Chemistry of Heterocyclic Compounds, Vol. 38, No. 11, 2002

SYNTHESIS AND BIOLOGICAL PROPERTIES OF ISOQUINOLINES SPIROFUSED WITH CARBOCYCLES AND HETEROCYCLES AT POSITION 4. (REVIEW)

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Published data on the synthesis and biological properties of isoquinolines spirofused with carbocycles and heterocycles at position 4 are reviewed. The methods of synthesis are classified according to the formation of the isoquinoline fragment or the carbocycle or heterocycle fused with it during the construction of the spirocyclic system. Data on the biological activity are arranged according to the types of action exhibited by the compounds.

Keywords: biologically active substances, heterocyclic spiranes, spirofused isoquinolines.

"Molecular design," which has been exploited vigorously by synthetic chemists in the last two decades, is probably suited no better than to spirocyclic compounds. Although esthetic concerns do not play a leading role in the activities of synthetic chemists, a major motivating force in the development of the chemistry of various types of organic compounds is still the prospect of a fruitful search for new substances having useful properties and, primarily, those having biological activity. In this sense spirocyclic and spiroheterocyclic compounds, in particular, provide a fertile subject for investigation.

Among the wide variety of heterocyclic derivatives it is possible to single out those for which the probability of discovering useful biological characteristics is so high that it is even possible to speak of the "pharmacophoric quality" of their heterocyclic nuclei. Accordingly, the development of methods for the synthesis of spirocyclic systems is often of practical value, as witnessed by the abundance of information on these questions. As an example it is possible to mention the vigorously developed chemistry of 4-spiropiperidines [1]. The same can be said of spiroisoquinolines. Their chemistry has been the subject of more than 600 original papers, many of which also treat some aspect of the biological activity of the compounds. However, since the appearance of a collection of reviews on the chemistry of isoquinolines [2] there has been no sufficiently comprehensive coverage of the synthesis and properties of spiroisoquinolines. The present review covers the available information on the construction and biological activity of the most widely studied compounds of this group, in which the isoquinoline fragment is spirofused with a carbocycle or a heterocycle at position 4. (For convenience they will subsequently be called 4-spiroisoquinolines.) It should be noted that fragments of the 4-spiroisoquinoline ring are encountered in subjects of natural origin. Thus, (-)-secoplicamine, the structure of which is based on the spiro[isoquinoline-4,1'-2-cyclohexane] system, was recently isolated from plants of the *Galanthus plicatus* family [3].

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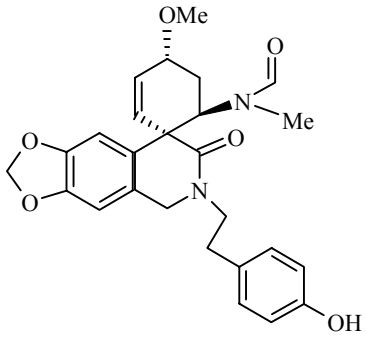


(-)-Secoplicamine

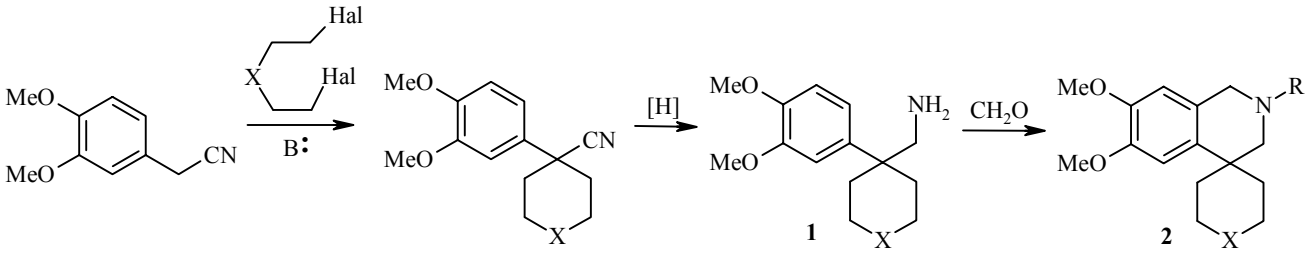
In view of the wide variety of the compounds examined in the review their individual chemical properties are not described. In a number of cases during description of methods for the synthesis of 4-spiroisoquinolines further transformations of the obtained products, directed as a rule toward modification of their structure with additional pharmacophoric groups, are briefly indicated. The methods used for such modification are described in greater detail in papers devoted to biologically active 4-spiroisoquinolines, cited in section 3 of the review.

Methods for the synthesis of 4-spiroisoquinolines are examined according to two familiar approaches to the construction of the system. The first involves the formation of the isoquinoline fragment by intramolecular cyclization of a compound representing the respective functionalized aryl-substituted carbo- or heterocycle (see Section 1). The second approach requires the use of isoquinoline intermediates in which the prerequisites for fusion with the carbo- or heterocycle at position 4 have been created (see Section 2).

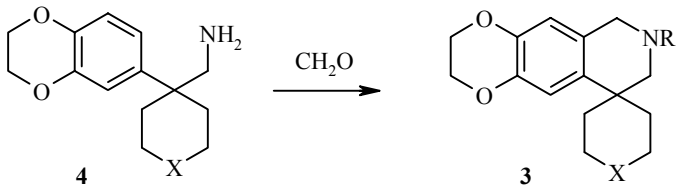
Information on the biological activity of 4-spiroisoquinolines are presented in section 3 and is arranged according to the type of activity of the compounds.

1. METHODS FOR THE SYNTHESIS OF 4-SPIROISOQUINOLINES BASED ON CONSTRUCTION OF THE ISOQUINOLINE FRAGMENT

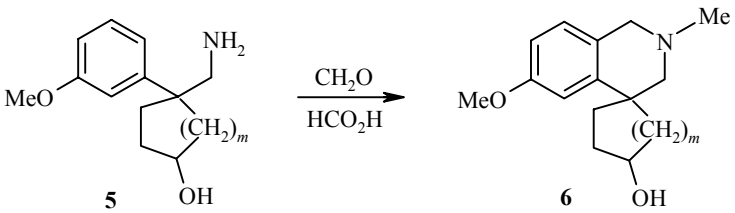
The usual pathways for construction of the isoquinoline system are widely used in the synthesis of 4-spiroisoquinolines [2, 4-9]. Thus, one of the key methods uses condensation of β-arylethylamines with formalin under the conditions of the Pictet–Spengler reaction. As a rule the amines are produced by the reaction of the respective acetonitriles with α,ω-dihalides followed by reduction of the nitrile group to amine by standard procedures. For example, the reaction of 3,4-dimethoxyphenylacetonitrile with 1,4-dibromobutane, 1,5-dibromopentane, or bis-2-chloroethyl ether in toluene with $NaNH_2$ as base gave the corresponding cycloalkylated nitriles, which were submitted to hydride reduction with lithium aluminum hydride or to catalytic hydrogenation to the amines **1**. Further condensation of the latter with formalin through a Schiff base by the Pictet–Spengler reaction led to high yields of the tetrahydro-4-spiroisoquinolines **2** (R = H, X = bond, CH_2, CH(OH), O) [10-16].



This approach was also used for the production of new heterocyclic systems, i.e., 9-spirofused dihydroxyisoquinolines **3** (R = H, X = bond, O), from cycloalkylated β-(2,3-dihydro-1,4-benzodioxin-6-yl)ethylamines **4** [17].

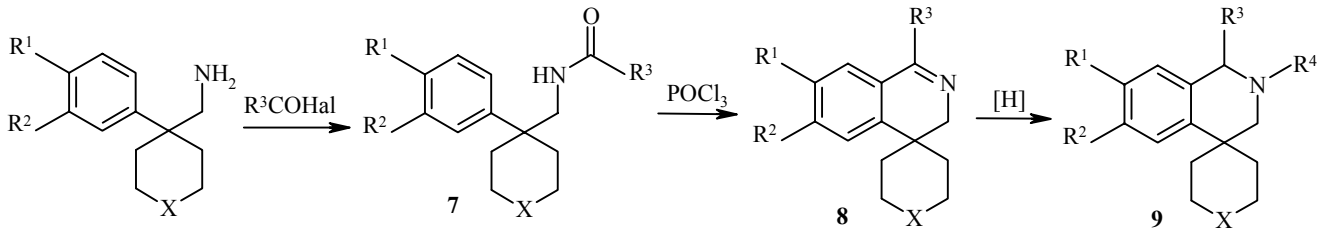


Under the conditions of the Eschweiler–Clarke reaction (the formaldehyde–formic acid system) the amines **4** are converted with quantitative yields into the corresponding N-methyl-substituted spiranes **3** (R = Me, X = bond, O) [17]. 4-Aminomethyl-4-(3,4-dimethyloxyphenyl)-substituted tetrahydropyran **1** (X = O) and cyclohexanol **1** (X = CH(OH)) were subjected to a similar transformation for the production of the corresponding 2-methylspiro[isoquinoline-4,4'-pyran] **2** (R = Me, X = O) [18] and 2-methylspiro[isoquinoline-4,1'-cyclohexan]-4-ol **2** (R = Me, X = CH(OH)) [19]. Under the same conditions 1-(methoxyphenyl)-3(4)-aminomethylcycloalkanols **5** undergo cyclization to 2-methyl-1,2,3,4-tetrahydrospiro-[isoquinoline-4,1'-cycloalkan]ols **6** (*m* = 1-3) [20-22], which together with their O-acetyl derivatives are of interest as potential analgesics – structural analogs of the alkaloid galanthamine [23].



5, 6 *m* = 1-3

Another classical method for the construction of the isoquinoline system is widely used in the synthesis of 4-spiroisoquinolines, i.e., the Bischler–Napieralski reaction. Here N-acylated aryl (aminomethyl) carbocycles or heterocycles **7** undergo cyclization, catalyzed by acidic condensing agents ($POCl_3$, H_3PO_4, PPA, and others), to the corresponding 2,3-dihydro-4-spiroisoquinolines **8**. This method was used to obtain derivatives of spiro[isoquinoline-4,1'-cyclopentane] **8** (X = bond) [17, 24-29], spiro[isoquinoline-4,1'-cyclohexane] **8** (X = CH_2) [15, 17, 29-33], spiro[isoquinoline-4,4'-pyran] **8** (X = O) [17, 25, 29], and spiro[isoquinoline-4,4'-piperidine] **8** (X = –NMe–) [34, 35]. The general scheme of the described syntheses is given below.



