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Pyrido- and pyrimidoisoindoles: methods of synthesis and properties

A A Pokholenko, Z V Voitenko, V A Kovtunenko

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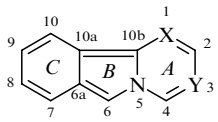
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Abstract. The data on the synthesis, structures and chemical properties of pyrido- and pyrimidoisoindole derivatives with an azine ring annelated to a pyrrole ring, which have been published over the last two decades, are generalised. The structure of the π-electron system and the high reactivities of azinoisoindoles are discussed. Special attention is given to aromatic pyrido- and pyrimidoisoindoles. The bibliography includes 86 references.

I. Introduction

The heterocyclic isoindole system attracts the attention of chemists involved in both synthetic and theoretical chemistry. A combination of high reactivity with pronounced aromatic properties is the main distinguishing feature of isoindole derivatives.[1–3] Several quantum-chemical approaches to the estimation of aromaticity and description of the 10π-electron system of the isoindole ring have been proposed. It was found that the concept based on the calculation of valence activities of its fragments reflects the structures and properties of such *ortho*-quinoid heteroaromatic compounds in the most adequate way.[4,5] This concept was confirmed experimentally for isoindole derivatives using X-ray diffraction analysis[4] and mass spectrometry.[6]

The present review is devoted to the methods of synthesis and chemical properties of three types of isoindole systems fused at the pyrrole ring and containing a junction nitrogen atom, *viz*., pyrido[2,1-*a*]- (**1**),† pyrimido[2,1-*a*]- (**2**) and pyrimido[6,1-*a*]isoindole (**3**) derivatives.



1: X = Y = CH;
2: X = N, Y = CH;
3: X = CH, Y = N

The annelation, to the electron-donating isoindole ring, of an additional acceptor azine ring strongly influences the structures and reactivities of these tricyclic systems, and unusual chemical properties can be expected. To date, investigations of *a*-fused isoindole systems are scarce. Some publications are devoted to original approaches to the synthesis of such derivatives, their biological activities and other useful properties. A review[2] devoted to the synthesis and properties of simple isoindoles provides but few examples of preparation of fused isoindole systems. Thus a small chapter in the monograph[1] published in 1983 is virtually the only literature source devoted to the chemistry of azinoisoindoles, whereas a recently published review[7] deals with the description of fused triazolo- and tetrazoloisoindoles. The present review surveys the data on the methods for the synthesis and properties of pyrido- and pyrimidoisoindoles published over the last two decades and includes some earlier publications, which enables the comprehensive presentation and systematisation of the data published on the subject.

II. Methods of synthesis of pyrido- and pyrimidoisoindoles

The uniqueness of the chemistry of azinoisoindoles can well be illustrated by some specially developed synthetic methods. As a rule, the starting compounds contained a benzene ring (*C*) to which a heterocyclic system [a pyrrole (*B*) or an azine (*A*) ring or both rings simultaneously] was attached. The data on the annelation of the benzene ring to indolizine derivatives (or their aza analogues) yielding azinoisoindoles are unavailable in the literature published over the last two decades, although several syntheses of this kind were described earlier.[1]

1. Synthesis of pyrido[2,1-*a*]isoindole derivatives

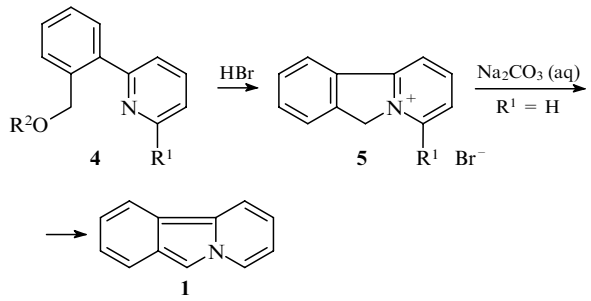
a. Closure of the pyrrole ring with formation of the N(5) – C(6) bond

The closure of the pyrrole ring with the concomitant formation of the N(5) – C(6) bond is one of the general approaches to the synthesis of aromatic isoindole systems. There are only a few examples of the synthesis of pyrido[2,1-*a*]isoindoles prepared by this method. Thus the intramolecular alkylation of the pyridine nitrogen atom is based on the formation of 2-[(*o*-halogenomethylaryl)]pyridines and has only been applied to the synthesis of pyrido[2,1-*a*]isoindole[8] and its methyl derivative.[9] Treatment of pyridines **4** with HBr affords pyrido[2,1-*a*]isoindolium bromide **5** in good yields. The dehydrobromination of the salt **5** (R^1 = H) with an aqueous solution of sodium carbonate gives a base (**1**) which is unstable in air, but can be used for further conversions.

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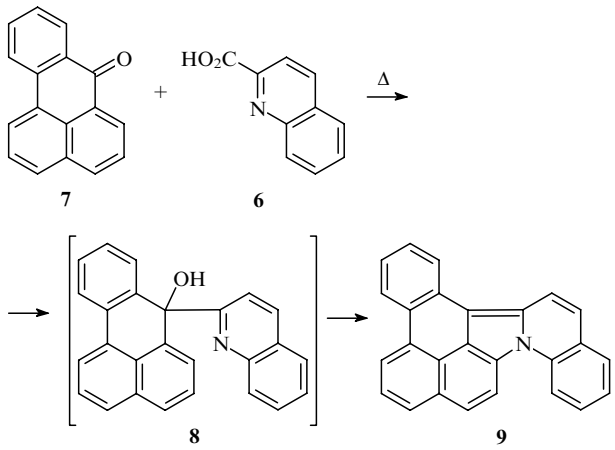
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Uspekhi Khimii **73** (8) 833 – 848 (2004); translated by R L Birnova

† These systems can also be regarded as benzo[*a*]indolizine derivatives; however, in general, we shall consider isoindole as the base fragment.



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

A heptacyclic heteroaromatic system with a junction nitrogen atom containing a pyrido[2,1-*a*]isoindole fragment has been synthesised.[10] Upon thermal decarboxylation of quinaldinic acid (**6**) in the presence of *meso*-benzanthrone (**7**), the intermediate 2-(7-hydroxy-7-benzanthryl)quinoline (**8**) eliminates a water molecule and cyclises into compound **9**.

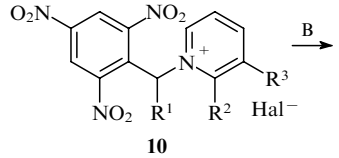


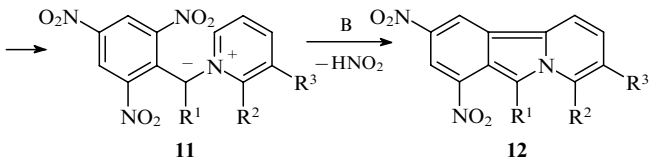
In this case, the formation of the N(5)–C(6) bond is preceded by the formation of the C(10a)–C(10b) bond, which results in the closure of the pyrrole ring and the formation of a fused pyrido[2,1-*a*]isoindole system.

b. Closure of the pyrrole ring with formation of the C(10a)–C(10b) bond

The most popular procedures for the synthesis of the pyridoisoindole system are based on the use of readily available *N*-substituted pyridine derivatives as the starting compounds. Two main types of cyclisation mechanisms are possible: one of them involves the formation of an ionic intermediate, while the second consists of the formation of a radical intermediate. Reactions *via* organometallic intermediates can be singled out into a separate group.

The Kröhnke cyclisation of pyridinium ylides. This cyclisation was discovered by Kröhnke[11] and is characteristic of ylides generated from pyridinium salts **10**. This served as the basis for the development of a general method for the formation of an isoindole fragment of nitrogenous heterocycles which was considered in detail in the monograph. [1] On treatment with a base, *e.g.*, an excess of piperidine in DMSO, pyridinium ylide **11** is converted into pyridoisoindole **12**.



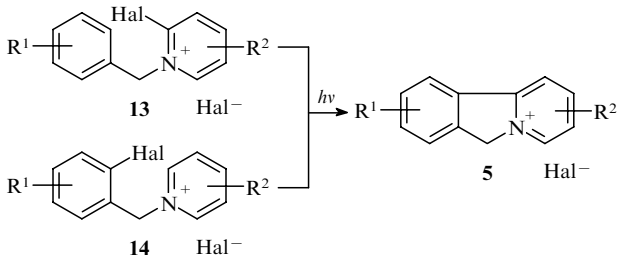


R^1 = H, ArCO; R^2, R^3 = H, Alk; B is a base.

This procedure, *viz*., short-term heating in aqueous methanol with 2 equiv. NaOH, is used for the preparation of 7,9-dinitropyrido[2,1-*a*]isoindole **12a** (R^1, R^2, R^3 = H) in 97% yield.

Cyclisation of radicals generated from aryl halides. Two approaches to the generation of free radicals, *viz*., photochemical and initiator-induced, are considered below.

Intramolecular photocyclisation enables the preparation of pyridoisoindoles containing halogens and alkyl substituents in both benzene and pyridine rings. The pyrido[2,1-*a*]isoindolium salt **5** (R^1 = R^2 = H) was synthesised for the first time by cyclisation of the isomeric pyridinium salts **13** (R^1 = R^2 = H) and **14** (R^1 = R^2 = H) upon UV irradiation of their aqueous solutions.[12]

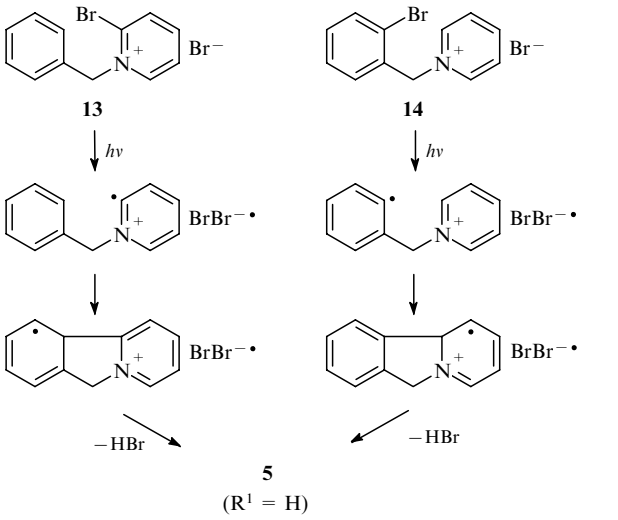


Hal = Cl, Br; R^1, R^2 = H, Me, Cl, Br.

