanetidine exhibiting the characteristics of adrenoblockers and hypotensive agents, and also tripamide **61**, which is a modern hypotensive drug and an effective diuretic [11-13, 86-92], were obtained in this way.



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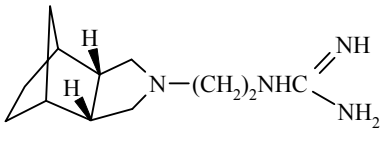

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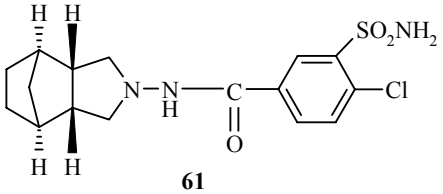
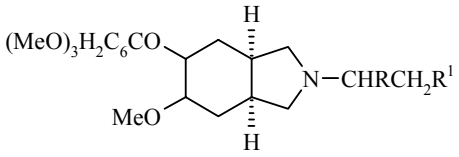


61

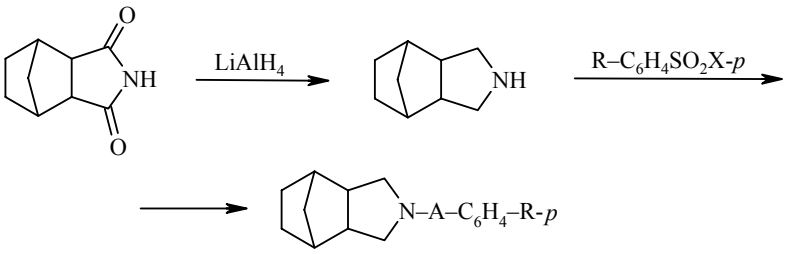
In [71] stereospecific syntheses of reserpine-like derivatives of *cis*-octahydroisoindole **62** from N-substituted tetrahydrophthalimides through epoxidation of the latter were described:



62

R = H, Me; R^1 = Ph, 3-indolyl, 1-naphthyl

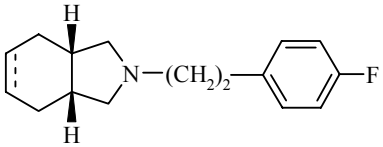
Methods for the production of highly active diuretic and psychotropic agents based on hexa- and octahydroisoindoles (and methanoisoindoles) **63**, starting from phthalimides and phthalimidines, have been patented [10, 93-95], for example [10]:



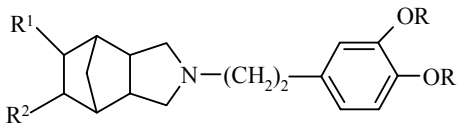
63

R = NH_2, NO_2, $MeSO_2$, MeCO, MeCONH; X = NH_2, NCO, NHCOOEt, NHCOCl;
A = SO_2NHCO, SO_2NH, $SO_2NHCONH$

Neuropsychotropic agents as analogs of dopamine **64** and **65** [74, 76], analgesics **66** [97], antidepressants **67** [98], and medicines for the treatment of diabetes **68** [99-103] were synthesized in a similar way:

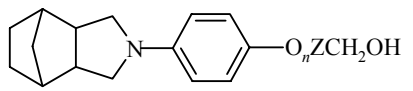


64, **65**



66

R = Me, Ac; R^1 = H; R^2 = Ph; R^1R^2 = bond



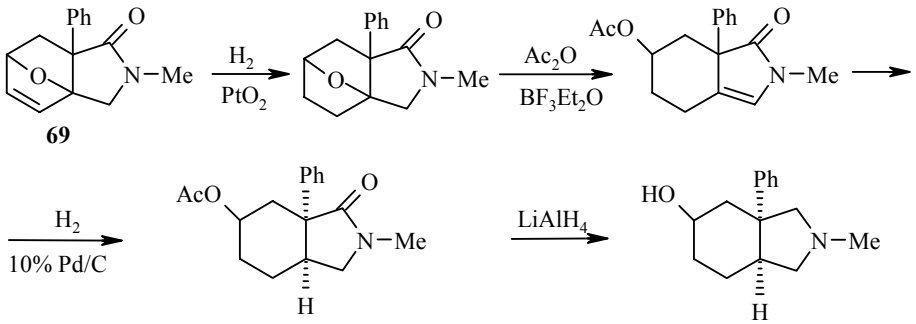
67

n = 0, 1; Z = bond, CH_2, CHMe, CH_2CH_2

68

n = 0, 1; R = Ac, AcNH, NO_2, $MeSO_2$

A method for the production of analogs of the analgesic profadol **70** was based on the transformations of 2-methyl-7a-phenyl-3a,b-epoxy-2,3,6,7-tetrahydroisoindol-1-one (**69**) [104]. One of the stages is reduction of the carbonyl group with lithium aluminum hydride.