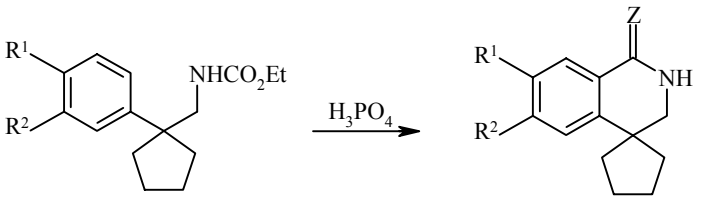
The nature of the substituent R^3 in compounds **8** is determined by the structure of the initial amide **7** and can vary within wide limits: lower Alk [17, 32, 33, 35], Ar [17, 24, 27, 33], aralkyl [24, 26, 31, 33, 34], aralkenyl [25].

The yields of the desired spirans **8** here fluctuate over a wide range from 30 to 80%, but if the benzene ring of the initial amide **7** contains electron-donating substituents (such as, R^2 = OAlk, and especially $R^1 = R^2$ = OAlk, $R^1R^2 = O(CH_2)O$), the yields are as a rule extremely high. The 3,4-dihydro-4-spiroisoquinolines **8** obtained in this way can be reduced to the 1,2,3,4-tetrahydro derivatives **9** (R^4 = H) with lithium aluminum hydride [24-28], sodium borohydride [29, 31-33], and tin in hydrochloric acid [30] or by hydrogenation over platinum according to Adams [34].

It should be noted that in a number of cases compounds **8** (X = bond, $R^1 = R^2$ = H, R^3 = *p*-alkoxy-substituted or unsubstituted Ar) were submitted without isolation to reduction with lithium aluminum hydride to the corresponding tetrahydro derivatives **9** (R^4 = H). The yields in two stages were 30-60% [27].

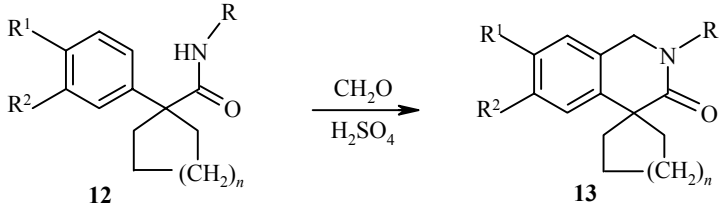
By using the Bischler–Napieralski reaction it is possible to vary the substituent R^3 at position 1 of the isoquinoline ring within wide limits, restricted essentially only by the availability of the respect carboxylic acids or chlorides. This distinguishes this method favorably from the synthesis of 4-spiroisoquinolines by the Pictet–Schlenger reaction, which has only been used for the production of 1-unsubstituted tetrahydro-4-spiroisoquinolines. However, the usual general limitations [4-6] for the synthesis of 4-spiroisoquinolines by any of the described methods naturally also apply to the 4-spiroisoquinolines. Particular demands are made of the electron donating power of the aromatic ring in the initial phenylethylamines. It is no accident that most of the 4-spiroisoquinolines synthesized by these methods contain electron-donating substituents (R^1, R^2 = OH, OAlk; $R^1R^2 = O(CH_2)_2O$) at positions 6 and also 7. The use of Ar-unsubstituted β-phenylethylamines **7** ($R^1 = R^2$ = H) is possible, but the yields here are lower (e.g., see [15, 27]). In [34] the possibility of obtaining Ar-unsubstituted 1'-methylspiro[isoquinoline-4,4'-piperidines] from 4-aminomethyl-1-methyl-4-phenylpiperidine under the conditions of the Pictet–Spengler, Eschweiler–Clarke, and Bischler–Napieralski reactions was demonstrated. The use of any of these methods for the production of 4-spiroisoquinolines with electron-withdrawing substituents in the aromatic ring has not been mentioned in the literature.

The cyclization of alkyl carbamates is also possible under the conditions of the Bischler–Napieralski reaction, and this makes it possible to insert a carbonyl group at position 1 of the isoquinoline ring. Thus, the spiro[isoquinoline-4,1'-cyclopentane]-1-ones **11** (Z = O) were obtained by heating ethyl (1-arylcyclopentyl)methylcarbamates **10** (R^1 = H, R^2 = H, OMe, OEt; $R^1R^2 = OCH_2O$) in the presence of phosphoric acid. The products, together with the thiones **11** (Z = S) formed from them by the action of P_2S_5, exhibit hypolipemic activity [36, 37].



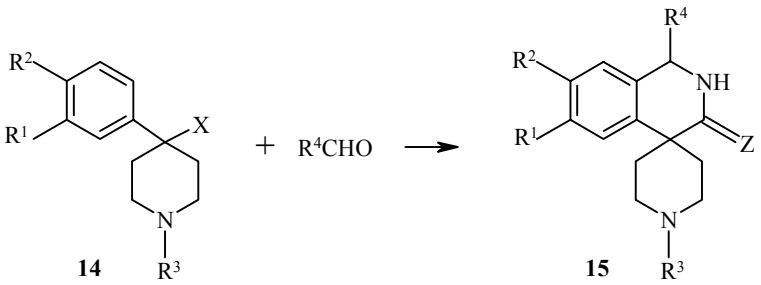
10 **11**

The acid-catalyzed cyclocondensation of 1-phenylcycloalkanecarboxamides **12** with paraformaldehyde demonstrates the wider possibilities of the Pictet–Spengler reaction in the production of spiro[isoquinoline-4,1'-cycloalkan]-3-ones **13** (*n* = 1, 2; R = aminoalkyl), which have found use as products for the treatment of psychic and psychosomatic illnesses [38].

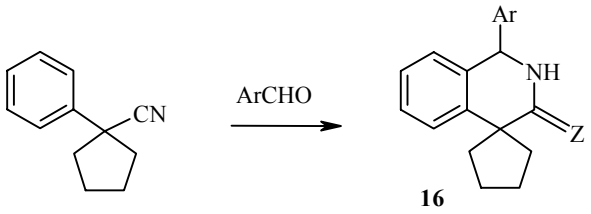


12 **13**

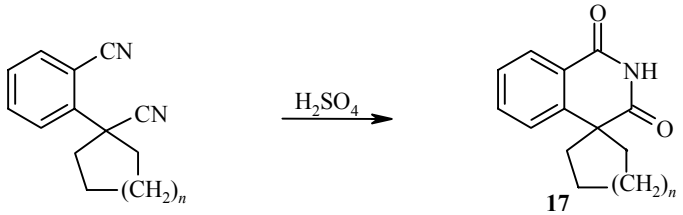
The cyclocondensation of the thioamides **14** (X = $CSNH_2$) with heteroaromatic and aromatic aldehydes in polyphosphoric acid under the influence of P_2O_5, leading to spiro[isoquinoline-4,4'-piperidine]-3-thiones **15** (Z = S, R^1 = R^2 = H, OMe; R^3 = H, Me; R^4 = H, Ar, 4-pyridyl), can be regarded as a variant of the Pictet–Spengler synthesis [39]. Cyclization of the nitriles (X = CN), leading to spiro[isoquinoline-4,4'-piperidin]-3-ones **15** (Z = O), is possible under the same conditions [39, 40]. The same products can also be obtained by desulfurization of the thiones **15** (Z = S) by the action of SeO_2 or HCl, while compounds **15** (Z = O) are transformed by the successive action of P_2S_5 or of PCl_5 and H_2S into the thiones **15** (Z = S) [39]. The spiro[isoquinoline-4,4'-piperidines] **15** and their structural analogs isoquinoline-3-(thi)ones with β-aminoethyl substituents at position 4 synthesized in this way have been reported as antiarhythmic agents [30] and anticonvulsants [40].



The spiro[isoquinoline-4,1'-cyclopentan]-3-ones **16** (Z = O), obtained under the same conditions from 1-phenylcyclopentanecarbonitrile and aromatic aldehydes, and the corresponding thiones **16** (Z = S) formed from them by the action of P_2O_5 have antidiabetic and anticholesteremic activity [41].

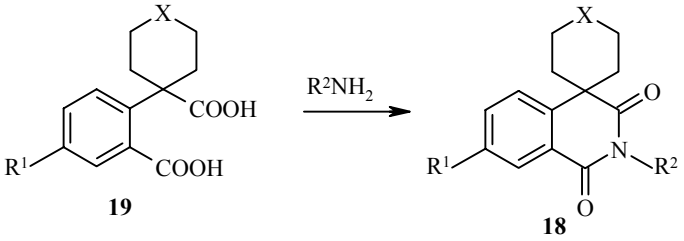


Homophthalic acid and its derivatives are widely used in the synthesis of isoquinolines. They have found use in the synthesis of spirocyclic isoquinolines and their cycloalkylated analogs. Thus, treatment of 1-(2-cyanophenyl)cycloalkanecarbonitriles with 90% sulfuric acid gave spiro[isoquinoline-4,1'-cyclobutane]-, spiro[isoquinoline-4,1'-cyclopentane]-, and spiro[isoquinoline-4,1'-cyclohexane]-1,3-diones **17** (*n* = 1-3) with yields of 34, 46, and 58% respectively. The products were used as intermediates in the synthesis of cardiotonic and antihypertensive drugs [42].



The spiro[isoquinoline-4,1'-cycloalkane]-1,3-diones **18** (X = bond, CH_2, CH(OH); R^1 = H, Hal, NO_2, R^2 = H) can also be obtained by ammonolysis of the corresponding 1-(2-carboxyphenyl)-cycloalkanecarboxylic acids **19** (R^1 = Cl, NO_2) [43]. Their N-hydroxy derivatives **18** (with X = bond; R^1 = H,

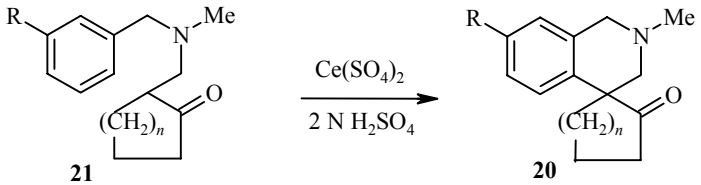
R^2 = OH, yield 82%) were synthesized with the hydroxylamine base as amino component, which was produced *in situ* from its hydrochloride by the action of sodium methoxide in methanol solution [44]. In the same papers the behavior of the O-tosyl derivatives **18** (R^2 = OTs) under the conditions of the Lossen rearrangement and of the spirocyclic homophthalimides **18** (R^2 = H) under the conditions of the Hofmann rearrangement, leading to the corresponding spirocyclic indolinones and/or isoindolinones, was studied.