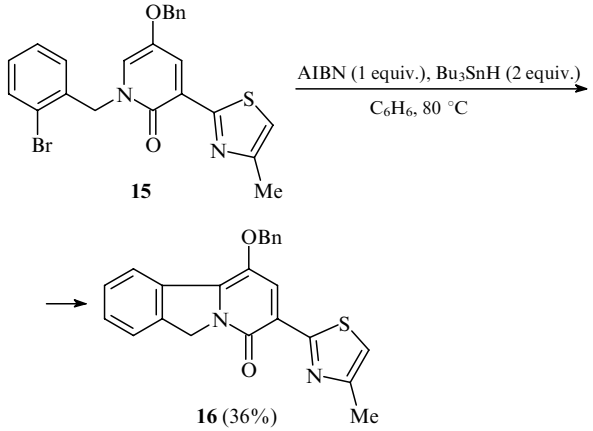
Later, this method was extended to substituted pyridinium salts.[13, 14] The best yields of reaction products were obtained upon monochromatic irradiation of the substrate at the absorption wavelengths of the starting salt (~260–280 nm).[14] It was found that *N*-benzyl-2-halogenopyridinium salts **13** are more reactive than their isomers **14**. The effects of the substituents in the benzene and pyridine rings on the reaction rates and product yields have been investigated. No photocyclisation takes place, if the benzene ring of the starting salt contains a nitro group [12] or if alcohols, *e.g.*, methanol or ethanol, are used as solvents.[14]

The intermediates and products of laser-induced flash photolysis (a laser pulse at 266 nm) of the isomers **13** and **14** have been studied [15] and the following reaction mechanism has been proposed: the initial photohomolytic cleavage of the C–Hal bond is followed by radical arylation and proton elimination (Scheme 1).

Scheme 1

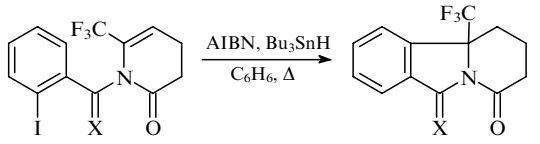


A method for the preparation of pyridoisoindoles by radical cyclisation of the corresponding *N*-(*o*-bromobenzyl)pyridone derivatives in the presence of an initiator has been developed.[16] Thus treatment of aryl bromide **15** with azobisisobutyronitrile (AIBN) and Bu_3SnH (benzene, 80 °C) results in the generation of an aryl radical which is intramolecularly attached to the pyridone ring at position 6. Retention of the double bond in compound **16** is interpreted as spontaneous oxidation of the intermediate radical addition product. This reaction occurs through a non-chain mechanism, so the initiator is used in an equimolar amount.



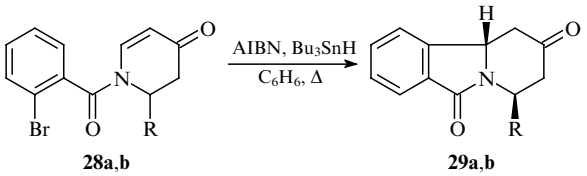
Hydrogenated pyrido[2,1-*a*]isoindoles are formed similarly from tetrahydro- and dihydropyridine derivatives containing a 5,6-double bond. Thus starting from *N*-(*o*-halobenzyl)pyridines **17** compounds **18** are formed under radical initiation conditions, whereas derivatives **19** (R = H) give rise to the isomers **20** and **21** in total yields 34% – 52%.[17] In these reactions, reductive debromination affords compounds **22** and **23** as side products (Scheme 2).

N-(*o*-Iodobenzyl and *o*-iodobenzoyl)-3,4-dihydro-2-pyridones (**24** and **25**, respectively) also undergo cyclisation under the action of the system Bu_3SnH – AIBN.[18] This reaction requires catalytic amounts of the initiator; the reaction time increases to 8 – 10 h, and the corresponding products **26** and **27** are formed in high yields.



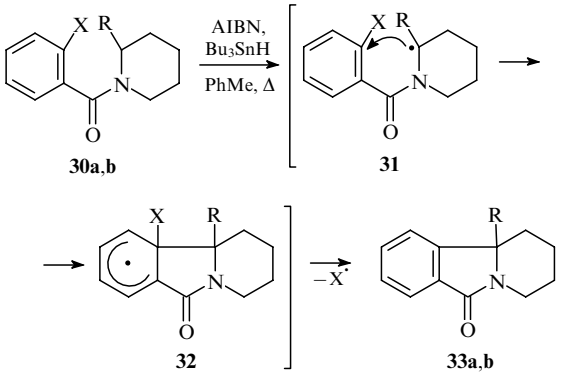
X = 2 H (**24**, **26**); O (**25**, **27**).

The radical cyclisation of 2-substituted 2,3-dihydro-4-pyridones **28** containing an *o*-bromobenzoyl group at the nitrogen atom occurs in good yields and with high diastereoselectivities. The pyridonoisoindolinones **29** formed were isolated as *trans*-isomers with a pseudo-axial position of the substituent R. The stereochemistry of the derivative **29a** was confirmed by data from X-ray diffraction analysis.[19]



R = Ph (**a**, 91%), Me (**b**, 86%).

In contrast to the previous examples, *N*-benzoylpiperidines **30** do not contain a double bond as the site for the addition of a phenyl radical. However, these substrates can eliminate the hydrogen atom from the α-position to the nitrogen atom with a subsequent attack of the benzene ring. Such products were isolated from the reaction mixture upon radical cyclisation of compounds **30** under the action of the system AIBN – Bu_3SnH.[20] A stepwise formation of two radical intermediates, **31** and **32**, eventually resulting in the pyridoisoindole derivatives **33** was suggested.

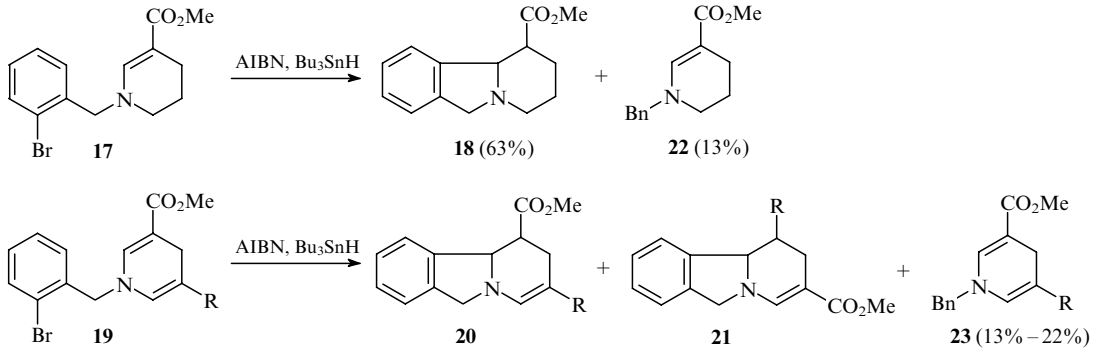


X = H, R = All (**a**, 10%); X = I, R = $CH_2C{\equiv}CSiMe_3$ (**b**, 18%).

This approach was used in the synthesis of a series of pyrido[1,2-*a*]isoindoles containing various functional groups in the pyridine ring.[21]

Intramolecular cyclisation of organometallic intermediates. The Heck intramolecular cyclisation is the most popular reaction of this type. Cyclisation of arylpalladium intermediates involving the double bonds of the tetrahydropyridine ring is the key step of this reaction. An unsuccessful attempt at cyclisation of substituted aryl bromide **15** under conditions of the Heck reaction has been described.[16] The use of the system $Pd(OAc)_2$ – PPh_3 – K_2CO_3 –

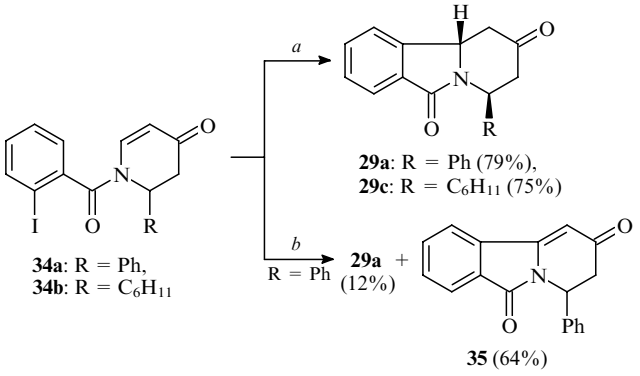
Scheme 2



R = H, CO_2Me.

Et_4NCl led only to the reduction and decomposition of the substrate.

However, the intramolecular cyclisation using arylpalladium reagents was successfully applied to *N*-acyltetrahydropyridones **34** (see Refs 22 and 23).

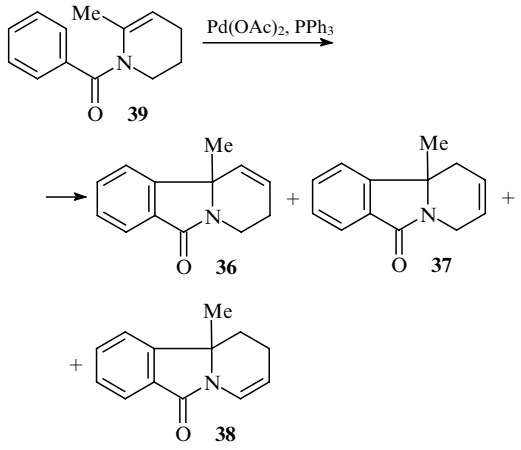


(*a*) $(Ph_3P)_2Pd(OAc)_2$, HCO_2H, Et_3N, DMF, 80 °C;

(*b*) $(Ph_3P)_2Pd(OAc)_2$, Bu_4NBr, NaOAc, molecular sieves 4 Å, DMF, 80 °C.

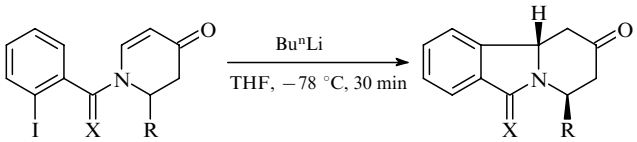
In the presence of formic acid (conditions *a*), this reaction occurs regio- and stereoselectively and yields only the *trans*-diastereomer **29** as in the case of the radical cyclisation of this substrate.[19] In the absence of a proton source (conditions *b*), the dehydrogenated derivative **35** is the main product. The carbonyl group of the amide bond is essential in this reaction; in its absence, only the dehalogenation of the substrate takes place.[22]

The competitive formation of three isomeric tetrahydropyrido[2,1-*a*]isoindolones **36**–**38** is observed in the intramolecular cyclisation of *N*-(*o*-iodobenzoyl)-2-methyltetrahydropyridine **39** *via* arylpalladium complexes. However, by varying reaction conditions one can change the ratio of the reaction products and even make this process regiospecific.[24, 25]



Conditions	*T* /°C	Time	Yield (%)	Selectivity (%)			Ref.
				36	**37**	**38**	
MeCN	–	–	–	39	34	27	24
K_2CO_3, Et_4NCl, DMF	30	2 h	72	68	32	–	25
TlOAc, MeCN	80	4 days	65	100	–	–	24

The cyclisation mechanism of 2-substituted *N*-(2-lithiobenzoyl- and 2-lithiobenzyl)-2,3-dihydro-4-pyridones formed upon treatment of substituted pyridones **34** and **40**, respectively, with butyllithium is similar to that of the Heck reaction. Rapid substitution of lithium for the halogen is followed by intramolecular nucleophilic addition.[26] This reaction is characterised by a high degree of stereoselectivity (compounds **29** and **41** were isolated as *trans*-isomers) and has found sufficiently broad synthetic application.

