Chemistry of Heterocyclic Compounds, Vol. 42, No. 8, 2006

METHODS FOR THE CONSTRUCTION OF [1,2]ISOINDOLO-CONDENSED BENZAZEPINES, BENZAZOCINES, QUINOLINES, AND ISOQUINOLINES. 2*. ISOINDOLOQUINOLINES, ISOINDOLO-ISOQUINOLINES. (REVIEW)

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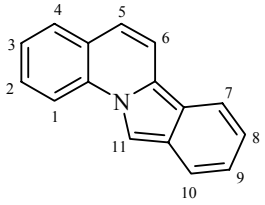
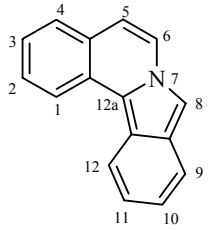
Data for 1966-2004 on methods for the construction of tetracyclic systems in which an isoindole ring is condensed with quinoline and isoquinoline fragments on the [1,2] side are reviewed. Methods and conditions for the synthesis of isoindoloquinolines and isoindoloisoquinolines are examined. Examples of the synthesis of physiologically active natural alkaloids possessing the structure of these condensed isoindoles are presented.

Keywords: alkaloids, isoindoloisoquinolines, isoindoloquinolines, synthesis methods.

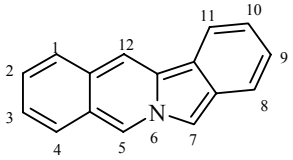
The formation of three condensed heterocyclic systems is theoretically possible during the fusion of isoindole and quinoline (isoquinoline) rings.



Isoindolo[2,1-*a*]quinoline



Isoindolo[1,2-*a*]isoquinoline



Isoindolo[2,1-*b*]isoquinoline

* For Part 1, see [70].

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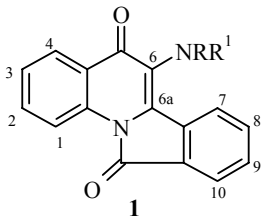
All the above-mentioned tetracycles except the last have been studied adequately in so far as the derivatives of isoindolo[2,1-*a*]quinolines and isoindolo[1,2-*a*]isoquinolines have a wide spectrum of biological activity while the isoindolo[1,2*a*]isoquinoline skeleton represents the framework of more than ten alkaloids (see section 2.1).

1. SYNTHESIS OF ISOINDOLO[2,1-*a*]QUINOLINES

The development of methods for the synthesis of various isoindolo[2,1-*a*]quinolines is of interest from the standpoint of both the pharmacology (antihypoxia products **1** [1], topoisomerase inhibitors **2**) and the synthesis of other heterocyclic structures of practical interest from them.



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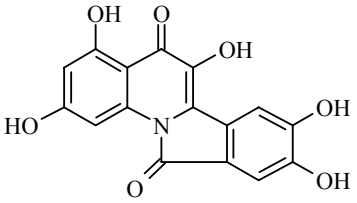


2

R, R^1 = Me, Et, Bn, Het

These tetracyclic systems can be constructed in two ways, i.e., by annelation of the quinoline fragment to the isoindole ring or, conversely, annelation of the isoindole to the quinoline. The first approach is used more widely on account of the greater accessibility of the isoindoles.

1.1. Synthesis of Isoindolo[2,1-*a*]quinolines from Substituted Isoindoles

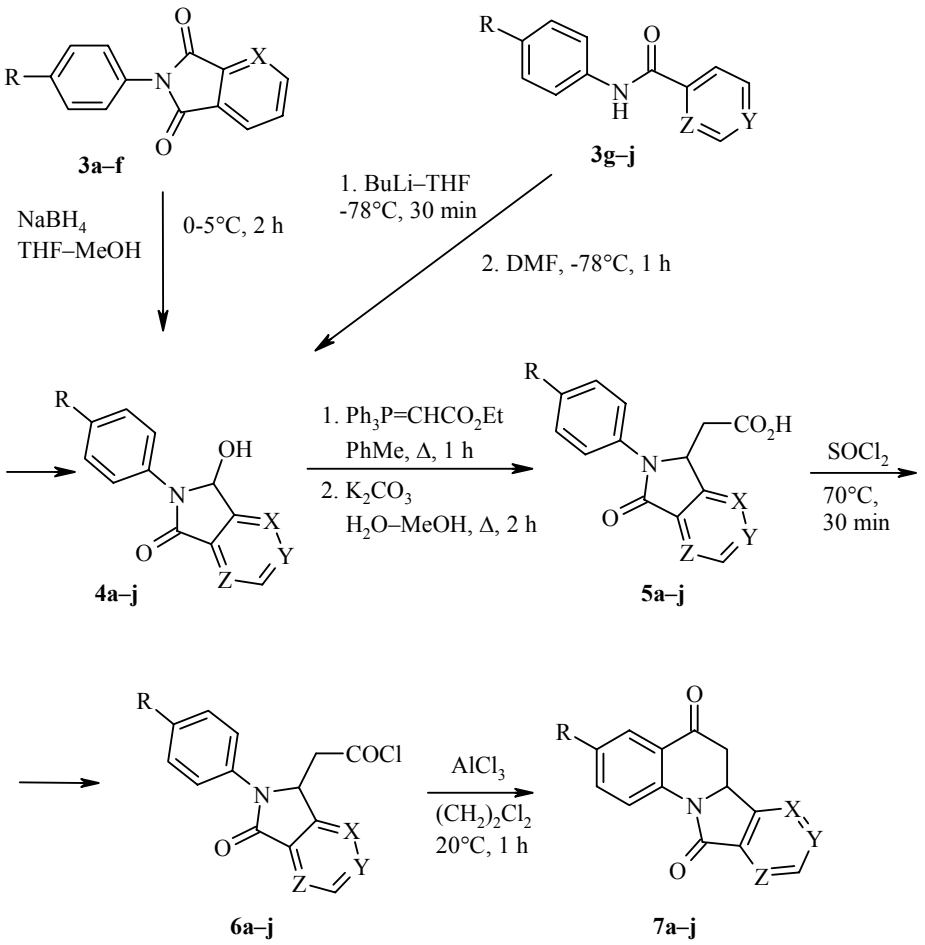
An intramolecular Friedel–Crafts reaction with 2-aryl-2,3-dihydro-3-oxo-1H-isoindolo-1-acetyl chlorides **6** leads to isoindolo[2,1-*a*]quinolines and their aza analogs **7** [1,3]. The starting compounds for the synthesis of the acetyl chlorides **6a-f** are N-arylphthalimides **3a-f**, which are converted into the required acid

TABLE 1. The Yields of Compounds **4-7**

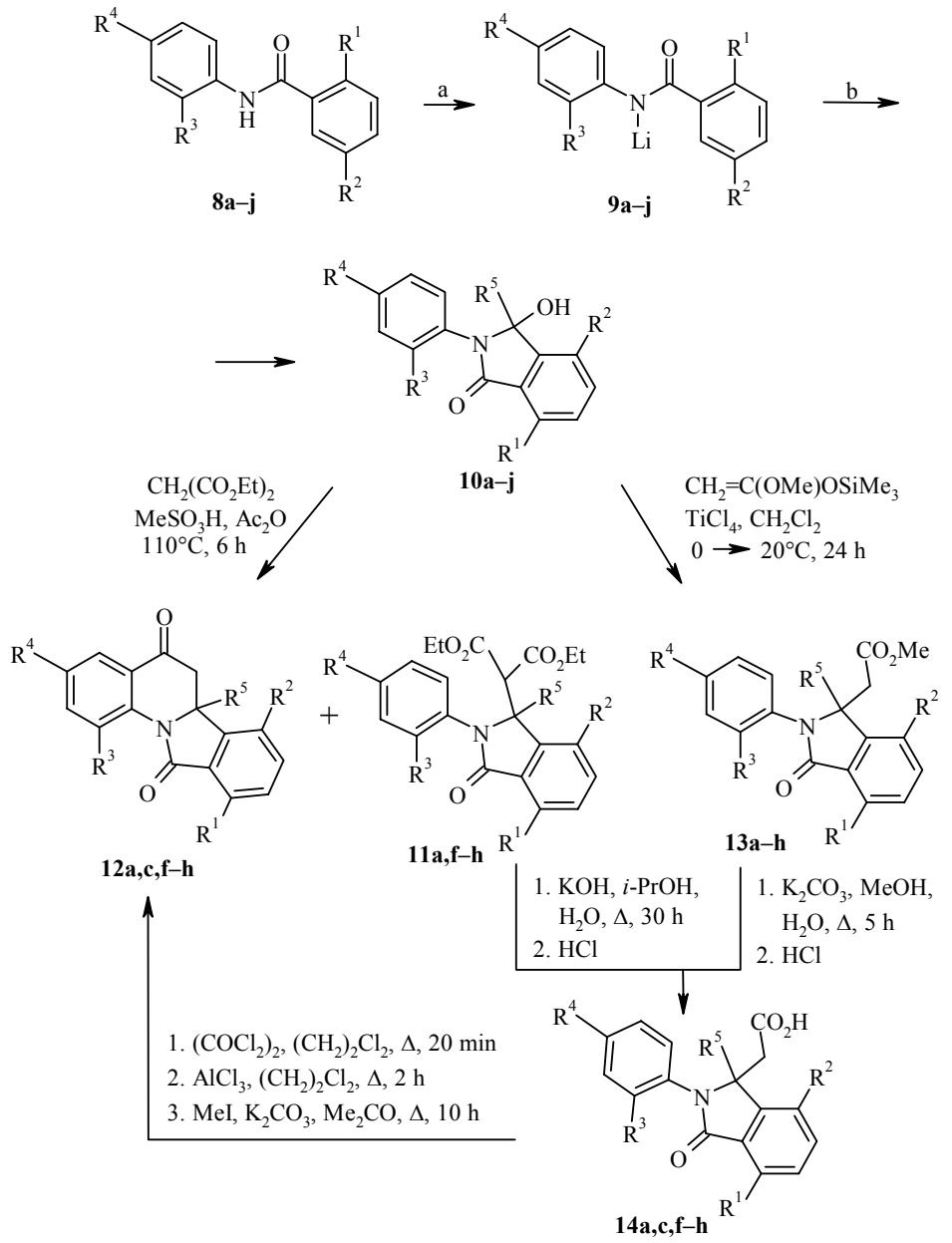
Compound **3-7**	Substitutents				Yield, %			
	R	X	Y	Z	**4**	**5**	**6***	**7**
a	H	C	C	C	90	71	87	95
b	F	C	C	C	86	75	97	97
c	Cl	C	C	C	94	70	99	96
d	Me	C	C	C	79	81	96	91
e	OMe	C	C	C	95	72	82	99
f	H	N	C	C	—	78		35
g	H	C	C	N	58	74		48
h	OMe	C	C	N	51	87		40
i	H	C	N	C	70	95		46
j	OMe	C	N	C	86	86		45

***** Compounds **6f-j** were not isolated in the individual form.

chlorides **6** by successive sodium borohydride reduction, the action of the Wittig reagent, and the action of thionyl chloride [1]. The starting compounds for the synthesis of the aza derivatives **6g-j** are picoline and isonicotine anilides **3g-j**, the reaction of which with butyllithium and DMF gives the intermediate 2-aryl-3-hydroxy-2,3-dihydroazaisoindol-1-ones **4g-j** [3].



Isoindolo[2,1-*a*]quinolines can be obtained in one stage from 2-aryl-3-hydroxyisoindol-1-ones **10** [4]. The initial isoindolones **10** are synthesized by the lithiation of benzanilides with butyllithium in THF followed by reaction of the obtained salts **9** with carbonyl compounds. In acetic anhydride in the presence of methanesulfonic acid the hydroxyisoindolinones **10a**,**f-h** ($R^5 \neq H$) react with diethyl malonate to form a mixture of isoindol-1-one 3-malonates **11** and dihydroisoindolo[2,1-*a*]quinoline-5,11-diones **12**. It was not possible to shift the reaction toward the preferential formation of the diones by increasing the reaction time. The reaction does not take place in the case of the isoindolones **10i**,**j** (R^5 = 4-nitrophenyl or 4-pyridyl) (Table 2). This is probably explained by the decrease in the stability of the intermediate N-acyliminium cations on account of the strong electron-withdrawing effect of the substituent R^5.



a) BuLi, THF, -78°C, 30 min or 0°C, 6 min; b) R^5X, THF, -78°C, 30 min → 20°C, 1 h

In reaction with diethyl malonate the isoindolones **10c**,**e** (R^5 = H) give mixtures of unidentified compounds. This prompted the search for other methods for the synthesis of the isoindoloquinolines **12**. The reaction of compounds **10** with 1-methoxy-1-trimethylsilyloxyethene in the presence of $TiCl_4$ leads to the formation of 3-carboxymethylphthalimides **13** with high yields.

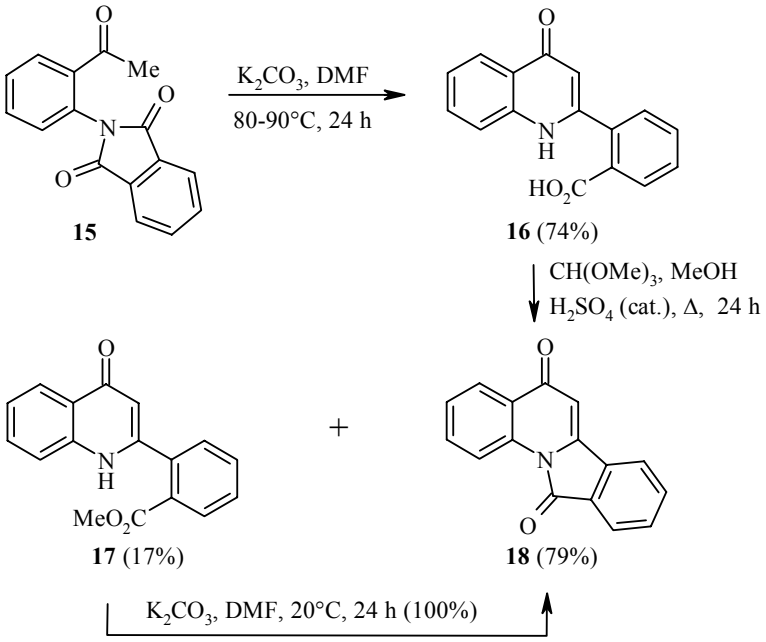
The decarboxylation of the malonates **11** or alkaline hydrolysis of the phthalimides **13** leads to the formation of 3-carboxymethylphthalimides **14** with quantitative yields. Treatment of the acids **14** with oxalyl chloride followed by electrophilic cyclization by the action of aluminum chloride gives the isoindolo[2,1-*a*]-quinolines **12**. The cyclization is accompanied by partial demethylation, but alkylation of the reaction mixture with methyl iodide at the last stage leads to the formation of the fully methylated derivatives **12**.