19 **18**

The acetamides **18** (R^2 = $CH_2CONR^3R^4$), obtained by N-alkylation of the spirocyclic homophthalimides **18** (R^2 = H) by N,N-dialkylchloroacetamides in the presence of sodium hydride, together with the homophthalimides **18** (R^2 = $(CH_2)_nNR^3R^4$), synthesized by the cyclocondensation of the dicarboxylic acids **19** with ω-dialkylaminoalkylamines, were patented as products for the treatment of psychic disturbances [45, 46].

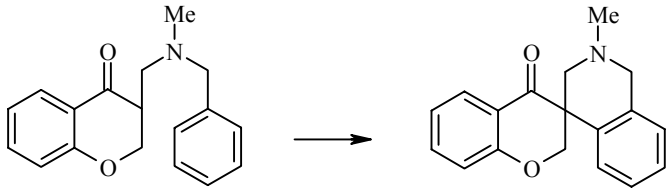
A convenient approach was proposed to the synthesis of spiroisoquinolines **20** by oxidative cyclization of the Mannich bases **21** from cycloalkanones and secondary benzylamines heated for 5-6 h (40°C) in the $Ce(SO_4)_2$–2N H_2SO_4 system [47].



21 **20**

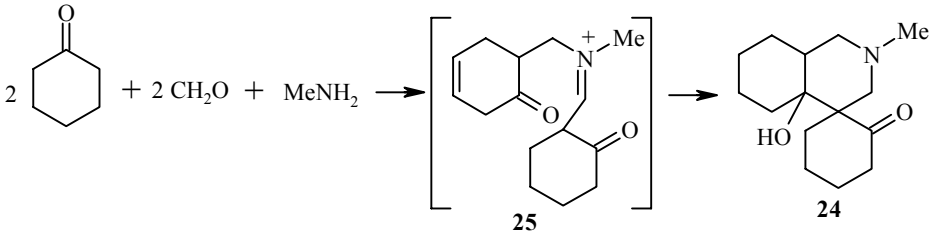
n = 1–3; R = H, NO_2

Under these conditions the Mannich base **22** based on 2,3-dihydrochromen-4-one undergoes cyclization to spiro[isoquinoline-4,3'(2H)-chromen]-4'-one **23** with a yield of 27%.



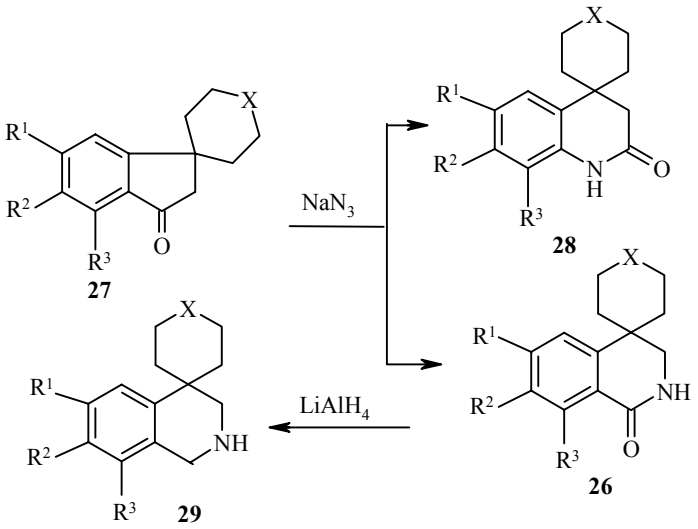
22 **23**

In [48] it was shown that the product from the condensation of methylamine, cyclohexanone, and formaldehyde in molar ratios of 1:2:2 had the spirocyclic structure of 4a-hydroxydecahydrospiro[isoquinoline-4,1'-cyclohexan]-2'-one (**24**) and not the Mannich base **25**, as considered earlier.

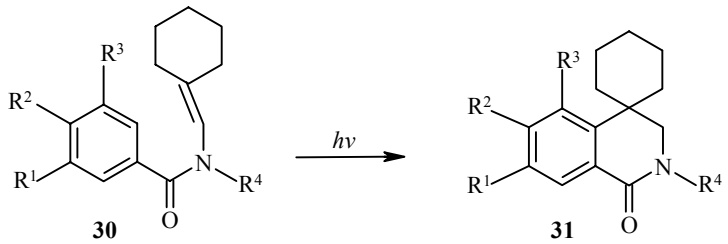


25 **24**

The spirocyclic isoquinolin-1-ones **26** (X = CH_2, CH(OH), NMe; R^1–R^3 = H, OMe, lower Alk, Hal) can be obtained by a Schmidt rearrangement of the corresponding spiroindanones **27** [49-54]. However, this method for their synthesis can hardly pretend to be preparative, since there is always the alternative rearrangement path leading to 4-spiroquinolin-2-ones **28**. In [50] the effect of substituents in the benzene ring of the spirocyclic indane on the ratio of the isomeric rearrangement products was specially investigated. Nevertheless, the method makes it possible to synthesize 4-spiroisoquinolin-1-ones with substitution in the aromatic ring that is impossible in the above-mentioned Bischler–Napieralski cyclization of alkyl carbamates [36, 37]. This fact has acquired particular significance in connection with the fact that the products from hydride reduction of the lactam group, i.e., tetrahydrospiro[isoquinoline-4,1'-cyclohexanes] **29** (X = CH_2; R^1 = OH, OMe; R^2 = R^3 = H), are of interest as inhibitors of cholinesterase [52]; for spiro[isoquinoline-4,4'-piperidines] **29** (X = N(COY); COY = dipeptide residues with a terminal amino group that was free or was alkylated by lower alkyls; R^1-R^3 = H, lower Alk, Hal) the ability to promote the release of growth hormone in humans and animals was demonstrated [53, 54].

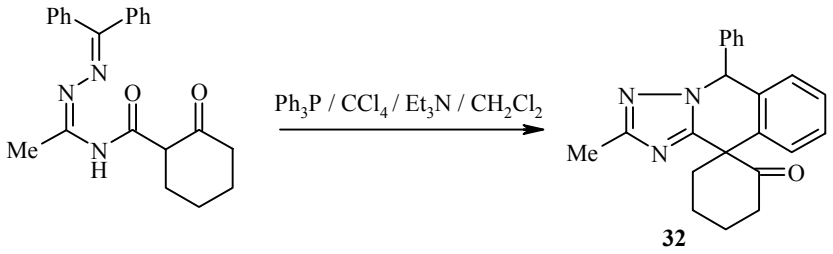


Photochemical methods for the synthesis of spiroisoquinolines have also been described. Thus, the enamides **30** (obtained with yields of 50-98% by the condensation of cyclohexanecarbaldehyde with aroyl chlorides and primary amines) are converted by irradiation of their solutions in cyclohexane or methanol with a mercury lamp for 6 h into the spiro[isoquinoline-4,1'-cyclohexan]-1-ones **31** (R^1 – R^3 = H, OMe; R^1,R^2 = OCH_2O, R^3 = H; R^4 = CH_2Ph, C_6H_4OMe-4, CHMePh, $CHPh_2$) with yields of 55-96% [55, 56].



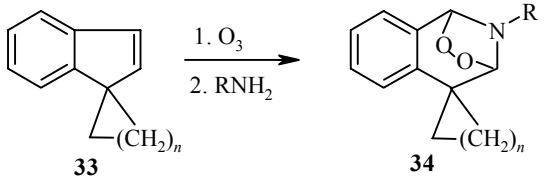
This approach was recently used for the synthesis of 2-benzylspiro[isoquinoline-4,1'-cycloalkane]-1,2'-diones and 2-methylspiro[isoquinoline-4,1'-cyclohex-3-en]-1-one and, from the latter, 2-methylspiro-[isoquinoline-4,1'-cyclohexan]-3'(2')-ols as structural analogs of the alkaloids lycoramine and the above-mentioned galanthamine [57].

In the literature there numerous examples of the synthesis of derivatives of spirocyclic systems in which the 4-isoquinoline fragment is in more complex condensed or bridged systems. Thus, the formation of spiro[1,2,4-triazolo[1,5-*b*]isoquinoline-10,1'-cyclohexan]-2'-one **32** with a yield of 9% under the conditions of the Appel reaction as a result of prolonged heating of N'-(diphenylmethylene)-N-(2-oxocyclohexylcarbonyl)ethanehydrazonamide in a mixture of triphenylphosphine, carbon tetrachloride, triethylamine, and methylene chloride has been described [58]. The mechanism of the process is discussed in the same paper.



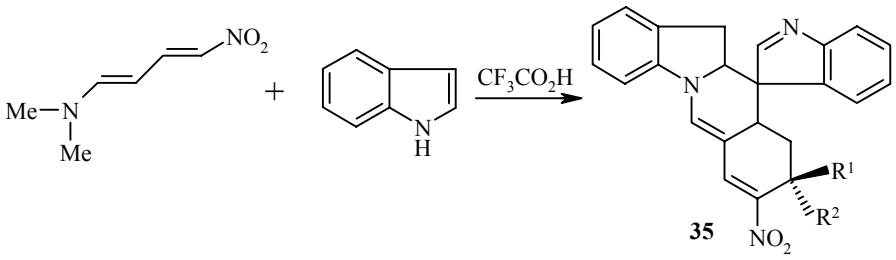
32

The low-temperature ozonolysis (-70°C) of the spiroindenes **33** (R = Bu, Ph, CH_2Ph, cyclohexyl) in the presence of primary amines is accompanied by recyclization, leading finally to the spiranes **34** (*n* = 1, 3) with yields of 78-89% [59].



33 **34**

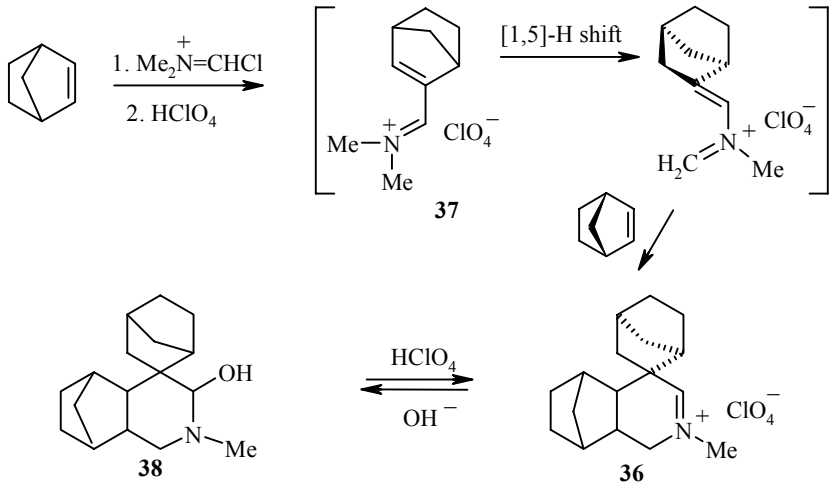
The condensation of a nitrodienamine with indole in trifluoroacetic acid leads to stereoisomeric products with the structure of spiro[indole-2',11-indolo[1,2-*b*]isoquinolines] **35** (R^1, R^2 = H, CH_2NO_2) with an overall yield of 75% [60].