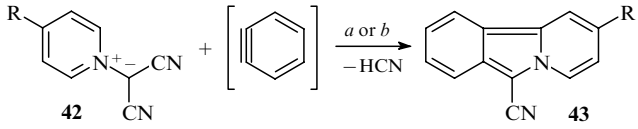


X = O (**29**, **34**); 2 H (**40**, **41**).

Compound	X	R	Yield (%)
29	O	Ph	91
	O	C_6H_{11}	86
	O	$CH_2=CH$	89
	O	$CH\equiv C$	88
	O	$C_4H_9C\equiv C$	86
41	2 H	H	50

c. Closure of the pyrrole ring with simultaneous formation of the C(5) – C(6) and C(10a) – C (10b) bonds

Heterocyclisation involving dehydrobenzene is an approach to the construction of the azinoisoindole system. 1,3-Dipolar addition of 4-substituted pyridinium dicyanomethylides **42** to dehydrobenzene results in 2-R-6-cyanopyrido[2,1-*a*]isoindoles **43** in moderate yields.[27–30] Dehydrobenzene can be generated by pyrolysis of diphenyliodonium-2-carboxylate or reaction of anthranilic acid with isoamyl nitrite. The derivatives **43** formed can themselves be used as 1,3-dipolar reagents (see Section IV.1.c). 6-Cyanopyrazino[2,1-*a*]isoindole is prepared from pyrazinium dicyanomethylide in a similar way, whereas pyrimidinium dicyanomethylide does not generate the corresponding heterocycles under these conditions.



R = H, Me, Ph, COPh, COMe, CO_2Me;

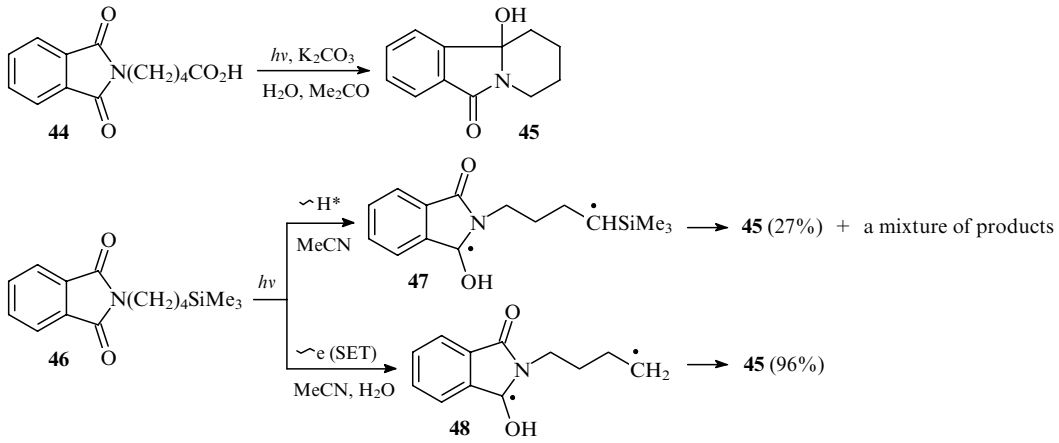
(*a*) 190–200 °C; (*b*) chloroform – acetone, Δ.

d. Closure of the pyridine ring with formation of the C(1) – C(10b) bond

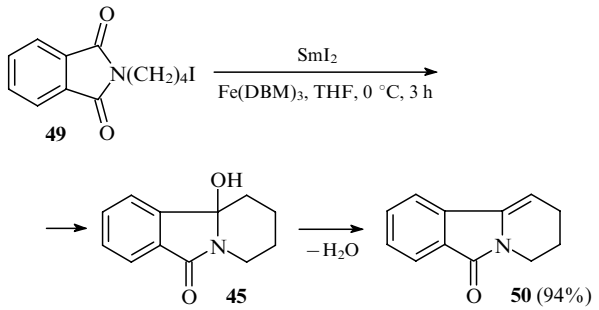
This methodology for the synthesis of a pyrido[2,1-*a*]isoindole structure is based on the use of *N*-substituted phthalimides and their analogues as the starting compounds. Two heterocyclisation principles are possible depending on the type of the intermediate formed.

Radical cyclisation. Several examples of cyclisations yielding saturated pyridoisoindoles are documented. Thus irradiation of the phthalimide derivative **44** results in photochemical triplet-sensitised decarboxylation. The intermediate biradical generated upon the electron transfer (the SET-mechanism) from the carboxylate anion to one of the carbonyl groups of the phthalimide eliminates CO_2 and undergoes cyclisation to give compound **45**.[31, 32] Irradiation of *N*-[4-(trimethylsilyl)butyl]phthalimide **46** in acetonitrile yields a mixture of products, since these conditions favour the simultaneous realisation of two mechanisms, *viz*., intramolecular abstraction of the hydrogen atom by the carbonyl group of phthalimide resulting in the formation of the biradical **47** followed by its subsequent conversions and cleavage of the trimethylsilyl group with a single-electron transfer resulting in the biradical **48**. If the reaction is carried out in an acetonitrile – water (35% of water) mixture, the second mechanism predominates and compound **45** is the only product (yield 94%) (Scheme 3).[33]

Scheme 3

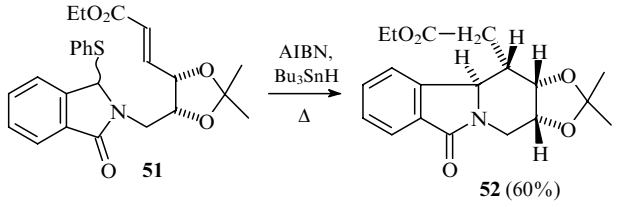


Cyclisation of the imide **49** under the action of SmI_2 (radical reduction) and subsequent spontaneous dehydration result in compound **50**.[34]

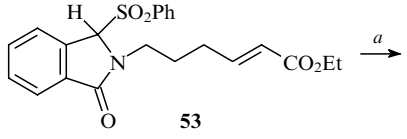


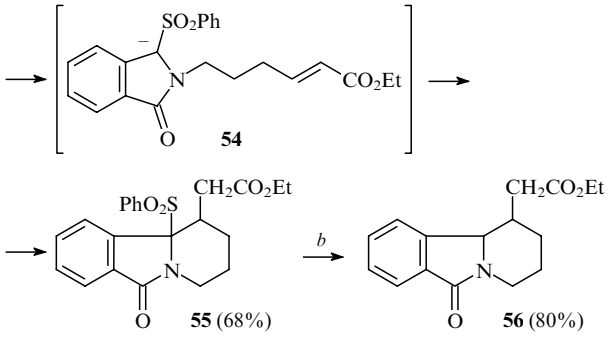
DBM is dibenzoylmethane.

Six-membered *exo*-cyclisation of the α-aminoacyl radical generated upon cleavage of the phenylthio group from phthalimidine **51** yields a functionalised saturated pyrido[2,1-*a*]isoindole derivative **52**.[35]



Cyclisation involving anionic intermediates. Among other reactions of formation of the pyridoisoindole system, this method is illustrated by the largest number of examples. Under the action of bases, substituted phthalimidine **53**, which is structurally close to the aforementioned derivative **51**, generates the α-aminoacyl-α-sulfoaryl anion **54**, which undergoes a Michael-type intramolecular addition to the double bond of the α,β-unsaturated ester substituent.[36] The tricyclic sulfone **55** is reduced to partially saturated isoindolone **56** upon treatment with Raney nickel.

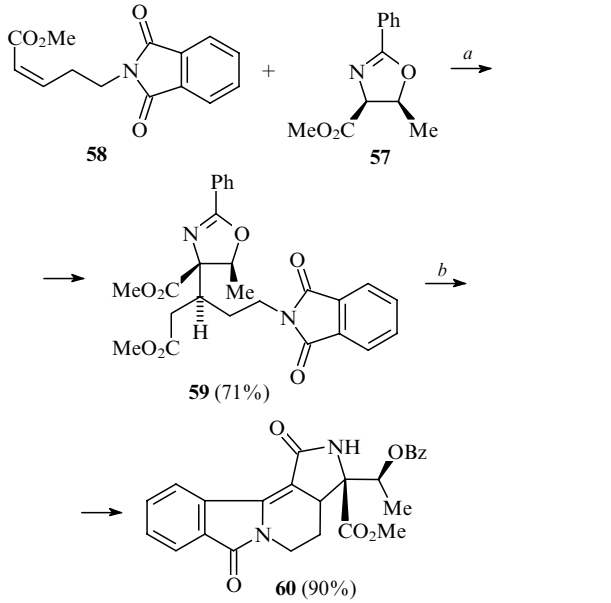




(*a*) NaH, DMSO, THF, 20 °C, 20 min;
(*b*) Ni/Re, EtOH, ultrasound, 5 min.

The formation of a nitrogen-containing tetracyclic system, which incorporates a pyridoisoindole fragment, was observed [37] in the recyclisation of the Michael addition products of a lithium derivative of the oxazoline **57** to α,β-unsaturated esters.

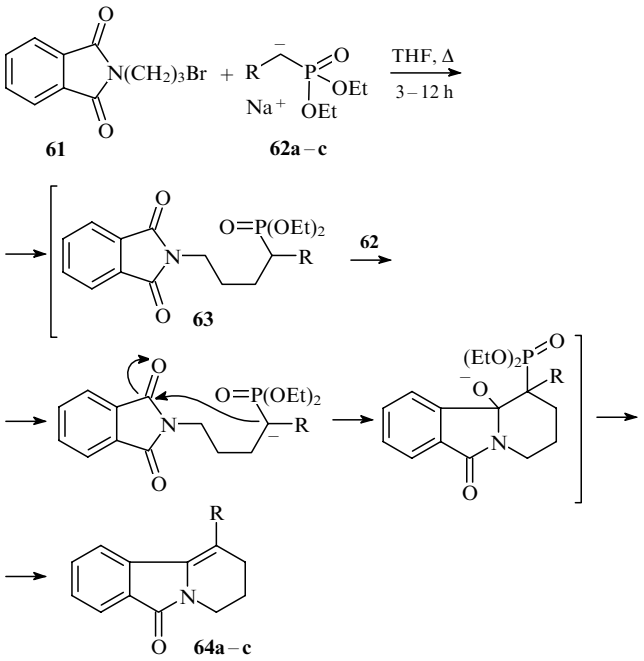
The adduct of the oxazoline anion to (*Z*)-ω-phthalimidopent-2-enoate **58**, *i.e.*, compound **59**, is converted into the tetracycle **60** in high yield under acidic conditions.[37]



(*a*) LDA, DME, −78 °C; (*b*) CF_3CO_2H, Na_2SO_4, H_2O, THF.