TABLE 2. The Yields of Compounds **11-14***

11-14	R^5	R^5X	Yield, %				
			11+**12** from **10**	**12** from **14**	**13**	**14** from **11**	**14** from **13**
a	Ph	$PhCO_2Me$	59+21	53	85	98	98
b	4-ClC_6H_4	4-$ClC_6H_4CO_2Me$	—	—	66	—	—
c	H	DMF	Resinification	42	60	—	97
d	4-ClC_6H_4	4-$ClC_6H_4CO_2Me$	—	—	60	—	—
e	H	DMF	Resinification	—	80	—	—
f	Ph	PhCOMe	52+28	94	85	97	97
g	4-ClC_6H_4	4-$ClC_6H_4CO_2Me$	49+26	88	60	94	94
h	Ph	$PhCO_2Me$	56+26	57	80	77	90
i	4-$O_2NC_6H_4$	4-$O_2NC_6H_4CO_2Me$	0	—	—	—	—
j	4-Py	4-$PyCONMe_2$	0	—	—	—	—

* **a-d** R^1 = H, **e-j** R^1 = OMe; **a**,**b**,**e-j** R^2 = H, **c**,**d** R^2 = OMe; **a**,**c-j** R^3 = H, **b** R^3 = Me; **a**,**h** R^4 = OMe, **b-g**,**i**,**j** R = H.

In 1997 [5] a method was proposed for the synthesis of isoindolo[2,1-*a*]quinolines based on the cyclization of *o*-amidoacetophenones **15** in an alkaline medium. A mixture of the quinolone **17** and isoindolo[2,1-*a*]quinoline **18** is formed in the reaction of quinolonecarboxylic acid **16** with orthoesther. The ester **17** is converted quantitatively into the required compound **18** when treated with potassium carbonate in DMF.



The initial ketone imide **15** was obtained by the reaction of *o*-bromoacetone with phthalimide (99%).

Later [2, 6, 7] attempts were made to modify the conditions for the cyclization of various N-(2-acetylaryl)phthalimides in order to optimize the yield of the required isoindolo[2,1-*a*]quinolines. Thus, the isoindolo[2,1-*a*]quinolines **23a-g** are formed when the substituted 2-aminoacetophenones **19a**,**b** and substituted phthalic anhydrides **20a-e** are boiled in xylene in the presence of a base [2]. The initial methoxyacetanilides **19** are obtained by the regiospecific acylation of the corresponding aromatic amines with methoxyacetonitrile (catalyst BCl_3).

In the case of phthalic anhydrides not containing strong electron-donating groups the isoindoloquinolines **23** are formed with good or satisfactory yields. In the case of the quinoline **23f** (R^1 = 2,4-$(OMe)_2$, R^2 = 8,9-$(OMe)_2$) the intermediate (the phthalimide **22**) was isolated, due probably to the low reactivity of its carbonyl groups. This imide was converted into the corresponding isoindoloquinoline **23f** by heating at 200°C in a Parr bomb. The isolation of the intermediate imide **22** indicates that the quinoline ring is formed at the last stage of cyclization. The yield of compound **23g** is substantially smaller than that of **23a**, due to the strong electron-withdrawing effect of the fluorine atom. In the case of the 3-*t*-butyl-substituted phthalic anhydride **20c** a mixture of two regioisomers **23c** and **23d** in approximately equal proportions is formed.

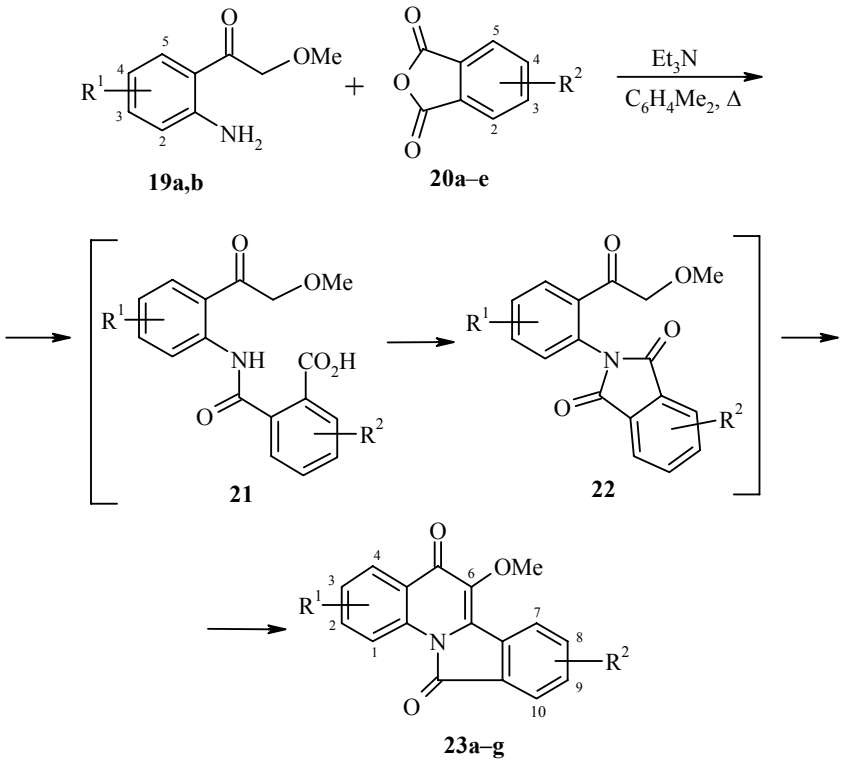
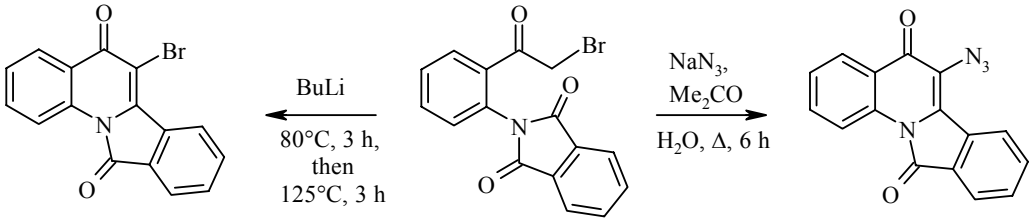


TABLE 3. The Yields of Compounds **23**

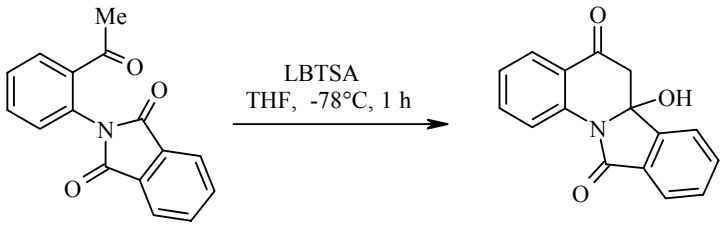
Initial compounds	Reaction product	R^1	R^2	Yield **23**, %
19a + 20a	**23a**	2,4-$(OMe)_2$	H	59
19a + 20b	**23b**	2,4-$(OMe)_2$	8,9-Cl_2	74
19a + 20c	**23c/23d**	2,4-$(OMe)_2$	9-*t*-Bu/8-*t*-Bu	21/16
19a + 20d	**23e**	2,4-$(OMe)_2$	8,9-Me_2	35
19a + 20e	**23f**	2,4-$(OMe)_2$	8,9-$(OMe)_2$	65
19b + 20a	**23g**	2,4-F_2	H	35

In 1997 *o*-phthalimidobromoacetophenone **24** was converted into the corresponding isoindolo[2,1-*a*]-quinolines **25a**,**b** by the action of butyllithium or sodium azide.



25a (72%) **24** **25b** (76%)

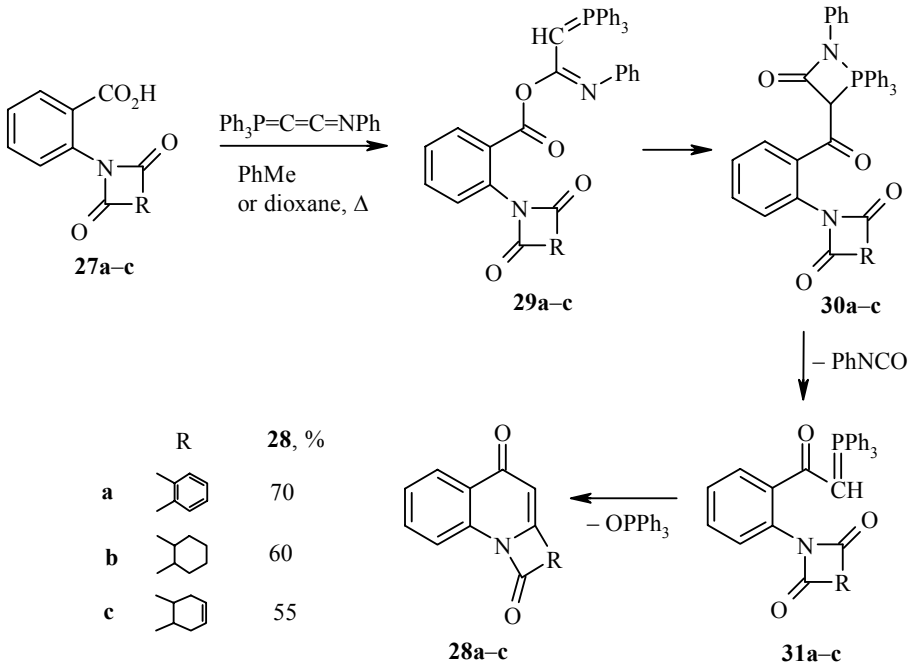
The intramolecular cyclization of *o*-phthalimidoacetophenone **15** takes place best in the presence of lithium bistrimethylsilylamide and leads to the formation of the required isoindolo[2,1-*a*]quinoline **26** with a yield close to quantitative [7].



15 **26** (90%)

LBTSA = lithium bistrimethylsilylamide

The reaction of the 2-imidobenzoic acids **27a-c** with N-phenyl(triphenylphosphoranylidene)ethene imine leads to the formation of the corresponding isoindolo[2,1-*a*]quinolines **28** [8]. The proposed mechanism of this transformation includes the addition of the carboxyl group of compound **27** at the C=C bond of the ylide with the formation of the O-acylimidate **29** and the elimination of phenyl isocyanate, leading to the acylphosphorane **31**, which then undergoes cyclization by the Wittig reaction to the isoindoloquinoline **28**.

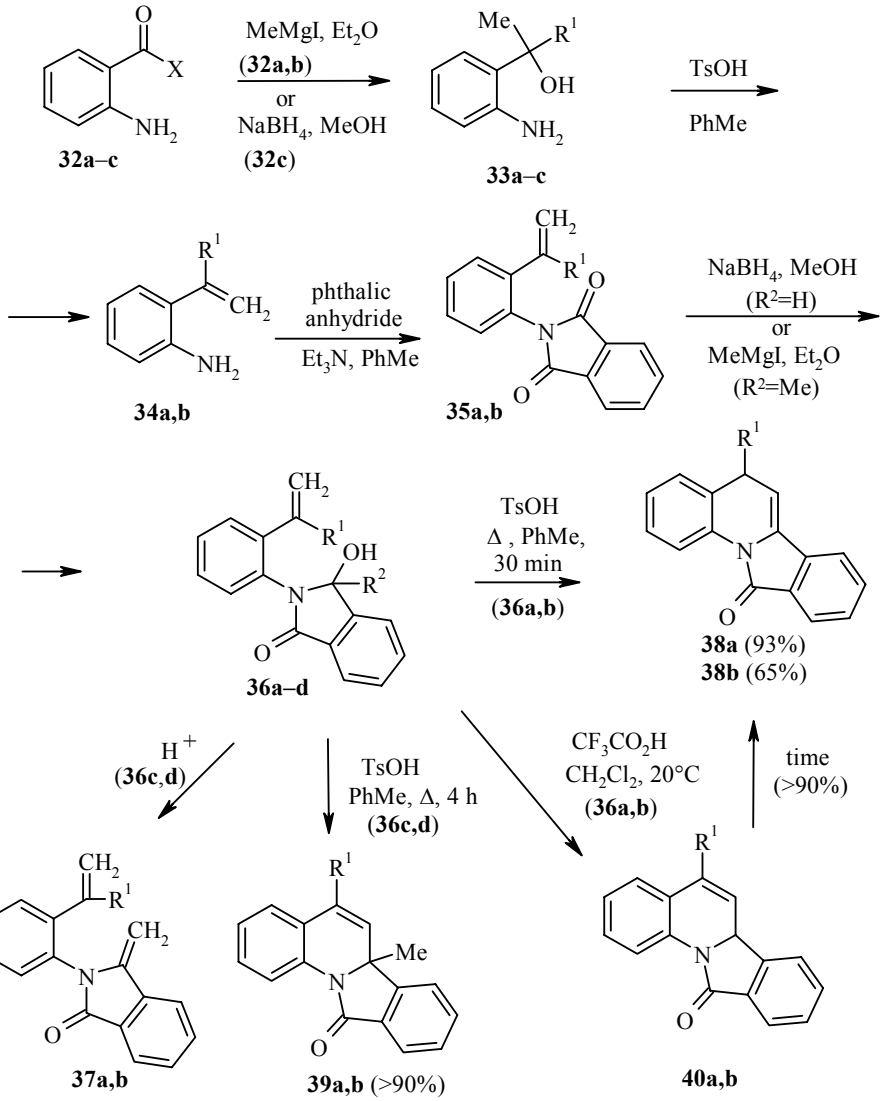


27a–c **29a–c** **30a–c** **31a–c** **28a–c**

	R	**28**, %
a		70
b		60
c		55

The initial imides **27** were synthesized from anthranilic acid and the respective anhydrides.

