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

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Data on methods for the construction of tetracyclic systems in which an isoindole ring is condensed with benzazepines and benzazocines on the [1,2] side are reviewed. The reaction conditions and approaches leading to isoindolobenzazepines and isoindolobenzazocines are discussed. Examples of the synthesis of physiologically active natural alkaloids with the structure of the above-mentioned condensed isoindoles are presented. Data for 1959-2004 are included.

Keywords: alkaloids, isoindolobenzazepines, isoindolobenzazocines, synthesis methods.

The interest in the development of methods for the synthesis of tetracyclic structures in which an isoindole fragment is annelated with quinoline, isoquinoline, or benzazepine fragments is due to the wide spectrum of physiological activity and the widespread occurrence of such structures in nature.

In spite of the considerable amount of experimental data there are no papers summarizing methods for the construction of such structures.

In the present review data on the synthesis of isoindolobenz-3- and isoindolobenz-2-azepines, isoindoloazocines, isoindoloquinolines, and isoindoloisoquinolines are examined systematically. The review is structured in this way because isoindolo[1,2-*b*]benz-3-azepines form the main structural fragment in a large number of alkaloids and the available information on their synthesis is the most comprehensive. In addition to the methods of synthesis, the review contains certain information on the occurrence of the condensed isoindoles in nature and on their physiological activity.

1. ISOINDOLOBENZAZEPINES

The formation of four condensed heterocyclic systems containing an isoindolobenzazepine fragment during the fusion of benzazepine and isoindole rings is theoretically possible: 6H-Isoindolo[2,1-*a*]benz-1-azepine (**1**), 7H-isoindolo[1,2-*a*]benz-2-azepine (**2**), 5H-isoindolo[2,1-*b*]benz-2-azepine (**3**), and 5H-isoindolo[1,2-*b*]benz-3-azepine (**4**).

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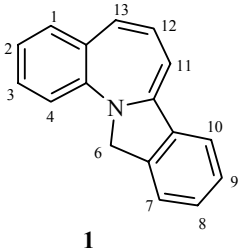

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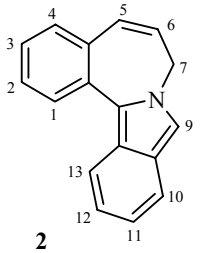

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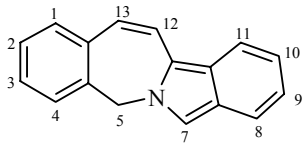

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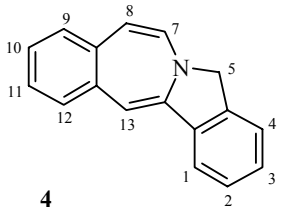

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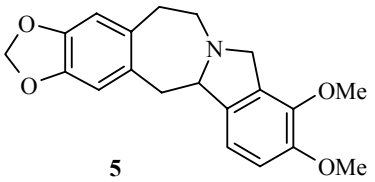
Of the heterocycles **1**-**4** only compound **4** has been studied sufficiently at the present time. Information on methods for the construction of and the chemical characteristics of the polycycles **1** and **2** can be gleaned from a limited number of publications [1-4]. We were only able to find mention of derivatives of isoindolo[2,1-*b*]benz-2-azepines **3** in nine papers [5-13], four of which are patents (10-13).

1.1. Synthesis of Isoindolo[1,2-*b*]benz-3-azepines

A compound containing an isoindolobenzazepine skeleton was first synthesized by Schöpf and Schweickert [14] and was called the "Schöpf–Schweickert base VI" **5**. This amine was later isolated [15] from a plant of the berberis family (*Berberis darwinii*) and was called chilenamine.

In the 1980s a series of isoindolobenzazepine alkaloids [(±)-chilenine **6**, (±)-palmanine **7**, (±)-deoxychilenine **8**, pictonamine **9**, chileninone **10**, and (±)-lennoxamine **11**] were isolated from the same family of plants (*B. empetrifolia*, *B. actinacantha Mart. ex Schult.*, *B. darwinii Hook*, and *B. valdiviana Phil.*) [15-17].

In the same years [18, 19] it was found that isoindolo[1,2-*b*]benz-3-azepin-5-ones **12** exhibit cytotoxic activity toward cells affected by leukemia.



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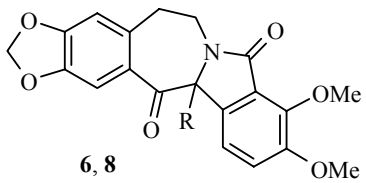
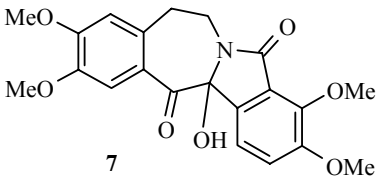


6, **8**

6 R = OH, **8** R = H



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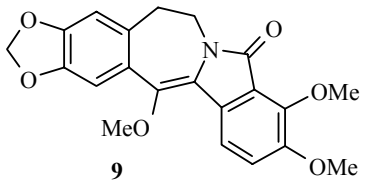

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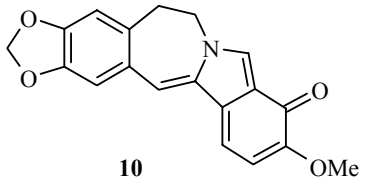

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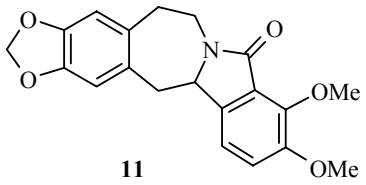

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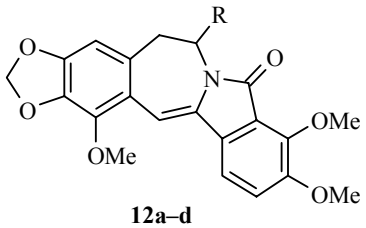


12a–d

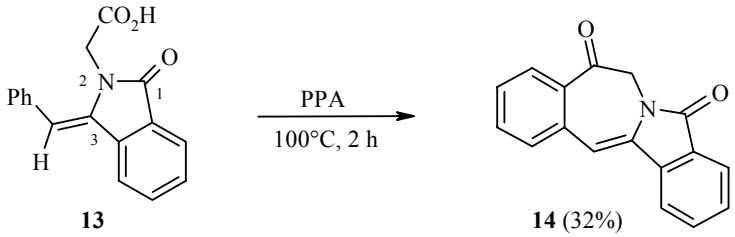
12 **a** R = OH, **b** R = OMe, **c** R = OEt, **d** R = NMe_2

The last fact and also the unique structure make these compounds interesting subjects for the synthesis of various biologically active compounds. All this, together with the discovery of a large number of natural compounds, aroused the interest of chemists in the isoindolobenzazepine system, and this led in turn to the development of methods for the construction of the isoindolo[1,2-*b*]benz-3-azepine skeleton.

The principal methods for the synthesis of isoindolo[1,2-*b*]benz-3-azepines can be divided into three groups, i.e., annelation of the azepine fragment to an already existing isoindole fragment or *vice versa* or synthesis of the isoindolobenzazepines from a natural raw material (the readily obtainable berberine alkaloids). In recent years original methods have appeared for the synthesis of isoindolobenzazepines from ten-membered lactams, diazoketamides, by rearrangement of isoindoloquinolines, and these are summarized in sections 1.1.5-1.1.7.

1.1.1. Synthesis of Isoindolo[1,2-*b*]benz-3-azepines from Isoindole Derivatives. Syntheses of isoindolobenzazepines based on various phthalimidines have found widespread use on account of their simplicity, the relatively small number of stages, and the high yields.

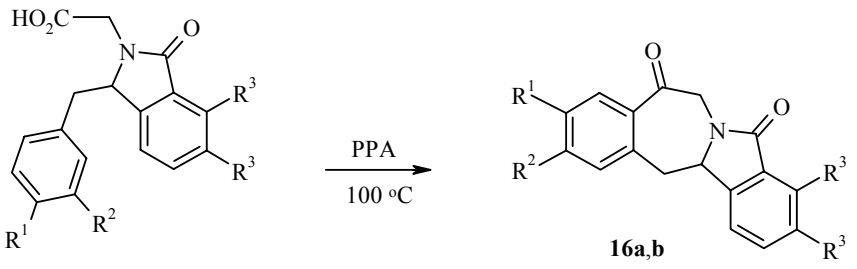
When *Z*-2-carboxymethyl-3-benzylidenephthalimidine (**13**), synthesized from 3-benzylidene-phthalimidine and sodium glycinate, is heated in PPA, dihydroisoindolo[1,2-*b*]benz-3-azepine (**14**) is formed [20].



13 **14** (32%)

For the synthesis of tetrahydroisoindolo[1,2-*b*]benz-3-azepines **16** it is possible to use the substituted carboxymethyl-3-benzylphthalimidines **15**, obtained by catalytic reduction of the corresponding 2-carboxymethyl-3-benzylidenephthalimidines [21, 22].

In the case of compound **15c** it was not possible to select suitable cyclization conditions. In all the experiments either mixtures of unidentifiable compounds were obtained or the initial acid **15c** was recovered.

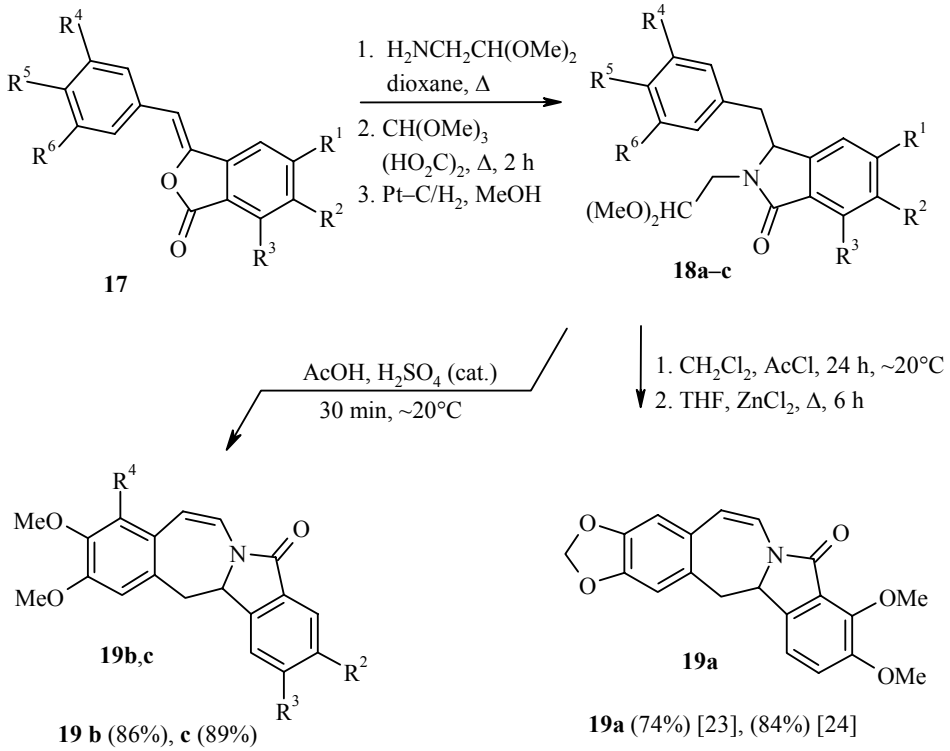


15a–c **16a**,**b**

16 a (64%), **b** (81%)

a $R^1 = R^2 = OMe$, $R^3 = H$; **b** $R^1 = R^2 = R^3 = OMe$; **c** $R^1+R^2 = OCH_2O$, $R^3 = OMe$

Dihydroisoindolo[1,2-*b*]benz-3-azepine (**19a**) was obtained from N-2,2-dimethoxyethyl-3-benzylphthalimidine (**18a**) in the presence of zinc chloride [23]. Cyclization of the analogous acetals **18b**,**c** was later realized by the action of catalytic amounts of sulfuric acid [24].

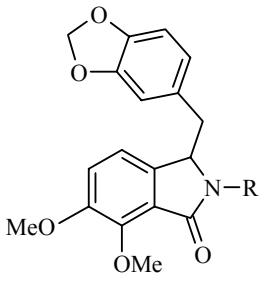


17 **18a–c** **19b**,**c** **19a**

19 b (86%), **c** (89%) **19a** (74%) [23], (84%) [24]

19 a $R^1 = R^2 = OMe$, $R^3 = R^4 = H$, $R^5+R^6 = OCH_2O$; **b** $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = R^6 = OMe$;
c $R^1 = H$, $R^2+R^3 = OCH_2O$, $R^4 = R^5 = R^6 = OMe$

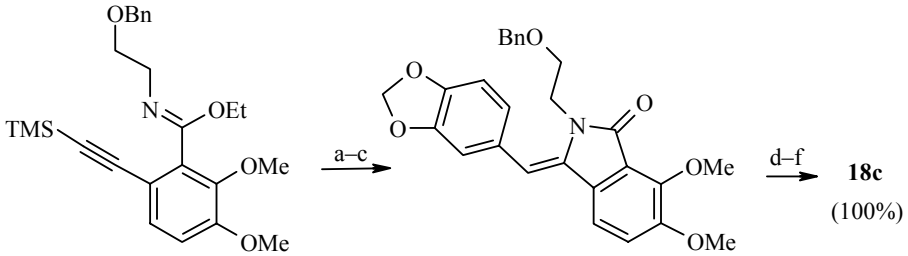
It should be noted that only hydrolysis of the acetal group of compound **18a** is observed under the normal conditions for the cyclization of aminoacetals (treatment with formic or sulfuric acids). Resin formation is observed if the temperature is increased or boron trifluoride etherate is used. A small yield of the desired compound **19a** is only obtained if TsOH is used as catalyst. It was only possible to obtain an acceptable yield of the isoindoloazepine **19a** by successive reaction of the initial acetal **18a** with acetyl chloride and zinc chloride. The authors suggest that the reaction of the isoindolone **18** with acetyl chloride leads to the formation of a mixture of chloromethoxy and vinyl derivatives **18d**,**e**, which then undergo cyclization under the influence of the Lewis acid [23].