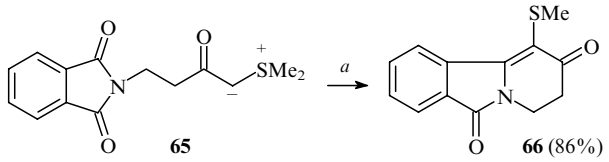
Studies of alkylation of *N*-(3-bromopropyl)phthalimide **61** under the action of an excess of the anions **62** have shown that the closure of the pyridine ring in the intermediate phosphonates **63**

formed occurs by the Horner – Wadsworth – Emmons reaction to yield the pyridoisoindole derivatives **64**.[38]



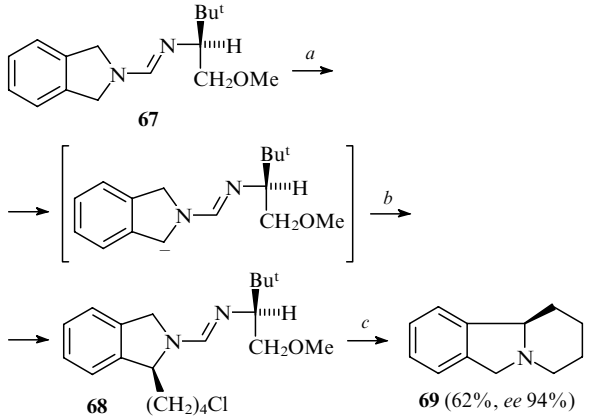
R = P(O)(OEt)$_2$ [**a** (78%)], CO_2Et [**b** (92%)], CN [**c** (95%)].

Closure of the C(1) – C(10b) bond of the pyridoisoindole system was also observed upon intramolecular cyclisation of ketone-stabilised sulfur ylides with a phthalimide substituent.[39–41] For example, cyclisation of the ylide **65** (prepared in four steps from β-alanine) in the presence of an equimolar amount of benzoic acid gave substituted pyrimidoisoindoledione **66**.[40]



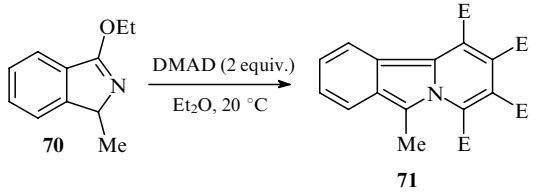
(*a*) $PhCO_2H$, PhMe, Δ.

Asymmetric mono-C-alkylation of chiral amidine **67** with 1,4-dichlorobutane gave compound **68**; the latter underwent easy intramolecular cyclisation to give an optically active hydrogenated pyridoisoindole **69** following hydrazinolysis.[42]



(*a*) Bu^{n}Li, THF, −78 °C; (*b*) $Cl(CH_2)_4Cl$, THF, −100 °C, 30 min; (*c*) N_2H_4, 20 °C, 5 – 10 min.

Pyridoisoindoles were also synthesised from substituted isoindole; in this case, the pyridine ring is 'made complete' using an addition reaction. Thus 3-ethoxy-1-methyl-1*H*-isoindole **70** reacts with dimethyl acetylenedicarboxylate (DMAD) (molar ratio 1 : 2) at room temperature to give 1,2,3,4-tetramethoxycarbonyl-6-methylpyrido[2,1-*a*]isoindole **71**.[43]

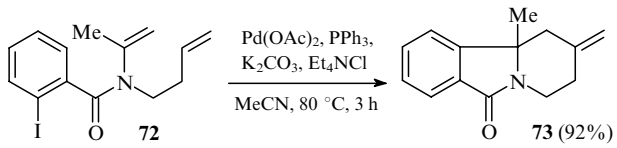


E = CO_2Me.

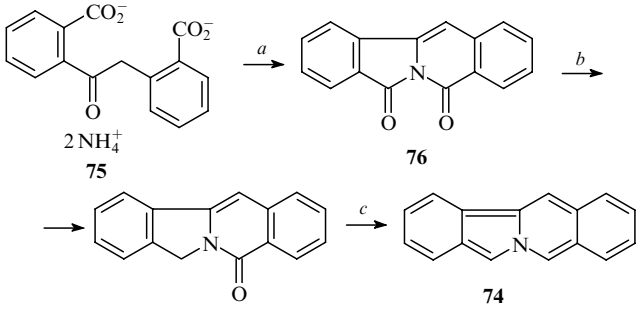
Hence, this method allows one to synthesise both saturated and aromatic pyridoisoindole derivatives.

e. Simultaneous closure of two rings

In this Section, we provide examples of several different approaches to the formation of a pyridoisoindole system. Thus aryl iodide **72** enters the so-called 'tandem' reaction with simultaneous closure of both heterocyclic rings, *viz*., pyrrole and pyridine, under conditions of the Heck reaction.[44] In terms of a hypothetical mechanism of such a double cyclisation, a palladium complex plays the role of a catalyst. Treatment of the starting iodide with palladium acetate in the presence of triphenylphosphine (2 equiv.) yields an arylpalladium intermediate where the palladium atom migrates from the aryl carbon atom to the alkyl carbon atom. This alkylpalladium complex contains no hydrogen atoms in the β-position with respect to the palladium atom which might be eliminated; therefore, it reacts with the second double bond present in the molecule. These conditions favour the transfer of the palladium atom to another alkyl carbon atom, its subsequent splitting as the initial palladium complex and formation of hydrogenated pyridoisoindolone **73**.

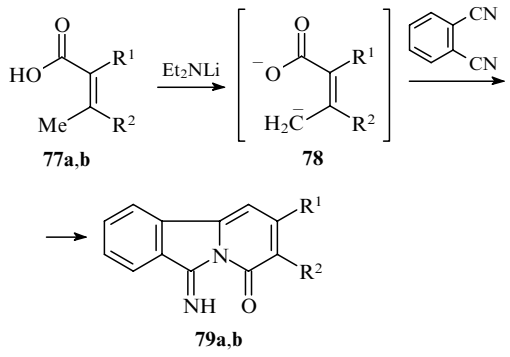


Synthesis of isoindolo[2,1-*b*]isoquinoline **74** where simultaneous formation of two heterocyclic rings also occurs has been described.[45] Heating of dry diammonium salt of 2,2′-dicarboxydeoxybenzoin **75** results in its cyclisation into 5,7-dihydroisoindolo[2,1-*b*]isoquinoline-5,7-dione **76**, which is reduced to the heteroaromatic system **74** in a two-step reaction.



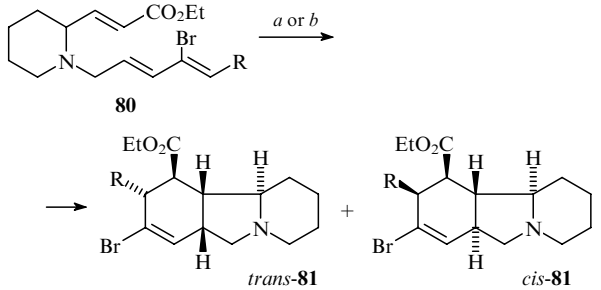
(*a*) Ph_2NH, 240 °C; (*b*) Zn, HCl, AcOH; (*c*) $LiAlH_4$, Et_2O, Δ, 3 h.

Treatment of 2- or 3-methylcrotonic acid **77** with lithium diethylamide gives the dianions **78**; their reactions with phthalodinitrile result in 6-iminopyrido[2,1-*a*]isoindolones **79**.[46] The yields of the conversion products depend on the type of the unsaturated acid used.



R^1 = Me, R^2 = H (*E*) [**a** (9%)]; R^1 = H, R^2 = Me [**b** (39%)].

The intramolecular Diels–Alder reaction in the substrates **80** also afforded partially saturated pyridoisoindoles. The starting molecule contains a piperidine ring, while the pyrrole and aliphatic rings are being constructed. The decahydropyrido-[2,1-*a*]isoindole structure is formed in a quantitative yield as a mixture of two diastereomeric pairs **81** (*cis*- and *trans*-isomers, the latter being predominant). This reaction occurs quantitatively both upon heating and under the action of a catalyst ($TiCl_4$).[47,48]



R = Me, Pr^i;

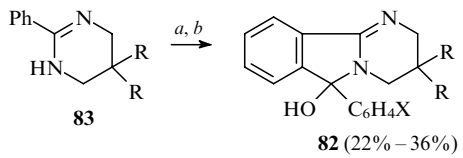
(*a*) PhMe, Ar, 100–150 °C, 16.5 h; (*b*) $TiCl_4$, CH_2Cl_2, 20 °C, 1 day.

2. Synthesis of pyrimido[2,1-*a*]isoindole derivatives

Systems containing fused isoindole and pyrimidine rings have received much less attention than pyrido[2,1-*a*]isoindoles. However, pyrimido[2,1-*a*]isoindole derivatives have recently been synthesised using both novel reactions and traditional approaches.

a. Closure of the pyrrole ring

Houlihan *et al.*[49] have performed synthesis of a series of 6-aryl-substituted 2,3,4,6-tetrahydropyrimido[2,1-*a*]isoindol-6-oles **82**. The *N*,*o*-dilithium derivatives prepared by treatment of 2-phenyl-1,4,5,6-tetrahydropyrimidines **83** with butyllithium reacted with methyl esters of halo-substituted benzoic acids. Compounds **82** represent structural analogues of the medicinal drug Mazindol (see Section V).



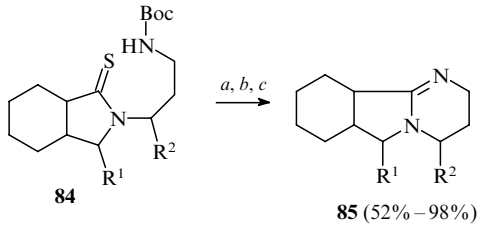
X = Cl, F; R = H, Me;

(*a*) Bu^nLi, THF, 50 °C, 3 h; (*b*) $XC_6H_4CO_2Me$, THF, 50 °C, 6 h.

Not only was this approach to the construction of the isoindole structure employed in the synthesis of annelated pyrimidine analogues, but it was also extended to imidazole and diazepine derivatives.[49]

b. Closure of the pyrimidine ring

Conventional cyclisation of thiolactams **84** into amidines[50] has recently been used for the synthesis of a series of the derivatives **85** containing a hydrogenated pyrimido[2,1-*a*]isoindole system with hydroxyalkyl substituents in positions 4 and/or 6.[51,52] This reaction includes several steps, *viz*., *S*-methylation of the starting thiolactam with methyl iodide to yield a methylthioimmonium salt, deprotection of the terminal amino group by treatment with trifluoroacetic acid and final spontaneous cyclisation into amidine **85** following deprotonation of the intermediate ammonium salt with a base.