35

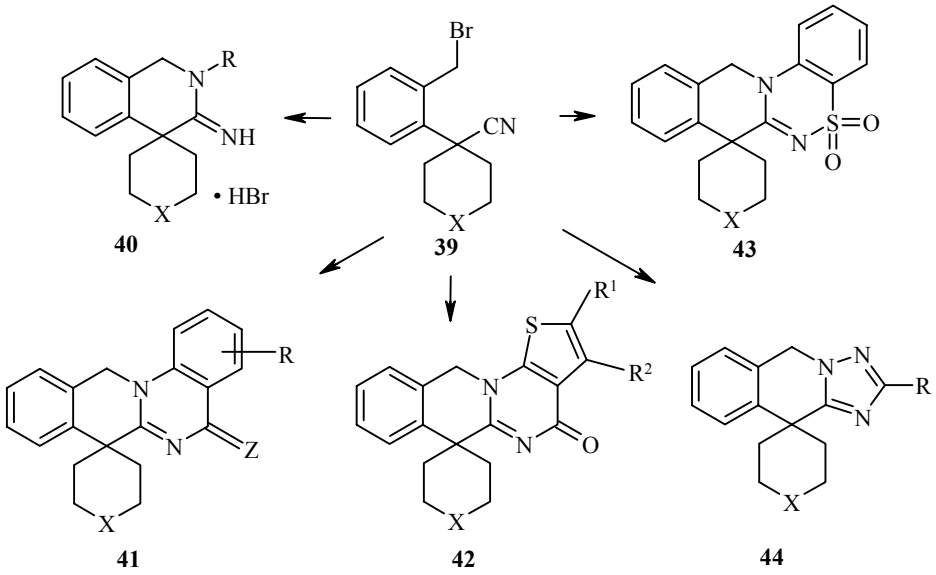
A significant case of the formation of a bridge system **36**, containing the spiro[isoquinoline-4,1'-cyclohexane] system as structural fragment, was described in [61]. It was shown that norbornene is transformed under Vilsmeier formylation conditions (the DMF–$POCl_3$ complex followed by treatment with perchloric acid) into 4-methyl-4-aziniumtricyclo[6.2.1.$0^{2.7}$]undec-4-ene-6-spiro-2'-bicyclo[2.2.1]heptane perchlorate (**36**) as a result of a [1,5]-H shift in the initially formed immonium salt **37** and a Diels–Alder reaction of the salt that arises here as diene with an excess of norbornene.

The structure of the perchlorate **36** was confirmed by X-ray crystallographic investigation. It is converted reversibly by the action of aqueous alkali into the unstable adduct **38**, characterized by data from the IR and high-resolution mass spectra (chemical ionization).



Unfortunately, the analogous synthesis of the octahydrospiro[isoquinoline-4,1'-cyclohexane]-2-ium salt could not be realized, since cyclohexene behaves ambiguously under the indicated conditions. However, under the influence of the N-formylmorpholine–$POCl_3$ complex it undergoes formylation with the formation of a moderate yield of 1-cyclohexene-1-carbaldehyde like other nonactivated olefins. On the other hand, this formylating system proved ineffective with respect to norbornene.

Recently [62, 63] a new convenient approach was proposed for the synthesis of 4-spiroisoquinolines based on the reaction of α,α-cycloalkylated *o*-bromomethylphenylacetonitriles **39** with primary amines. It made it possible to obtain spiro[isoquinoline-4,4'-tetrahydropyran]-3-imines **40** (X = O) and spiro[isoquinoline-4,1'-cyclopentane]-3-imines **40** (X = bond) with substituents R that could be varied within wide limits (Alk, Ar, (het)arylalkyl) at position 2 of the isoquinoline fragment (yields 40-93%).

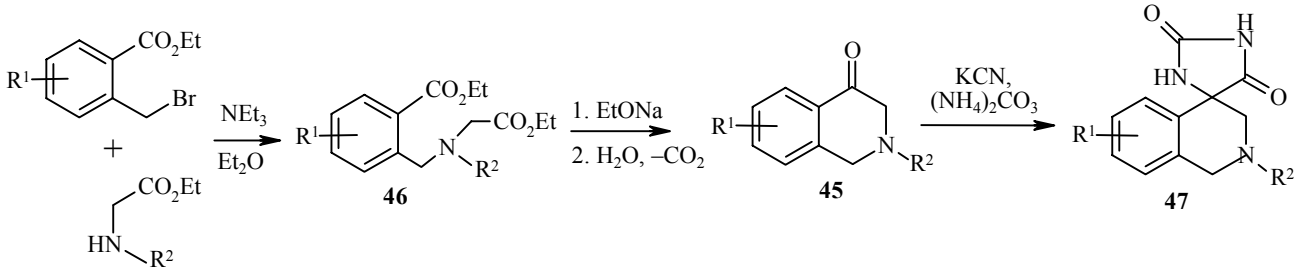


The potential of this approach lies in the possibility of synthesizing condensed systems containing a 4-spiroisoquinoline ring with the use of bifunctional amines. Thus, condensation of the bromo nitriles **39** with substituted and unsubstituted anthranilic acids (or their esters) and anthranilonitrile resulted in the formation of the spirocyclic isoquino[2,3-*a*]quinazolin-3-ones **41** (X = O, bond; Z = O; R = H, 1-3-Hal, 3-Me) and their

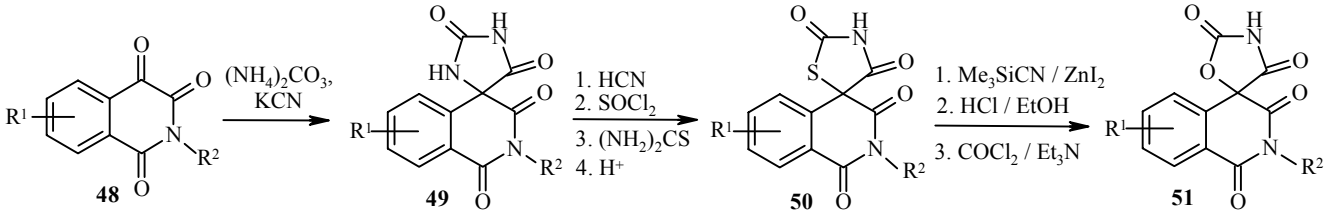
3-imines **41** (X = O, bond; Z = NH; R = H) with yields of 50-90%. With the esters of 2-aminothiophene-3-carboxylic acids it gave 4H-thieno[3',2':5,6]pyrimido[1,2-*b*]isoquinolines **42** (X = O, bond; R^1 = Alk; R^2 = H, Alk; R^1R^2 = $(CH_2)_n$; *n* = 3, 4) with yields of 55-94% [63, 64]. The analogous condensation with *o*-aminobenzenesulfonamide led with 55-94% yields to spirocyclic benzo[5,6][1,2,4]thiadiazino[4,3-*b*]-isoquinolines **43** (X = O, bond) [65]. The reaction of bromo nitriles with hydrazine and with the hydrazides of carboxylic acids gave 2-(acyl)amino-4-spiroisoquinolines, which were converted into spirocyclic [1,2,4]triazolo[1,5-*b*]isoquinolines **44** (X = O, bond; R = H, Me, Ar) (with R = Ar the yields were 52-77%) [66].

2. METHODS FOR SYNTHESIS OF 4-SPIROISOQUINOLINES BASED ON ISOQUINOLINE INTERMEDIATES

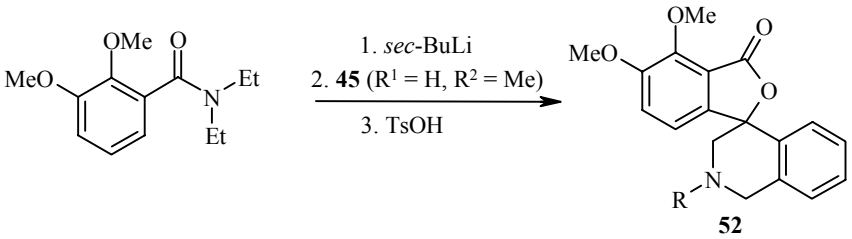
The pathways for the production of 4-spiroisoquinolines examined below are based on the use of isoquinoline derivatives in which position 4 has been prepared functionally in the appropriate manner for spirofusion with various carbo- and heterocycles. Such requirements were created, in particular, in 1,2,3,4-tetrahydroisoquinolin-4-ones **45**, produced by the Dieckmann cyclization of the ethyl esters of N-substituted N-(2-ethoxycarbonyl)benzylglycines **46** followed by hydrolysis and decarboxylation of the intermediately formed keto esters. The cyclocondensation of compounds **45** with ammonium carbonate and potassium cyanide secures the production of a spirofused hydantoin ring and the formation of the spiranes **47** (R^1 = H, OH, OMe, Hal; R^2 = H, alkyl, phenylalkyl, alkanoyl, Ts) according to the scheme [67, 68]:



The analogous transformation of isoquinoline-1,3,4-triones **48** (R^1 = H, Alk, OAlk, Hal, CF_3, NO_2, Ar, OAr, etc.; R^2 = H, Alk, Ar, (het)arylalkyl, etc.) led to the corresponding spirocyclic hydantoins **49** [69]. By a sequence of transformations in the hydantoin ring of compounds **49** it was possible to synthesize derivatives of spiro[isoquinoline-4,5'-thiazole]-1,2',3,4'-tetrones **50** and spiro[isoquinoline-4,5'-oxazole]-1,2',3,4'-tetrones **51**.