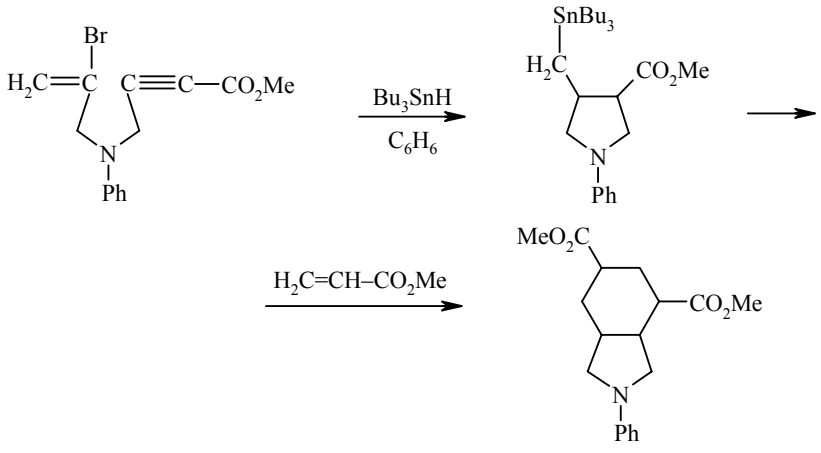
69

70

R = H, OH, OAc

2.2. Intra- and Intermolecular Heterocyclization of Acyclic and Alicyclic Systems

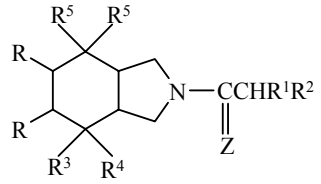
An original method for construction of the octahydroisoindole ring **71** using organotin and organopalladium reagents was described in [105].



71

During a study of the stereoselectivity of the Diels–Alder reaction in the series of 4-azanonatrienes [106] and 1-R-2,3-methoxycarbonylaziridines with norbornene [32] tetra- and octahydroisoindoles (and methanoisoindoles) were obtained. In [32] the yield of octahydromethanoisoindole **37** amounted to 94%.

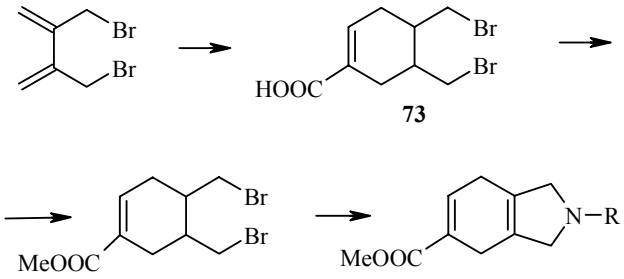
The synthesis of a large group of entiomerically pure octahydroisoindoles, obtained as antagonists of substance P [75-77, 107-110], is based on the cyclocondensation of 4,4-diphenylcyclohexen-2-one with $PhCH_2N(CH_2OBu)CH_2SiMe_3$. Subsequent transformations lead to various isoindoles with general formula **72**.



72

R = H, RR = bond; R^1 = Ph, cyclohexyl, naphthyl, heterocyclyl;
R^2 = H, Hal, OH, alkyl, alkNH, alkO-, alkyl-S-, acyloxy, carboxy, NH_2, AcNH, benzyloxycarbonyl; R^3 = Hal, OH; R^4= H, Hal; R^5= Hal, Me, Ph; Z= O, NH

The adduct of 2,3-bis(bromomethyl)-1,3-butadiene **73** with propiolic acid can be converted into hydrogenated N-substituted isoindoles **74** [111].