18d,e

d R = –$CH_2CH(Cl)OMe$, **e** R = –$CH{=}CH_2$

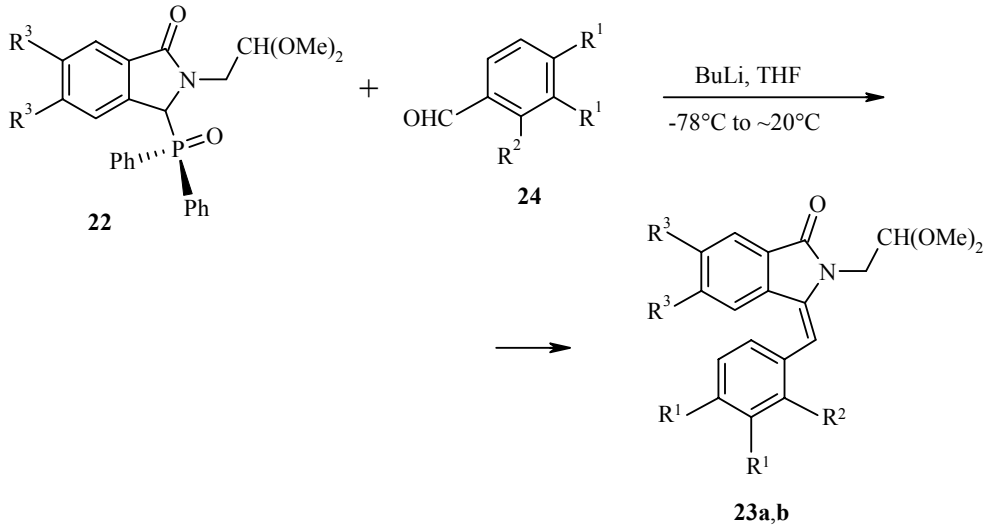
The initial dimethyl acetals **18** were obtained from the substituted 3-benzylidenephthalide (**17**) [23]. A different method was later proposed for the synthesis of the phthalimidines **18** [25], in which the key stage was intramolecular cyclization of the alkynes **20**, taking place through the intermediate alkylidenelactams **21**.



20 **21** (90%) **18c** (100%)

a) trimethylchlorosilane, NaI, MeCN, 0 → ~20°C, 12 h; b) $Pd(OAc)_2$, PPh_3, Ag_2CO_3, Et_3N, 1-I-2,3-$(OCH_2O)C_6H_3$, Bu_4NCl, THF, ~20°C, 3 h; c) hexamethyldisilazanyllithium, THF, 0 → ~20°C, 1 h; d) Pd–C/H_2, THF–MeOH–AcOH, ~20°C, 36 h; e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 → 0°C; f) TsOH, $CH(OMe)_3$, MeOH, Δ

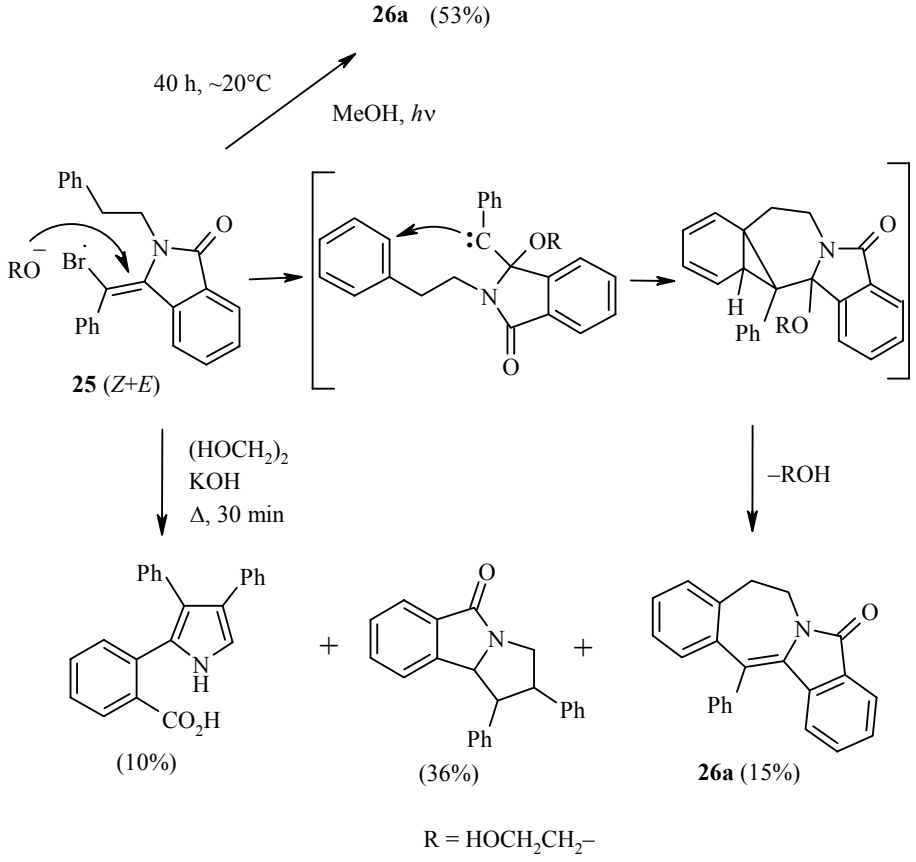
The 3-benzylidenephthalimidines **23** can also be obtained by the Horner reaction [24] from the readily obtainable substituted benzaldehydes **24** and phosphorylated isoindolinones **22**, containing a dimethyl acetal group.



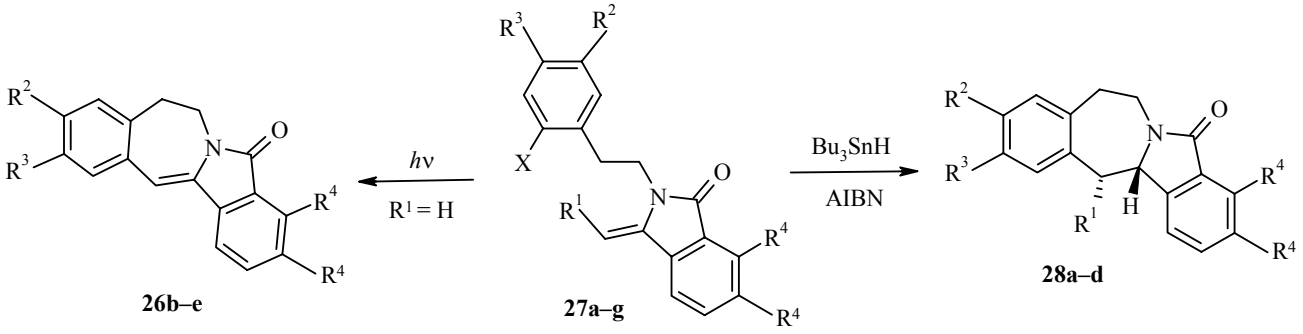
22 **24** **23a**,**b**

23 a R^1 = OMe, $R^2 = R^3$ = H (89%); **b** $R^1 = R^2$ = OMe (95%), $2R^3 = OCH_2O$

Three compounds, one of which is dihydroisoindolo[1,2-*b*]benz-3-azepine **26a** (15%), are formed when 3-(α-bromobenzylidene)-2-phenethylphthalimidine (**25**) is heated in ethylene glycol in the presence of alkali; only isoindolobenzazepine **26a** (53%) is formed when a methanol solution of the phthalimidine **25** is irradiated with a mercury lamp [26]. The authors propose a mechanism for the rearrangement of the phthalimidine **25** under alkaline conditions,



Irradiation of benzene solutions of N-[α-(2-halophenethyl)]phthalimidines **27a-e** in the presence of triethylamine [27] or under the conditions of the Heck reaction [28] leads to the formation of the dihydroisoindolo[1,2-*b*]benz-3-azepine **26b-e**. Radical cyclization of N-[α-(2-bromophenethyl)]phthalimidines **27a**,**b**,**f**,**g** leads to tetrahydroisoindolo[1,2-*b*]benz-3-azepines **28a-d** [29, 30].



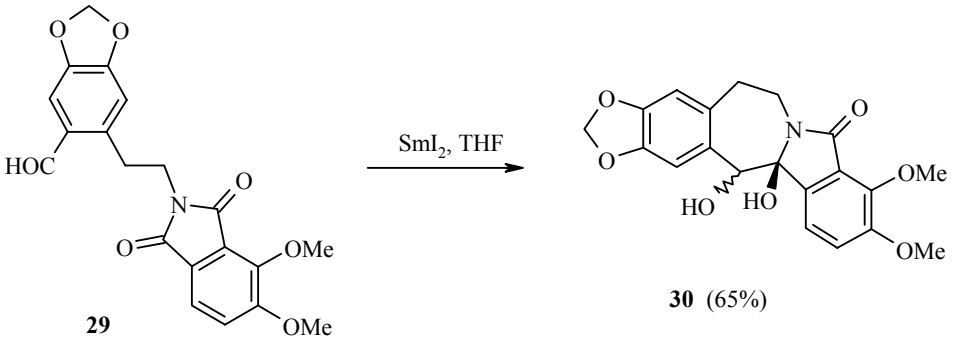
AIBN – azobis(isobutyronitrile)

TABLE 1. The Preparation Conditions and Yields of Compounds **26** and **28***

27	R^2	R^3	R^4	Cyclization conditions	Produkt	Yield, %
a	OMe	OMe	H	*hν*, 2537 Å, PhH, NEt_3	**26b**	20
				Bu_3SnH, AIBN, PhH, Δ	**28a**	81
b	OCH_2O		OMe	*hν*, 2537 Å, PhH, NEt_3	**26c**	22
				Bu_3SnH, AIBN, PhH, Δ	**28b**	61
c	OMe	OMe	OMe	*hν*, 2537 Å, PhH, NEt_3	**26d**	Not indicated
d	H	H	H	$Pd(OAc)_2$, K_2CO_3, LiCl, 120°C, DMF	**26e**	70
e	OCH_2O		OMe	$Pd(OAc)_2$, K_2CO_3, LiCl, 120°C, DMF	**26c**	10
				$Pd(OAc)_2$, Bu_4NCl, $NaHCO_3$, DMF, 110°C, 18 h		50
				$Pd(OAc)_2$, Bu_4NCl, $NaHCO_3$, 3 Å MS*[2], MeCN, Δ, 16 h		28
				$Pd(OAc)_2$, Bu_4NCl, KOAc, 3 Å MS, DMF, 110°C, 18 h		34
				$Pd(OAc)_2$, Bu_4NCl, KOAc, DMF, 110°C, 18 h		54
f	OMe	OBn	H	Bu_3SnH, AIBN, PhH, Δ, 6 h	**28c**	40
g	OMe	OMe	H	Bu_3SnH, AIBN, PhH, Δ	**28d**	93

* **27 a** R^1 = H, **g** R^1 = Ph; **a-c**, **f**, **g** X = Br, **d**, **e** X = I.
*[2] MS – molecular sieves.

In 2002 Japanese chemists [31] proposed a new approach to the synthesis of isoindolo[1,2-*b*]benz-2-azepines, the key stage of which was intramolecular cyclization of N-[α-(2-formylphenethyl)]phthalimidine **29** in the presence of samarium(II) iodide. The reaction is stereoselective, and a 3:1 mixture of the *cis* and *trans* diastereomers of isoindolobenzazepine **30** is formed.

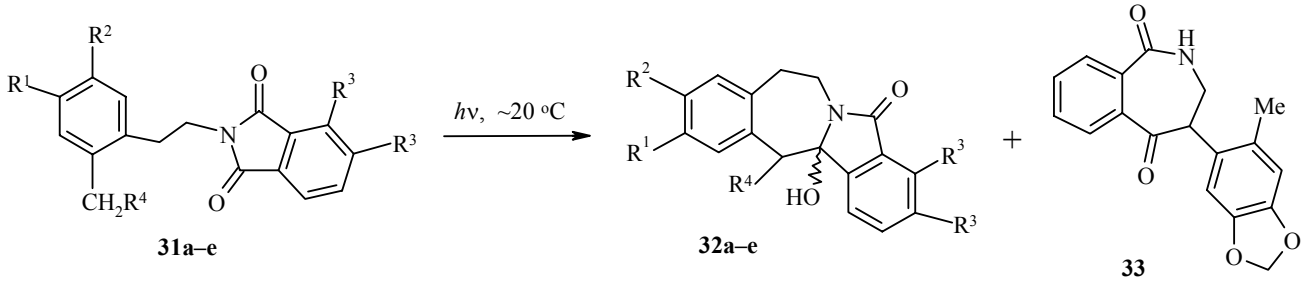


29 **30** (65%)

The photocyclization of the phthalimidines **31**, containing an *o*-methylphenyl substituent in the N-side chain, leads to the formation of isoindolo[1,2-*b*]benz-3-azepines **32** [32, 33]. In the case of compound **31c** the benz-2-azepine **33** is formed as a side product with a yield that depends on the reaction conditions. The sulfide **32e** is unstable and undergoes dehydration during isolation. The initial phthalimidines **31a-d** are synthesized by the reaction of the respective phthalic anhydrides and β-phenylethylamines at 150°C. The thioether **31e** is easily formed from compound **31b** by the action of *t*-BuSH (HOAc, $HClO_4$).