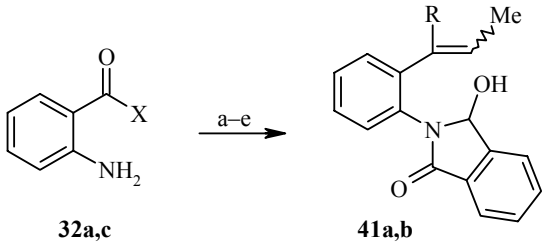
The key stage of a new method for the synthesis of isoindolo[2,1-*a*]quinolines from *o*-acetyl-substituted anilines [9, 10] is the formation of the N-acyliminium ion from the isoindole fragment of the molecule. According to this approach, the *o*-substituted anilines **32** are converted by the action of methylmagnesium iodide or sodium borohydride into the alcohols **53** with quantitative yields. Dehydration of the alcohols **33a**,**b** in the presence of TsOH in toluene leads to the aminostyrenes **34a**,**b**, the acylation of which with phthalic anhydride gives the phthalimides **35a**,**b**. Total resinification of the reaction mixture occurs during attempts at the dehydration of compound **33c**. The reaction of N-arylphthalimides **35a**,**b** with sodium borohydride or the Grignard reagent leads to the formation of the hydroxylactams **36a**,**b** (R^2 = H) or **36c**,**d** (R^2 = Me) respectively. They show high susceptibility to dehydration, and their partial transformation into the enamides **37a**,**b** (**36** + **37** > 95%) is observed even during treatment of the reaction mass. When boiled in toluene in the presence of TsOH the hydroxylactams **36** undergo cyclization to the isoindolo[2,1-*a*]quinolines **38a**,**b** or **39a**,**b** respectively.



32 a X = OEt, **b** X = Ph, **c** X = Me; **33 a** R^1 = Me, **b** R^1 = Ph, **c** R^1 = H;
34, 35, 37-40 a R^1 = Me, **b** R^1 = Ph; **36 a** R^1 = Me, R^2 = H; **b** R^1 = Ph, R^2 = H;
c R^1 = R^2 = Me; **d** R^1 = Ph, R^2 = Me

Cyclization of the alkenes **36a**,**b** by the action of dichloromethane at 20°C leads to the isoindoloquinolines **40a**,**b**, which in the course of time isomerize quantitatively to the corresponding enamides **38a**,**b**.

Replacement of methylmagnesium iodide by ethylmagnesium iodide leads to the formation of the hydroxylactams **41a**,**b**, which are analogs of the aminostyrenes **36**, as mixtures of the *Z*- and *E*-isomers [10].

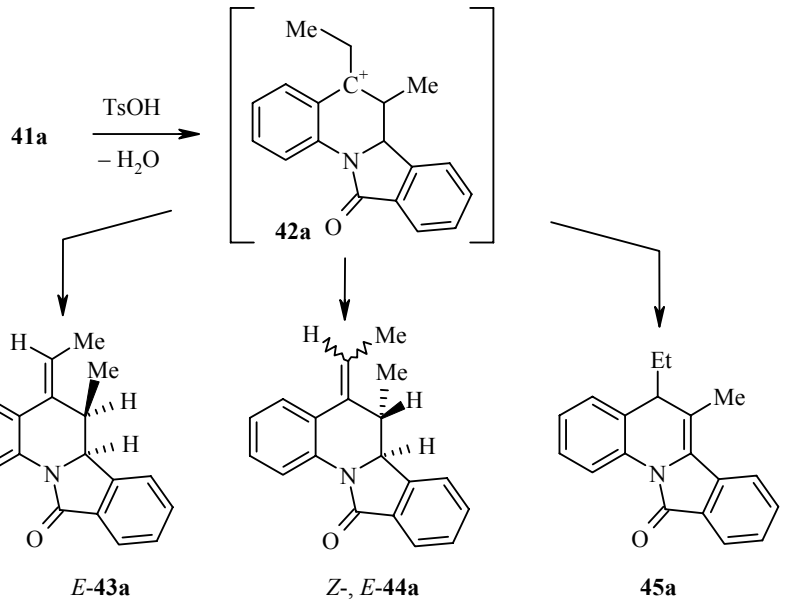


32a,c **41a,b**

a R = Et (88%), **b** R = Me (86%)

a) EtMgI, Et_2O, 20°C, 24 h; b) PhMe, H^+, Δ, 45 min; c) phthalic anhydride, NEt_3, PhMe, Δ, 48 h; d) PPA, PhMe, Δ, 48 h; e) $NaBH_4$, MeOH, 10°C

During the action of catalytic amounts of TsOH the hydroxylactam **41a** is converted after 40 min into a mixture of isoindoloquinolines **44a** (*Z*-, *E*-) and **43a** (*E*-) in ratios of 14:14:72 with an overall yield of 90%. Here trace quantities of compound **45a** were detected. If the reaction time is increased, the content of the **45a** isomer increases: After 10 days **45a** (21%), *E*-**43a** (57%), *E*-**44a** (11%), *Z*-**44a** (11%); after 25 days **45a** (42%), *E*-**43a** (48%), *E*-**44a** (5%), *Z*-**44a** (5%).

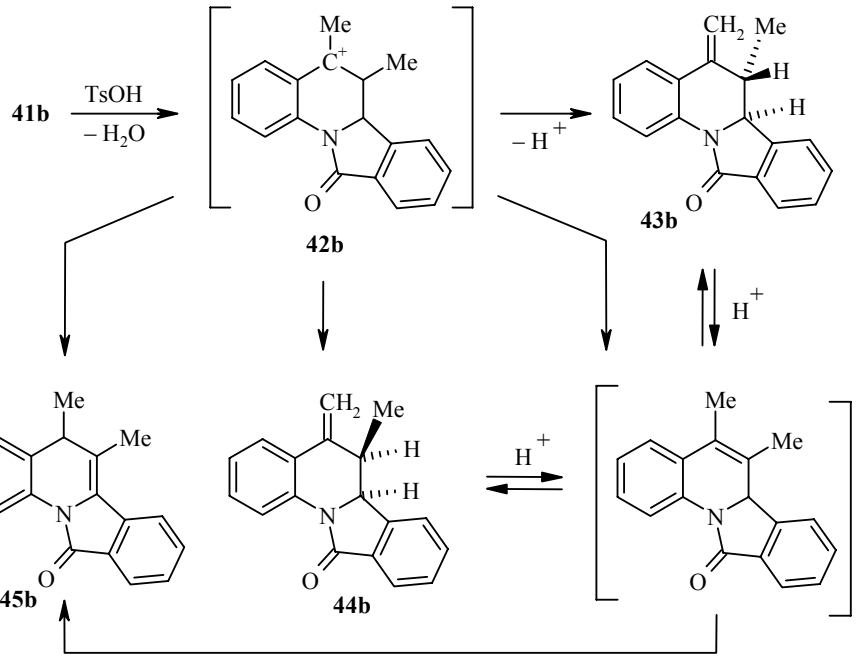


E-**43a** *Z*-, *E*-**44a** **45a**

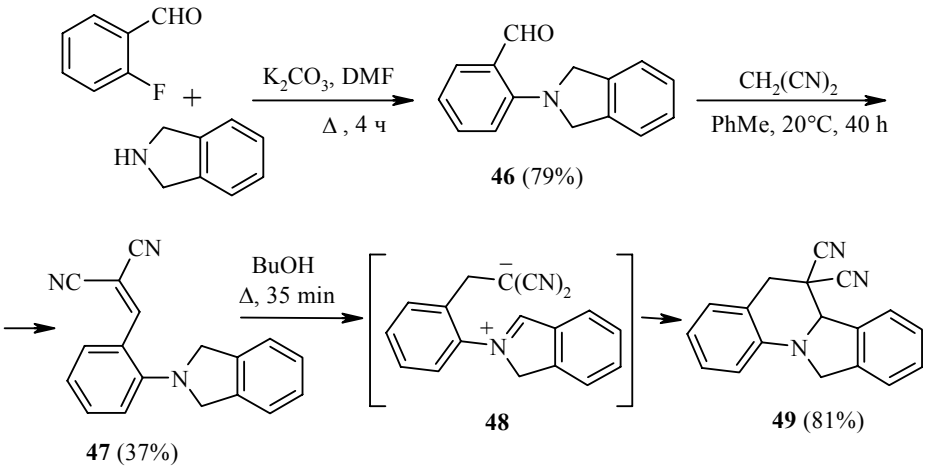
If the cyclization is carried out in the presence of 1 eq. of TsOH, a 22:68:5:5 mixture of **45a**, *E*-**43a**, *E*-**44a**, and *Z*-**44a** is formed. Resinification is observed, and this becomes stronger with increase in the reaction time.

The carbocation **42b** is formed from N-(*o*-butenylphenyl)hydroxylactam **41b** in the presence of catalytic amounts of TsOH, and its deprotonation leads to the formation of three isoindoloquinolines **43b** (33%), **44b** (33%), and **45b** (34%). After 3 h the percentage ratios of the reaction products change to 27:27:46 respectively,

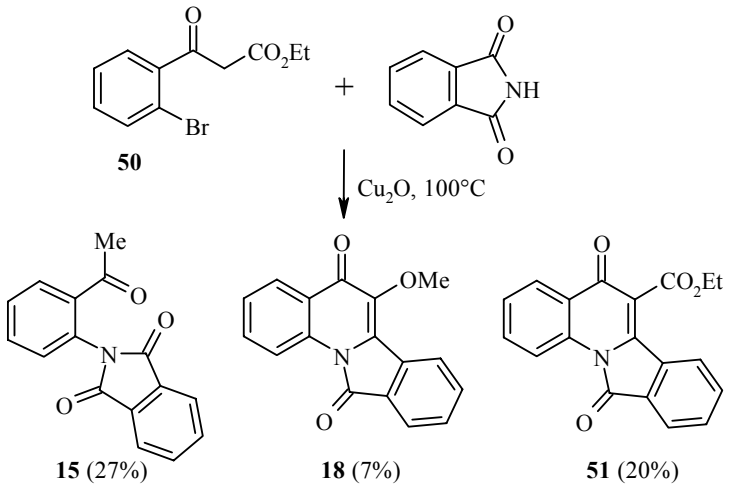
and after 24 h only the isoindoloquinoline **45b** remains in the reaction mixture. It was isolated with a yield of 48%. If 1 eq. of TsOH is used, only the isoindoloquinoline **45b** is formed with a yield of 75% after 30 min.



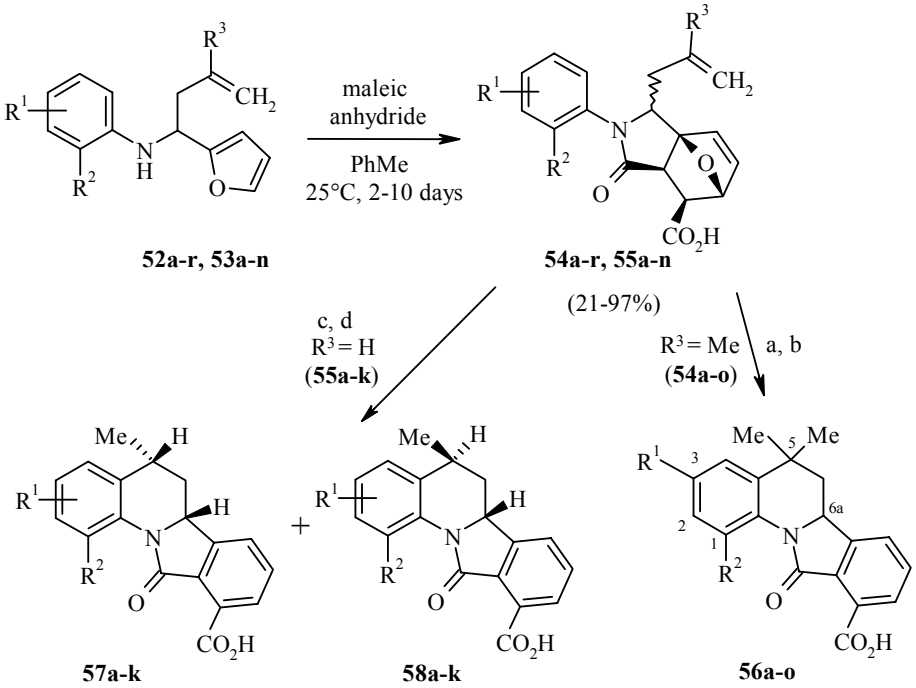
The isoindolo[2,1-*a*]quinoline **49** is formed when the dinitrile **47** is boiled in butanol. The initial isoindole **47** is obtained by condensation of the aldehyde **46** with malononitrile in toluene. The cyclization of the benzylidene derivative **47** probably takes place through a [1,5]-shift of hydrogen and the formation of the dipolar intermediate **48** followed by addition of the carbanion at the iminium fragment [11].



The reaction of ethyl bromobenzoylacetate **50** with phthalimide in the presence of copper(I) oxide gives a mixture of 2-acetylphenylphthalimide **15** and 6-substituted isoindolo[2,1-*a*]quinolines **18** and **51** [5]. The reaction also takes place in the absence of the catalyst, but the yield is substantially lower.