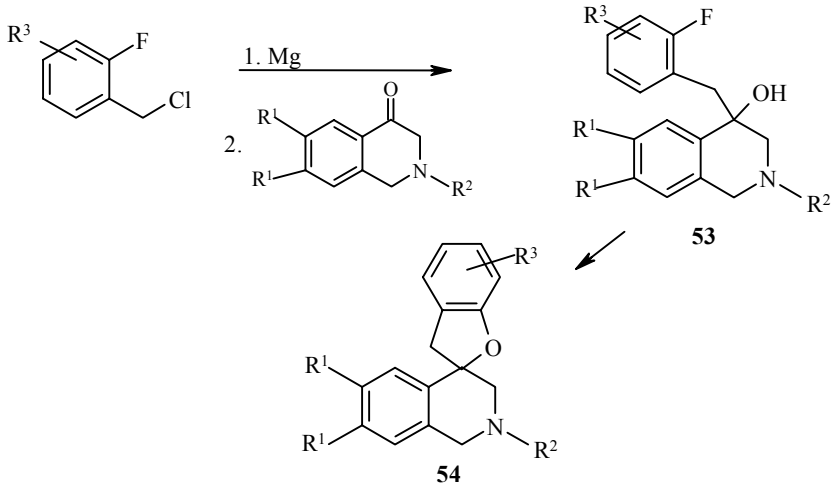


The lithium derivative obtained from 2,3-dimethoxy-N,N'-diethylbenzamide by the action of *sec*-butyllithium (ether, -78°C) is transformed as a result of condensation with the isoquinoline **45** (R^1 = H, R^2 = Me) followed by lactonization of the intermediately formed hydroxy acid (heating in the presence of TsOH) into spiro[isobenzofuran-1,4'-isoquinoline] **52** (R = Me) with a yield of 63% [70].

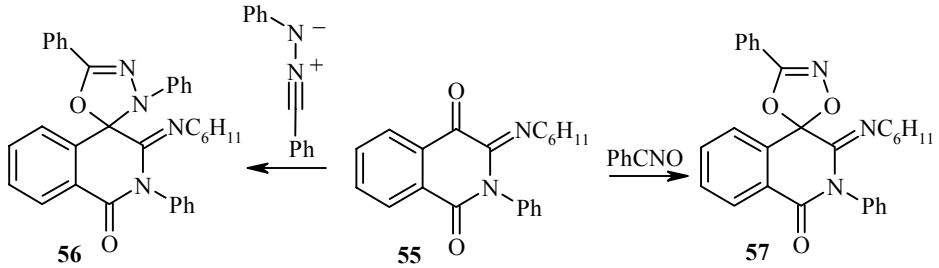


52

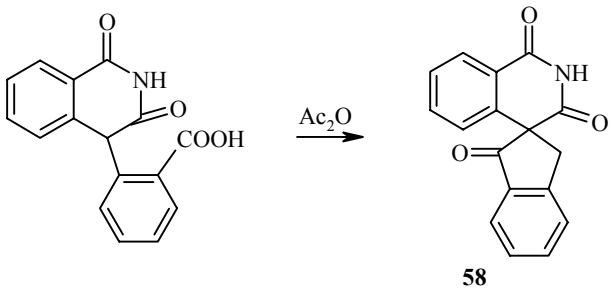
By a method close to that described above 4-(2-fluorobenzyl)tetrahydroisoquinolin-4-ols **53** (obtained by the Grignard reaction of magnesium derivatives of *o*-fluorobenzyl chlorides with 2-benzyl- and 6,7-dimethyloxy-2-benzyl-2,3-dihydro-4(1H)-isoquinolines) were transformed as a result of intramolecular nucleophilic arylation by the action of sodium hydride into tetrahydrospiro[benzofuran-2,4'-isoquinolines] **54** (R^1 = H, OMe; R^2 = Bn; R^3 = H, Hal) [71]. These compounds and also the extensive range of N(2')-substituted derivatives **54** (R^2 = alkyl, alkenyl, alkynyl, alkanoyl, aroyl) were patented as anticonvulsants, diuretics, and antihypertensives [72].



The ability of 3-(cyclohexylimino)-λ-phenylisoquinoline-1,4-dione (**55**) to enter into dipolar [2+3] addition at the 4-carbonyl group with N-phenylbenzonitrile imine and benzonitrile oxide in the presence of triethylamine, leading to the 4-spiroisoquinolines **56** (yield 82%) and **57** (yield 62%) fused with the 1,3,4-oxadiazole and 1,4,2-dioxazole fragments respectively, was demonstrated [73].

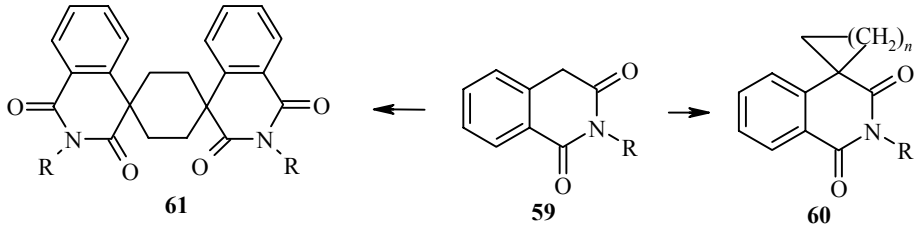


Of all the methods for the synthesis of 4-spiroisoquinolines the largest number are those in which the CH-acid characteristics of the appropriately activated isoquinolines are utilized. It is not by accident that the first mention of the synthesis of 4-spirocyclic isoquinolines is intramolecular acylation by the action of acetic anhydride in 3-(*o*-carboxybenzyl)homophthalimide, leading to spiro[isoquinoline-4,2'-indane]-1,1',3(2H)-trione (**58**) [74].



58

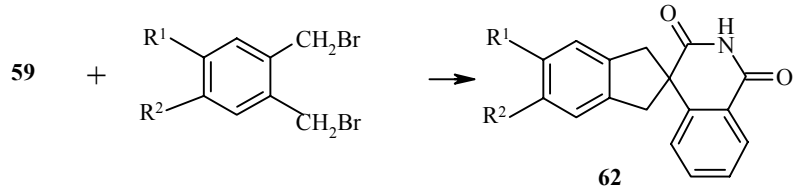
Homophthalimide itself [isoquinoline-1,3(2H,4H)-dione] **59** (R = H) and its N-substituted derivatives are used extremely widely in the synthesis of 4-spiroisoquinolines on account of the availability and of the high CH acidity of the $C_{(4)}H_2$ group. In the simplest cases the homophthalimides **59** undergo cycloalkylation by α,ω-dihalogenoalkanes, the length of the polymethine chain in which determines the size of the spirofused ring that forms. Thus, prolonged agitation (18-48 h) of a mixture of homophthalimide **59** (R = H, Me, or Ph) and 1-bromo-2-chloroethane in anhydrous DMF in the presence of potassium carbonate or sodium hydride at room temperature under excess nitrogen pressure leads to spiro[isoquinoline-4,1'-cyclopropane]-1,3-diones **60** (*n* = 1) with yields of 50-79% [75].



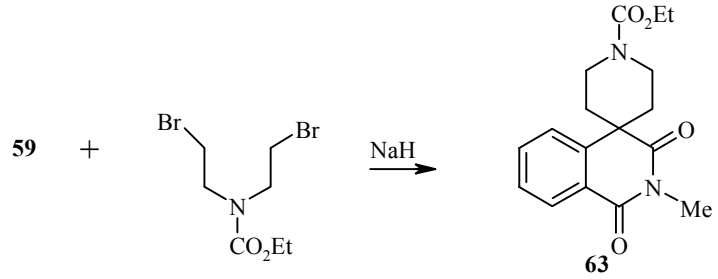
61 **59** **60**

Cycloalkylation of homophthalimide with 1,4-diiodobutane, realized by heating the reagents in DMF in the presence of potassium carbonate, leads with a yield of 50% to spiro[isoquinoline-4,1'-cyclopentane]-1,3(2H,4H)-dione **60** (*n* = 3, R = H), which exhibits anti-inflammatory and neuroleptic activity [76]. Together with this compound, the cyclocondensation of the homophthalimides (R = H, Me, Ph) with 1,4-dibromobutane and 1,5-dibromopentane gave the respective N-(un)substituted spiro[isoquinoline-4,1'-cyclopentane]- and spiro[isoquinoline-4,1'-cyclohexane]-1,3(2H,4H)-diones **60** (*n* = 3, 4; R = H, Me, Ph) [77-79]. However, the employed conditions of cycloalkylation (heating for 0.5 h, the homophthalimide–alcoholic potassium hydroxide–benzene–dibromoalkane system) secures only small yields (17-37%) of the spiran **60**. In [80] the cycloalkylation of N-benzylhomophthalimide **59** (R = Bn) by α,ω-dibromoalkanes in an alcohol solution of sodium hydroxide was studied. The highest yield (72%) of the spirocyclic product **60** (*n* = 3, R = Bn) was obtained with 1,4-dibromobutane. From 1,5-dibromopentane under the same conditions the corresponding dione **60** (*n* = 4, R = Bn) was obtained with a yield of 42%. The expected spirocyclobutane system was not formed at all from 1,3-dibromopropane. In the case of 1,2-dibromoethane the product **60** (*n* = 1) was obtained with a yield of 13%. The reaction of the homophthalimide **59** with twice the amount of 1,2-dibromoethane (anhydrous alcohol, triethylamine) led to dispiro[isoquinoline-4,1'-cyclohexane-4',4"-isoquinolines] **61** [78, 79].

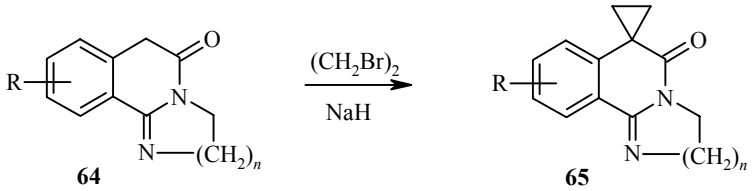
With the use of 1,2-bis(bromomethyl)benzene and 2,3-bis(bromomethyl)naphthalene for the cycloalkylation of the homophthalimides **59** (R = H, Me, Ph) it is possible to synthesize more complex spiran systems, i.e., spiro[isoquinoline-4,2'-indane]-1,3-diones **62** (R = H, Me, Ph; R^1 = R^2 = H) and spiro[benzo[*f*]indane-2,4'-isoquinoline]-1',3'-diones **62** (R = H, Me, Ph; R^1R^2 = $(CH{=}CH)_2$) respectively with yields of 50-60% [77, 79, 81].



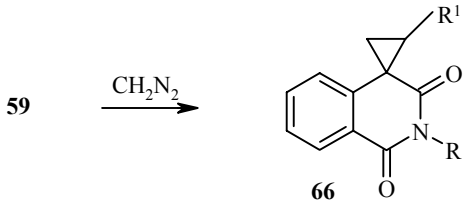
Spiro[isoquinoline-4,4'-piperidine]-1,3-dione **63** was obtained as a result of the reaction of the homophthalimide **59** (R = Me) with ethyl bis(2-bromoethyl)carbamate in anhydrous DMF in the presence of sodium hydride as base [82].