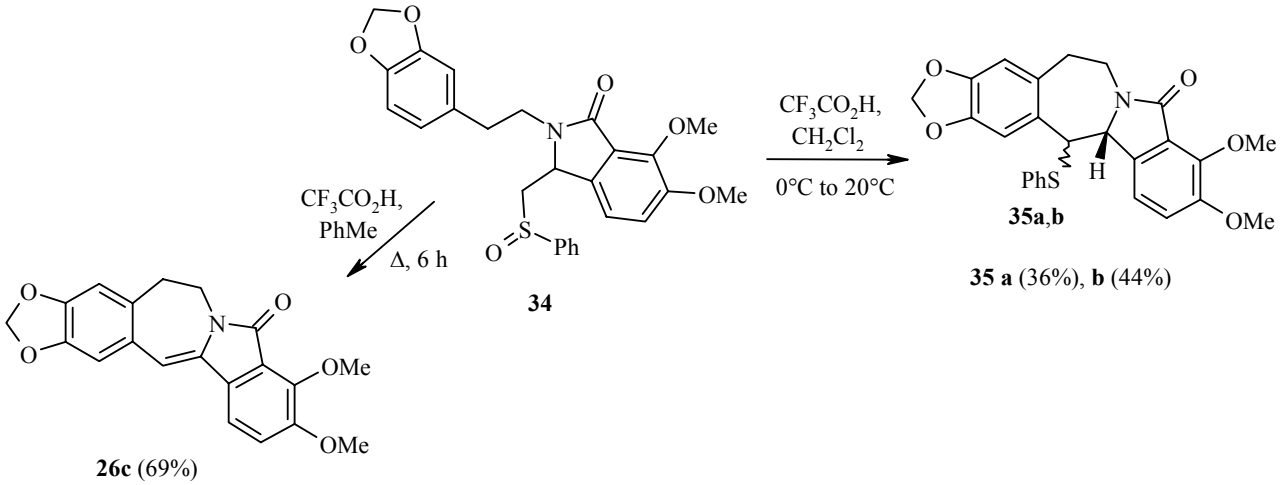
TABLE 2. The Preparation Conditions and Yields of Compounds **32** and **33**

31	R^1	R^2	R^3	R^4	Conditions (irradiation with mercury lamp)	Yield, %		
						32	**33**	**31** (recovery)
a	H	H	H	H	MeCN, 500 W, 7 h	5	—	29
b	OMe	OMe	H	H	Me_2CO, 500 W, 2 h 30 min	19	—	41
					Me_2CO, 1 kW (Pyrex), 1 h 30 min	27	—	55
c	OCH_2O		H	H	Me_2CO, 500 W, 35 min	9	10	30
					Me_2CO, 1 kW (Pyrex), 45 min	17	14	19
d	OMe	OMe	OMe	H	Me_2CO, 500 W	24	—	8
					Me_2CO, 1 kW (Pyrex)	35	—	21
e	OMe	OMe	H	*t*-BuS	Me_2CO	Not isolated	—	—



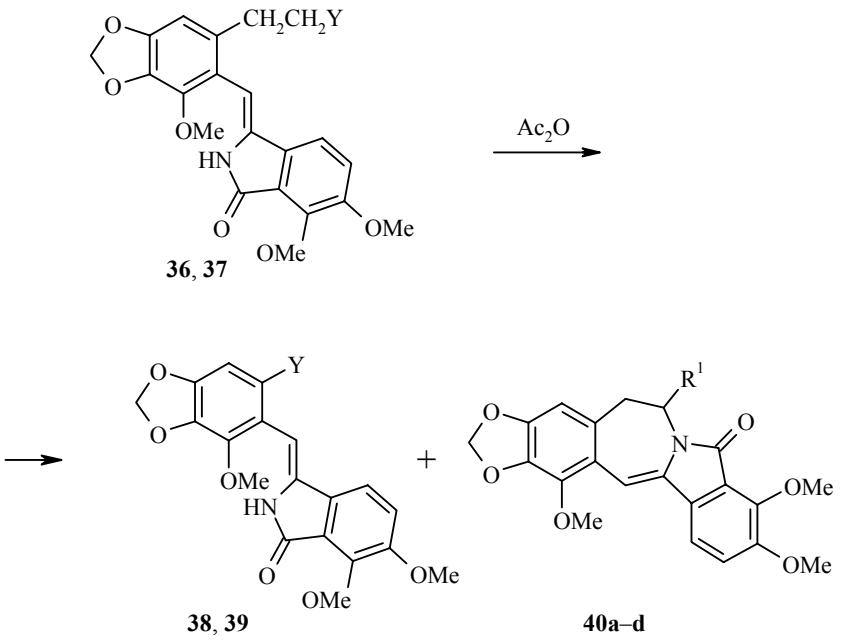
31a–e **32a–e** **33**

The reaction of the sulfoxide **34** with trifluoroacetic acid in dichloromethane leads to the formation of 13-phenylthioisoindolo[1,2-*b*]benz-3-azepine **35** in the form of a mixture of diastereomers **35a** (*cis*-SPh) and **35b** (*trans*-SPh). The authors suggest that this transformation takes place through a Pummerer rearrangement followed by intramolecular substitution of the obtained α-trifluoroacetoxy sulfide. Dihydro-isoindolobenzazepine **26c** was isolated when the reaction was carried out in boiling toluene. The reaction probably takes place through the formation of the phenylsulfanyl derivative **35**, which eliminates thiophenol under the reaction conditions [34, 35].



Isoindolobenzazepines can also be obtained from methyl iodide or *Z*-narceine imide [36-38]. Thus, in addition to the expected *Z*- and *E*-narceone imides **38** (R = –CH=CH_2) dihydroisoindolo[1,2-*b*]benz-3-azepine **40a** was isolated with a yield of 2% during the thermal decomposition of *Z*-narceine imide **36**.

The composition of the reaction products during the treatment of *Z*-narceine imide N-oxide **37** with acetic anhydride depends on the conditions. When the N-oxide **37** was heated with acetic anhydride [37] dihydroisoindolo[1,2-*b*]benz-3-azepine **40b** was formed with a yield of 54% instead of the expected dealkylation product. In chloroform at room temperature [38] a mixture of isoindolobenzazepines **40b**,**c** and the imide **39** is formed. If the reaction is carried out in the presence of pyridine [38] the isoindolobenzazepines **40b**,**d** are formed.



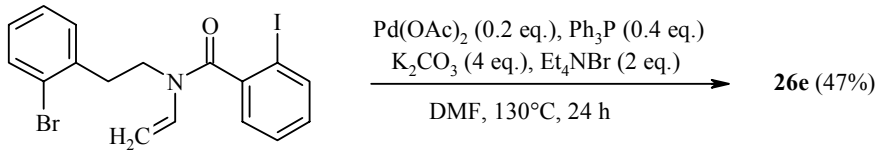
36 Y = NMe_3I; **37** Y = $N(O)Me_2$; **38** Y = –CH=CH_2; **39** Y = –$CH_2N(Me)Ac$;

40 a R^1 = H, **b** R^1 = NMe_2, **c** R^1 = OH, **d** R^1 = OAc

TABLE 3. The Preparation Conditions and Yields of Compounds **40**

Initial compound	Reaction condition	Reaction product	Yield, %
36	30% KOH, Δ, 7 h	**38**	92
		40a	2
37	Ac_2O, 40-70°C	**40b**	54
	Ac_2O, $CHCl_3$, 20°C, 50 h	**39**	23
		40b	19
		40c	5
	Ac_2O, PyH, $CHCl_3$, 20°C, 50 h	**40b**	22
		40d	7

Under the conditions of the Heck reaction the enamide undergoes successive cyclization to dihydroisoindolobenzazepine **26e** [39].



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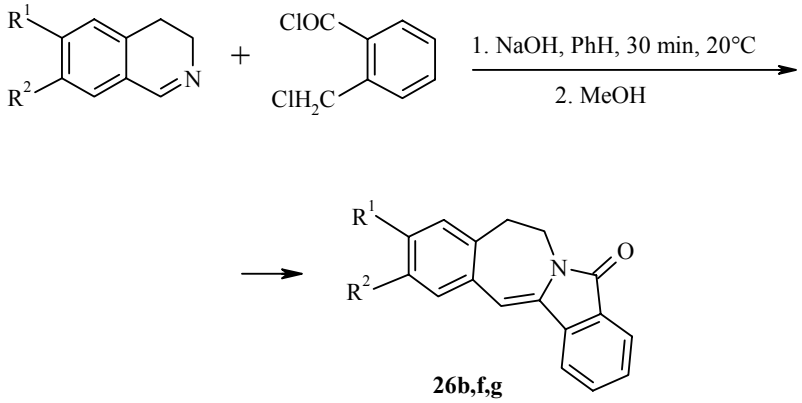
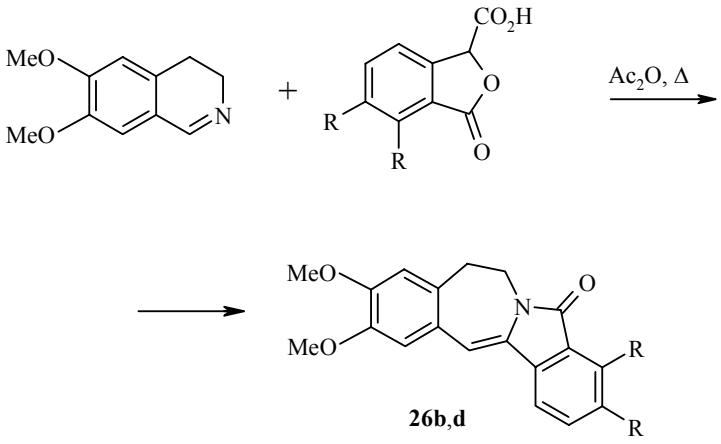
1.1.2. Synthesis of Isoindolo[1,2-*b*]benz-3-azepines from Substituted Isoquinolines. On the basis of a retrosynthetic analysis in 1984 an original single-stage method was proposed for the synthesis of isoindolo[1,2-*b*]benz-3-azepines **26b**,**f**,**g** [40]. It was established that the reaction requires the presence of an oxygen atom at position 6 of the isoquinoline.



26b,f,g

26 b $R^1 = R^2 =$ OMe (59%); **f** $R^1 =$ OMe, $R^2 =$ H (32%); **g** $R^1 + R^2 = OCH_2O$ (27%)

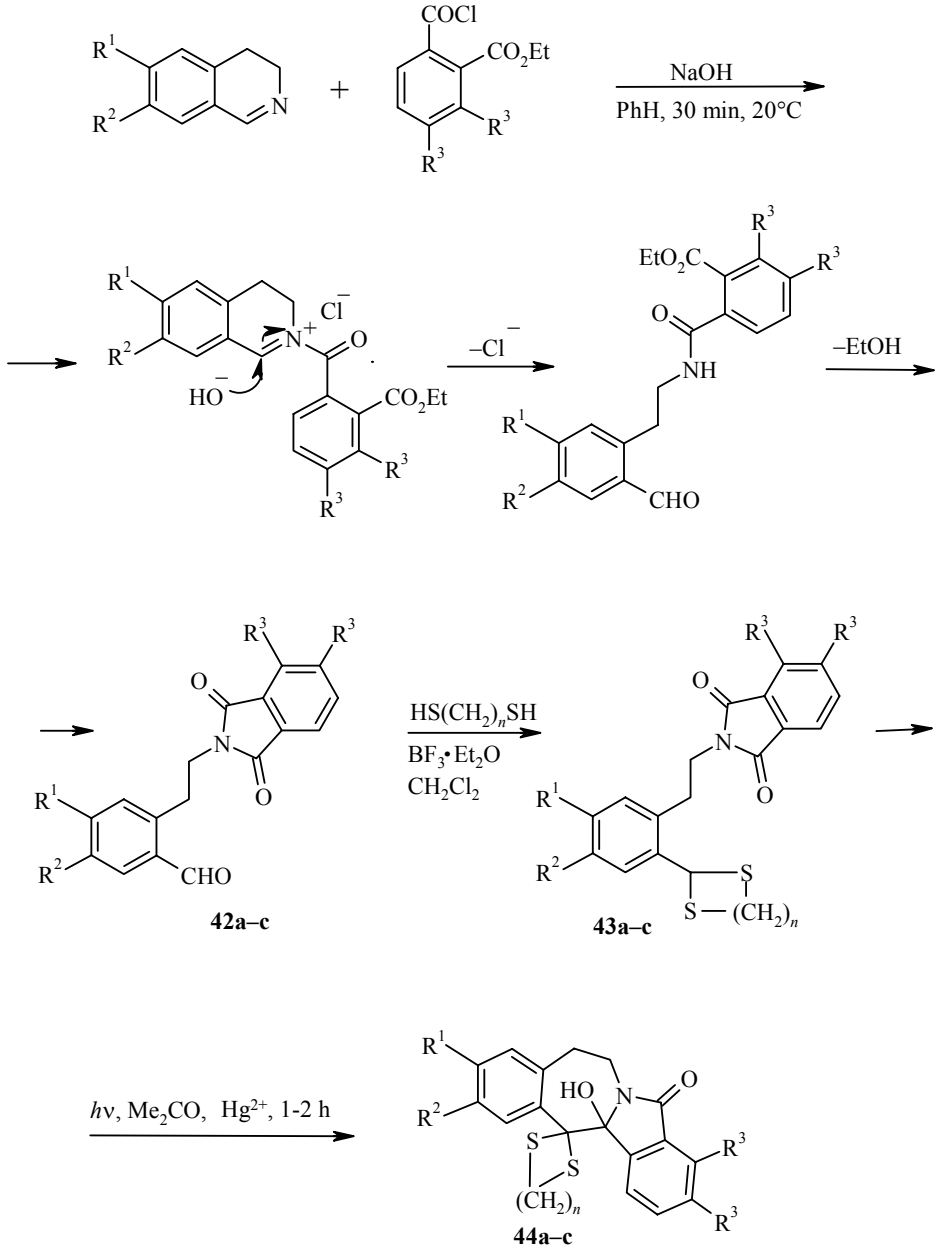
Dihydroisoindolo[1,2-*b*]benz-3-azepines **26b**,**d** are formed according to a similar scheme during the acylation of 3,4-dihydrosisoquinolines with phthalide-3-carboxylic acids [41, 42].



26b,**d**

26 b R = H (59%), **d** R = OMe (50%)

The aldehydes **42** are formed in the reaction of 3,4-dihydroisoquinolines with substituted 2-ethoxycarbonylbenzoyl chlorides in the presence of sodium hydroxide. Thioacetyl protection of the products followed by photocyclization gives tetrahydroisoindolo[1,2-*b*]benz-3-azepines **44** [43, 44]. It was not possible to realize cyclization in the case of the sulfides **43d**,**e** [44].