A single-stage method was recently proposed [12-15] for the synthesis of isoindolo[2,1-*a*]quinolines by the acid-catalyzed intramolecular electrophilic cyclization of 2-alkenyl-substituted tricyclodec-8-enes **54** and **55**. The initial tricyclodecenes are obtained by reaction of the furyl-substituted homoallylamines **52** and **53** with maleic anhydride. Cyclization of the N-*p*-aryl- and N-*o*-aryl-substituted tricycles **54a-o** and **55a-k** by the action of sulfuric and/or phosphoric acids takes stereospecifically at the free *ortho* position of the phenyl ring with the formation of the isoindoloquinolinecarboxylic acids **56-58** [12-14]. In the case of the 2-methallyl-substituted adducts **54a-o** the obtained tetracycles **56a-o** are individual substances, while in the case of the 2-allyl-substituted compounds **55a-k** they are mixtures of geometric isomers *cis*-**57a-k** and *trans*-**58a-k** with respect to the arrangement of the 5-Me group and the H-6a proton with a preference for the first isomer.



a) H_3PO_4, 75-85°C, 45 min (R^1 and R^2 = Alk or OAlk); b) H_3PO_4/H_2SO_4 (3:1), 125-140°C, 1-2 h (R^1 and R^2 = Hal);
c) H_3PO_4/H_2SO_4 (3:1), 100-120°C (R^1 and R^2 = Alk or OAlk);
d) H_3PO_4/H_2SO_4 (3:1), 145-155°C (R^1 and R^2 = Hal)

TABLE 4. The Yields of compounds **56-58**

56	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**	**l**	**m**	**n**	**o**
R^1	H	H	Me	H	H	MeO	H	Me	*i*-Pr	Cl	Br	F	H	H	H
R^2	H	Me	H	Et	MeO	H	Bn	Me	H	H	H	H	Cl	Br	F
Yield **56**, %	68	31	50	45	34	72	32	61	67	41	51	62	50	31	40

57+58	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**
R^1	H	H	H	MeO-3	Me-2	Cl-3	Br-3	F-3	H	H	H
R^2	H	Me	MeO	H	Me	H	H	H	Cl	Br	F
57/58	4/1	4.5/1	3.5/1	12/1	6/1	3.5/1	3/1	3.6/1	4.2/1	1.6/1	8/1
Yield **57**+**58**, %	52	49	32	31	55	41	63	54	44	40	30

The intramolecular alkylation of the N-*m*-aryl-substituted tricycles **54p-r** and **55l-n** takes place at both free *ortho* positions of the phenyl radical with the formation of mixtures of regioisomers [15]. In the case of the cyclization of the allyl-substituted adducts **55l-n** each regioisomer exists in the form of a mixture of diastereomers with a pseudoequatorial **57**+**57'l-n** and pseudoaxial **58**+**58'l-n** 5-Me group.

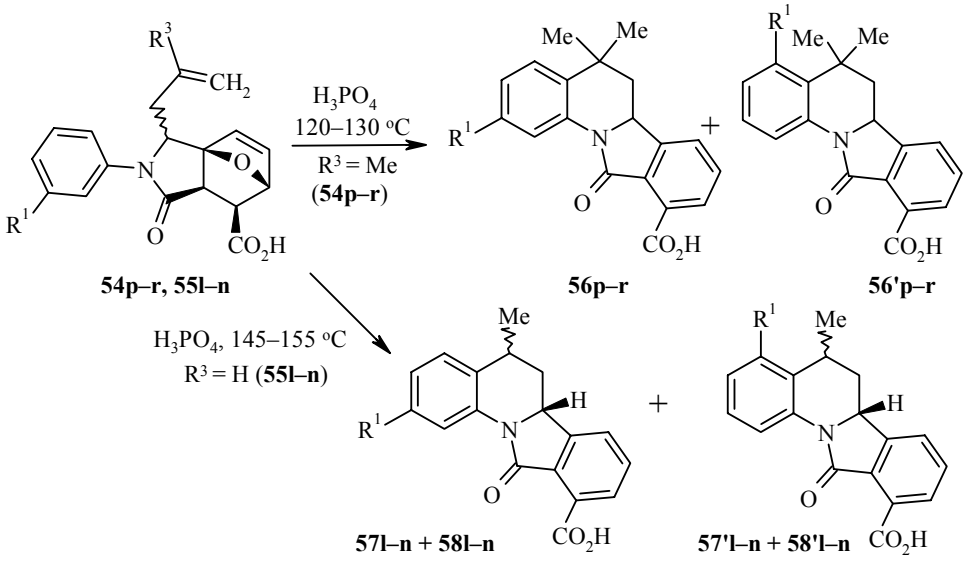


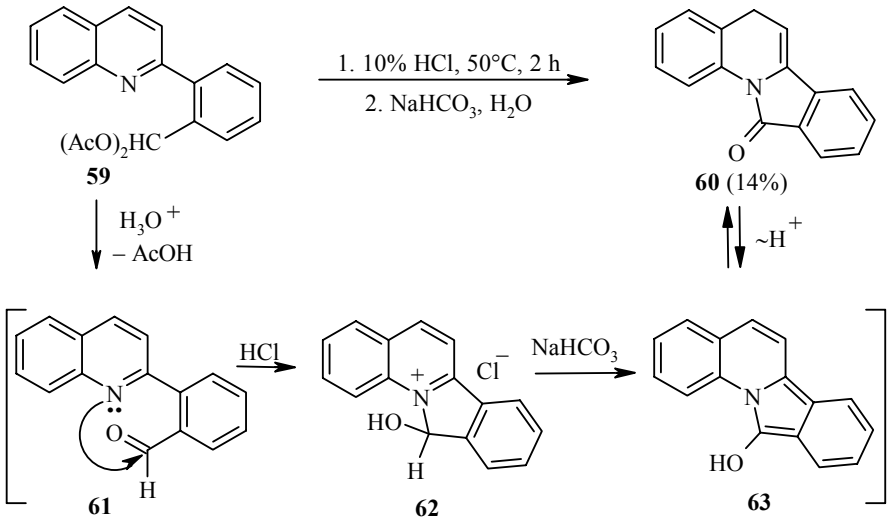
TABLE 5. The Yields and Ratios of the Isomers **56-58**

Compound **56**, **56'**	R^1	**56** : **56'**	Yield, %
p	Me	2 : 1	52
q	MeO	4.5 : 1	57
r	Cl	1 : 1.6	63

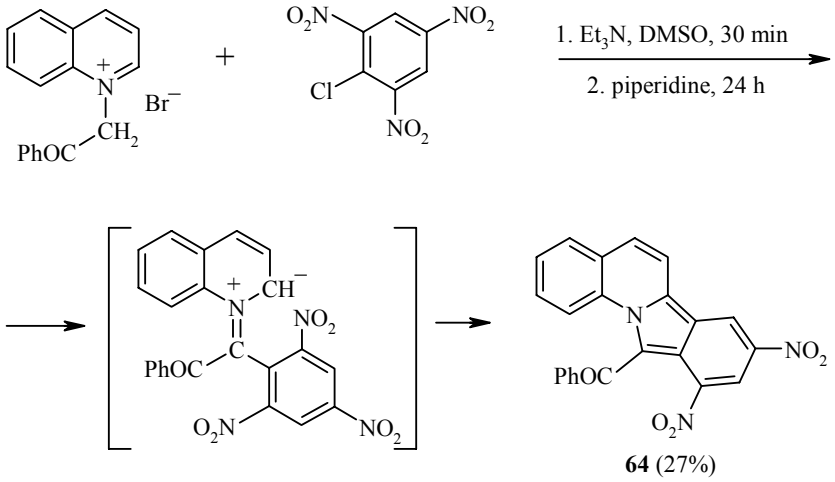
Compound **57, 57', 58, 58'**	R^1	**57** : **58** : **57'** : **58'**	Overall yield, %
l	Me	35 : 11 : 5 : 1	41
m	MeO	18 : 7 : 2.5 : 1	40
n	Cl	1.3 : 1:1 : 0	44

1.2. Synthesis of Isoindolo[2,1-*a*]quinolines from Substituted Quinolines

Treatment of *o*-(α-quinolyl)benzylidene diacetate **59** with dilute hydrochloric acid leads to the formation of 5H-isoindolo[2,1-*a*]quinolin-11-one **60**. The transformation includes nucleophilic addition of the nitrogen atom at the aldehyde group of the quinoline **61**. Further treatment with a base leads to prototropic isomerization to the stable isoindoloquinoline **60**.



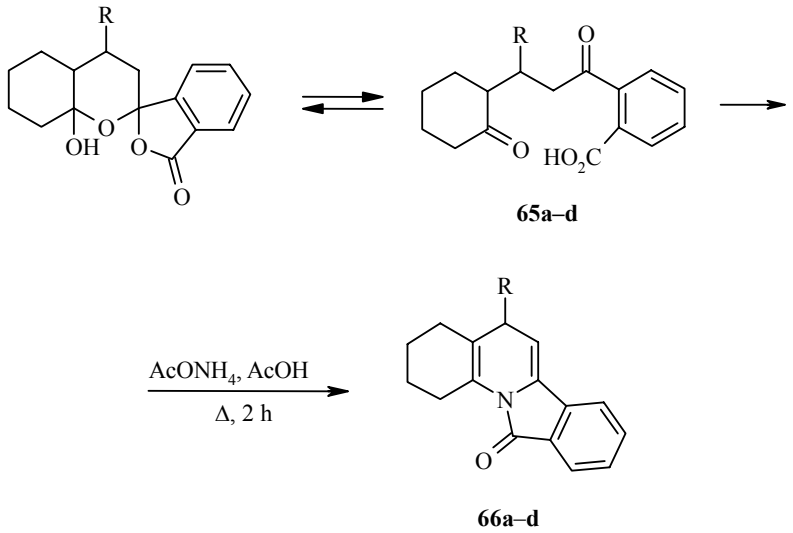
Cycloimmonium salts containing an active N-methylene group react with picryl chloride to form benz[*a*]indolizines and their annelated analogs. Thus, 11-benzoyl-8,10-dinitroisoindolo[2,1-*a*]quinoline **64** is formed in the reaction of N-phenacylquinolinium bromide with picryl chloride in a basic medium [17].



1.3. Synthesis of Isoindolo[2,1-*a*]quinolines from Diketones

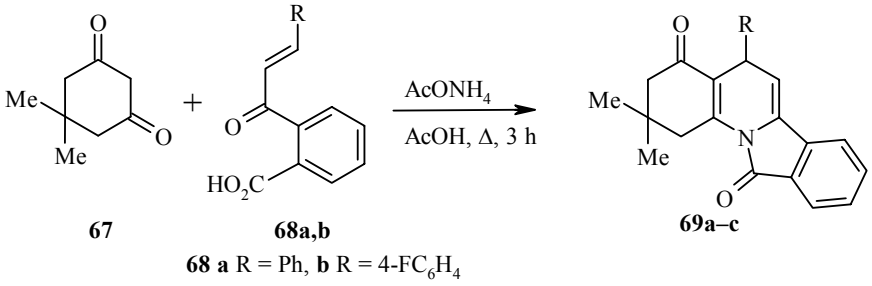
A group of Russian scientists [18-20] proposed some original methods for the synthesis of isoindolo[2,1-*a*]quinolines based on the transformations of α-aryl-substituted 1,5-diketones. Thus, hydrogenated isoindolo[2,1-*a*]quinolines **66a-d** are formed in the reaction of substituted diketones **65** with ammonium acetate

in acetic acid (an "improved Chichibabin pyridine synthesis") [18]. The reaction takes place through intramolecular acylation of the initially formed 2-*o*-carboxyphenyl-1,4-dihydropyridines.



66 a R = Ph (65%); **b** R = 4-$MeOC_6H_4$ (52%);
c R = 4-FC_6H_4 (48%); **d** R = 2,4-$Cl_2C_6H_3$ (70%)

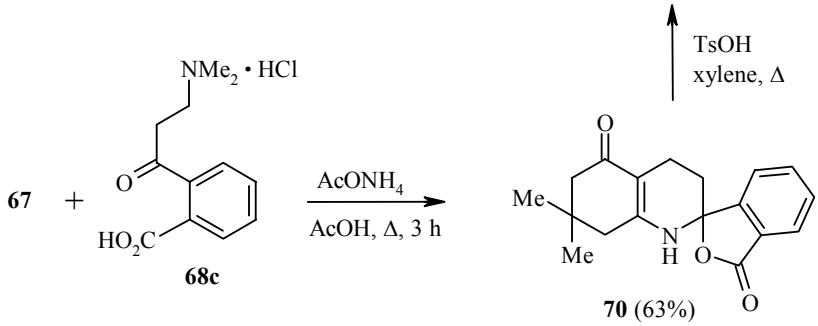
Later, the same group of authors developed a single-stage method for the synthesis of isoindolo[2,1-*a*]quinolines using 2-(3-arylacryloyl)benzoic acids **68a**,**b** or *o*-(3-dimethylaminopropionyl)benzoic acid **68c** as starting compounds [19]. The reaction of the acids **68a**,**b** with dimedone **67** leads to the formation of the required isoindolo[2,1-*a*]quinolines **69a**,**b**. Under the same conditions the hydrochloride of the Mannich base **68c** is transformed into octahydroquinoline-2-spirodihydrobenzofuran **70**, treatment of which with TsOH leads to recyclization to the ketone **69c**.