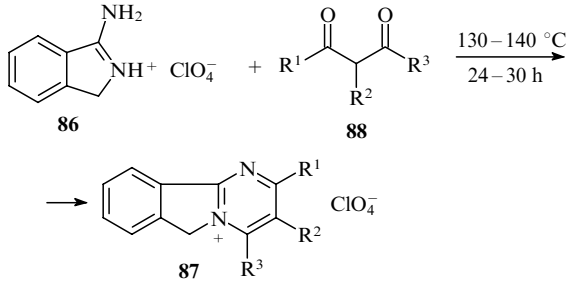
R^1 = R^2 = CH_2OH; R^2 = H: R^1 = $(CH_2)_2OH$, $CH_2CH(Ph)OH$;

(*a*) MeI, 20 °C, 17 h; (*b*) CF_3CO_2H, CH_2Cl_2, 0 °C;

(*c*) Et_3N or NaOH (solid), CH_2Cl_2, 0 °C, 2 h.

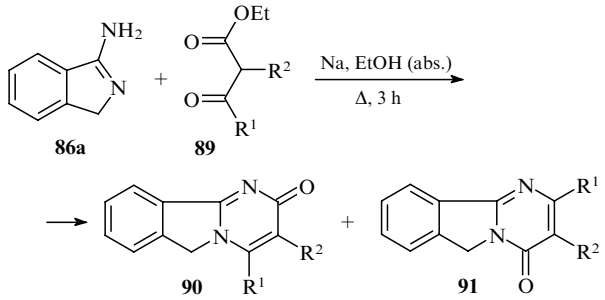
In the reactions of chiral starting thiolactams, enantiomerically pure hydroxyamidines **85** are formed, which proved to be very useful as catalysts in the asymmetric addition of nucleophiles to α,β-unsaturated ketones.

Cyclisation starting from 1-aminoisoindole. Construction of the pyrimidine ring fused to isoindole can also be performed starting from 1-aminoisoindole or its salts containing an N–C=N fragment. This methodology was initially applied to 1-aminoisoindolium perchlorate **86**. The pyrimido[2,1-*a*]isoindolium salts **87** substituted in the pyrimidine ring were prepared by its condensation with β-diketones **88**.[53,54]



R^1, R^2, R^3 = H, Me, Et.

The 1-aminoisoindole base reacts similarly with β-oxo esters **89** to give both 2-oxo (**90**) and 4-oxo isomers (**91**).[55,56] A detailed investigation into this reaction has made it possible to select the conditions for the isolation of each of the isomers. Thus it was found that the yield of 4-oxo derivatives increases with temperature.



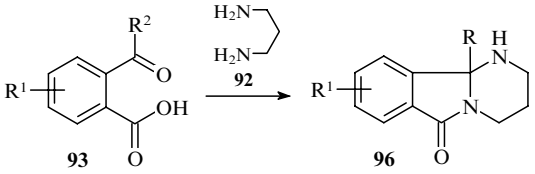
R^1–R^2 = $(CH_2)_n$; *n* = 3, 4.

c. Simultaneous closure of pyrrole and pyrimidine rings

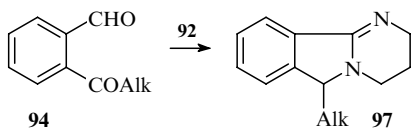
Condensation of *o*-acylbenzoic acids and related compounds with 1,3-diamino derivatives, which results in simultaneous closure of the pyrrole and pyrimidine rings, is the most efficient approach to the synthesis of the pyrimido[2,1-*a*]isoindole system and was

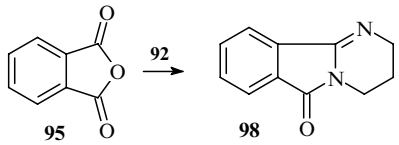
detailed in the monograph.[1] Here, the most typical examples of synthesis based on this approach are mentioned.

1,3-Diaminopropane **92** reacts with *o*-acylbenzoic acids **93**, *o*-acylbenzaldehydes **94** and phthalic anhydride **95** (but not with phthaloyl dichloride or phthalates[57]) to give hexahydropyrimido[2,1-*a*]isoindol-6-ones **96** or the tetrahydro derivatives **97** and **98**, respectively. This reaction usually occurs upon boiling of the reaction mixture in toluene or xylene with azeotropic distillation of water in the presence of catalytic amounts of toluene-*p*-sulfonic acid (for **93**, the yields exceed 60%).

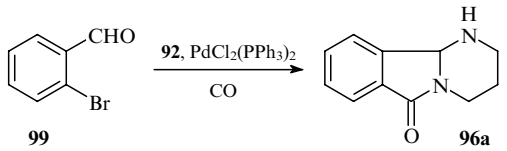


R^1 = H, Alk; R^2 = Alk, Ar.

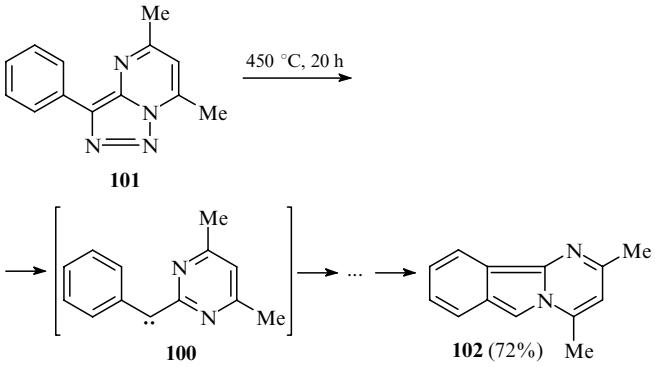




Carbonylation of 2-bromobenzaldehyde **99** with 1,3-diaminopropane **92** in the presence of a palladium catalyst also results in hexahydropyrimido[2,1-*a*]isoindol-6-ones.[58]

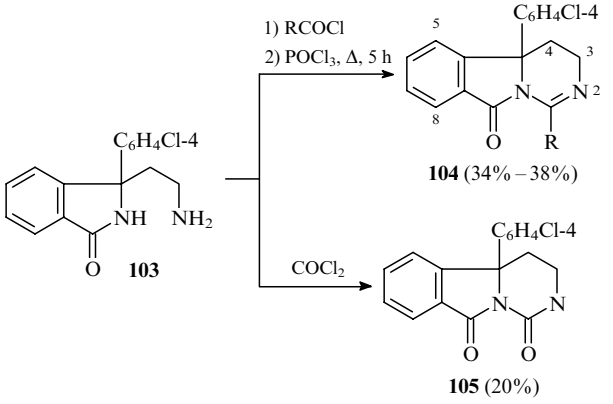


Heterocyclisation of carbene **100** formed upon gas-phase thermolysis of phenyltriazolo[1,5-*a*]pyrimidine **101** can also be related to this type. Pyrimido[2,1-*a*]isoindole **102** is the main reaction product.[59,60]



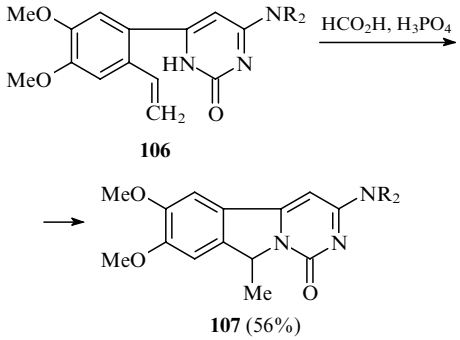
3. Synthesis of pyrimido[6,1-*a*]isoindole derivatives

The aromatic system of pyrimido[6,1-*a*]isoindole has not been synthesised so far; only a few examples of preparation of partially saturated derivatives of this heterocycle have been described. Thus cyclisation of diamides prepared by acylation of amine **103** leads to the closure of the azine ring of the pyrimido[6,1-*a*]isoindole **104**. Upon heating with phosgene, this amine forms compound **105**. The cyclic structure of the products **104** and **105** is confirmed by an upfield shift of a signal for the axial proton at the C(4) atom in the ^{1}H NMR spectra in comparison with the non-cyclic structure.[61]



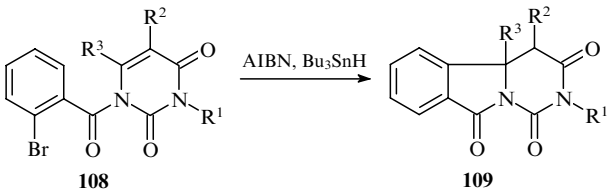
R = H, Me, 4-ClC_6H_4, CH_2Ph.

Treatment of pyrimidone **106** with formic and orthophosphoric acids results in the closure of the pyrrole ring and the formation of pyrimido[6,1-*a*]isoindole derivatives **107**.[62] Although the mechanism of this reaction has not been studied in detail, it can be assumed with a high degree of certainty that in acidic medium the arylmethyl carbocation, which is formed first, attacks either the carbon atom or the nitrogen atom of the enamine fragment. The direction of this reaction is determined by the presence, in the pyrimidine ring, of the *N*-methylpiperazine group which manifests electron-donating properties and induces strong activation of the nitrogen atom at position 1.



NR_2 is *N*-methylpiperazin-1-yl.

Treatment of the 1-(*o*-bromobenzoyl)pyrimidine derivatives **108** with Bu_3SnH or $(Me_3Si)_3SiH$ in the presence of catalytic amounts of AIBN afforded a series of tricyclic pyrimido[6,1-*a*]-isoindolinetriones **109** in good yields.[63] This synthetic approach is similar to the above-described radical heterocyclisation and allows the formation of the C(10a)–C(10b) bond and the closure of the pyrrole ring of hydrogenated pyrido[2,1-*a*]isoindolediones (see Section II.1.b).



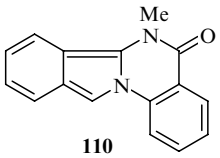
R^1	R^2	R^3	Yield (%)
Bu^s	Me	H	50
H	H	H	59
H	H	Me	80
H	H	CF_3	59

Thus, the choice of a synthetic procedure is determined by the structure of the desired azinoisoindolines.

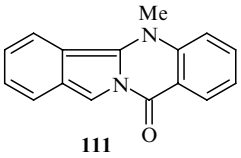
III. Electronic structures and spectral characteristics of aromatic azinoisoindoles

Quantum-chemical calculations of aromatic azinoisoindoles **1**–**3** have demonstrated that these compounds can be regarded as 14π-electron aromatic systems characterised by a high degree of internuclear conjugation and localisation of double bonds in both six-membered rings, *i.e.*, azine and benzene. The highest negative π-charge of the systems **1**–**3** is on the carbon atom 6 of the pyrrole ring and exceeds that on the nitrogen atoms.[5] These peculiarities of the electronic structure are responsible for the changes in the chemical properties of azinoisoindole compounds in comparison with isoindole itself.

It is of note that annelation of the quinazolone fragment to the side *a* of isoindole yields the corresponding isomeric 18π -electron isoindoloquinazolones **110** and **111**, which can be presented as two weakly interacting π-fragments, one of which represents the 10π-electron fragment of isoindole.