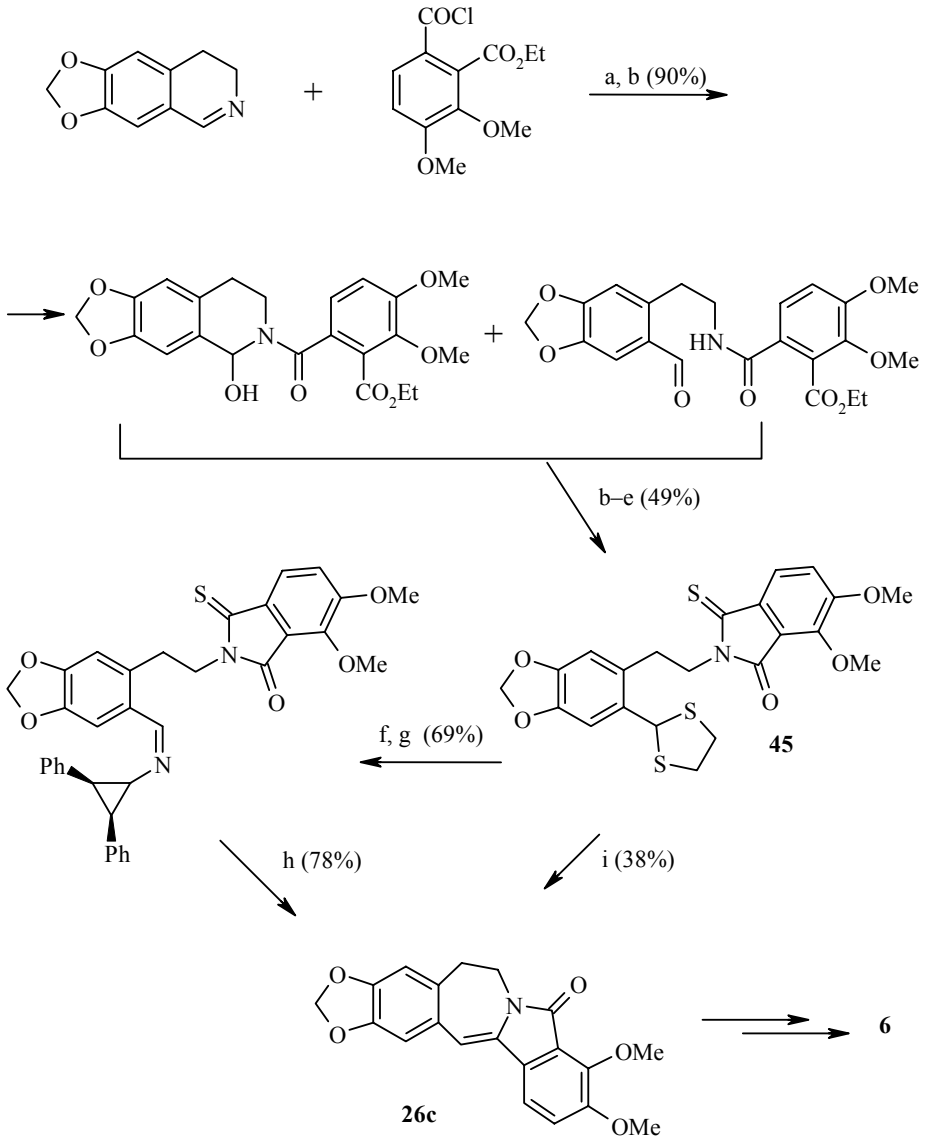
42a–c

43a–c

44a–c

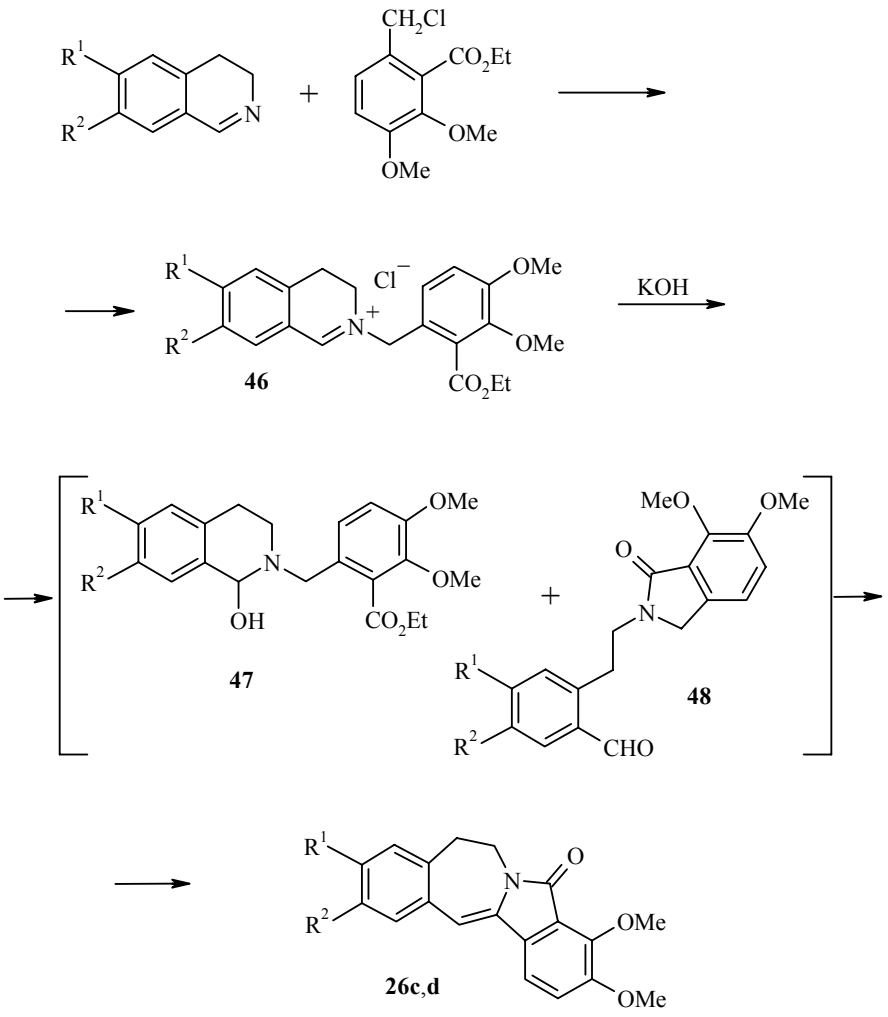
42 a $R^1 = R^2 = OMe$, $R^3 = H$ (78%); **b** $R^1+R^2 = OCH_2O$, $R^3 = H$ (79%); **c** $R^1+R^2 = OCH_2O$, $R^3 = OMe$ (80%);
43 a $R^1 = R^2 = OMe$, $R^3 = H$, $n = 2$ (86%); **b** $R^1 = R^2 = OMe$, $R^3 = H$, $n = 3$ (85%); **c** $R^1+R^2 = OCH_2O$, $R^3 = H$, $n = 3$ (86%);
d $R^1+R^2 = OCH_2O$, $R^3 = OMe$, $n = 2$ (87%); **e** $R^1+R^2 = OCH_2O$, $R^3 = OMe$, $n = 3$ (89%); **44 a** $R^1 = R^2 = OMe$, $R^3 = H$, $n = 2$ (50%);
b $R^1 = R^2 = OMe$, $R^3 = H$, $n = 3$ (30%); **c** $R^1+R^2 = OCH_2O$, $R^3 = H$, $n = 3$ (55%)

In 1989 a method was proposed for the synthesis of chilenine **6** from 6,7-methylenedioxy-3,4-dihydroisoquinoline and 3,4-dimethoxy-2-ethoxycarbonylbenzoyl chloride [45]. The key stage of the synthesis is the previously undescribed carbenoid monophthalimide coupling. Isoindolobenzazepine **26c** was obtained with a smaller yield directly from the thioacetal **45** by reaction with tungsten hexacarbonyl.



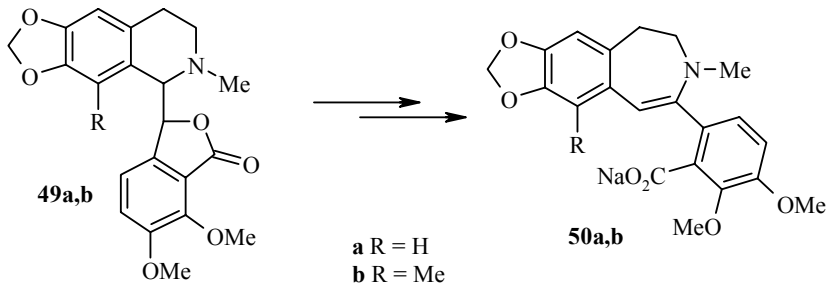
a) CH_2Cl_2, 0°C; b) $NaHCO_3$; c) $HS(CH_2)_2SH$, 0°C, CH_2Cl_2, $BF_3{\cdot}Et_2O$; d) THF, NaH (cat.); e) P_2S_5, PhH, Δ;
f) $CHOCO_2H$, AcOH, HCl (cat.); g) *trans*-1-amino-2,3-diphenylaziridine; h) $Rh(OAc)_2$ (cat.), PhMe, Δ; i) $W(CO)_6$, *o*-$C_6H_4Cl_2$

The alkylation of 6,7-methylenedioxy- or 6,7-dimethoxy-3,4-dihydroisoquinoline in acetonitrile leads to the formation of the iminium chlorides **46**, which undergo cyclization under the influence of bases to the dihydroisoindolo[1,2-*b*]benz-3-azepines **26c** or **26d** respectively [46]. The supposed intermediates (the pseudobase **47** and the lactam **48**) were not isolated.

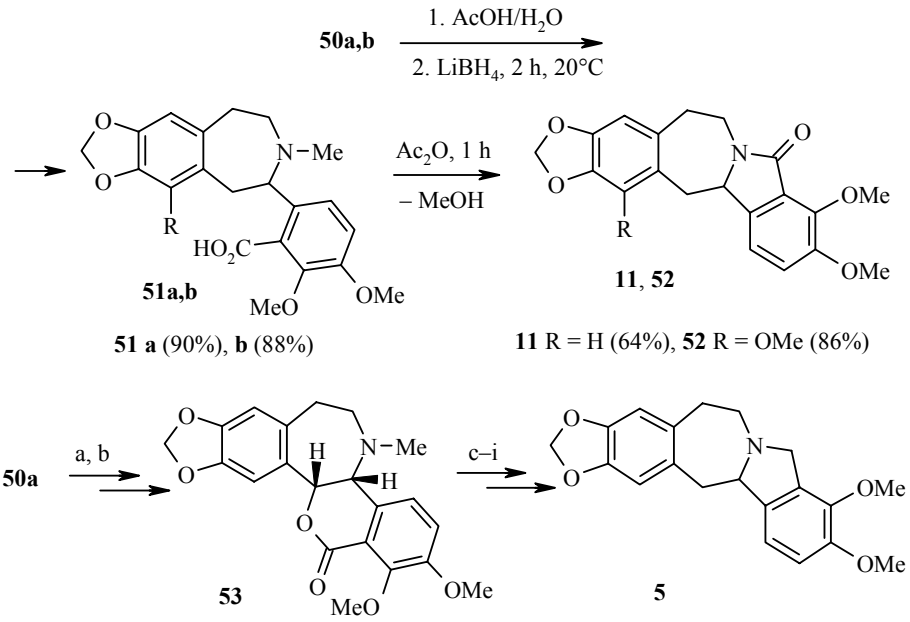


26 c $R^1 = R^2 = OCH_2O$ (73%), **d** $R^1 = R^2 = OMe$ (75%)

1.1.3. Synthesis of Isoindolo[1,2-*b*]benz-3-azepines from Substituted Benz-3-azepines. The successive treatment of sodium 2'-[2-(benz-3-azepine)]benzoates **50a**,**b**, obtained from (-)-β-hydrastine **49a** or (-)-α-narcotine **49b** [47-49], with acetic acid and lithium borohydride gives the saturated 2'-[2-(benz-3-azepine)]benzoic acids **51a**,**b**. Under the influence of acetic anhydride the products undergo N-demethylation and intramolecular cyclization to the isoindolobenzazepines **11** and **52** respectively. By a more complicated scheme, including the cyclization of sodium 2'-[2-(benz-3-azepine)]benzoate **50a** [49] to (-)-*cis*-11-methyl-6-oxorhoeadan **53**, the chilenamine **5** is obtained with a good overall yield.



a R = H
b R = Me

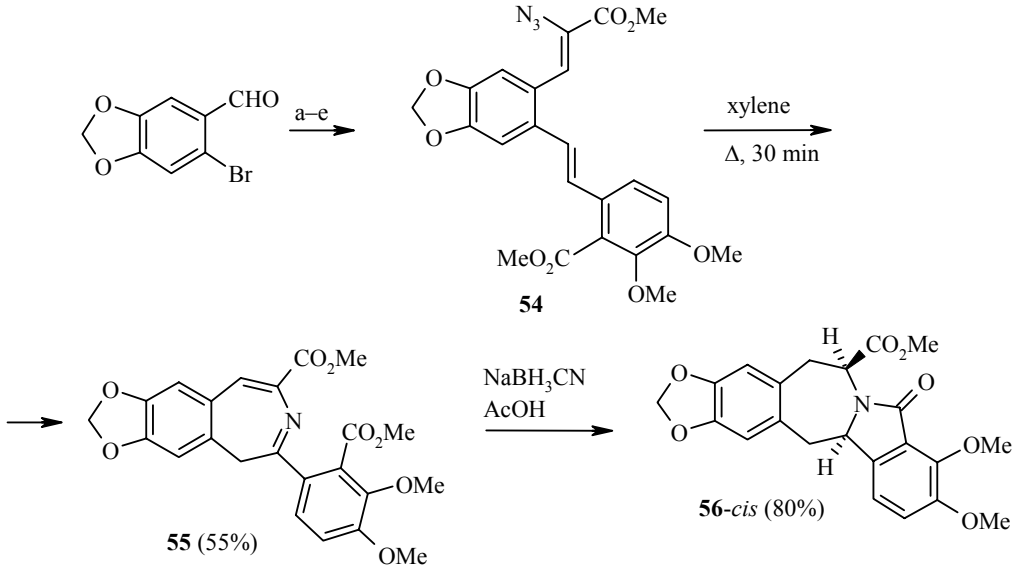


51 a (90%), **b** (88%)