67 **68a,b**

69a–c

68 a R = Ph, **b** R = 4-FC_6H_4

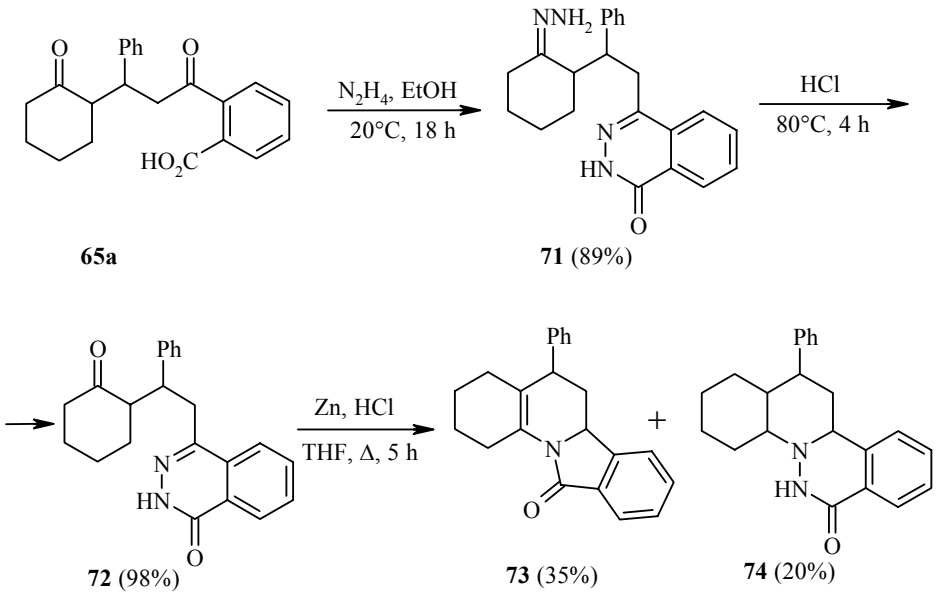


68c

70 (63%)

69 a R = Ph (54%), **b** R = 4-FC_6H_4 (45%), **c** R = H (43%)

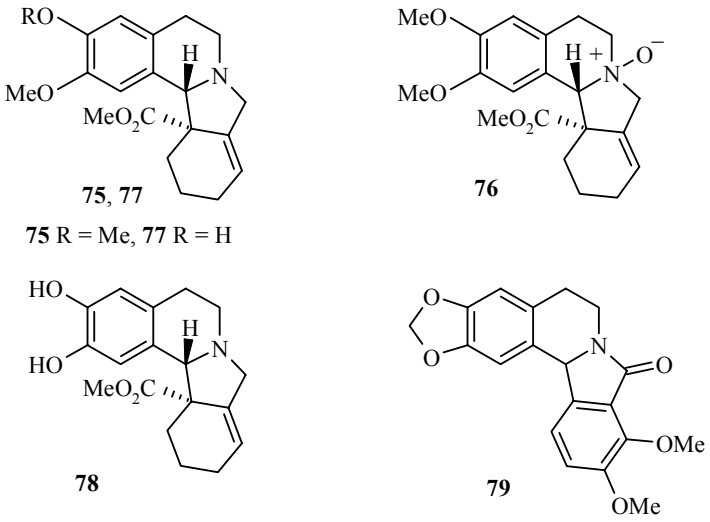
Acid hydrolysis of the hydrazone **71** gives the ketophthalazone **72**, reduction of which with zinc dust leads to the formation of a mixture of isoindolo[2,1-*a*]quinoline **73** and the 7,8-diaza-D-homosteroid **74** [20].



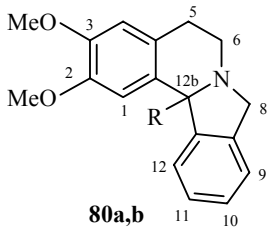
2. ISOINDOLOISOQUINOLINES

2.1. Synthesis of Isoindolo[1,2-*a*]isoquinolines

Compounds of this type are widely represented in nature. Thus, a whole series of alkaloids were isolated from the plant *Cocculus Hirsutus*, which grows in Pakistan and include jamtinine **75** [21, 22], jamtine N-oxide **76** [23], hirsutine **77** [24], and haiderine **78** [25]. The alkaloid nuevamine **79** was found in the shrub *Berberis darwinii Hook*, which grows in Chile [26, 27].



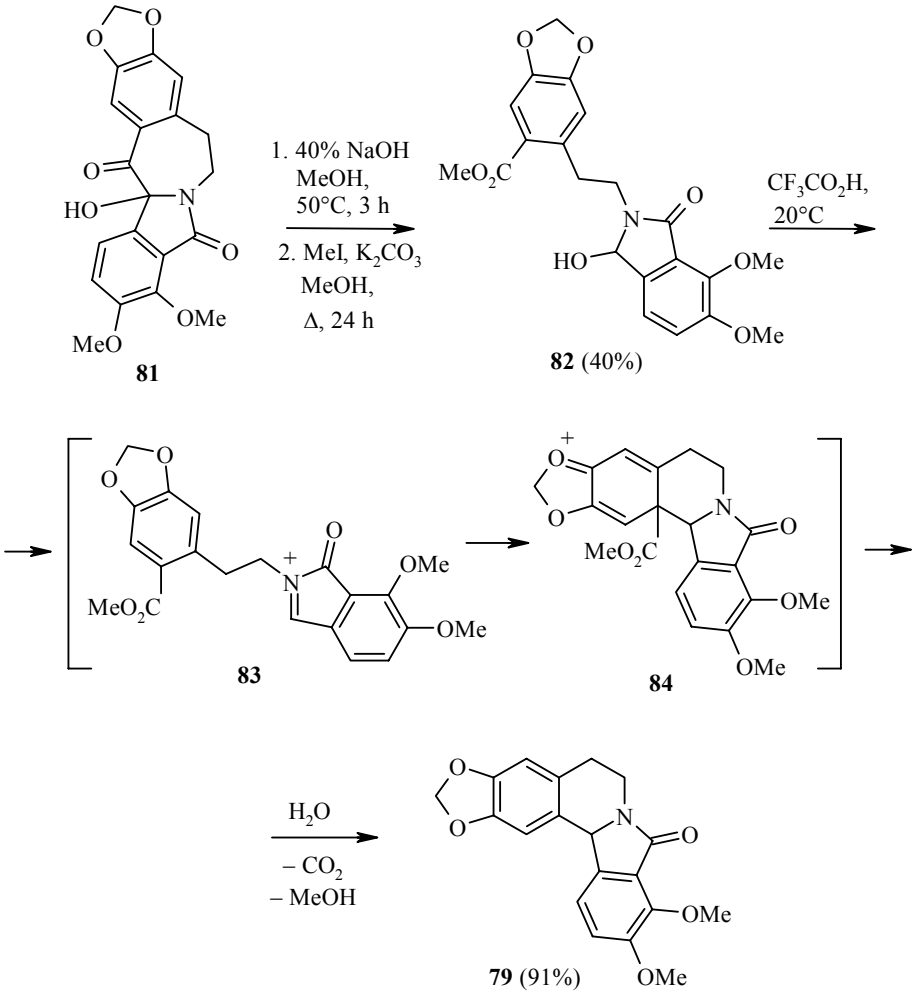
The interest in the synthesis of analogs of the above-mentioned alkaloids is due more to the fact that the isoindoloisoquinolines **80** are stimulants of the central nervous system and exhibit anti-inflammatory activity [28-30].



80a,b

80 a R = Ph, **b** R = $CH_2C_6H_4Cl$-*p*

A probable path for the biosynthesis of nuevamine was modelled *in vitro* by American scientists [31]. They contracted the ring in chilenine **81**, isolated from plants of the barberry family, and obtained nuevamine **79**.



81

82 (40%)

83

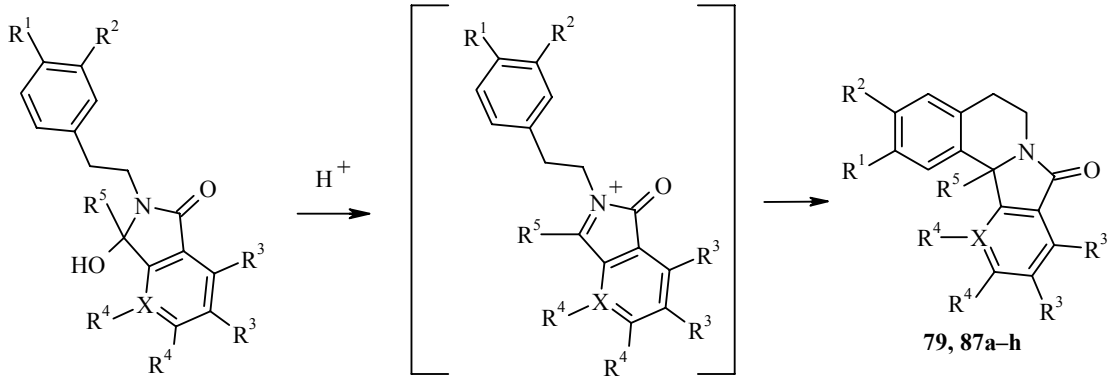
84

79 (91%)

The process includes cleavage of the azepine fragment of chilenine by the action of a base with the formation of the phthalimide **82** and subsequent recyclization in an acidic medium with the formation of nuevamine **79**.

It is possible to single out two main approaches to the synthesis of isoindolo[1,2-*a*]isoquinolines using isoindole derivatives or isoquinoline derivatives as starting compounds.

2.1.1. Synthesis of Isoindolo[1,2-*a*]isoquinolines from Isoindole Derivatives. Intramolecular alkylation, taking place through the acid-catalyzed cyclization of α-hydroxylactams, is a convenient method for the construction of condensed heterocycles [28, 32-35]. Thus, the lactams are converted under acidic conditions into the corresponding isoindoloquinolines **87a-f** and **79** [28, 32-34] and their aza analogs **87g**,**h** [35]. The reaction takes place through the formation of the N-acyliminium cation **86**. The initial hydroxylactams **85** were synthesized by reduction of the respective lactams or by condensation of primary amines with the corresponding 3-halogen-substituted phthalic anhydrides [28, 32-35].



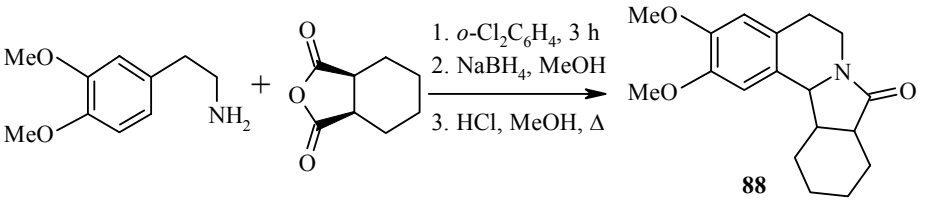
85a–h **86**

Octahydroisoindolo[1,2-*a*]isoquinoline **88** can be obtained by the procedure [29, 30] described for the synthesis of compounds **87**. In this case cyclohexane-1,2-dicarboxylic anhydride is used for the synthesis of the initial hydroxylactam.

TABLE 6. The Formation Conditions and Yields of Compounds **79** and **87**

Reaction product*	R^1	R^2	R^3	R^4	R^5	Condition	Yield, %
79	OCH_2O		OMe	H	H	CF_3CO_2H, CH_2Cl_2, 20°C	100
87a	H	H	H	H	Ph	H_2SO_4, 20°C, 2 h	65
87b	OMe	OMe	H	H	Ph	$POCl_3$, 50°C, 2 h	91
						HCl, MeOH, Δ, 3 h	Not indicated
87c	H	H	H	H	H	H_2SO_4, 20°C, 2 h	84
87d	OMe	OMe	H	H	H	CF_3CO_2H, CH_2Cl_2, 20°C	100
87e	OMe	OMe	OMe	H	H	CF_3CO_2H, CH_2Cl_2, 20°C	100
87f	OCH_2O		H	OMe	H	CF_3CO_2H, CH_2Cl_2, 20°C	100
87g	H	H	H	H	H	CF_3CO_2H, Δ, 3 h	93
87h	H	H	H	H	Ph	CF_3CO_2H, Δ, 3 h	72

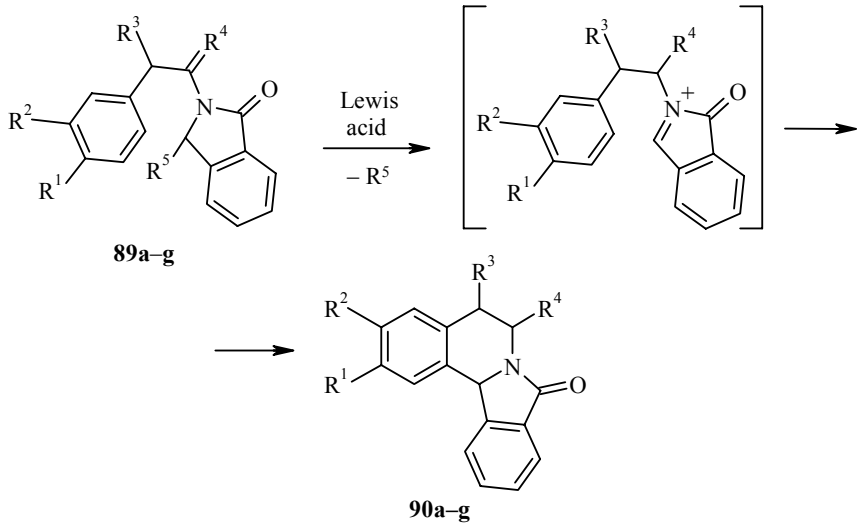
*** 79**, **87a-f** X = C, **87g**,**h** X = N.



88

Intramolecular cyclization of 3-methoxy(benzotriazolyl)-substituted 2-arylisoindol-1-ones **89** can be realized by the action of Lewis acids [36-38].

The chiral derivatives **89d**,**e** form compounds **90d**,**e** as mixtures of diastereomers. The initial benzotriazolyl-substituted isoindolones **89a-e** are obtained by the condensation of 2-arylethylamines, benzotriazole, and 2-carboxybenzaldehyde (toluene, Δ, azeotropic distillation of the water, 24 h) [38].