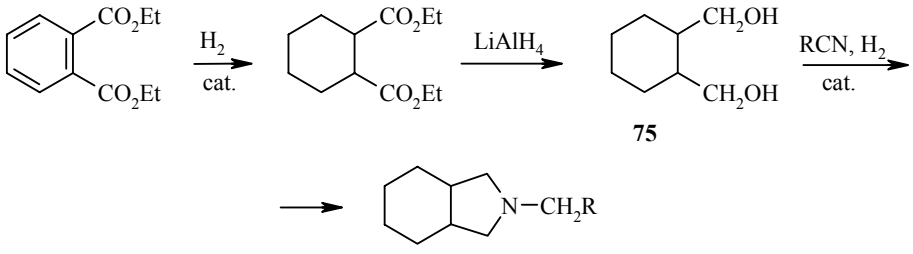
73

74

R = CH_2Ph, CH_2CH_2OH, $NHCO_2Me$

2.3. Catalytic Reductive Amination and Hydrogenation

A convenient method for the synthesis of octahydroisoindoles **76** was proposed in [112], i.e., the catalytic reductive amination of 1,2-bis(hydroxymethyl)cyclohexane **75** by aliphatic nitriles at an industrial copper–magnesium catalyst. The method is based on the use of the readily available diethyl phthalate as raw material.



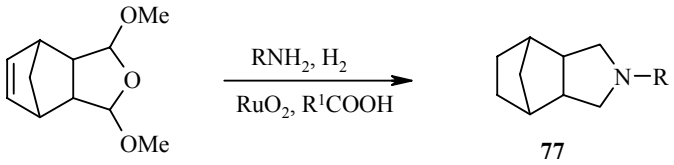
75

76 (~65%)

R = Alk

The optimum conditions for the reduction process are: 240°C, hydrogen pressure 1.5 MPa, volume delivery rate of reaction mixture 0.5 h^{-1}. The structure of compounds **76**, which represent a 1:1.5 mixture of *cis* and *trans* isomers, was confirmed by the data from IR, ^1H NMR, and mass spectra.

Catalytic reductive amination was used in the synthesis of octahydro-4,7-methanoisoindoles **77** [68] based on the adducts **40** and **41** obtained according to [45].

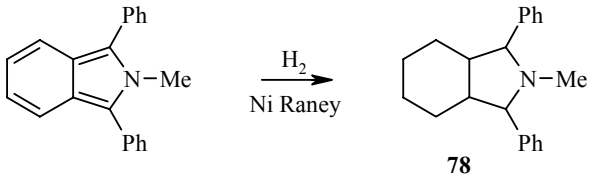


77

R = *t*-Bu, *c*-Hex, CH_2CH_2OH; R^1 = Me, Et

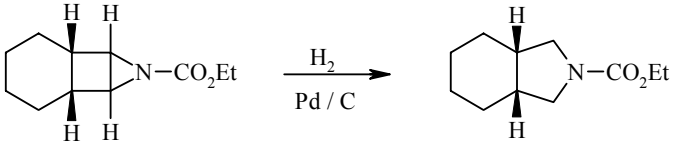
Compounds **77** were isolated in the form of mixtures of isomers with overall yields of 51-55%. The *endo-exo* isomers of octahydroisoindole (R = *t*-Bu) were isolated in the pure form, and their structures were supported by the data from the ^1H NMR spectra.

As a rule, the catalytic hydrogenation of isoindoles leads to isoindolines [2]. Under harsh conditions the reaction products may be octahydroisoindoles [113]. Thus, the hydrogenation of 2-methyl-1,3-diphenylisoindole at Raney nickel in dioxane gives the octahydro derivative **78**.