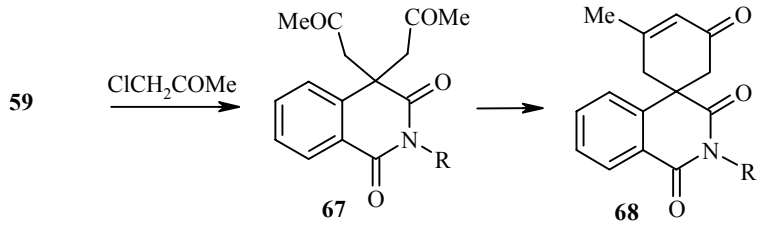
Cycloalkylation with dibromoethane was also applied to the condensed analogs of homophthalimide **64** for the synthesis of spirocyclopropanes **65** (R = H, Hal; *n* = 1-3), which exhibit antiasthmatic and broncholytic activity [83]. In particular, during treatment of the imidazoisoquinoline **64** (*n* = 1) with dibromoethane in the presence of sodium hydride the spiro[cyclopropane-1',6-imidazo[2,1-*a*]isoquinoline] **65** (R = H, *n* = 1) is formed with a low yield.



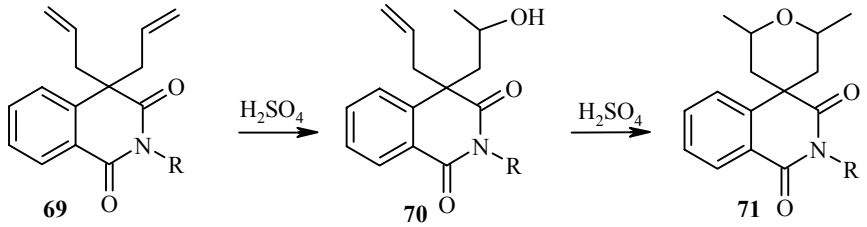
In connection with the construction of a spirofused cyclopropane ring it is necessary also to mention the unexpected direction in the reaction of N-methylhomophthalimide **59** (R = Me) with diazomethane in ether solution, leading to a mixture of 2-methyl- and 2,2'-dimethylspiro[isoquinoline-4,1'-cyclopropane]-1,3-diones **66** (R = Me, R^1 = H, Me) and a compound $C_{11}H_{11}N_3O_2$ with unestablished structure [84]. Trace quantities of the 2-dimethylamino derivatives **66** (R = NMe_2) were also detected during the reaction of 2-aminohomophthalimide **59** (R = NH_2) [85].



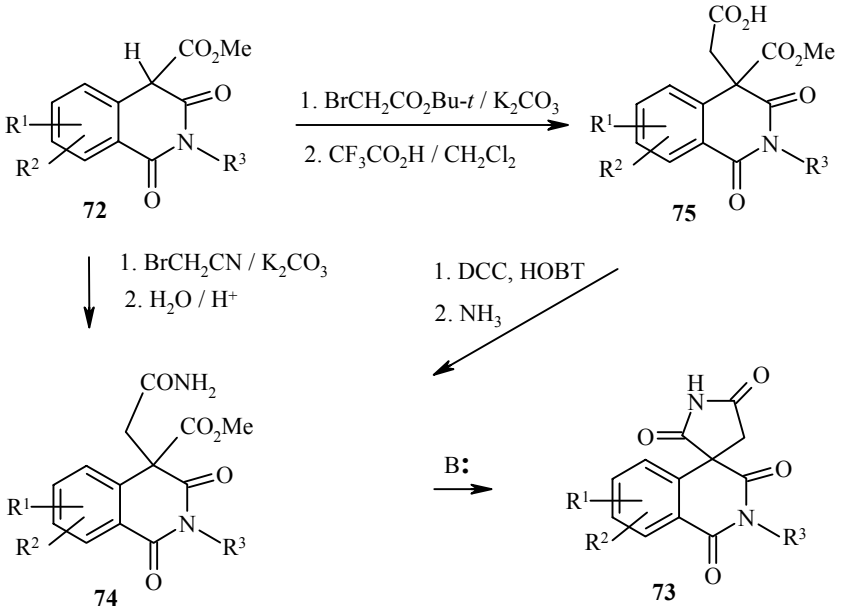
Another group of syntheses of spirocyclic compounds based on homophthalimides requires the insertion at position 4 of groups whose intramolecular condensation by standard procedures secures the formation of various spirofused rings. Thus, diacetonylhomophthalimides **67**, produced as a result of the alkylation of homophthalimides **59** (R = H, Me, Ph) with an excess of chloroacetone in an alcohol medium in the presence of triethylamine, undergo cyclization under the influence of *p*-toluenesulfonic acid in boiling toluene to the corresponding spiro[isoquinoline-4,1'-cyclohex-4'-ene]-1,3,3'-triones **68** [78, 79].



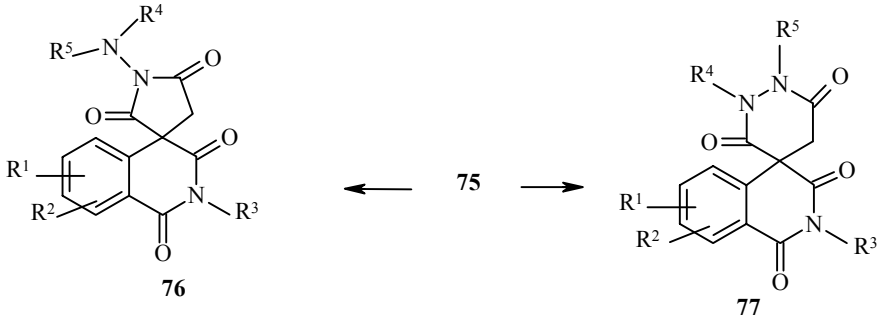
The 4,4-diallyl derivatives **69** (R = H, Me) synthesized from the homophthalimides **59** are converted as a result of hydration by the action of sulfuric acid for 1 h into 4-allyl-4-(2-hydroxypropyl)homophthalimides **70**. With increase in the reaction time to 90 h it is possible to obtain 2,6-dimethyl-2,3,5,6-tetrahydrospiro[isoquinoline-4,4'-4H-pyran]-1,3-diones **71** with yields of up to 70% [86-88].



In the last decade methods have been developed vigorously for the synthesis of 4-spiroisoquinolines based on the methyl esters of Ar-(un)substituted homophthalimide-4-carboxylic acids **72** (here and subsequently in structures **73-77** *n* = 1-6, R^1, R^2 = H, Hal, CF_3, NO_2, Alk, Ar, OAlk, OAr, R^3 = H, Alk, Ar, acyl, alkoxycarbonyl, $(CH_2)_nCO_2H$, dihalobenzyl, dihaloaralkyl, benzothiazolylmethyl), obtained in four stages from *o*-halobenzoic acids [69, 89-98]. In the synthesis of spiro[isoquinoline-4,3'-pyrrolidine]tetrones **73** the key intermediates were the amides of 4-carboxy-4-isoquinolineacetic acids **74** and were obtained by alkylation of the esters **72** with bromoacetonitrile or *tert*-butyl bromoacetate followed by the standard transformations shown in the scheme [69, 89-94]. The cyclization of the amides **74** to the spirocyclic succinimides **73** was realized by the action of strong bases such as sodium hydride in DMF or lithium hexamethylenedisilylamide in THF. A method for the production of optically pure spiro[isoquinoline-4,3'-pyrrolidine]tetrones **73** is also described in the patent [69].

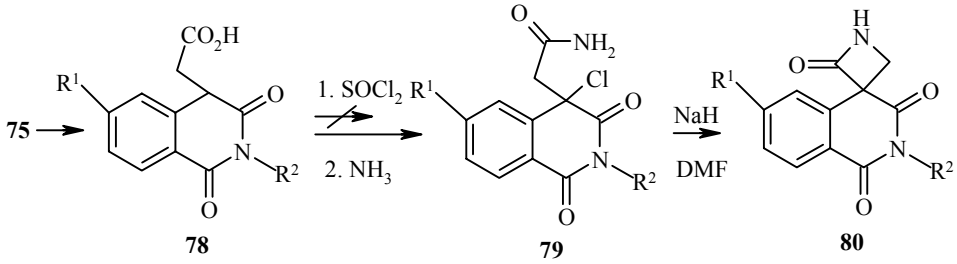


The amination of the acids **75** with (un)substituted hydrazines gave the corresponding hydrazides. Their cyclization by the action of the above-mentioned bases led, depending on the nature of substitution in the hydrazide, to spirofused 1-aminopyrrolidines **76** (R^4, R^5 = H, Alk, Ar, aralkyl, alkanoyl, aryl- and alkylsulfoxy, etc.) [95-98] or to the pyridazines **77** (R^4, R^5 = H, Alk, Ar, aralkyl, etc.) [99, 100].



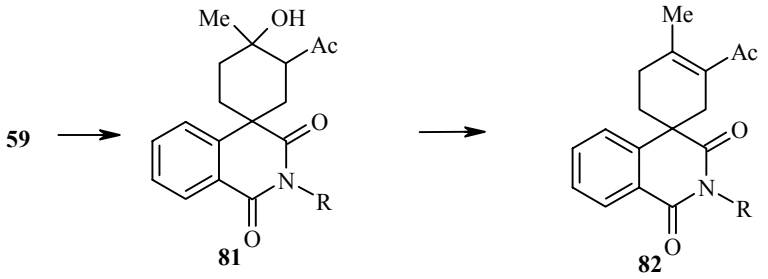
76 **75** **77**

The construction of a spirofused azetidine ring was realized on the basis of 4-methoxycarbonyl-4-isoquinolinylacetic acids **75**. Hydrolysis of the ester group in these compounds is accompanied by 4-decarboxylation of the intermediate dicarboxylic acids. The 4-isoquinolinylacetic acids **78** (R^1 = H, Hal, R^2 = Alk, dihalo-substituted Bn) formed here are converted as a result of successive treatment with thionyl chloride and ammonia into the corresponding 4-chloro-4-isoquinolinylacetamides **79**, the cyclization of which by the action of sodium hydride in DMF leads to spiro[isoquinoline-4,2'-azetidines] **80** [100-102]. Convincing evidence for the spiro structure of these compounds can be provided by the magnetic nonequivalence of the protons of the methylene group in the azetidine ring, while the *gem*-spin–spin coupling constants are increased by 2 Hz compared with the initial acetamide **79**.