89a–g

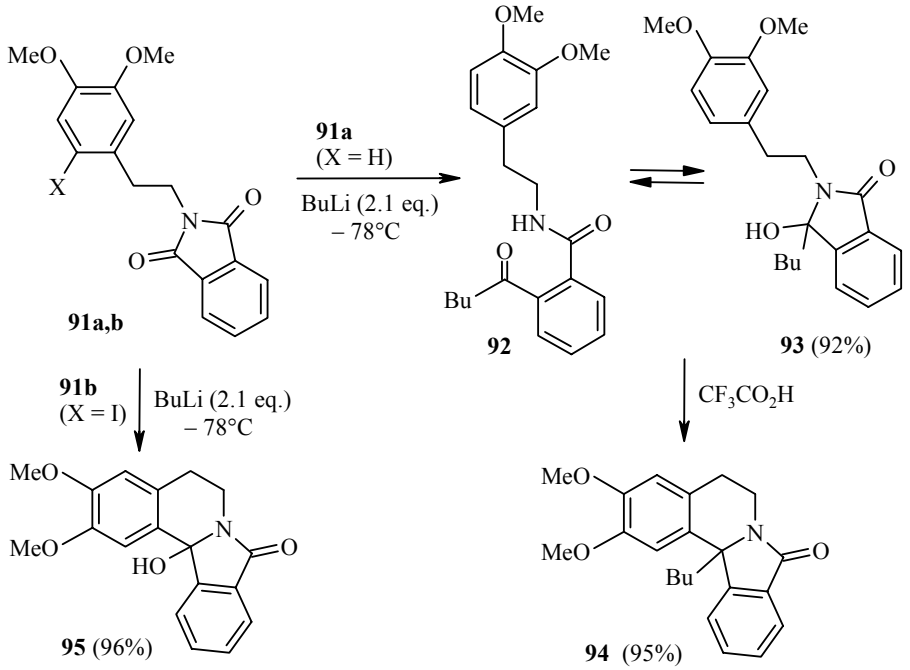
90a–g

TABLE 7. The Production Conditions and Yields of Compounds **90***

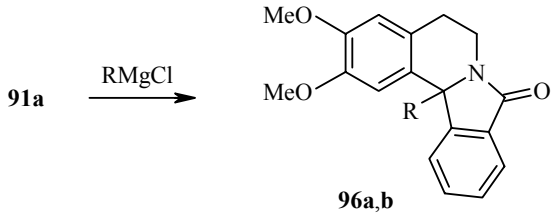
Com-pound	R^1	R^2	R^3	R^4	Conditions	Yield %
90a	H	H	H	H	$TiCl_4$, PhMe, Δ, 24 h	50
90b	OMe	H	H	H	$TiCl_4$, PhMe, Δ, 24 h	65
90c	OMe	OMe	H	H	$TiCl_4$, PhMe, Δ, 24 h	75
90d	H	H	(*S*)-CH_2OH	H	$TiCl_4$, PhMe, Δ, 24 h	60
90e	H	H	(*S*)-OH	(*R*)-Me	$TiCl_4$, PhMe, Δ, 24 h	65
90f	H	H	H	H	$TiCl_4$, CH_2Cl_2, -78→20°C, 24 h	100
90g	OMe	OMe	H	H	$TiCl_4$, CH_2Cl_2, -78→20°C, 24 h	100
					$Sc(OTf)_3$, CH_2Cl_2, 20°C, 3 h	54
					$Cu(OTf)_2$	56

* **89a-e** R^5 = benzotriazole, **89f**,**g** R^5 = OMe.

Isoindoloisoquinolines can be obtained by the reaction of N-arylphthalimides with butyllithium [39, 40]. Thus, treatment of the phthalimide **91a** with butyllithium in THF leads to the ketone **92**, which exists in tautomeric equilibrium with the cyclic form **93**. The amido alcohol **93** is converted by the action of trifluoroacetic acid into the isoindolo[1,2-*a*]isoquinoline **94**. The isoindoloisoquinoline **95** is obtained similarly from the 2-iodine-substituted phthalimide **91b** in one stage.

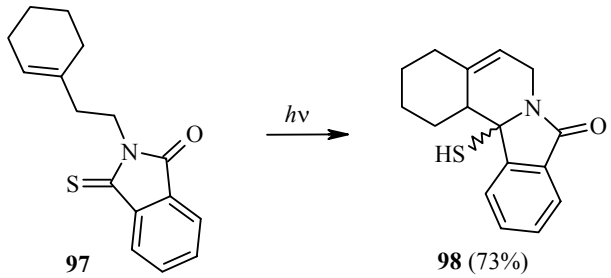


Grignard reagents can be used instead of butyllithium [28]. The phthalimide **91a** reacts with benzylmagnesium chloride or *p*-chlorobenzylmagnesium chloride, giving a moderate yield of 12*b*-R-isoindolo[1,2-*a*]isoquinolines **96a**,**b**.

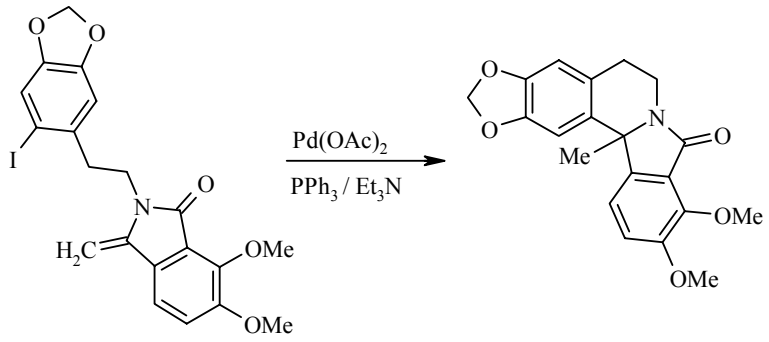


96 a R = Bn, **b** R = $CH_2C_6H_4Cl$-*p*

Photochemical cyclization of the thiooxophthalimide **97** leads to the formation of a mixture of diastereomers of 12*b*-mercapto-substituted isoindolo[1,2-*a*]isoquinolines **98** in a ratio of 1:1 [41].

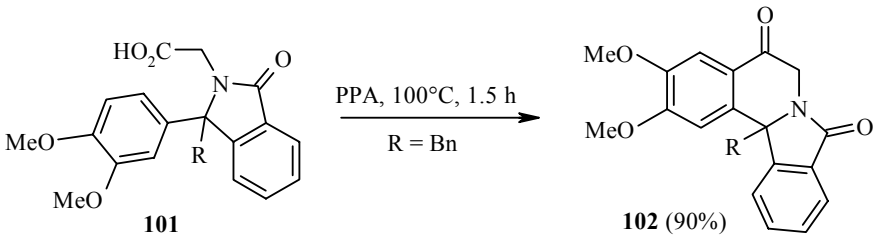


Under the conditions of the Heck reaction 2-[(*o*-iodo)-α-phenethyl]-3-methylenephthalimidine **99** gives a satisfactory yield of isoindoloisoquinoline **100** [42].



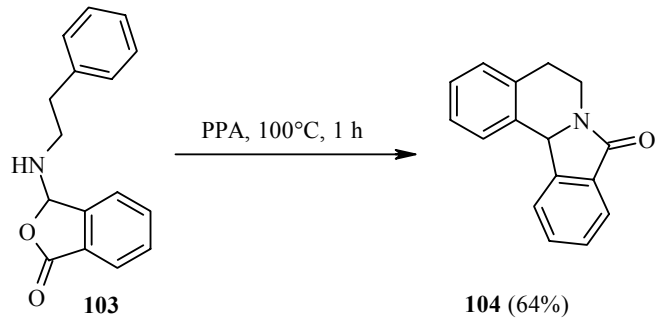
99 **100** (34–47%)

3-Benzyl-3-(3,4-dimethoxyphenyl)phthalimidine-2-acetic acid **101** is converted regiospecifically by the action of PPA into the corresponding 12*b*-benzylisoindolo[1,2-*a*]isoquinoline **102** [43]. The initial phthalimidine **101** was synthesized from 3-benzylidenephthalimidine-2-acetic acid and veratrole in the presence of perchloric acid.



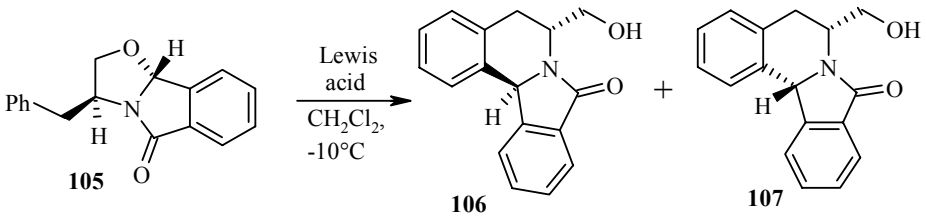
101 **102** (90%)

Polyphosphoric acid leads to intramolecular cyclization of 3-(β-phenylethylamino)phthalide **103** to 5,6-dihydroisoindolo[1,2-*a*]isoquinoline **104** [44]. The initial anhydride **103** is produced by the reaction of β-phenethylamine with *o*-formylbenzoic acid (toluene, Δ, 1 h).



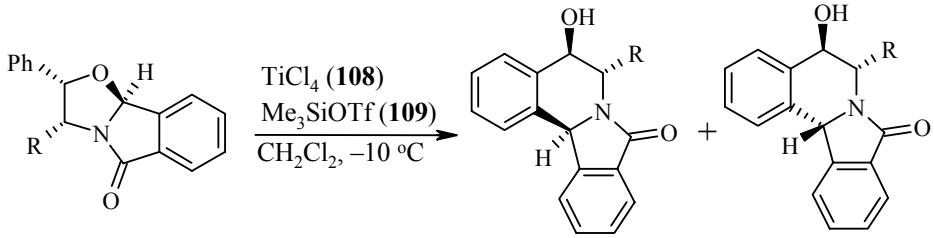
103 **104** (64%)

The optically active isoindolo[1,2-*a*]isoquinolines **106** and **107** can be obtained from the tricyclic oxazolidine **105** [45]. Under the influence of Lewis acids **105** generates an N-acyliminium cation, which undergoes cyclization to the aromatic ring. A 2-6-fold preference for the stereoisomer **106** is observed, depending on the catalyst. Trimethylsilyl triflate was the best catalyst from the standpoint of diastereoselectivity; the ratio of the alcohols **106** and **107** was ≥49:1.



Lewis acid = $SnCl_4$, $TiCl_4$, BF_3OEt_2, Me_3SiOTf, H_2SO_4

The method was used for recyclization of the tricyclic lactams **108** and **109**.

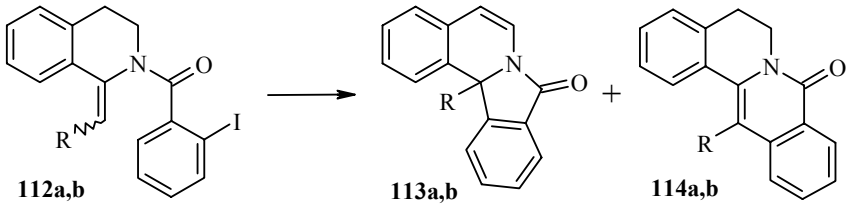


108 R = Ph
109 R = Me

110a
111a

110b (14:1) 94%
111b (26:1) 99%

2.1.2. Synthesis of Isoindolo[1,2-*a*]isoquinolines from Substituted Isoquinolines. The intramolecular Heck reaction of *o*-iodobenzamides **112** under the action of palladium(II) acetate leads to the formation of a mixture of the products from 5-*exo*-*trig*-cyclization **113** and 6-*exo*-*trig*-cyclization **114** [46-48]. The ratio of the products can be altered by varying the conditions.



112a,b

113a,b

114a,b

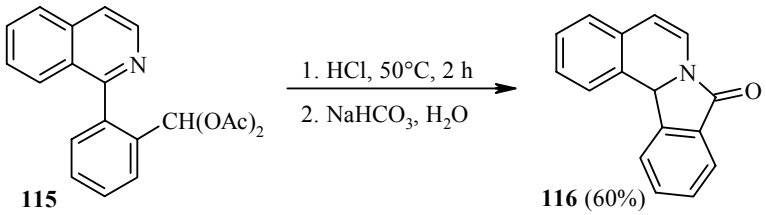
112 a R = Me, **b** R = H; **113 a** R = –CH=CH_2, **b** R = Me; **114 a** R = Me, **b** R = H

TABLE 8. The Production Conditions and Yields of Compounds **113** and **114**

Initial	Reaction conditions	**113**/**114**	Yield, %
112a	$Pd(OAc)_2$ (0.05 eq.), PPh_3 (0.1 eq.), DMF, 100°C, 2 h	6.7/1	84
	$Pd(OAc)_2$ (0.1 eq.), PPh_3 (0.2 eq.), Na_2CO_3 (2 eq.), DMF, 100°C, 1 h	3.9/1	80
	$Pd(OAc)_2$ (0.1 eq.), PPh_3 (0.2 eq.), Et_4NCl (1 eq.), MeCN, 80°C, 1 h	10/1	91
	$Pd(OAc)_2$ (0.12 eq.), PPh_3 (0.25 eq.), Et_4NCl (1 eq.), MeCN, 30-50°C, 168 h	13/1	83
112b	$Pd(OAc)_2$ (0.05 eq.), PPh_3 (0.1 eq.), HCO_2Na (1 eq.), DMF, 80°C, 24 h	2/1	74

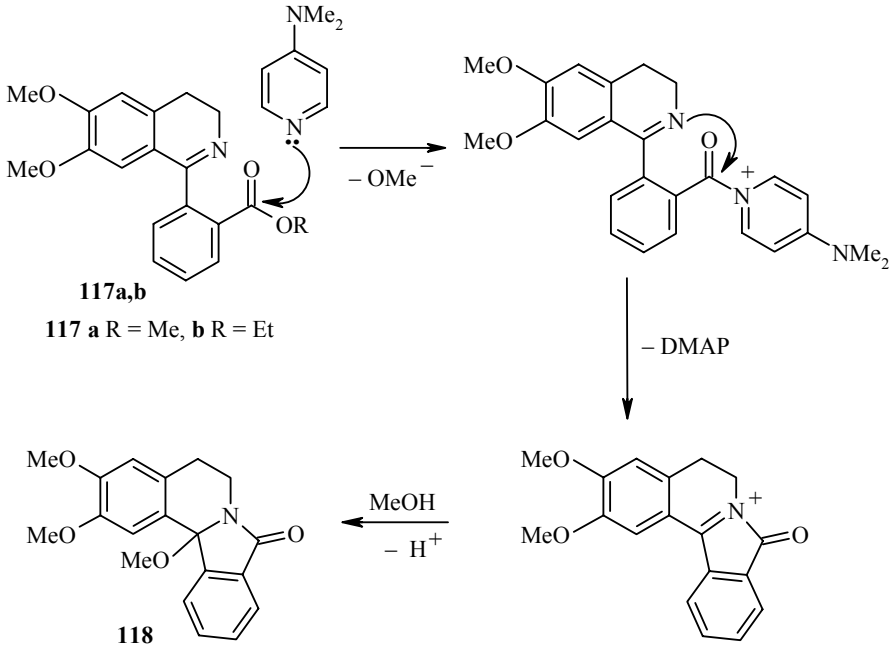
The initial enamides **112a**,**b** are obtained by the acylation of 1-alkenylidene-3,4-dihydroisoquinoline with *o*-iodobenzoyl chloride.