110

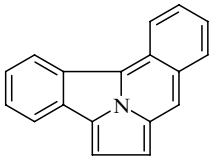


111

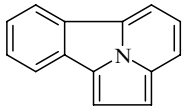
Consequently, their chemical behaviour should be similar to that of 1,2-disubstituted non-fused isoindoles.[5] The ability of isoindoloquinazolones to be involved in [4 + 2]cycloaddition reactions to give 1 : 1 adducts confirms this statement.

It is known that simple isoindoles behave as dienes in the Diels–Alder reaction involving the pyrrole ring.[1,2] Based on the results of quantum-chemical calculations, Kovtunenko *et al.*[64] attempted to predict the behaviour of various fused isoindoles in this reaction and in a competitive Michael addition in the α-position of the pyrrole ring. These calculations allowed one to suggest high activities of the compounds studied as dienes; the addition of dienophiles to all the azinoisoindoles under study (as in the case of isoindole) occurs most probably to the pyrrole diene fragment, *i.e.*, at positions 6 and 10b. The values of the static reactivity indices suggest that the activities of azinoisoindoles in both synchronous and non-synchronous cycloaddition reactions decrease in the following order: **110** = **111** > **1** > **3** > **2**.

No special studies of the spectral properties of azinoisoindoles have been carried out; however, the structures of all the derivatives synthesised were confirmed by ^{1}H NMR or, in some cases, ^{13}C NMR spectroscopy. Comparative data on the NMR spectra for six 2-R-6-cyanopyrido[2,1-*a*]isoindoles **43** are available.[29] Detailed assignment of signals in the ^{1}H and ^{13}C NMR spectra of benzo[1,2]pyrrolizino[3,4,5-*a*,*b*]isoquinolines (**112**)[65] and indolizino[3,4,5-*a*,*b*]isoindoles (**113**) was carried out based on the results of COSY, HMQC and HMBC experiments and the nuclear Overhauser effects.[66]

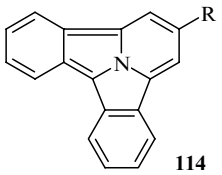


112



113

Matsumoto *et al.*[67] have measured the ESR spectra of the radical cations derived from benzo[*a*]isoindolo[1,2,3-*cd*]indolizine (1,2,3,4-dibenzocyclo[2,2,3]azine) **114** (R = H) upon its oxidation with $AgClO_4$ in dichloromethane at room temperature. It was found that despite high resonance stabilisation of the benzene rings these compounds containing a pyridoisoindole fragment as a structural element are related to the 18π-electron conjugated system.



114

R = H, D, Me, Ph, PhCO.

The redox potentials of the derivatives of compounds **114** have been studied.[68,69] It was shown that the presence of an electron-withdrawing substituent in this heteroaromatic system increases their oxidation potentials in comparison with the unsubstituted compound **114** (R = H), whereas the electron-donating and phenyl groups decrease it.

The mass-spectrometric behaviour of some fused isoindole derivatives has been described.[6] Studies of the fragmentation patterns of molecular ions of pyrido[2,1-*a*]- and pyrimido[2,1-*a*]-isoindoles suggest their aromaticity. The specific pathways of their fragmentation under electron impact have been studied.

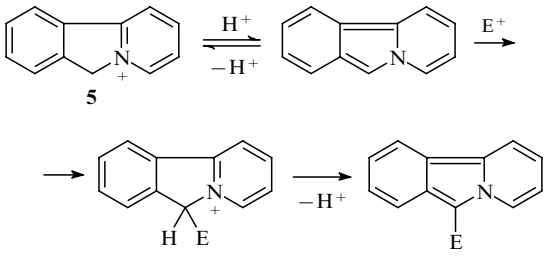
IV. Chemical properties

1. Reactions of pyrido[2,1-*a*]isoindoles

Like isoindole, aromatic pyrido[2,1-*a*]isoindoles demonstrate high reactivities. Reactions with electrophiles and addition of unsaturated compounds are the most characteristic for aromatic pyridoisoindoles.

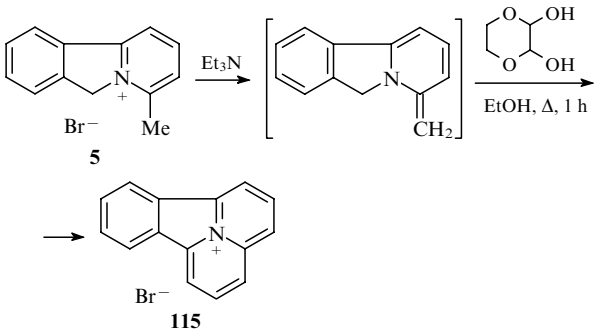
a. Reactions with electrophiles

Aromatic pyrido[2,1-*a*]isoindoles as such are unstable compounds, therefore, the stable 6*H*-protonated forms, *i.e.*, pyridoisoindolinium salts of the type **5**, are usually employed in reactions with electrophilic reagents. The electrophilic attack occurs at the most electron-excessive position 6 of the pyrrole ring. Examples of such reactions (acylation, arylation, diazotisation, *etc.*) are described in the monograph.[1]



5

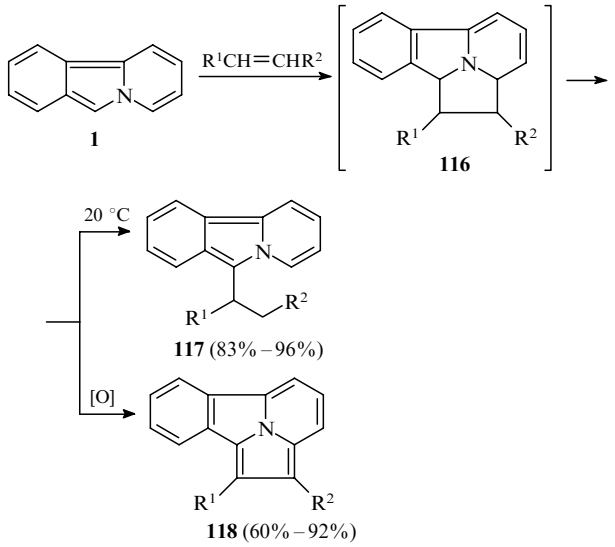
The reaction of 4-methylpyridoisoindolinium salt **5** (R^2 = 4-Me) with 2,3-dihydroxy-1,4-dioxane as the glyoxal synthon in ethanol in the presence of triethylamine (the molar ratio of the reagents is = 1 : 1 : 1), which yields compound **115** as a double condensation product at the side methyl group and at position 6 of pyridoisoindole,[9] can also be assigned to reactions of this kind. Apparently, the initial deprotonation involves the more CH-acidic methyl group.



115

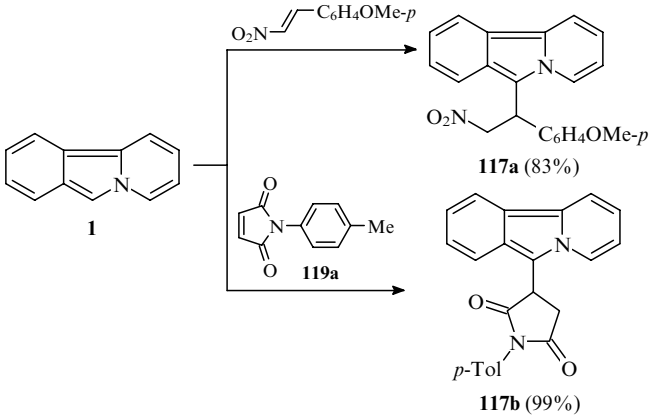
b. Addition of electron-deficient alkenes

The formation of the cyclic adducts **116** upon reactions of pyrido[2,1-*a*]isoindole **1** with compounds containing an activated double bond, *viz*., maleic, fumaric and acrylic esters and acrylonitrile, at 0 °C was established by ^{1}H NMR spectroscopy.[8] Spectral analysis revealed that the dienophile adds to the substrate at positions 4 and 6 in accordance with the [3 + 2](8π + 2π)-cycloaddition mechanism. These cycloadducts are extremely labile and at room temperature are gradually converted into the Michael adducts at position 6, *viz*., compounds **117**. Oxidation of the cycloadducts **116** with chloranil yields the indolizino[3,4,5-*ab*]-isoindole derivatives **118**.

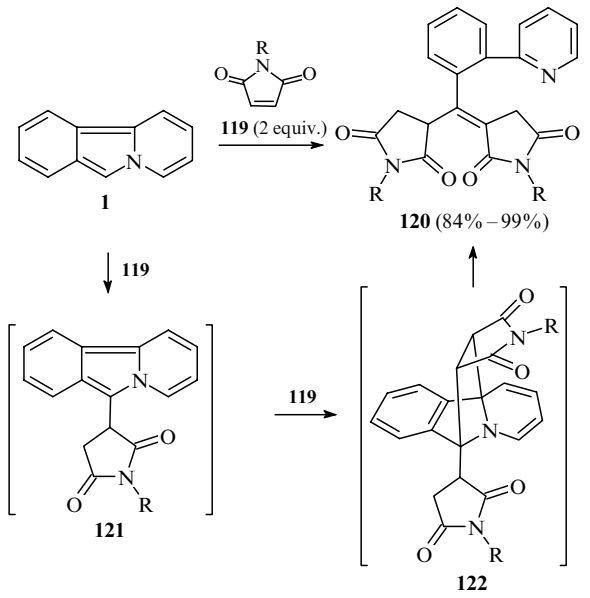


R^1 = H: R^2 = CN, CO_2Me; R^1 = R^2 = CO_2Me.

Unexpectedly, the reaction of pyrido[2,1-*a*]isoindole **1** with (*E*)-1-(4-methoxyphenyl)-2-nitroethene and *N*-(*p*-tolyl)maleimide (**119a**) at 0 °C gave directly the corresponding Michael adducts **117**. Thus, the cycloadducts represent kinetic products.[8]



Recently, it has been shown that the reaction of pyrido[2,1-*a*]-isoindole **1** with maleinimides (2 equiv.) under conditions of thermodynamic control (boiling in propan-2-ol) yields the 1 : 2 adducts **120**. Their structures were investigated by spectroscopic methods and X-ray diffraction analysis, which revealed that the reaction is quite unusual. The following mechanism has been proposed: after the formation of the Michael adduct at position 6 of one alkene molecule (**121**) (the latter is similar to compound **117b**), the second maleimide molecule is added at positions 6 and 10b (the Diels – Alder reaction). The 7-azanorbornene system in the intermediate **122** is very sterically strained due to simultaneous annelation of three rings. This leads to the rearrangement of the bonds, which is accompanied by opening of two rings, aromatisation of the pyridine fragment and formation of an exocyclic double bond.[70, 71] Such a rearrangement has been documented for neither simple isoindole systems nor for fused systems.

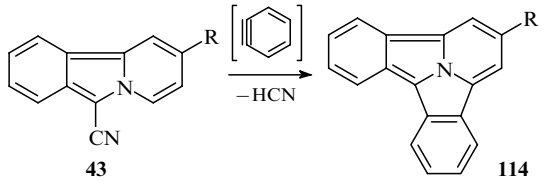


R = H, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, Bn, naphthyl.