11 R = H (64%), **52** R = OMe (86%)

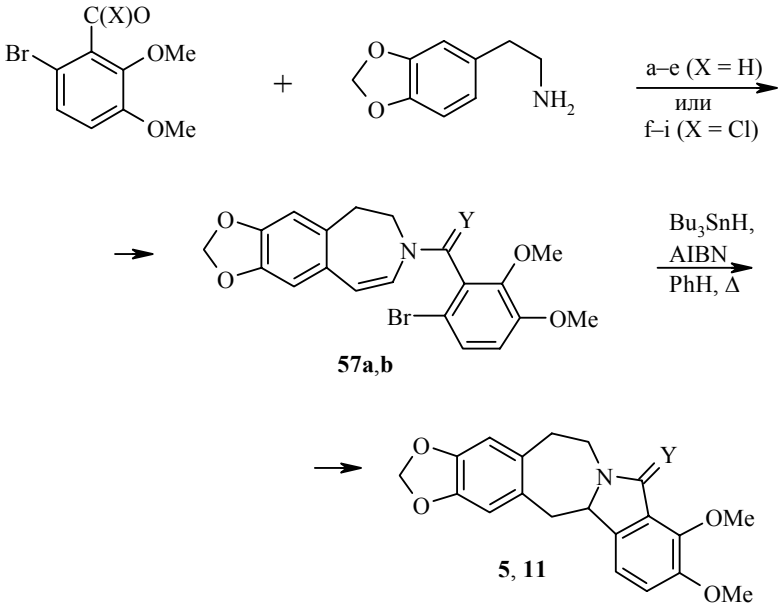
a) H_2O, AcOH, CH_2Cl_2, then EtOH, Ph_2CO, *hν* (46%); b) THF, $LiBH_4$, 20°C, 6 h, then AcOH/Ac_2O, 20°C, 16 h (85%); c) $CHCl_3$, *m*-chloroperbenzoic acid, 20°C, 14 h, then 15% K_2CO_3, 0°C, 1 h (99%); d) $CHCl_3$, $(CF_3CO)_2O$ (49%); e) THF, *p*-tolylsulfonyl isocyanate, 30°C, 15 min (99%); f) THF, 70% Red-al® solution of sodium bis(2-methoxyethoxy)aluminum dihydride $NaAlH_2(OCH_2CH_2OMe)_2$), 15 min, then $CHCl_3/H_2O$, H_2SO_4, -10°C (83%); g) MeOH, $HC(OMe)_3$, $H_2C_2O_4$, 0°C, 14 h (57%); h) MeOH, N_2, then NaOH, 0°C, 10 min (99%); i) EtOH, HCl, N_2, 95°C, 10 min, then EtOH, PtO_2/H_2 (80%)

When boiled in xylene the azidocinnamate **54** undergoes cyclization to 2-arylbenz-3-azepine **55**, the reduction of which with sodium cyanoborohydride in acetic acid followed by nucleophilic attack by the nitrogen atom on the ester group leads to the formation of the isoindolobenzazepine **56** [51, 52]. The initial azidocinnamate **54** was obtained from 2-bromopiperonal by successive transformations.



a) $(HOCH_2)_2$, TsOH (cat.), PhMe, Δ; b) BuLi, Et_2O, -60°C, then DMF; c) $(MeO)_2P(O)$-2-methoxycarbonyl-3,4-methoxyphenyl), *t*-BuOK, THF; d) HCl, CH_2Cl_2; e) $MeO_2CCH_2N_3$, NaOMe, MeOH/THF, 5°C

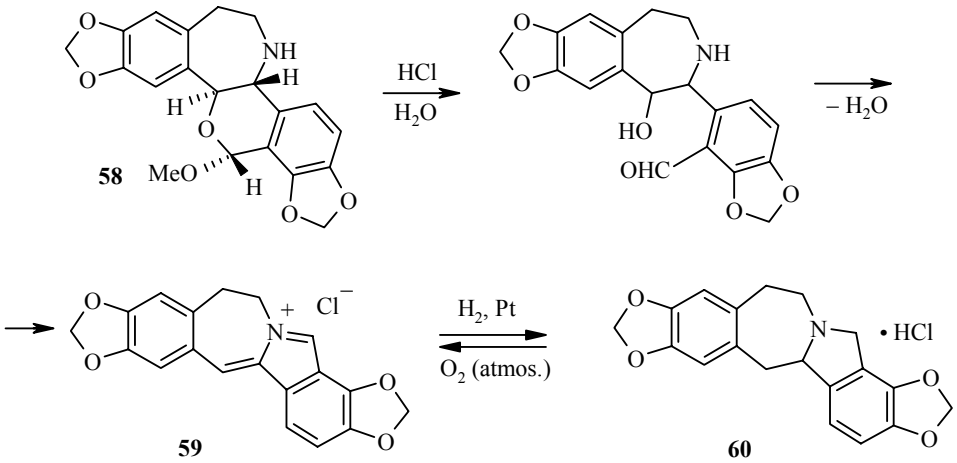
The substituted N-benzyl-4,5-dihydrobenz-3-azepine **57a**, obtained from 2-bromo-5,6-dimethoxybenzaldehyde and β-(3,4-methylenedioxyphenyl)ethylamine, is converted by the action of Bu_3SnH in the presence of azobisisobutyronitrile into chilenamine **5** with a yield of 95% [53]. A similar approach was used for the synthesis of lennoxamine **11** (58%) starting from 2-bromo-5,6-dimethoxybenzoyl chloride [54].



57 a Y = 2H, **b** Y = O; **5** Y = 2H; **11** Y = O

AIBN = azobisisobutyronitrile.
a) CH_2Cl_2, MS (molecular sieves); b) $NaBH_4$, MeOH; c) α-chloro-α-methylthioacetyl chloride, $SnCl_2$, CH_2Cl_2;
d) Zn, AcOH, Δ; e) diisobutylaluminum hydride, THF, -78°C; f) 2,2-dimethyl-1,3-dioxan-5-one, PhMe, MS, then Hunig's base (N,N-diisopropylethylamine), 20 °C, 18 ч; g) $BF_3 \cdot Et_2O$, MeCN, 20°C, 12 h; h) $NaClO_2$, 0°C, 1 h;
i) $Pb(OAc)_4$, $Cu(OAc)_2$, DMF, 105 °C

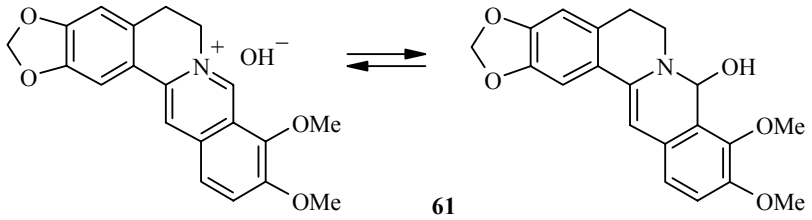
The intense-red iminium salt **59** is formed during the treatment of papaverrubin A **58** with dilute hydrochloric acid. Catalytic reduction of this salt leads to the formation of the leuco base **60**, which is easily oxidized back to compound **59** in air [55, 56].



Such colored iminium salts are form by all the papaverrubin alkaloids. This property of these compounds has been used as a test for opium, since papaverrubin alkaloids are always present in opium [56].

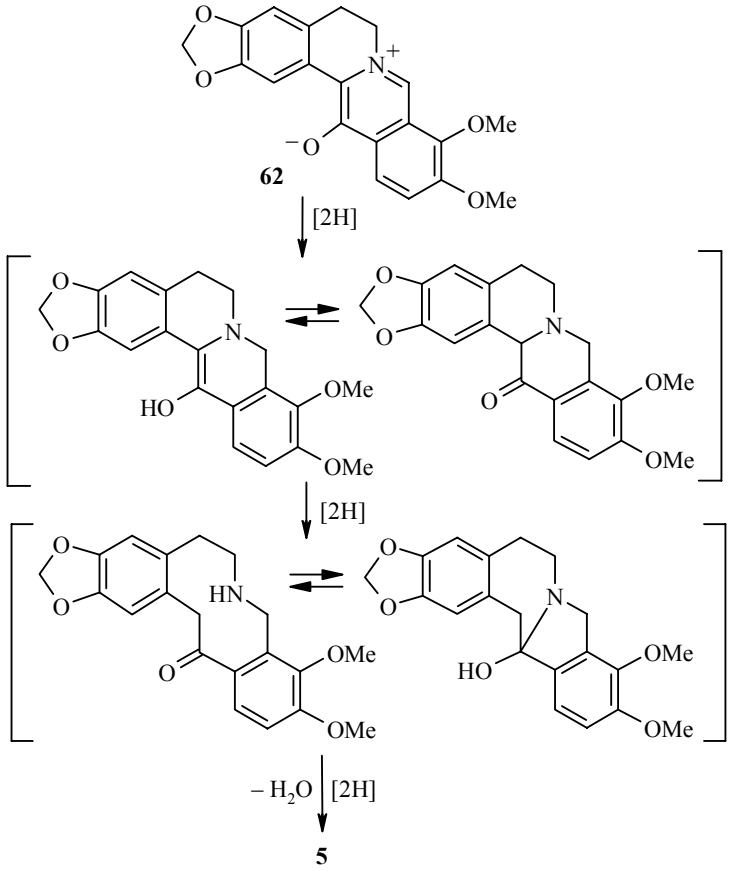
1.1.4. Synthesis of Isoindolo[1,2-*b*]benz-3-azepines from Derivatives of Berberine. Various derivatives of berberine are commercially available substances and can therefore provide suitable starting materials for the synthesis of isoindolo[1,2-*b*]benz-3-azepines.

The most important representative of this class of alkaloids is berberine **61**, which is present in significant amounts in plants of the *Ranunculaceae* (crowfoot), *Berberidaceae* (barberry), and *Rutaceae* (rue) families [56].



61

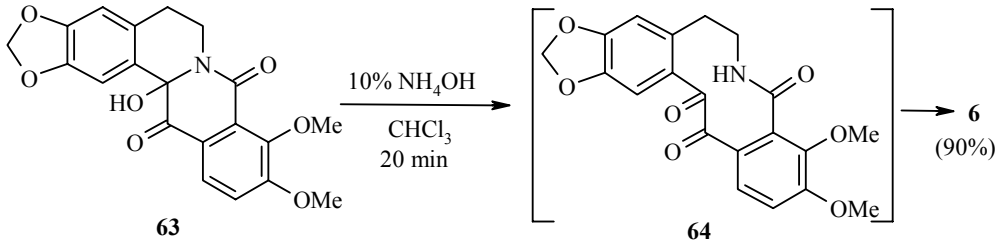
As mentioned above [14], in 1965 the first representative of the class of isoindolo[1,2-*b*]benz-3-azepines, the "Schöpf–Schweickert base VI" **5**, was obtained by the reduction of berberinephenolbetaine **62**.



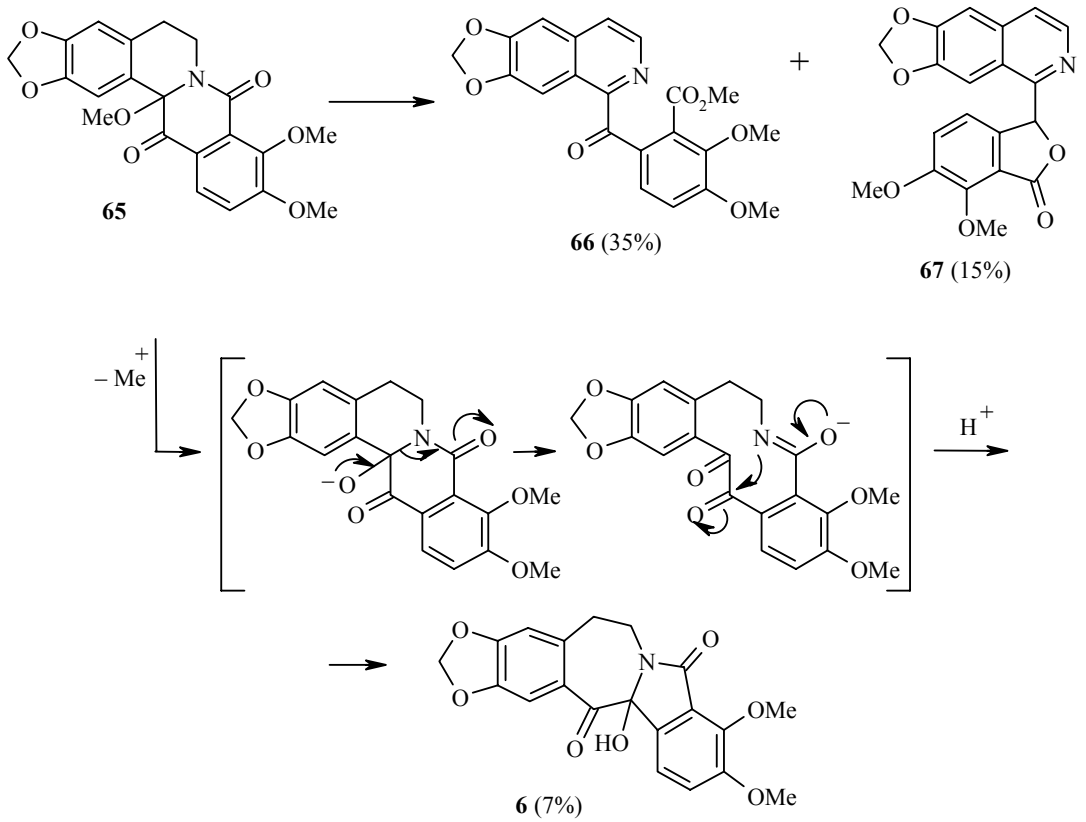
62

5

A skeletal rearrangement, leading to the formation of (±)-chilenine **6**, occurs when a solution of 8,13-dioxo-14-hydroxycanadine **63**, present in plants of the barberry family [57-62], is treated with ammonium hydroxide in chloroform. It is suggested that the rearrangement takes place through the formation of the intermediate **64**.