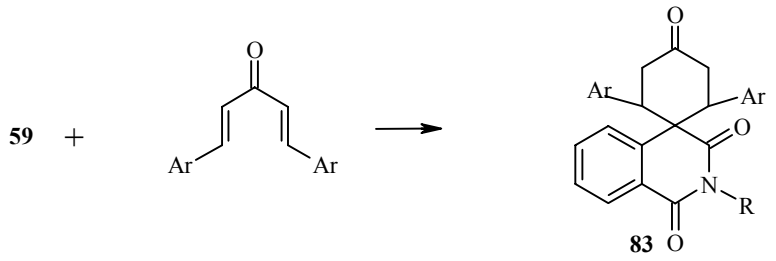
78 **79** **80**

Further possibilities in the synthesis of spiroisoquinolines are opened up by the use of the Michael reaction with homophthalimides, which can act as donors or acceptors (in the form of the products from their condensation with carbonyl compounds). In the first case they start from 4-unsubstituted homophthalimides **59** (R = H, Me, Ph) and vinyl ketones or their synthetic equivalents. Thus, the reaction of the indicated imides **59** with a twofold excess of 4-diethylamino-2-butanone methiodide by the action of an alcohol solution of potassium hydroxide does not stop at the stage of the respective diketones but leads to 4'-hydroxy-4'-methyl-3'-acetylspiro[isoquinoline-4,1'-cyclohexane]-1,3-diones **81** with yields of 53-66%. Dehydration of the latter by the action of *p*-toluenesulfonic acid makes it possible to obtain the corresponding spirocyclic cyclohexenes **82** [78].

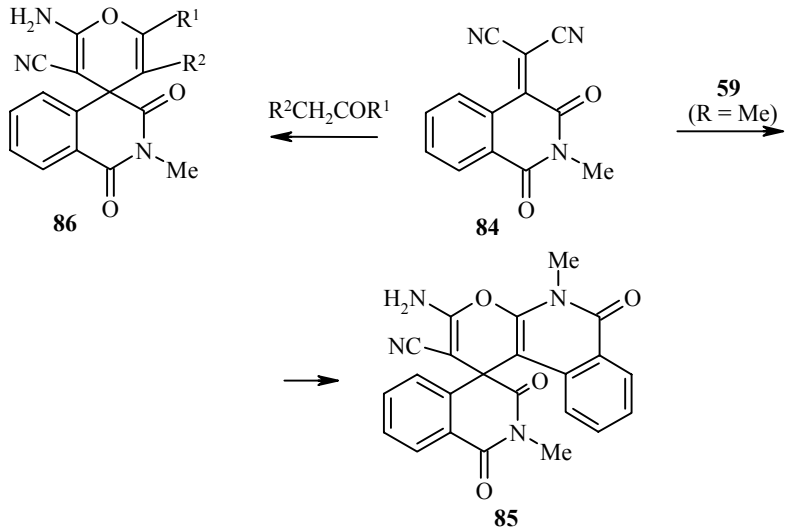


59 **81** **82**

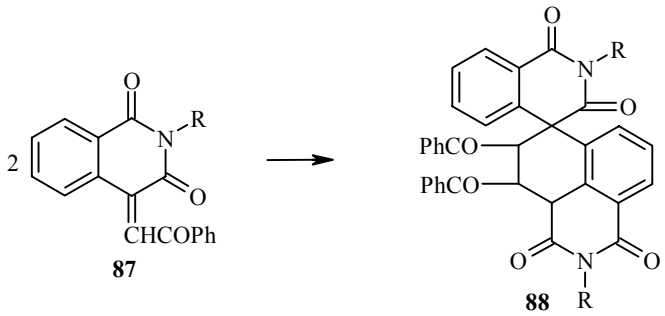
Double Michael cycloaddition of diarylidene derivatives of acetone (Ar = Ph, C_6H_4OMe-*p*) to the homophthalimides **59** (R = H, Me, Ph, Bn) leads to the corresponding spiro[isoquinoline-4,1'-cyclohexane]-1,3,4'-triones **83** [103]:



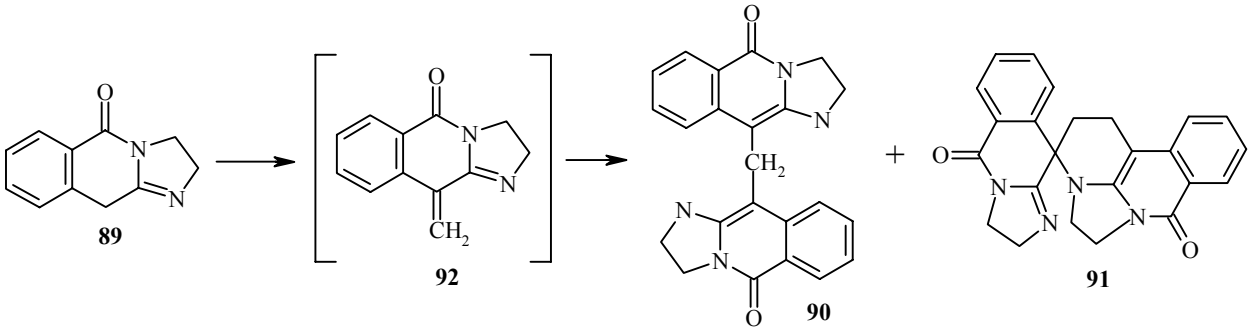
The condensed spirane **85** was obtained with a quantitative yield from 4-dicyanomethylenehomophthalimide (**84**) and compound **59** (R = Me) [104]. In the same paper the enamino nitriles **86** (R^1 = Me, Ph, CO_2Me; R^2 = H, COMe, CO_2Et) of the spiro[isoquinoline-4,4'-pyran] series were synthesized as a result of nucleophilic Michael addition of methylene-active carbonyl compounds to the dinitrile **84**.



As a result of treatment at 215°C for 5 min or boiling in acetic acid for 1-5 h the 4-phenacylidenehomophthalimides **87** (R = H, Me) dimerize to the pentacyclic spiranes (**88**) (R = H, Me) with high yields [105, 106].

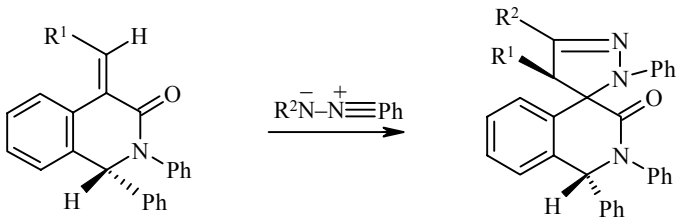


Some analogy with these transformations was observed in [107], devoted to investigation of the enamine characteristics of 2,3-dihydroimidazo[1,2-*b*]isoquinolin-5(1H)-one (**89**) in a series of other tricyclic enamines of the 1(2H)-isoquinolone series. Thus, bis(imidazoisoquinolyl)methane **90** and, quite unexpectedly, spiro[benzo[*c*]imidazo[1,2,3-*ij*][1,8]naphthiridine-3,10'-imidazo[1,2-*b*]isoquinoline] **91** were obtained in commensurable amounts from compound **89** under the conditions of the Mannich reaction (the dioxane–formalin–morpholine system). The formation of **91** was regarded as resulting from [2+4] addition, in which the roles of dienophile and azadiene are played by two molecules of the intermediately formed methylene derivative **92**.



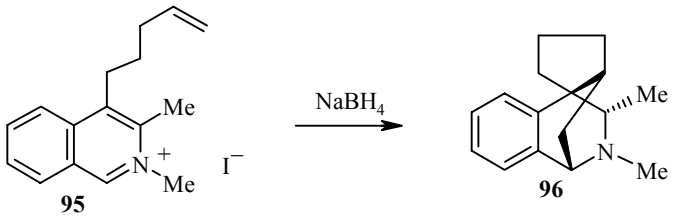
89 **92** **90** **91**

Like the derivatives of 4-isoquinoline **55** mentioned above, the 4-arylidene derivatives of 1,2-diphenyl-1,2,3,4-tetrahydroisoquinolin-3-one **93** are capable of entering into 1,3-dipolar cycloaddition to diarylnitrile imines, which is characterized by high regioselectivity. The products formed here have the structure of spiro[isoquinoline-4,3'-pyrazole]-3-ones **94** (R^1, R^2 = Ph, Ar) [108].



93 **94**

It is also necessary to mention the interesting transformation of 2,3-dimethyl-4-(4-pentenyl)isoquinolinium iodide (**95**) during the action of sodium borohydride, as a result of which the formation of the methylene bridge is accompanied by spirofusion of the isoquinoline and cyclopentane fragments. Here, the racemate of 1,2,3,4-tetrahydro-2,3-dimethyl-1,2'-methanospiro[isoquinoline-4,1'-cyclopentane] (**96**) is formed with a yield of 89% [109].



95 **96**

3. BIOLOGICAL CHARACTERISTICS OF 4-SPIROISOQUINOLINES

Biological tests on 4-spiroisoquinolines have demonstrated the broad spectrum of their activity, in which the inhibiting effect on both the peripheral and the central parts of the nervous system dominate. Data on the activity will be examined below in association with the nature of the mode of action of the compounds.

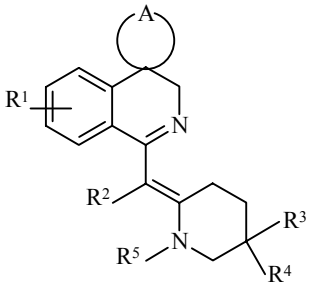
Depressants of the Central Nervous System. An extensive group of 4-spiroisoquinolines have a depressing effect on the central nervous system. Hypnotic effects have been described for spiro[isoquinoline-4,1-cyclopentanes] **9** (X = bond; R^1 = OAlk; $R^2 = R^4 = H$; $R^3 = CH_2C_6H_3(OMe)_2$-3,4) [26]. It is interesting to note that allyl(2-hydroxypropyl)homophthalimide **70** has clearly defined hypnotic activity, whereas its spirocyclization leads, together with reduced toxicity, to a change in the nature of its action: spiro[isoquinoline-4(1H)4'-4(H)-pyran] **71** (R = H) exhibits sedative activity [86-88]. For the diones **71** (R = H, Me) the doses at which they exhibit sedative but not soporific activity were determined [86-88, 110]. It was shown that the same compounds also possess depressant characteristics, while the introduction of substituents at the nitrogen atom ($R = CH_2CH_2NEt_2$, All) increases both the biological activity and the toxicity [111]. Animal tests indicated antispasmodic activity for compounds of type **9** (X = bond, (CH_2), O; $R^1 = R^2$ = OMe; R^3, R^4 = H, Me) [29], **15** (Z = O; R^1, R^2 = H, OMe; R^3 = Me; R^4 = H, Ar) [40], and **54** ($R^1 = R^3$ = H; R^2 = H, alkyl, alkenyl, etc.) [72]. Tetrahydrospiro[isoquinoline-4,4'-pyrans] **2** (X = O; R = Ar) [112] and spiro[isoquinoline-4,1'-cyclohexan]-4'-ols **2** (X = CH(OH); R = H, Me) [113] and also spiro[isobenzofuran-1,4'-isoquinolines] **52** (R = H, Me) (as agonists of dopamine receptors) [70] behaved as potential antiparkinsonian agents (central cholinolytics). From the results of a series of tests spiro-3,4-dihydroisoquinolines **8** (X = bond, O; $R^1 = R^2$ = OMe; R^3 = aralkyl; R^4 = H) were classified as potential neuroleptics [25].