The conversion products **120** present interest with regard to their stereochemistry. In the solid state, they have a 'twisted' double bond (the winding angle is equal to 7 – 10°), whereas in solution they represent a mixture of atropodiastereomers due to the presence of an asymmetric carbon atom and hindered rotation around the C – C bond between the exocyclic double bond and the 2-(α-pyridyl)phenylene fragment.[70] This phenomenon was studied in detail using ^{1}H NMR spectroscopy and the possibility of atropoisomerism in this type of compounds was confirmed by quantum-chemical calculations.[72]

c. Reactions with activated alkynes

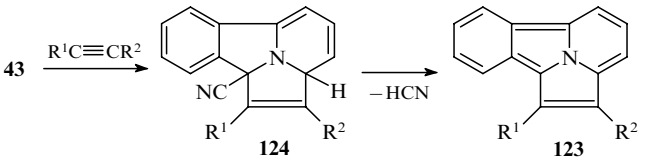
These reactions have already been mentioned in the section devoted to the synthesis of pyrido[2,1-*a*]isoindoles. Thus the preparation of 2-substituted 6-cyanopyrido[2,1-*a*]isoindoles using 1,3-dipolar addition of dehydrobenzene to 4-substituted pyridinium dicyanomethylides **42** is accompanied by the formation of benzo[*a*]isoindolo[1,2,3-*cd*]indolizines **114** as side products. Although the yields of the latter did not exceed 4% and no corresponding compounds were isolated in the case of R = CO_2Me, it is evident that 6-cyanopyrido[2,1-*a*]isoindole **43** was further coupled with dehydrobenzene with the elimination of HCN.[29, 30]



R = H, Me, Ph, PhCO, CO_2Me, MeCO.

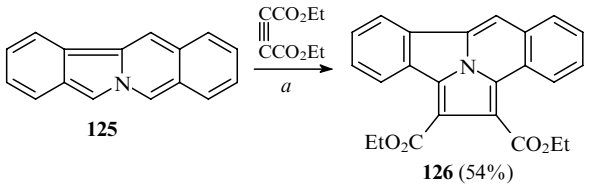
It is of interest that the change in the mode of generation of dehydrobenzene (the reaction of anthranilic acid with isoamyl nitrite was used instead of pyrolysis of diphenyliodonium-2-carboxylate) and the decrease in the reaction temperature increase the yield of the corresponding benzoyl derivative of benzo[*a*]-isoindolo[1,2,3-*cd*]indolizine **114** (R = PhCO) (up to 17%) without any significant changes in the yields of the products with other substituents.[30] If compounds **43** isolated in the individual state reacted with dehydrobenzene generated by pyrolysis of diphenyliodonium-2-carboxylate, the yields of the products **114** were 18% – 39%.

6-Cyanopyrido[2,1-*a*]isoindoles **43** as 1,3-dipolar agents also add alkynes activated by at least one electron-withdrawing group at positions 4 and 6.[27, 29, 73, 74] The yields of compounds **123** (sometimes, in a mixture with their precursors **124**) depend on the nature of the alkyne and reaction conditions; regioisomers **123** in various ratios are obtained from non-symmetrical alkynes.[74]



R^1, R^2 = H, COMe, COPh, CO_2Me, CO_2Bu^t, Ph, $SiMe_3$.

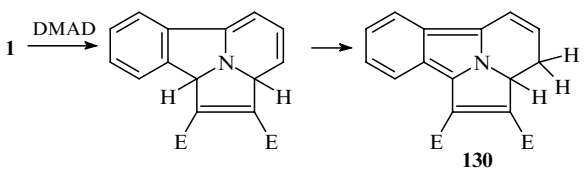
Numerous examples of reactions of fused pyridoisoindoles with dimethyl and diethyl acetylenedicarboxylates are documented. It was found[43] that isoquinolino[3,2-*a*]isoindole **125** reacts with diethyl acetylenedicarboxylate with the formation of benzoindolizino[3,4,5-*a*,*b*]isoindole **126**.



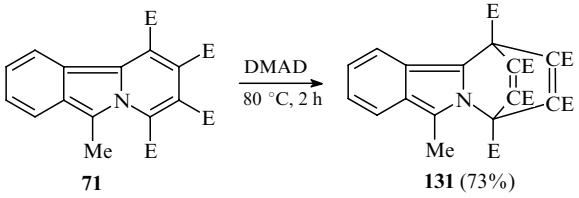
(*a*) 10% Pd/C, hydroquinone, PhMe, Δ, 14 h.

The data on the reaction of 6-cyanoisoindolo[1,2-*ab*]-isoquinoline **127** with dimethyl acetylenedicarboxylate are contradictory. Thus a product similar to the tetracycle **123** is formed in the presence of acetic acid (yield 26%),[75] whereas adducts with the composition 1 : 2 are formed in its absence (see Refs 73 and 75). The data on the structures of the latter are ambiguous. According to Matsumoto *et al.*,[73] they represent [5 + 2]-cycloaddition products which undergo further rearrangements into pyrroles **128** (3-cyanoindolizines react with DMAD in a similar way to yield pyrroles), whereas Tominaga *et al.*[75] prepared [3 + 2 + 2]-cycloadducts that underwent subsequent [1,5]-hydride shift, *i.e.*, compound **129** (an analogous reaction of 3-cyanoindolizine with DMAD has been described [73]) (Scheme 4).

Pyrido[2,1-*a*]isoindole itself reacts with DMAD involving positions 4 and 6, which is followed by a hydride shift.[8] Such structural conversion violates aromaticity of the benzene ring in favour of isoindole **130** with a quinoid structure containing a chain of conjugated double bonds.



In contrast to the above examples, 1,2,3,4-tetramethoxycarbonyl-6-methylpyrido[2,1-*a*]isoindole **71** (for the synthesis, see above) reacts with DMAD at positions 1 and 4 as a diene to give the adduct **131**.[43] This result is quite unexpected: it could not be predicted either on the basis of the general theoretical concepts of the Diels – Alder reaction (since the isoindole fragment possesses more pronounced donor properties than the pyridine one and geometrical considerations suggest that the triple bond is preferably added synchronously to the five-membered pyrrole ring) or on the basis of calculations of the reactivity indices of such derivatives.[64]

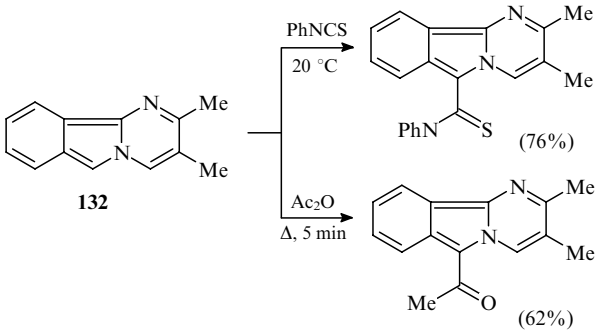


2. Chemical properties of pyrimido[2,1-*a*]isoindoles

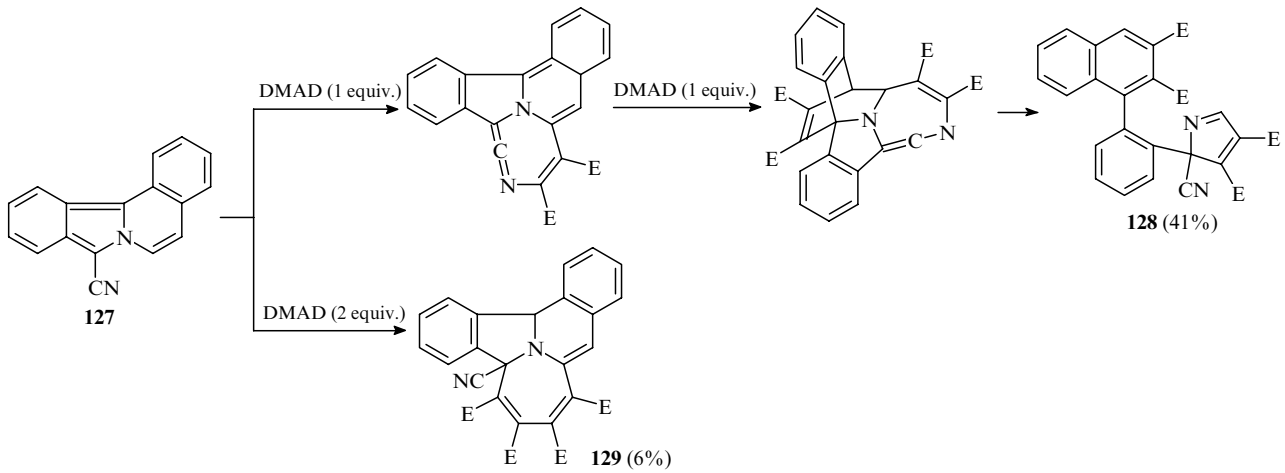
These systems are still insufficiently studied; nevertheless, reactions with pyrimidino[2,1-*a*]isoindoles or their fused derivatives as substrates can be found in the literature.

a. Reactions with electrophiles

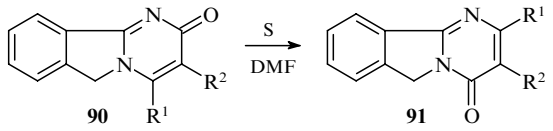
Electrophilic substitution of 2,4-dimethylpyrimido[2,1-*a*]isoindole **132** at position 6 occurs upon its treatment with phenyl isothiocyanate or acetic anhydride.[54]



Scheme 4



Rearrangement of pyrimido[2,1-*a*]isoindol-2-ones (**90**) into 4-isomers (**91**) was observed in 1985[76] and their properties including reactions with electrophilic reagents were studied. The rearrangement takes place upon heating of compounds **90** with sulfur in DMF. A similar reaction occurred upon heating with selenium; however, it was less efficient. The mechanism of this rearrangement has not been established yet.[77]



R^2 = H: R^1 = Me, Ph; R^1–R^2 = $(CH_2)_n$; n = 3, 4.

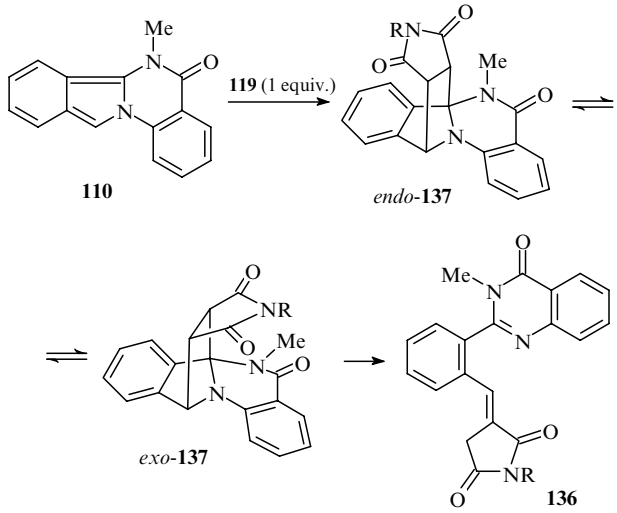
Presumably, in the initial step sulfur electrophilically attacks the position 6 of isoindole. The hemithioaminal formed undergoes recyclisation (*via* thioaldehyde) into an intermediate, which yields the isomer **91** following extrusion of sulfur.