The treatment of *o*-(1-isoquinolyl)benzylidene diacetate **115** with dilute hydrochloric acid leads to the formation of isoindolo[1,2-*a*]isoquinolin-12*b*H-8-one **116** [16].



115 **116** (60%)

Substituted 1-aryl-3,4-dihydroisoquinolines **117** are converted by reaction with 4-dimethylaminopyridine in methanol solution into the acylaminol **118** [49].



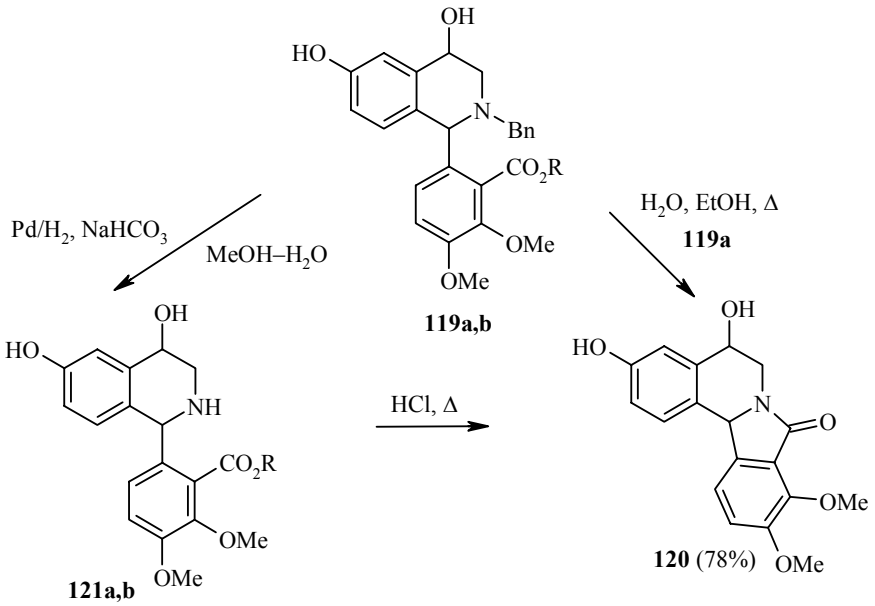
117a,b

117 a R = Me, **b** R = Et

118

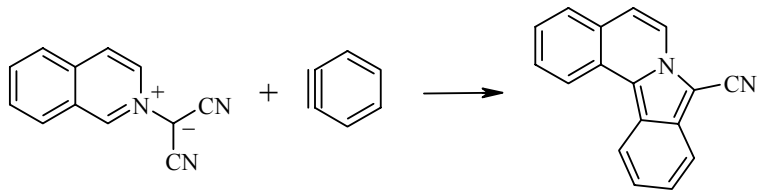
DMAP = 4-dimethylaminopyridine

When a water–alcohol solution of 6-(4,6-dihydroxy-1,2,3,4-tetrahydro-1-isoquinolyl)-2,3-dimethoxybenzoic acid **119a** is heated, isoindolo[1,2-*a*]isoquinoline **120** is formed instead of the expected debenzylation product [50]. Isoquinolines **121a**,**b** unsubstituted at the nitrogen atom, obtained from the N-benzyl derivatives **119a**,**b** by catalytic hydrogenation, are converted into the corresponding isoindoloisoquinolines **120** when heated with hydrochloric acid.



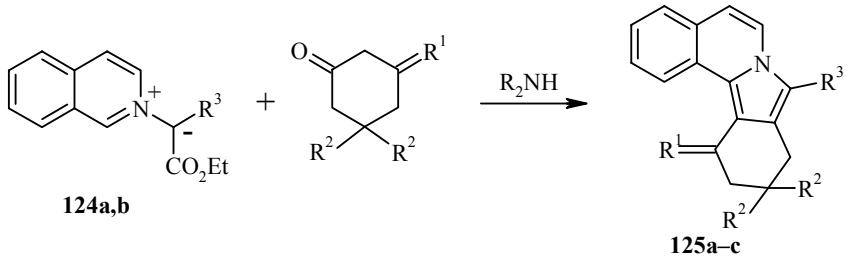
121 a R = H, **b** R = Et

The 8-cyanoisoindolo[1,2-*a*]isoquinoline is formed in the reaction of isoquinolinium dicyanomethylide **122** (obtained from isoquinoline and epoxytetracyanoethylene) with dehydrobenzene [51].



122 **123** (74%)

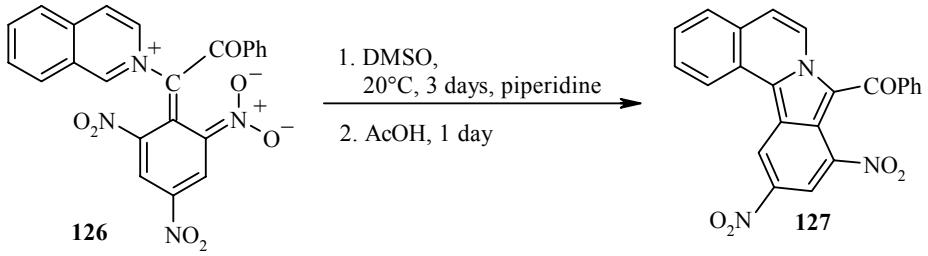
The partly hydrogenated isoindoloisoquinolines **125a-c** can be obtained by the cycloaddition of isoquinolinium ylides **124a**,**b** to cyclohexanone or dimedone in the presence of secondary amines [52, 53].



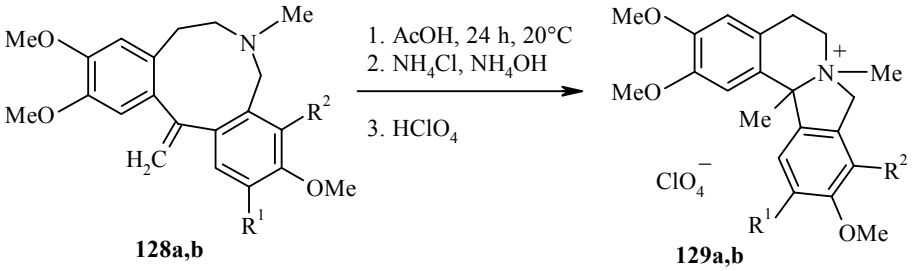
124a,b **125a–c**

124 a $R^3 = CO_2Et$, **b** $R^3 = CN$; **125 a** $R^1 = R^2 = H$, $R^3 = CO_2Et$;
b $R^1 = R^2 = H$, $R^3 = CN$; **c** $R^1 = O$, $R^2 = Me$, $R^3 = CO_2Et$

The betaine **126** is converted by the action of a base into the dinitroisoindoloisoquinoline **127** [54].



The action of acetic acid on the nine-membered unsaturated amines **128** leads to intramolecular transannular addition of the amino group to the exocyclic methylene fragment with the formation of 12*b*-methylisoindolo[1,2-*a*]isoquinolines **129** [55], isolated as the perchlorates.

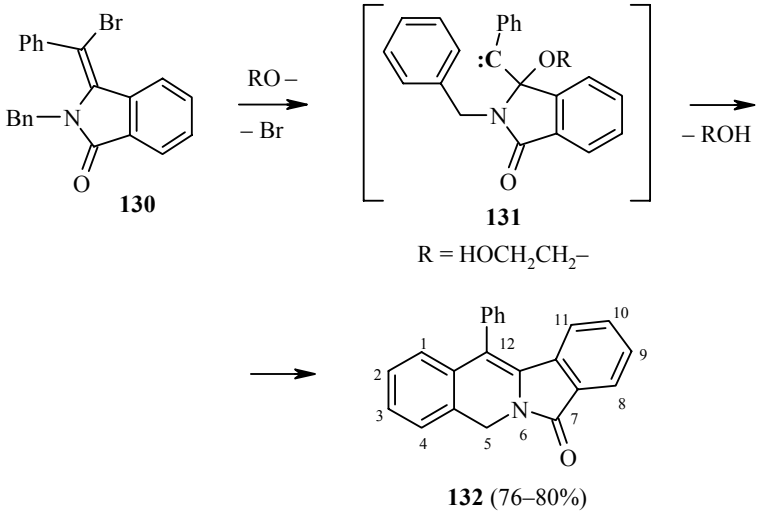


128 a R^1 = OMe, R^2 = H, **b** R^1 = H, R^2 = OMe; **129 a** (76%), **b** (83%)

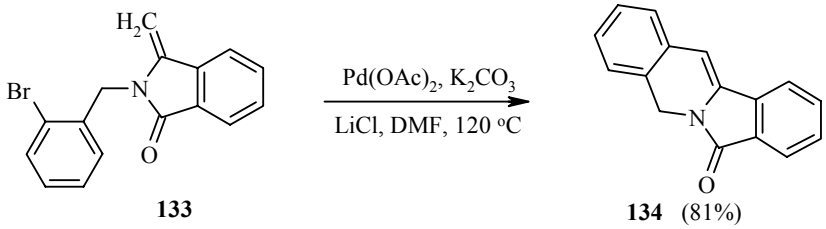
2.2. Synthesis of Isoindolo[2,1-*b*]isoquinolines

As for the type of compound described above, both isoindole derivatives and isoquinoline derivatives can be used for the synthesis of isoindolo[2,1-*b*]isoquinolines. In addition, a series of specific methods, described in section 2.2.3, have been developed for the construction of this heterocyclic system.

2.2.1. Synthesis of Isoindolo[2,1-*b*]isoquinolines from Isoindole Derivatives. Isoindolo[2,1-*b*]isoquinolines are produced by the intramolecular cyclization of various enamides of the isoindole series [42, 56, 57]. Thus, 2-benzyl-3-(α-bromobenzylidene)phthalimidine **130** is transformed into 12-phenylisoindolo[2,1-*b*]isoquinoline **132** when boiled in ethylene glycol in the presence of a base or during photolysis [56, 57].

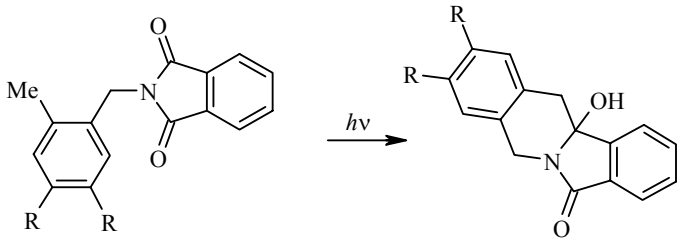


The Heck reaction of 3-methylenephthalimidine **133**, produced by the reaction of 2-acetylbenzoic acid with 2-bromobenzylamine (toluene, Δ, 85%), leads to the isoindoloisoquinoline **134** [42].



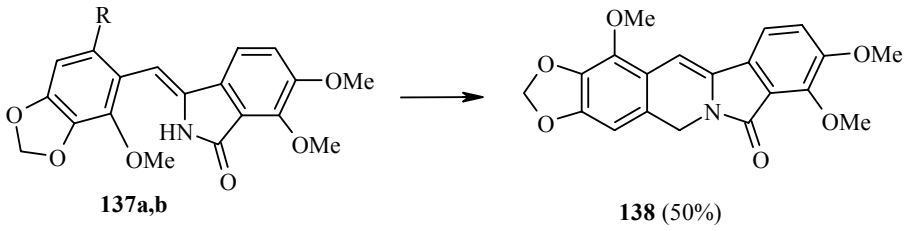
133 **134** (81%)

The photocyclization of 2-(*o*-methylbenzyl)phthalimides **135** to the corresponding 11*b*-hydroxyisoindolo[2,1-*b*]isoquinolines **136** takes place with 44-80% conversion and a low yield [58].



135a–c **136a–c**

The polymethoxy-substituted tetracycle **138** is formed from narceine imide methyl iodide **137a** by the action of silver oxide [59] or from the vinyl analog **137b** by boiling in a water–alcohol solution [60].