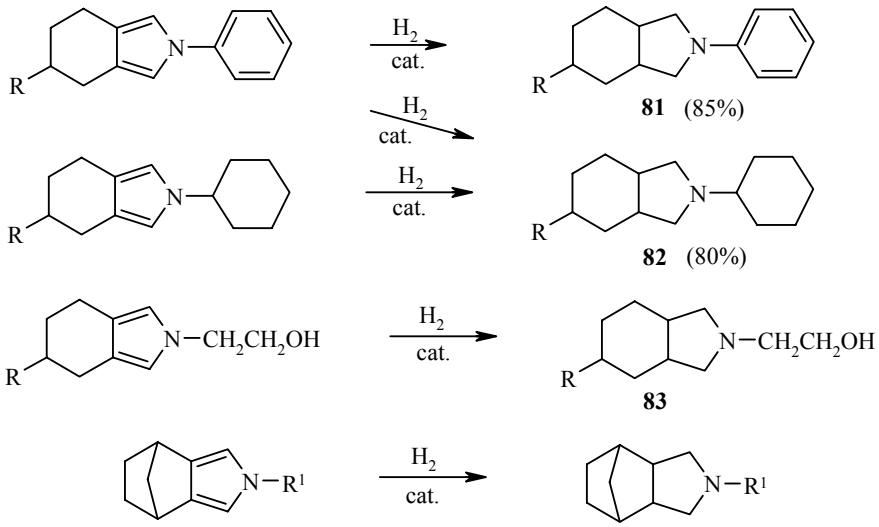
78

The catalytic reduction of N-ethoxycarbonyl-8-azatricyclo[4,3,0,$0^{7,9}$]nonane (**79**) leads to cleavage of the ring with the formation of octahydroisoindole **80** [114].



79 **80**

As a result of the hydrogenation (at initial hydrogen pressure 10 MPa) of 4,5,6,7-tetrahydroisoindoles **43**, synthesized by the methods in [40-42], the octahydroisoindoles **81**-**84** were obtained and used for pharmacological investigation [65, 115].



R = H, Me; R^1 = *t*-Bu, CH_2CH_2OH, Ph

The effect of temperature, the type of catalyst (Raney nickel, RuO_2, PtO_2, Rh/Al_2O_3), the nature of the solvent (acetic acid, ethanol, isopropyl alcohol), and the nature of the substituent at the nitrogen atom on the direction of the reaction and the yield of the products was determined.

At the ruthenium and rhodium catalysts at 60°C simultaneous reduction of the pyrrole and benzene rings occurs. Under these conditions in the "bridged" isoindole **84** the phenyl substituent remains unchanged even at 100-120°C. Platinum dioxide exhibits selectivity at room temperature, making it possible to reduce the pyrrole ring without affecting the benzene ring. In the presence of PtO_2 compounds **82** are only formed at 100°C. The effect of the solvent on the yield of the final products is insignificant, but the isomeric composition of the octahydroisoindoles depends on it. The nature of the substituent at the nitrogen determines the duration of reduction; under identical conditions compounds with a hydroxyethyl group are hydrogenated more slowly than the cyclohexyl and phenyl derivatives. The isomeric composition of the reaction products was determined from the data of GLC and the ^1H NMR spectra.

3. BIOLOGICAL CHARACTERISTICS OF HYDROGENATED ISOINDOLES

A large amount of factual information has now accumulated from study of the biological characteristics of hydrogenated isoindoles. The types of physiological activity and their applications in medicine have been mentioned in previous sections. Among them there are compounds with sets of important properties: hypotensive agents with a strong diuretic effect [10, 93-95]; psychotropic [74, 96] and antidiabetic [29, 103] agents; inhibitors of phosphodiesterase and antithrombotic substances [116]; anticancer and simultaneously antibacterial compounds [117]. Natural isoindole and its analogs are characterized by high bactericidal activity [17]. Hydrogenated isoindoles condensed with benzene, quinoline, cyclohexane, and other fragments exhibit significant activity against rhinoviruses [118, 119], and among them there are also analgesics and antidepressants [120, 121].

We made a systematic pharmacological study of the biological characteristics of isoindoles [43, 59-67, 69]. As a result of the tests substances with neurotropic, hypotensive, radioprotective, diuretic, bactericidal, antihelminthic, and fungicidal characteristics were found. The low toxicity of hydrogenated isoindoles was noted. Their biological activity is determined by the degree of saturation of the ring and by the nature of the substituent at the nitrogen atom [61]. It is necessary to mention particularly the methanoisoindoles, which exhibit a significant diuretic effect in trials on mice, rats, and dogs [62-64]. Certain compounds, by withdrawing sodium, simultaneously reduce the excretion of potassium, which distinguishes them favorably from usual diuretics.

Thus, to summarize all the foregoing a conclusion can be drawn about the significance of investigations in this region and the expediency of comprehensive study of the biological and other useful characteristics of hydrogenated isoindoles.

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