Among other reactions with electrophiles, protonation and methylation of both isomers have been studied. According to IR spectroscopic data, compounds **90** are protonated at the oxygen atom in the formation of hydrobromides, while compounds **91** undergo protonation at the nitrogen atom at position 1. In reactions with dimethyl sulfate or methyl toluene-*p*-sulfonate, pyrimido[2,1-*a*]isoindol-4-ones **91** are methylated at the nitrogen atom at position 1. The structure of the methylation products of the 2-isomers depends on reaction temperature: at temperatures up to 100 °C, methylation occurs at the oxygen atom, whereas that at 130 °C occurs at the nitrogen atom at position 1 (see Ref. 78). Pyrimido[2,1-*a*]isoindol-2-ones **90** differ from the 4-isomers in having lower chromatographic mobilities and lower stretching vibration frequency of the C=O group in the IR spectra. Pyrimido[2,1-*a*]isoindol-4-ones **91** are characterised by a bathochromic shift in the UV spectra.[79] Other differences in physicochemical properties of these isomers have also been established.[79,80]

b. Reactions with activated unsaturated compounds

Recently, it has been found that reaction of 2,4-dimethylpyrimido[2,1-*a*]isoindole **133** with maleimides **119** yields a mixture of products (Scheme 5) from which benzo[*f*]isoindole derivatives **134** were isolated.[81,82] Their yields depended on the reaction conditions and the nature of the substituent in the imide fragment. A mechanism for the formation of these products was proposed in which extrusion of the bridging nitrogen atom from the intermediate Michael–Diels–Alder adducts **135** was the key step (see Scheme 5).

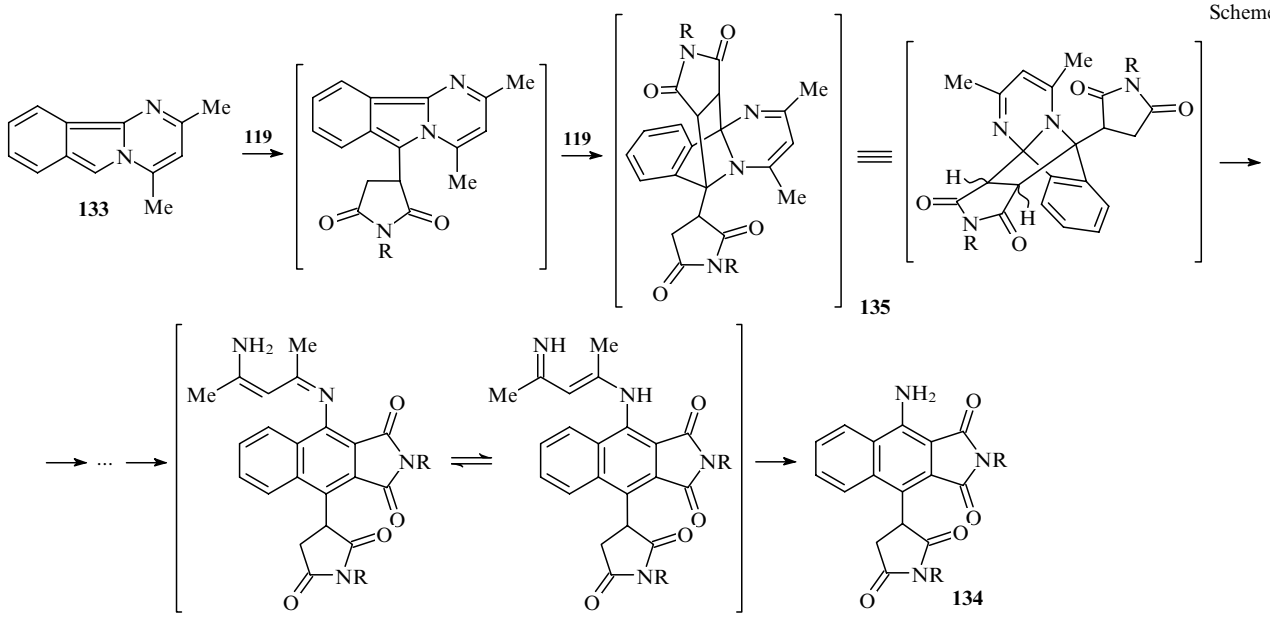
Interesting results were obtained in the study of reactions of isoindolo[2,1-*a*]quinazolin-5-ones **110** formally containing a pyrimido[2,1-*a*]isoindole fragment with maleimide derivatives. If the reagents are used at equimolar ratios, the rearranged adducts **136** are formed in high yields. This reaction occurs upon heating or brief boiling of the reactants in various solvents ($CHCl_3$, CH_2Cl_2, EtOH, Pr^iOH, PhMe). In order to establish the mechanism of this conversion under conditions of kinetic control, the intermediates **137**, which represent *endo*-Diels–Alder adducts, were isolated in the pure state. The conversion of the intermediate **137** into the final product **136** *via* the *exo*-isomer was confirmed by ^{1}H NMR spectroscopy.[83–85]



R = H, Bn, Ar.

With 2 equiv. of maleimide, the reaction under similar conditions follows another pathway: the Michael addition at the α-position of the pyrrole ring is the primary step, and the Michael adduct formed is involved in the Diels–Alder addition with the formation of stable tricyclic 7-azanorbornenes **138**. The structures of the products **136** and **138** were confirmed by X-ray diffraction analysis. No such rearrangement was observed for simple iso-

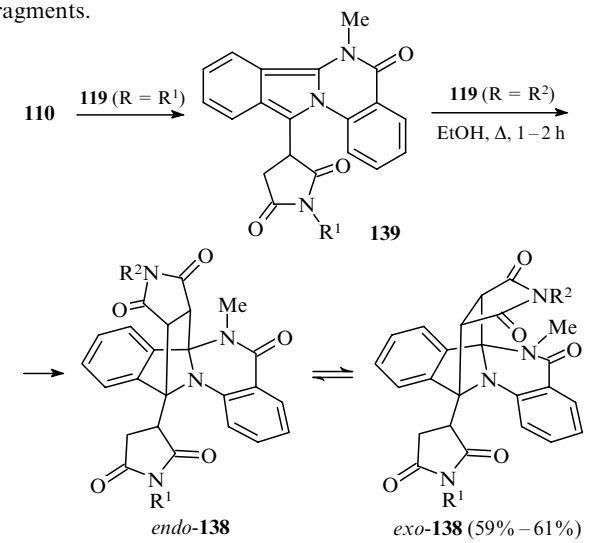
Scheme 5



R = H, 4-MeC_6H_4, 2-MeC_6H_4, 4-$MeOC_6H_4$, 1-naphthyl.

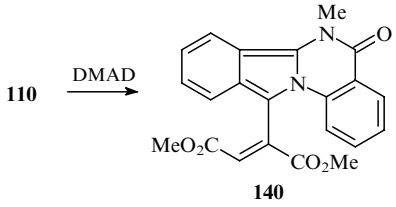
indoles (including fused ones). Compounds **138** appeared to be the first stable representatives of tricyclic 7-azanorbornene derivatives.

Compound **110b**, which represents the adduct of compound **110a** with maleimide, contains a succinimide fragment as a substituent R and can further react with maleimides. The adducts **138** or **139** formed may contain various substituents in the imide fragments.



R^1, R^2 = H, Bn, Ar.

The reaction of 6-methyl-5,6-dihydroisoindolo[2,1-*a*]quinazolin-5-one **110a** with DMAD affords the Michael adduct **140**.

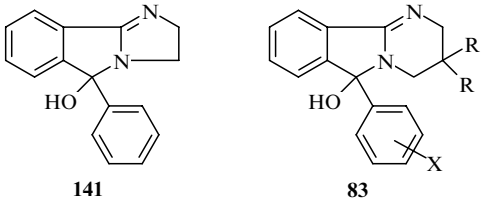


Studies of the chemical properties of various azinoisoindole compounds are under way.

V. Biological activity

Various isoindole derivatives have found application in many areas, particularly for production of polymeric materials possessing valuable properties or as biological markers and analytical reagents for chemistry and medicine. Numerous biologically active substances with a broad spectrum of activity have been found among compounds with the isoindole structure. Tricyclic isoindole derivatives (including azinoisoindoles) manifest antiviral, anti-inflammatory, analgesic and other physiological activities.[1]

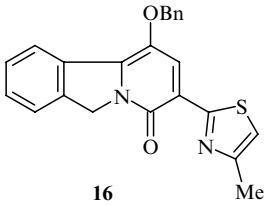
Various analogues of Mazindol **141** (a psychotropic drug recently introduced into clinical practice) have been extensively investigated in the past decade. They include a series of partially unsaturated azinoisoindoles **83**, which manifested high activity in neuronal tests.[49]



R = H: X = H, 2-F, 3-F, 4-F, 3-Cl, 4-Cl; R = Me, X = 4-Cl.

Compounds **83** inhibit the reverse capture of dopamine more efficiently than cocaine and Mazindol and by several orders of magnitude more selectively than serotonin.

Compound **16**, an analogue of known $GABA_A$ receptor agonists, was synthesised within the framework of a search for tricyclic non-sedative anxiolytic agents of the pyridine series.[21] This compound appeared to be efficient for both therapy and prophylaxis of CNS diseases.



Among other newly established biological properties of pyrimidoisoindoles, special mention can be made of the bactericidal activity of the fused derivative **140**.[86]

Other examples of practical applications of isoindole derivatives can be found in the monograph [1] and reviews.[2, 7]

* * *

It should be noted in conclusion that despite the sufficiently large number of examples of formation of the pyridoisoindole system published in the literature, the portion of direct syntheses of aromatic pyrido[2,1-*a*]isoindoles is extremely small. Deprotonation of the corresponding 6*H*-salts is still the main route to the synthesis of aromatic pyrido[2,1-*a*]isoindole derivatives. Pyrimido[2,1-*a*]isoindole and its derivatives are studied to an even lesser extent, while aromatic pyrimido[6,1-*a*]isoindole systems are presently unknown.

It thus appears that the azinoisoindoles considered above are insufficiently studied, although calculations and the recently described reactions with dienophiles demonstrate their high synthetic potential. Of particular interest is the possibility of a transition to various classes of organic compounds as a result of recently discovered rearrangements. The known reactions of azinoisoindoles with maleimides suggest their high reactivities in addition reactions occurring at position 6 of the pyrrole fragment.

Systematic synthetic, spectroscopic (including X-ray diffraction analysis) and biological studies into pyrido- and pyrimidoisoindole derivatives and the products of their diverse conversions represent a promising field of research in the chemistry of heterocyclic compounds.

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