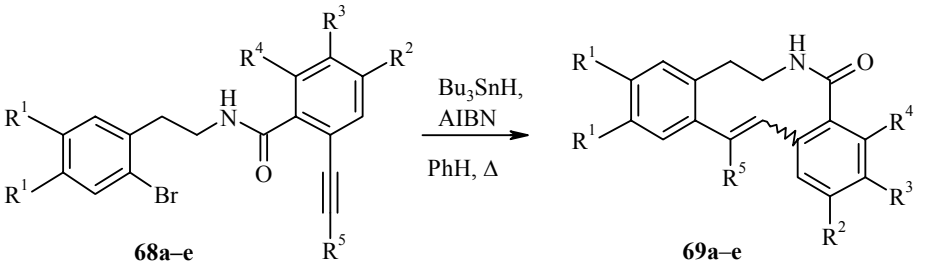
Three substances, one of which is (±)-chilenine **6**, are formed when 8,13-dioxo-14-methoxycanadine **65** is heated (175°C, 20 min) at reduced pressure. A mechanism for the formation of the tetracycle **6** was proposed in [62].



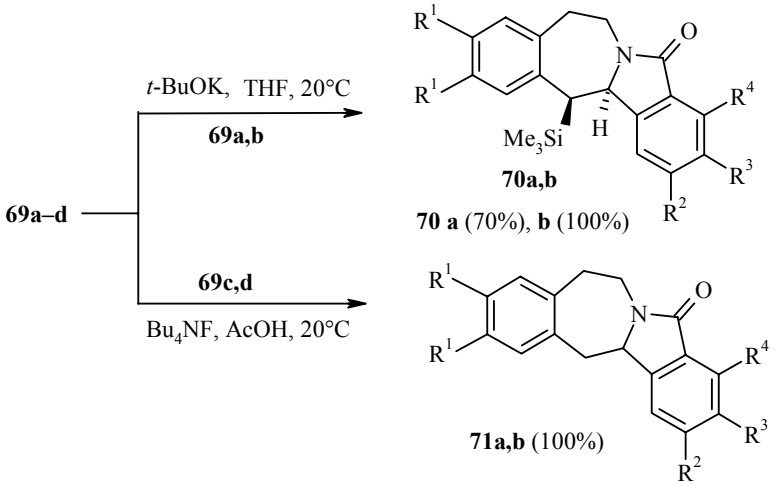
1.1.5. Synthesis of Isoindolo[1,2-*b*]benz-3-azepines from Ten-membered Lactams. Isoindolo[1,2-*b*]-benz-3-azepines **70** and **71** can be obtained by [7,5]-transannular cyclization of ten-membered lactams **69a-e**. The initial macrolactams **69** are synthesized from *o*-(trimethylsilylethynyl)benzamides **68a-d** [29, 63, 64] of unsubstituted *o*-ethynylbenzamide **68e** [65] by radical 10-*endo*-macrocyclization.

In the case of the alkynes **68a-d** cyclization takes place stereoselectively with the formation of only the *Z*-isomer, while in the case of compound **68e** a mixture of *Z*- and *E*-isomers (47:24) of the polycycles **69** is formed.

13-Trimethylsilyl-substituted **70** or 13-unsubstituted **71** isoindolo[1,2-*b*]benz-3-azepines can be obtained from the amides **69a-d**, depending on the reaction conditions.

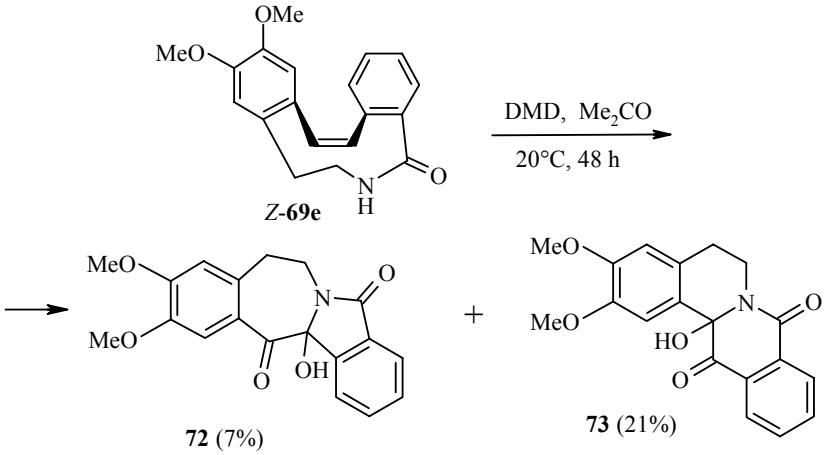


69 a (60%), **b** (74%), **c** (75%), **d** (70%), **e** (*Z* + *E*) (71%)



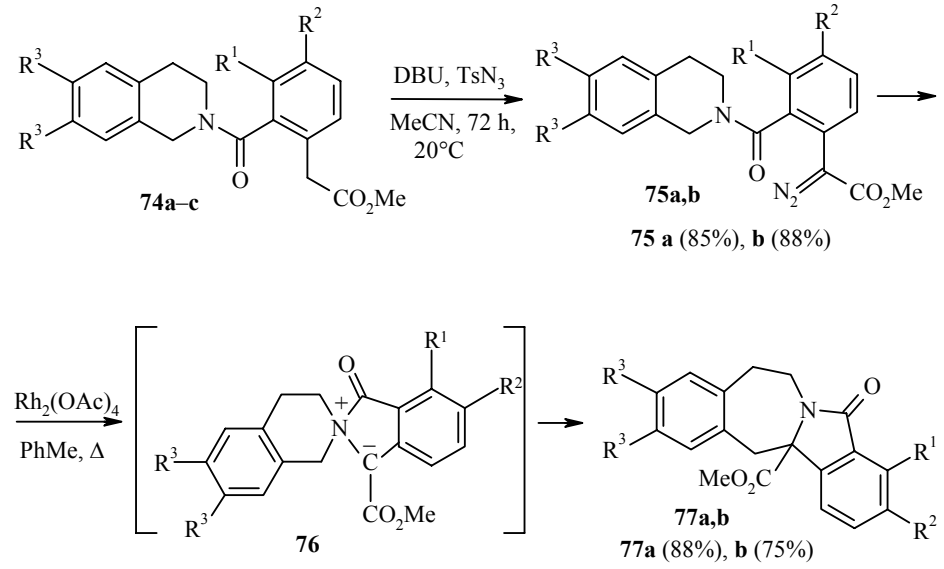
69, **70 a** $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = SiMe_3$; **b** $R^1 = OCH_2O$, $R^2 = H$, $R^3 = R^4 = OMe$, $R^5 = SiMe_3$; **69c**, **71a** $R^1 = OMe$, $R^2 = R^3 = R^4 = H$, **69d**, **71b** $R^1 = R^4 = H$, $R^2 = R^3 = OMe$, **69 c**, **d** $R^5 = SiMe_3$; **69e** $R^1 = OMe$, $R^2 = R^3 = R^4 = R^5 = H$

Treatment of the *E*-isomer **69e** with dimethyldioxirane leads to a mixture of 13-hydroxy-2,3-dimethoxy-6,8,13,13a-tetrahydro-5H-isoquino[3,2-*a*]isoquinolin-8-one and 2,3-dimethoxy-5,6-dihydro-8H-isoquino[3,2-*a*]-isoquinolin-8-one. From the *Z*-isomer **69e** under these conditions isoindolobenzazepine **72** is formed as side product in addition to isoquino[3,2-*a*]isoquinolinone **73** [65].



DMD – dimethyldioxirane

1.1.6. Synthesis of Isoindolo[1,2-*b*]benz-3-azepines from Diazoketamides. In 2001 it was proposed to use a sequence of reactions including the formation of an ammonium ylide and subsequent Stevens rearrangement for the construction of isoindolo[1,2-*b*]benz-3-azepines [66]. The reaction of the diazoketamides **75** with rhodium(II) acetate leads to the formation of isoindolo[1,2-*b*]benz-3-azepines **77**. The reaction mechanism requires the formation of an intermediate spirocyclic ammonium ylide **76**, which undergoes a Stevens [1,2]-shift of the benzylic carbon atom.



DBU – 1,8-diazabicyclo[5.4.0]undec-7-ene

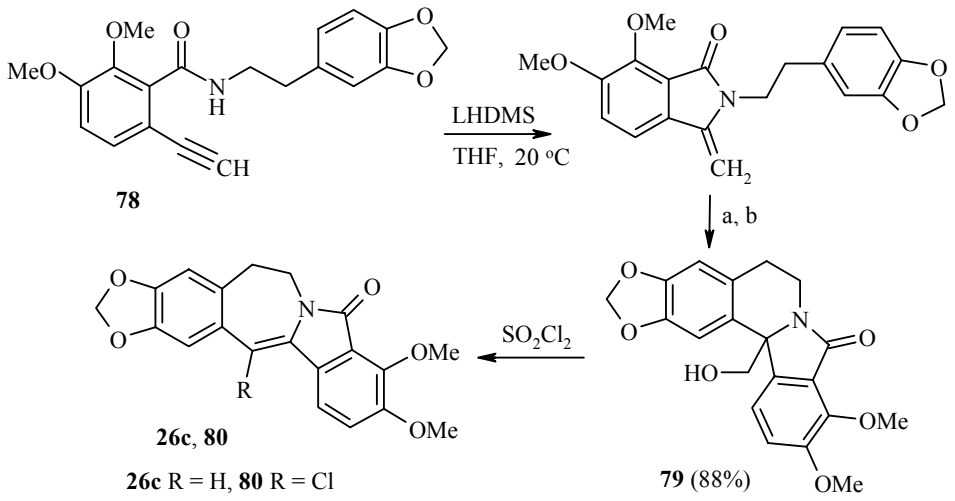
74-77 a $R^1 = R^2 = R^3 = H$; **b** $R^1 = OMe$, $R^2 = H$, $R^3 = OCH_2O$; **c** $R^1 = R^2 = OMe$, $R^3 = OCH_2O$

The initial diazoketamides **75a**,**b** are obtained from the corresponding esters **74a**,**b**. In the case of **74c** the diazoketamide was not obtained due to the strong electron-donating effect of the methoxy group at position 5, which leads to a decrease in the acidity of the benzylic protons.

1.1.7. Synthesis of Isoindolo[1,2-*b*]benz-3-azepines from Isoindoloisoquinolines. A new method for the production of the isoindolo[1,2-*b*]benz-3-azepine skeleton [67, 68] includes the production of isoindolo-[1,2-*a*]isoquinoline **79** from *o*-ethynylbenzamide **78** and its subsequent rearrangement by the action of SO_2Cl_2. Various reagents were tried to enlarge the ring of compound **79** (HBr/AcOH, conc. H_2SO_4, PPA, CF_3SO_3H), but the desired result was only obtained with sulfonyl chloride. Either isoindolobenzazepine **26c** or its chlorine derivative **80** can be obtained depending on the reaction conditions.

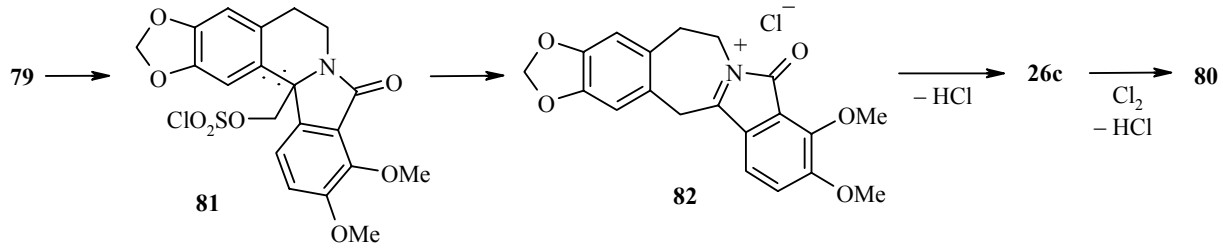
TABLE 4. The Reaction Conditions and the Yields of Compounds **26c** and **80**

Molar excess of SO_2Cl_2	Reaction conditions	Yield, %	
		26c	**80**
1.5	$CHCl_3$: PyH (1:1)	0	Traces
1.5	DMF : Et_3N (1:1)	No reaction	
3.0	$CHCl_3$: Et_3N (4:1)	45	0
3.0	$CHCl_3$: PyH (4:1), Et_3N (5 eq.)	75	0
3.0 + 1.5	$CHCl_3$: PyH (4:1), Et_3N (5 eq.)	0	76



LHDMS – hexamethyldisilazanyllithium
a) DMD, MeOH/Me_2CO (2:1), -78 → -30°C, then 10% $Na_2S_2O_3$ or DMD, Me_2CO, -70 → -35°C; b) 2 eq. $BF_3 \cdot Et_2O$, CH_2Cl_2, -45 → 0°C

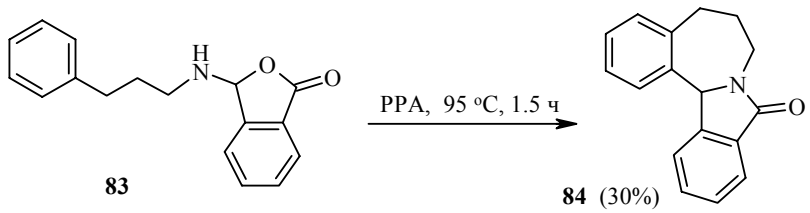
The mechanism of ring enlargement in the isoquinoline **79** involves chlorosulfonation of the hydroxyl group with the formation of the ether **81**, which is converted as a result of migration of the 2,3-methylenedioxyphenyl fragment into the iminium salt **82**, tautomeric with the hydrochloride **26c** [67, 68].