The ability to depress psychomotor activity has been described for spiro[isoquinoline-4,1'-cyclopentane]-1,3(2H,4H)-dione **60** (*n* = 3, R = H) [76]. On the basis of analysis of the results from tests on 4-spiroisoquinolines **2** (X = bond, O; R = ω-amino- and ω-(dialkylamino)alkyl) it was concluded that the introduction of rings spirofused with the isoquinoline system strengthens the depressant effect on the nervous system [114].

Spirocyclic homophthalimides **18** (X = bond, CH_2; R = $(CH_2)_nNR^2R^3$, $CH_2CONR^2R^3$; *n* = 1-3, NR^2R^3 = dimethylamino, 4-methylpiperazino] [46] were described as antidepressants but without defining the type of activity, while 4-spiroisoquinolin-1-ones **26** (X = CH_2, CH(OH); R^1 = OMe; $R^2 = R^3$ = H; R^4 = H, Me) were proposed as antidepressant-thymoerectics [51, 52].

Among the 4-spiroisoquinolines there are also compounds possessing analgesic activity of opiate type [25, 115, 116]. Anti-inflammatory activity is characteristic of spiroisoquinolines **60** (*n* = 3, R = H) [76] and **9** (X = bond, O; $R^1 = R^2$ = OMe; R^3 = H, Me; R^4 = Me) [29]. At Merck derivatives of spiro[isoquinoline-4,4'-piperidine] that modulate chemokinine receptor activity show up well against HIV infections and certain forms of AIDS have been studied in detail [117-119]. Spiro[isoquinoline-4,1'-cycloalkanes] with structure **97**, containing 2-piperidinylidenemethyl substituents (A = alicycle; R^1 = Hal, OH, Alk, Ar, R^2 = H, Alk, OAlk, Ph; R^3, R^4 = H, Alk; R^5 = H, Alk, CH_2OH) at position 1, and also the bisspirocyclic compound **98** were proposed as antiinflammatory preparations on the basis of the results of biochemical tests on the inhibition of previously stimulated ion channels [120, 121].

Stimulants of the Central Nervous System. The derivatives of only three spiroisoquinoline systems – spiro[isoquinoline-4,1'-cyclopentane] [45, 46, 122], spiro[isoquinoline-4,4'-pyran] [122], and spiro[isoquinoline-4,4'-cyclohexane] [45, 46] – behaved as stimulants of the central nervous system during tests on antagonism to the action of reserpine.



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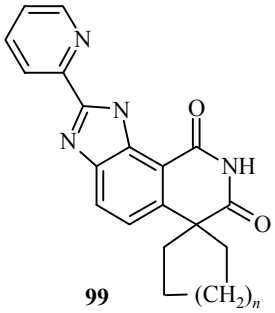

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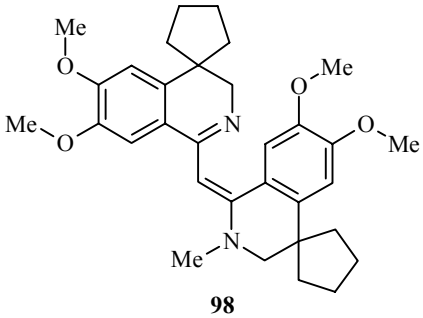

98

A = alicycle, R = Hal, OH, Alk, Ar; R^2 = H, Alk, OAlk, Ph; R^3, R^4 = H, Alk; R^5 = H, Alk, CH_2OH

Action on the peripheral nervous system is characteristic of a large number of spiroisoquinolines.

Considerable attention has been paid to efferent innervation; in addition to the establishment of weak adreno- and cholinolytic action for spirotetrahydroisoquinolines **2** (X = O, CH(OH); R = H) [10, 13] and **9** (X = CH_2; R^1 = R^2 = OMe; R^3 = aryl, aralkyl; R^4 = H) [31], a distinct spasmolytic effect was recorded for compounds **9** (X = bond; R^1 = R^2 = R^4 = H; R^3 = Ar [27]; X = bond, CH_2, O; R^3,R^4 = H, Me; R^1 = R^2 = OMe) [29] and 3,4-dihydroisoquinolines **8** (X = bond, O; R^1 = R^2 = OMe; R^3 = CH=CHAr) [25]. Adrenomimetic characteristics were described in compound **2** (X = $CH[OCH_2CH(OH)CH_2NAlk_2]$, R = Me) [19], and some compounds with the general formula **2** behaved as β-adrenolytics [110].

Substances Affecting the Function of the Respiratory Organs. A stimulant effect on respiration was described in compounds of type **71** (R = All, CH_2CH_2NEt) [111], and compounds **65** (*n* = 1-3, R = H, Hal, Alk) were proposed as bronchodilators [83]. Bronchoconstriction (assessed from the inhibition of the bonding of neurocanine during study of antagonism to the NK_2 receptor) was detected for an extensive range of 4-spirocyclic piperidines, including spiro[isoquinoline-4,4'-piperidines] [124, 125].

Substances Affecting the Cardiovascular System. Cardiotonic characteristics are exhibited by the spirocyclic imidazoisoquinolines **99** synthesized on the basis of the spirans **17** (*n* = 1-3) [42] and also by spiro[isoquinoline-4,4'-piperidin]-1-ones [126]. Antiarhythmic activity was observed in a series of spirocyclic isoquinolines with cyclopentane [123], cyclohexane [31], tetrahydropyran [10, 123], and piperidine [39]. Hypotensive activity is typical of the spiroisoquinolines **9** (X = bond; R^1 = H, OAlk; R^2 = R^4 = H; R^3 = aryl, aralkyl) [26, 27], spiro[isoquinoline-4,1'-cycloalkane]-1,3-diones **17** (*n* = 1-3) [42], and spiro[benzofuran-2,4'-isoquinolines] **54** (R^1 = R^3 = H; R^2 = H, alkyl, alkenyl, etc.) [72]. The spiroisoquinolines **9** (X = bond; R^1 = R^2 = OMe; R^3 = aralkyl; R^4 = H) strengthen the blood stream, expanding the coronary vessels [15, 29].

Substances Affecting Tissue Exchange Processes. According to data from Hoechst AG, the spiro[isoquinoline-4,1'-cyclopentanes] **11** and **16** (Z = O, S; R = Ar; R^1 = H; R^2 = H, OAlk; R^1R^2 = OCH_2O) were recommended as prospective hypolipemics – substances that prevent the deposition of cholesterol [36, 37, 41]. Compounds of type **93** inhibit the penetration of lipoproteides across the endothelium in the subendothelial space of smooth muscle cells [121]. In a large number of papers by researchers at American Home Products experiments with spiroisoquinolines of types **50**, **73**, **76**, **77**, and **80**, which exhibited the characteristics of inhibitors of aldose (e.g., galactose) reductases, are described [89, 90, 93-101]. These substances reduce the accumulation of dulcitol in eye tissues and thereby prevent the development of cataracts. These characteristics are also exhibited by isoquinoline-containing spirocyclic hydantoins **47** (R^1, = H, OH,

OMe, Hal; R^2 = H, alkyl, phenylalkyl, alkanoyl, tosyl) [67, 68], spiro[isoquinoline-4,1'-cyclopentane]-3-ones and the corresponding 3-thiones **16** (Z = O, S; R = Ar) [41], and spiro[isoquinoline-4,3-pyrrolidines] [127-129], proposed as peroral substitutes for pancreatic hormone preparations (insulin). For compounds **54** (R^1 = H, OMe; R^2 = H, alkyl, alkenyl, alkynyl, alkanoyl, aroyl; R^3 = H, Hal) diuretic activity was also detected in addition to the valuable characteristics mentioned above [72]. Compounds **97** and **98** inhibit the penetration of lipoproteides through the epithelium into the subendothelial space of smooth-muscle cells [120]. They were proposed for the treatment of ulcerative colitis and Crohn's disease [130]. An extensive series of 4-spirocyclic piperidines N-acylated by dipeptide residues, including the corresponding spiro[isoquinoline-4,4'-piperidines] exhibit the capacity for the secretion of growth hormones [53, 54].

Papers in which there are data on the biological activity of 4-spiroisoquinolines are listed below.

In conclusion it is necessary to draw attention to the intensive development of investigations into the chemistry of the spirocyclic compounds of isoquinolines and, in particular, their biological characteristics. Thus, almost half the references to 4-spiroisoquinolines in the literature have appeared during the last decade. It is clear that on account of the interesting and practically significant results that they will continue attract the attention of both synthetic chemists and pharmacologists.

TABLE 1. List of References to Types of Biological Activity of 4-Spiroisoquinolines

Type of biological activity	Reference
Depressants of the CNS	
Hypnotic action	26
Sedative action	86, 88, 111
Anticonvulsive action	29, 40, 72
M-Cholinolytic activity	113, 114
Neuroleptic activity	25
Psychotropic, depressant activity	76, 112, 115
Antidepressants	46
Agonists of dopamine D_1	70
Analgesic activity	25, 116, 117
Anti-inflammatory activity	29, 76, 118-122
Stimulants of the CNS	
Antagonism to reserpine	45, 123
Compounds active in the region of neuron ending	
Cholinolytic activity	13, 124, 125
Anticholinesterase activity	51, 52
Spasmolytic activity	10, 25, 27, 29, 31
Adrenolytic activity	13, 19, 106
Antiasthmatic, bronchodilating action	83, 112
Compounds acting on the cardiovascular system	
Antiarhythmic activity	10, 31, 123, 126
Hypotensive action	10, 27, 31, 42, 72
Increase of coronary blood flow	15, 29
Cardiotonic activity	42, 126
Production of short-term hypertensive effect	26
Substances acting on tissue exchange	
Hypolipidemic activity	36, 37, 89, 90, 93-101
Anticholinesteremic activity	41
Antidiabetic activity	41, 67, 68, 127–129
Promotion of growth hormone	53, 54
Antiulcer activity	130
Antiproliferative activity	121
Diuretic activity	72
Immunomodulator action	118–120

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