137a,b **138** (50%)

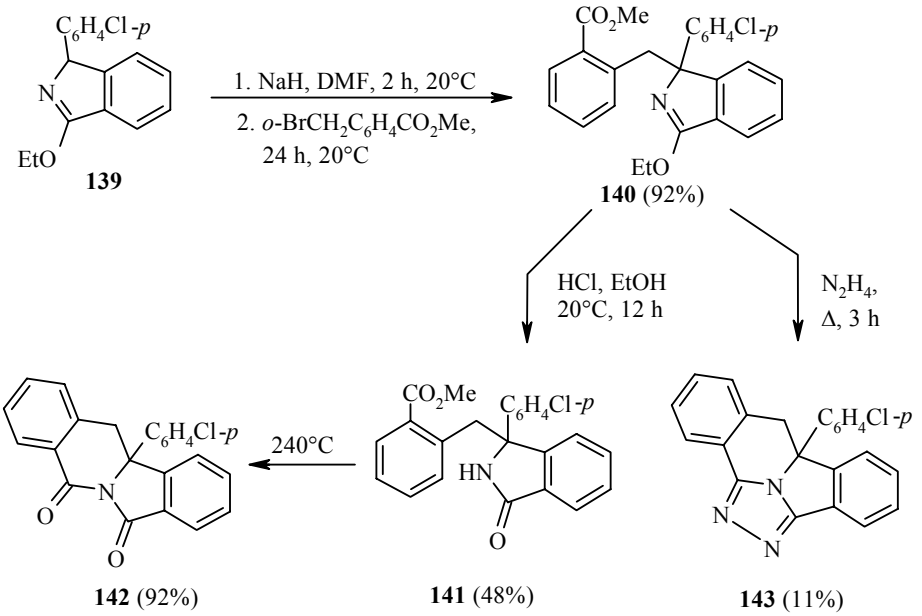
137 a R = $-CH_2CH_2\overset{+}{N}Me_3\overset{-}{I}$, **b** R = –CH=$CH_2$

Compound **138** exhibits coccidiostatic activity [59] (coccidia are intracellular parasites giving rise to coccidiosis – an invasive disease of humans and animals – and mainly parasitize the epithelium of the digestive system).

TABLE 9. The Production Conditions and Yields of Compounds **136**

Initial compound	R	Conditions (mercury lamp)	Yield **136**, %	Recovery of **135**, %
135a	H	MeCN, 7 h, 20°C, 1 kW	18	52
135b	OMe	Me_2CO, 50 min, 20°C, 500 W	52	28
135c	OCH_2O	Me_2CO, 1-5 h, 20°C, 500 W	25	20

Lactim ethers can be used for the synthesis of isoindolo[2,1-*b*]isoquinolines [61, 62]. Thus, the reaction of the carbanion generated from 1-(*p*-chlorophenyl)-3-ethoxy-1H-isoindole (**139**) with *o*-bromomethylbenzoic ester leads to the benzyl derivative **140**, the acid hydrolysis and pyrolysis of which give isoindolo[2,1-*b*]-isoquinoline **142**. Treatment of the iminoester **140** with hydrazine leads to a sequence of transformations, ending up in the formation of the triazole **143** [61].



139

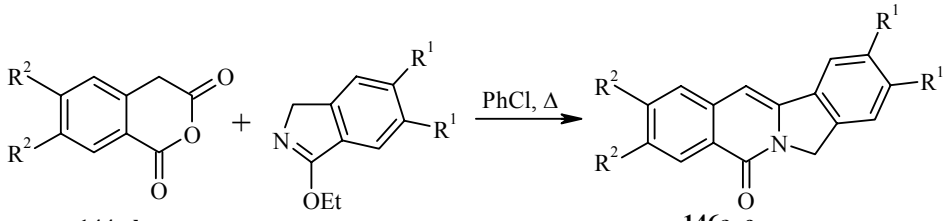
140 (92%)

142 (92%)

141 (48%)

143 (11%)

Moderate yields of the isoindolo[2,1-*b*]isoquinolines **146** are obtained during the treatment of homophthalic anhydrides **144** with lactim ethers **145** [62].



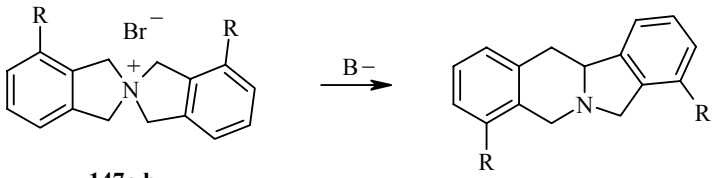
144a,b

145a,b

146a–c

144 a R^2 = H, **b** R^2 = OMe; **145 a** R^1 = H, **b** R^1 = OMe; **146 a** $R^1 = R^2$ = H (75%), **b** R^1 = H, R^2 = OMe (75%), **c** $R^1 = R^2$ = OMe (74%)

The Stevens rearrangement of quaternary spiroindane salts **147** with sodium hydride, phenyllithium, or sodium hydroxide leads to the formation of the isoindoloisoquinolines **148** with low yields [63]. The reaction is completely inhibited by the presence of accepting substituents in the initial compound (R = NO_2).

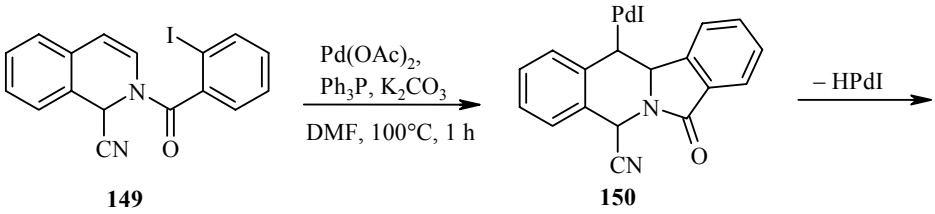


147a,b

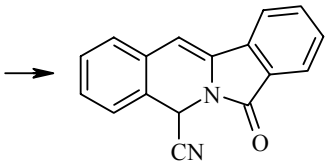
147 a R = H, **b** R = OMe

148a,b (11–41%)

2.2.2. Synthesis of Isoindolo[2,1-*b*]isoquinolines from Isoquinoline Derivatives. Isoindolo[2,1-*b*] **151** is formed as a result of 5-*exo*-*trig*-cyclization of 1-cyano-2-(*o*-iodobenzyl)-1,2-dihydroisoquinoline **149**, which takes place in the presence of palladium acetate through the intermediate **150** [46].

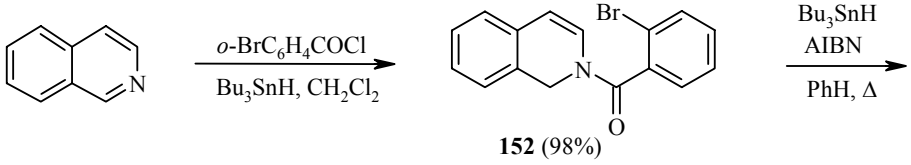


149 **150**

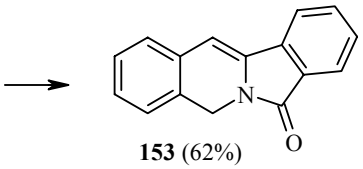


151 (59%)

Reductive acylation of isoquinoline with *o*-bromobenzoyl chloride in the presence of tributylstannane provides a convenient method for the synthesis of 1,2-dihydroisoquinoline **152**, which then undergoes radical cyclization to the hydrogenated isoindoloisoquinoline **153** [64]. The process can be realized in one synthetic stage by the addition of azobisisobutyronitrile and toluene to the intermediate isoquinoline **152**.



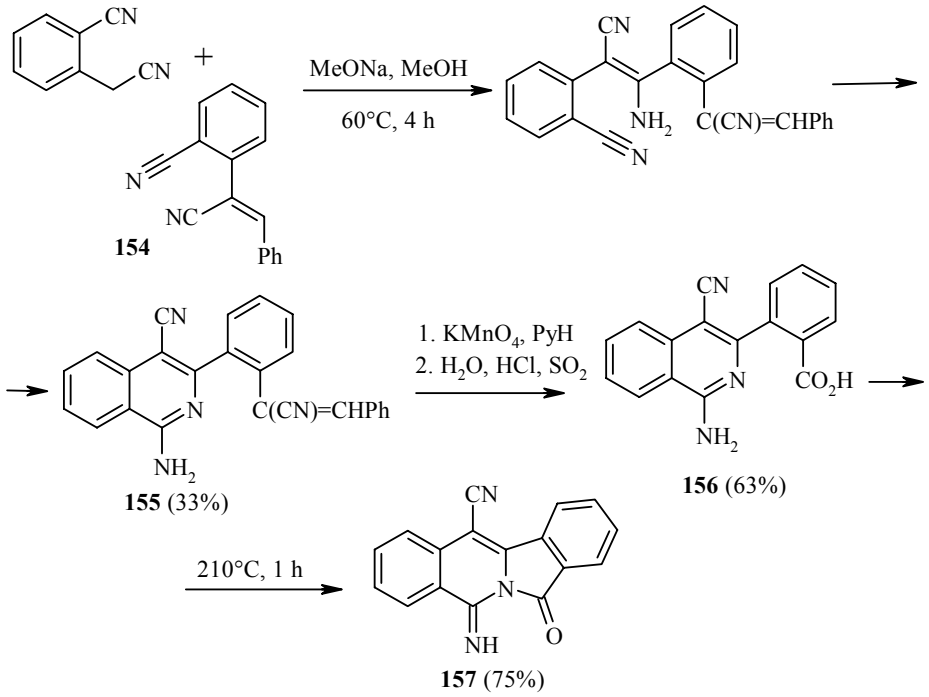
152 (98%)



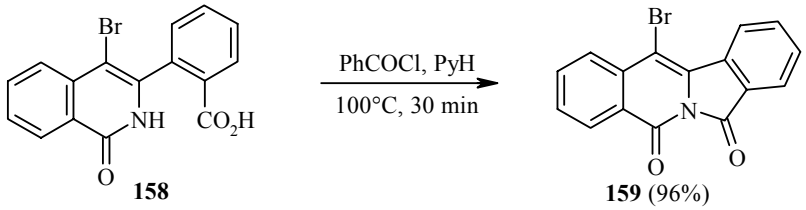
153 (62%)

AIBN = azobis(isobutyronitrile)

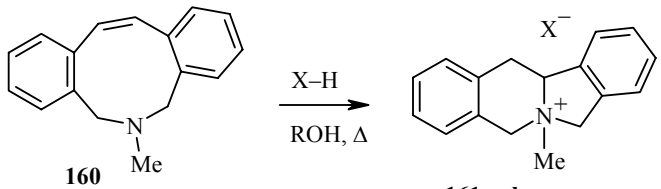
By oxidizing the 1-aminoisoquinoline **155**, obtained by the condensation of *o*-cyanobenzyl cyanide and α,*o*-dicyanostilbene **154** in the presence of sodium methoxide, with subsequent cyclization of the obtained acid **156** it is possible to obtain the polyfunctional isoindolo[2,1-*b*]isoquinoline **157** [65].



The intramolecular cyclization of 4-bromo-3-(*o*-carboxyphenyl)isoquinoline **158** by heating with benzoyl chloride in pyridine leads similarly to the diketo derivative **159** [66].

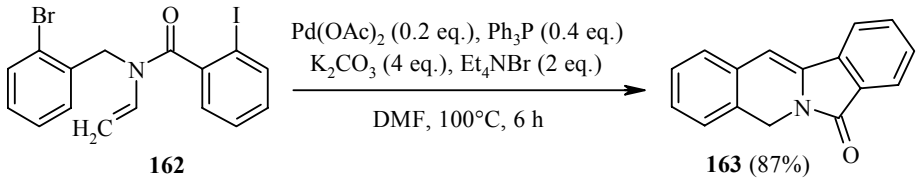


2.2.2. Other Methods for the Synthesis of Isoindolo[2,1-*b*]isoquinolines. Of the specific methods for the synthesis of isoindolo[2,1-*b*]isoquinolines it is necessary to mention the transannular cyclization of the nine-membered enamine **160** to quaternary isoindolo[2,1-*b*]isoquinolinium salts **161** [67].



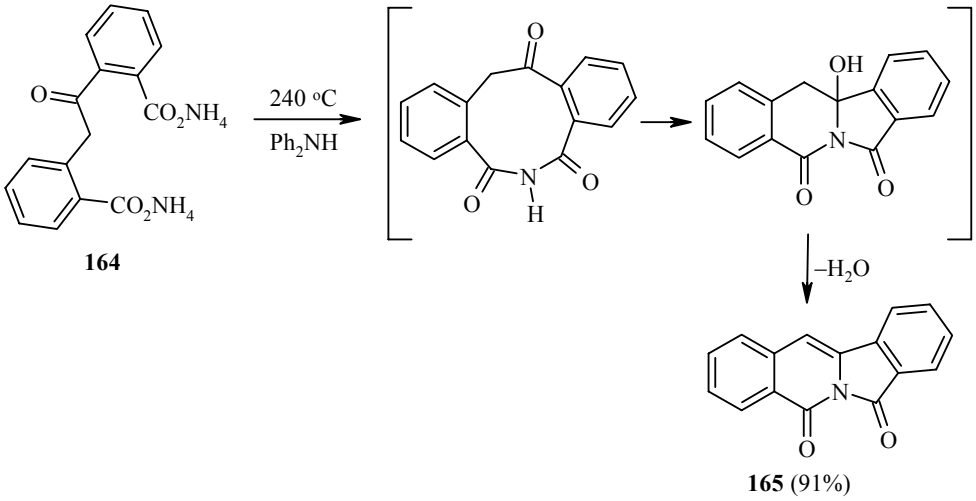
a X = I, **b** X = Br, **c** X = OH, **d** X = OMe, R = Me or Et

The unsaturated amide **162**, produced by the reaction of *o*-bromobenzylamine with acetaldehyde and *o*-iodobenzoyl chloride, is converted into isoindolo[2,1-*b*]isoquinoline **163** under the conditions of a standard Heck reaction [68].



162 **163** (87%)

When the diammonium salt of 2,2'-dicarboxydeoxybenzoin **164** is heated in diphenylamine the isoindolo[2,1-*b*]isoquinoline **165** is formed [69].



164

165 (91%)

By analyzing the data presented in both parts of this review it can be concluded that the most widely studied tetracycles containing an annelated [1,2]isoindole fragment are the isoindolo[1,2-*b*]benz-3-azepines. Chemists have also shown considerable interest in isoindolo[1,2-*a*]isoquinolines. There is hardly published information on the chemical transformations and synthesis of isoindolo[2,1-*b*]benz-2-azepines and isoindolo[2,1-*a*]quinolines, which are of interest in connection with their potential physiological activity.

The work was carried out with financial support from the Russian Fundamental Research Fund (grant No. 04-03-32433).

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