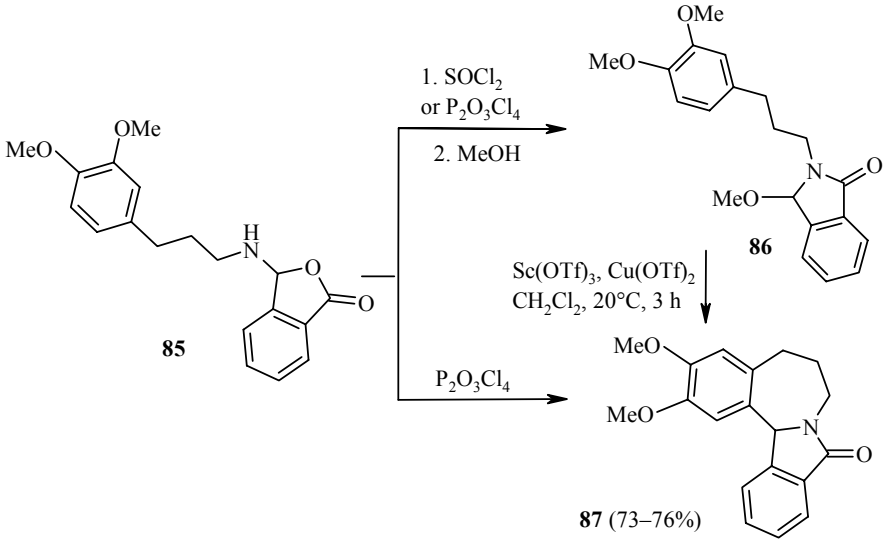
1.2. Synthesis of Isoindolo[1,2-*a*]benz-2-azepines

There have only been data on methods for the synthesis of isoindolo[1,2-*a*]benz-2-azepines in four publications [2-4, 69].

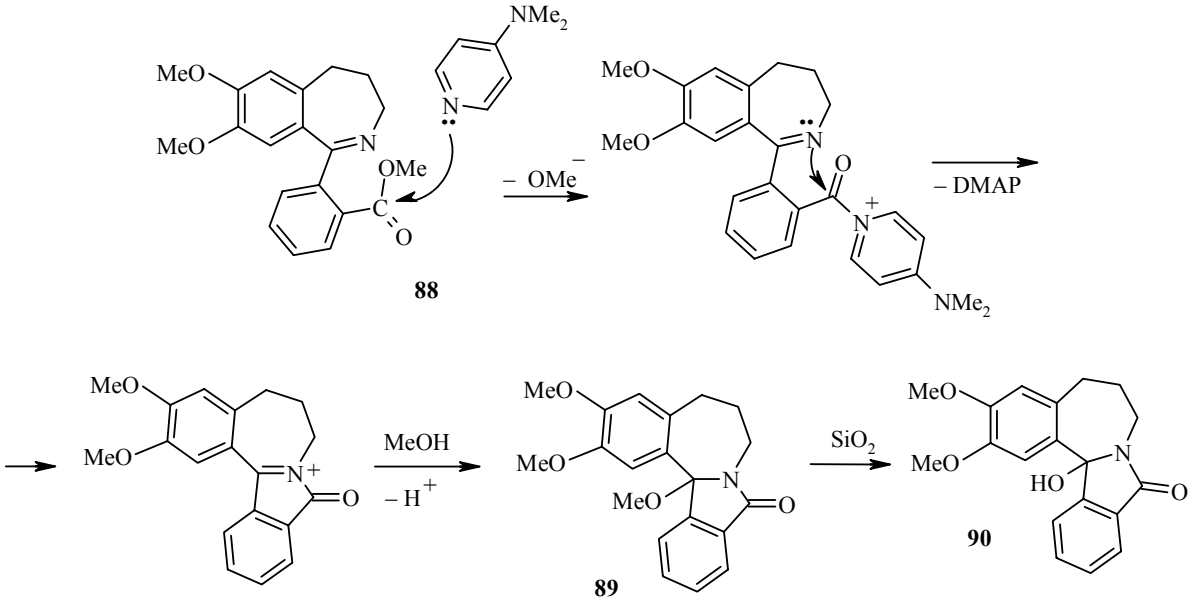
Isoindolo[1,2-*a*]benz-2-azepines can be obtained from 3-(γ-arylpropylamino)phthalides [2-4]. Thus, under the influence of PPA 3-(γ-phenylpropylamino)phthalide **83** undergoes cyclization to the corresponding isoindolo[1,2-*a*]benz-2-azepine **84** [2].



A similar method involves the reaction of 3-[γ-(3,4-dimethoxyphenyl)propylamino]phthalide **85** with thionyl chloride or pyrophosphoryl chloride to form the phthalimidine **86**. During the action of scandium or copper triflate compound **86** undergoes cyclization to isoindolo[1,2-*a*]benz-2-azepine **87**. Compound **85** can be converted into isoindolo[1,2-*a*]benz-2-azepine **87** in a single stage by the action of pyrophosphoryl chloride under more drastic conditions [3, 4].



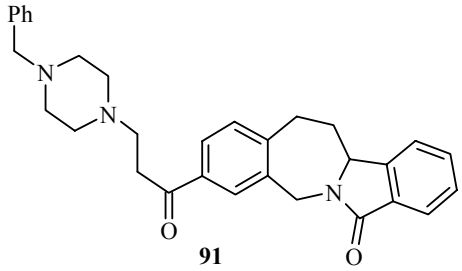
Derivatives of benz-2-azepine can be used for the synthesis of isoindolo[1,2-*a*]benz-2-azepines [69]. When heated in methanol in the presence of 4-(dimethylamino)pyridine the benz-2-azepine **88** is converted into oxoisoindolo[1,2-*a*]benz-2-azepine **89**. The latter is demethylated during chromatography on silica gel and converted into the isoindolobenzazepine **90**.



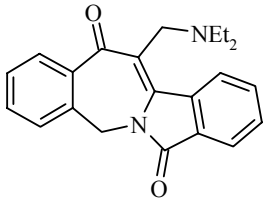
DMAP – 4-(dimethylamino)pyridine

1.3. Synthesis of Isoindolo[2,1-*a*]benz-2-azepines

Compounds of this type are of interest in connection with their physiological activity [6, 10-13]. For example, 5,11b,12,13-tetrahydro-3-{1-oxo-3-[1-(phenylmethyl)-4-piperidinyl]propyl}-7H-isoindolo[2,1-*b*]benz-2-azepin-7-one (**91**) is an inhibitor of acetylcholinesterase [10], while 12-diethylaminomethyl-5H-isoindolo-[2,1-*b*]benz-2-azepine-7,13-dione (**92**) has protective action against nitrogen hypoxia [6].

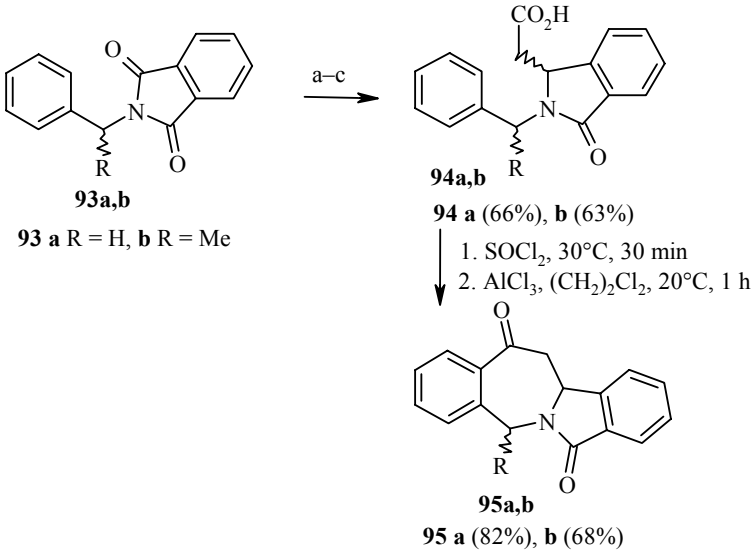


91



92

All the approaches to the synthesis of isoindolo[2,1-*b*]benz-2-azepines described in the literature are based on intramolecular cyclization of derivatives of N-benzylisoindole. Thus, isoindolo[2,1-*b*]benz-2-azepines **95** can be obtained from 2-aryl-2,3-dihydro-3-oxoisoindolo-1-acetates **94** by intramolecular Friedel–Crafts cyclization [6, 9]. The initial acids **94** are formed from N-benzylphthalimides **93** after reduction with sodium borohydride, a Wittig reaction, and alkaline hydrolysis.



93a,b

93 a R = H, **b** R = Me

a–c

94a,b

94 a (66%), **b** (63%)

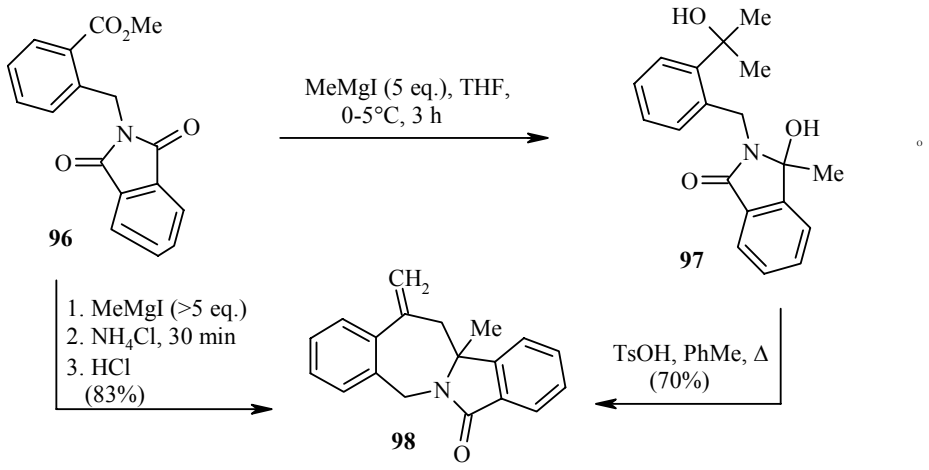
1. $SOCl_2$, 30°C, 30 min
2. $AlCl_3$, $(CH_2)_2Cl_2$, 20°C, 1 h

95a,b

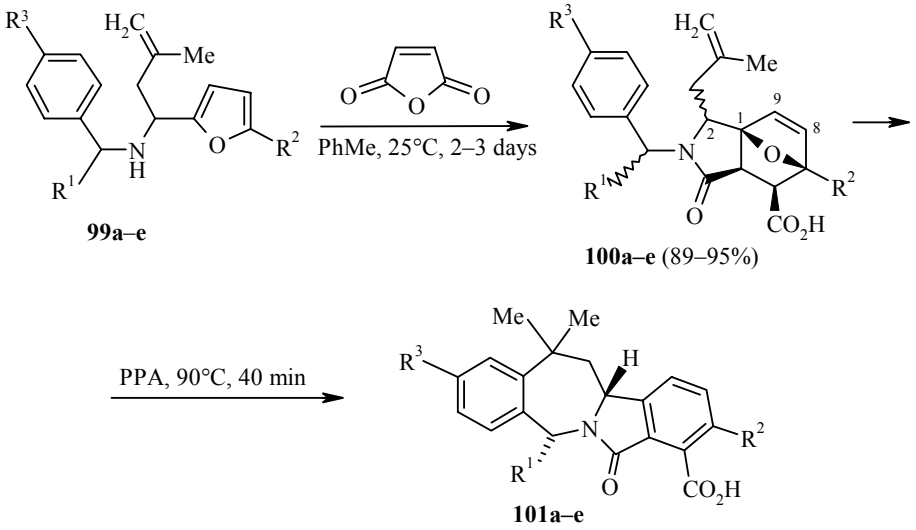
95 a (82%), **b** (68%)

a) $NaBH_4$, THF, MeOH, 0-5°C, 2 h; b) $Ph_3P{=}CHCO_2Et$, PhMe, Δ, 1 h;
c) K_2CO_3, H_2O–MeOH, Δ, 2 h

The unsaturated isoindolo[2,1-*b*]benz-2-azepine **98** can be obtained from the corresponding phthalimide **96**. In [7] two methods were proposed for this cyclization, i.e., a one-pot method and a two-stage method with the isolation of the hydroxylactam **97**. Reaction of the imidic ester **96** with methylmagnesium iodide followed by hydrolysis leads to the formation of the required compound **98** (83%). The azepine **98** is also formed when the hydroxylactam **97** is heated in toluene in the presence of TsOH (yield 70%).



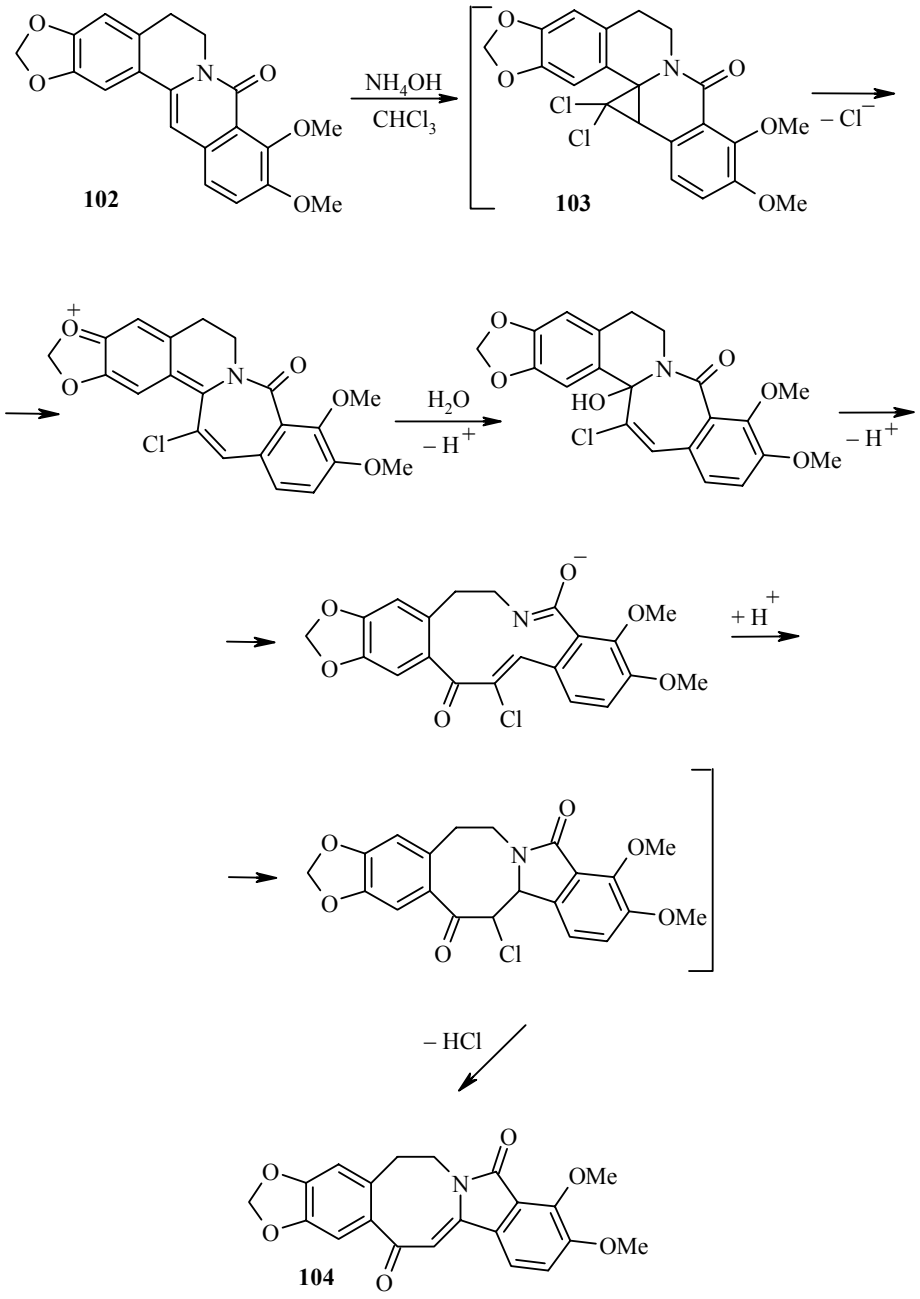
A single-stage method was recently proposed [70, 71] for the synthesis of isoindolo[2,1-*b*]benz-2-azepines **101** by the acid-catalyzed intramolecular electrophilic cyclization 2-alkenyl-substituted tricyclodec-8-enes **100**. The initial tricyclodecenes are obtained with quantitative yields by the reaction of furyl-substituted homoallylamines **99** with maleic anhydride.



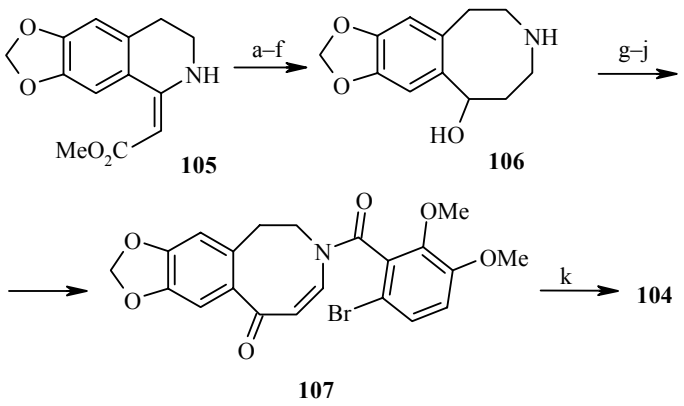
101 a $R^1 = R^2 = R^3 = H$ (75%); **b** $R^1 = R^3 = H$, $R^2 = Me$ (30%); **c** $R^1 = Me$, $R^2 = R^3 = H$ (31%);
d $R^1 = R^2 = H$, $R^3 = Me$ (48%); **e** $R^1 = R^2 = H$, $R^3 = OMe$ (48%)

2. SYNTHESIS OF ISOINDOLO[2,1-*c*]BENZ-3-AZOCINES

In the 1980s a new alkaloid with the unusual isoindolo[2,1-*c*]benz-3-azocine skeleton, called magallanesine **104**, was first synthesized from the plant *Berberis Darwinii Hook* [72]. This ketolactam can be obtained easily from oxoberberine **102** through the intermediate dichloro derivative **103** [73].

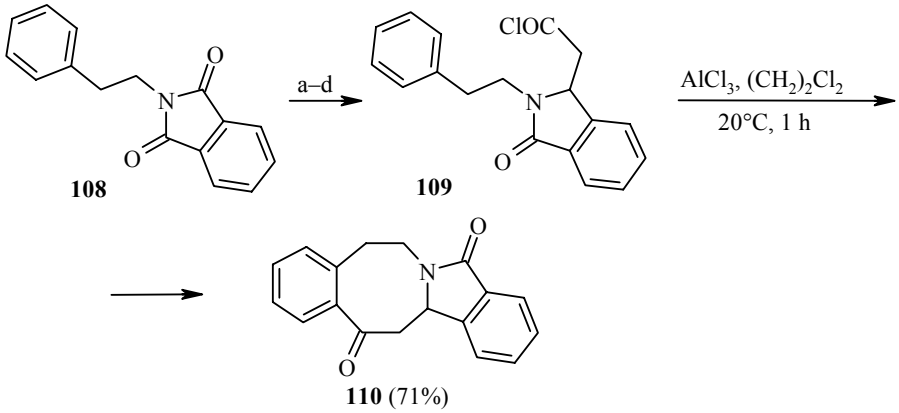


A total synthesis of magallanesine was realized from the hydrogenated isoquinoline **105** [74]. Hydroxybenz-3-azocine **106** (obtained in five stages from the ester **105**) is transformed into the N-benzoyl derivative **107**. Intramolecular cyclization of the latter under the conditions of a modified Heck reaction leads to the isoindolo[2,1-*c*]benz-3-azocine **104**.



a) Pd–C/H_2 4 kg/cm^2, AcOH–MeOH, 20°C (100%); b) $LiAlH_4$, THF, 0°C, 10 min (93%); c) $SOCl_2$, CH_2Cl_2, Δ, 2 h (97%); d) MeONa (1.5 eq.), MeOH, Δ, 1.5 h (72%); e) 35% H_2O_2, MeOH–$CHCl_3$, 20°C, 16 h; PtO_2 (0.01 eq.), 20°C, 5 h, then THF, Δ, 1 H (64%); f) Pd–C/H_2, MeOH, 1 kg/cm$_2$, 20°C (100%); g) 5-bromo-2,3-dimethoxybenzoyl chloride (1.2 eq.), 10% NaOH, $(CH_2OMe)_2$, 20°C (94%); h) Dess–Martin reagent [1,1,1-triacetoxy-1,2-dihydro-1,2-benziodoxol-3(1H)-one] (15% solution in CH_2Cl_2) (1.5 eq.), CH_2Cl_2, 20°C, 20 min (95%); i) lithium bistrimethylsilylamide, HMPTA, THF, -78°C, 20 min, then $(PhS)_2$ (2 eq.), -78→20°C, 1 h; j) *m*-chloroperbenzoic acid, CH_2Cl_2, 20°C, then PhMe, 20°C, 2 h (67%); k) $Pd(OAc)_2$ (10 mol %), Ph_3P (0.2 eq.), TlOAc (1.2 eq.), DMF, 130°C.

7,8,14,14*a*-Tetrahydroisoindolo[2,1-*c*]benz-3-azocine-5,13-dione (**110**) was synthesized from 3-oxo-2-phenethyl-2,3-dihydroisoindolo-1-acetyl chloride (**109**) by an intramolecular Friedel–Crafts reaction [6]. The initial acid chloride (**109**) was obtained from N-phenethylphthalimide (**108**) by analogy with compound (**95**) (see the scheme on p. 852).



a) $NaBH_4$, THF, MeOH, 0-5°C, 2 h (93%); b) $Ph_3P{=}CHCO_2Et$, PhMe, Δ, 1 h; c) K_2CO_3, H_2O–MeOH, 20°C, 2 h (54%); d) $SOCl_2$, 30°C, 30 min

There are no published data on isoindolobenzazocine rings with ring fusion other than the described [2,1-*c*].

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REFERENCES

1. P. Pigeon and B. Decroix, *Synth. Commun.*, **28**, 2507 (1998).
2. G. N. Walker, A. R. Engle, and R. J. Kempton, *J. Org. Chem.*, **37**, 3755 (1972).
3. H. Heaney and K. F, Shuhaibar, *Synlett*, 47 (1995).
4. M. T. El Gihani, H. Heaney, and K. F. Shuhaibar, *Synlett*, 871 (1996).
5. P. Pigeon and B. Decroix, *Tetrahedron Lett.*, **38**, 1041 (1997).
6. Y. Ishihara, Y. Kiyota, and G. Goto, *Chem. Pharm. Bull.*, **38**, 3024 (1990).
7. A. Dalch, S. Marchalin, P. Pigeon, and B. Decroix, *Tetrahedron Lett.*, **39**, 9187 (1998).
8. Y. Ishihara, T. Tanaka, S. Miwatashi, A. Fujishima, and G. Goto, *J. Chem. Soc., Perkin Trans. 1*, 2993 (1994).
9. A. Chihab-Eddine, A. Daich, A. Wale, and B. Decroix, *Heterocycles*, **58**, 449 (2002).
10. Y. Ishihara, T. Doi, H. Nagabukuro, and Y. Ishichi, WO Pat. 00/18391; http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO0018391&F=0&QPN=WO00183 91
11. Y. Ishihara, Y. Fujisawa, and N. Furuyama, WO Pat. 9846590; *Chem. Abstr.*, **129**, 330744 (1998).
12. G. Goto, Y. Ishihara, and M. Miyamoto, EP Pat. 655451; *Chem. Abstr.*, **123**, 198832 (1995).
13. G. Goto and Y. Ishihara, Jpn. Pat. 02042078; *Chem. Abstr.*, **113**, 40431 (1990).
14. C. Schöpf and M. Schweickert, *Chem. Ber.*, **99**, 2566 (1965).
15. E. Valencia, I. Weiss, S. Firdous, A. J. Freyer, M. Shamma, A. Urzsa, and V. Fajardo, *Tetrahedron*, **40**, 3957 (1984).
16. V. Fajardo, V. Elango, B. K. Cassels, and M. Shamma, *Tetrahedron Lett.*, **23**, 39 (1982).
17. E. Valencia, A. J. Freyer, M. Shamma, and V. Fajardo, *Tetrahedron Lett.*, **25**, 599 (1984).
18. J. Fuska, A. Fuskovi, and B. Proksa, *Pharmazie*, **37**, 443 (1982).
19. B. Proksa and J. Fuska, *Pharmazie*, **40**, 521 (1985).
20. V. Scartoni, R. Fiaschi, S. Catalano, I. Morelli, and A. Marsili, *J. Chem. Soc., Perkin Trans. 1*, 1547 (1979).
21. P. L. Barili, R. Fiaschi, E. Napolitano, L. Pistelli, V. Scartoni, and A. Marsili, *J. Chem. Soc., Perkin Trans. 1*, 1654 (1981).
22. E. Napolitano, R. Fiaschi, V. Scartoni, and A. Marsili, *J. Chem. Soc., Perkin Trans. 1*, 781 (1986).
23. E. Napolitano, G. Spinelli, R. Fiaschi, and A. Marsili, *J. Chem. Soc., Perkin Trans. 1*, 785 (1986).
24. A. Couture, E. Deniau, P. Grandclaudon, and C. Hoarau, *Tetrahedron*, **56**, 1491 (2000).
25. Y. Koseki and T. Nagasaka, *Chem. Pharm. Bull.*, **43**, 1604 (1995).
26. A. Marsili, V. Scartoni, I. Morelli, and P. Pierangeli, *J. Chem. Soc., Perkin Trans. 1*, 959 (1977).
27. H. O. Bernhard and V. Snieckus, *Tetrahedron Lett.*, 4867 (1971).
28. G. Kim, J. H. Kim, W.-J. Kim, and Y. A. Kim, *Tetrahedron Lett.*, **44**, 8207 (2003).
29. G. Rodriguez, M. M. Cid, C. Sai, L. Castedo, and D. Dominguez, *J. Org. Chem.*, **61**, 2780 (1996).
30. M. M. Cid, D. Domknguez, L. Castedo, E. M. Vizquez-Lopez, *Tetrahedron*, **55**, 5599 (1999).
31. H. Yoda, A. Nakahama, T. Koketsu, and K. Takabe, *Tetrahedron Lett.*, **43**, 4667 (2002).
32. P. H. Mazzocchi, C. R. King, and H. L. Amnion, *Tetrahedron Lett.*, **28**, 2473 (1987).
33. M. Machida, M. Nakamura, K. Oda, H. Takechi, K. Ohno, H. Nakai, Y. Sato, and Y. Kanaoka, *Heterocycles*, **26**, 2683 (1987).
34. H. Ishibashi, H. Kawanami, H. Iriyama, and M. Ikeda, *Tetrahedron Lett.*, **36**, 6733 (1995).
35. H. Ishibashi, H. Kawanami, and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 817 (1997).
36. J. Trojanek, Z. Koblicova, V. Suchan, and J. Holubek, *Collect. Czech. Chem. Commun.*, **40**, 681 (1975).
37. B. Proksa, Z. Votickz, and M. Stefek, *Chem. Zvesti*, **34**, 248 (1980).
38. B. Proska, J. Fuska, Z. Voticky, *Pharmazie*, **37**, 350 (1982).
39. A. Garcia, D. Rodriguez, L. Castedo, C. Sai, and D. Dominguez, *Tetrahedron Lett.*, **42**, 1903 (2001).

40. S. Ruchirawat, W. Lertwanawatana, S. Thianpatanagul, J. L. Cashaw, and V. E. Davis, *Tetrahedron Lett.*, **25**, 3485 (1984).
41. J. Chiefari, W. K. Janowski, and R. H. Prager, *Tetrahedron Lett.*, **27**, 6119 (1986).
42. J. Chiefari, W. K. Janowski, and R. H. Prager, *Aust. J. Chem.*, **42**, 49 (1989).
43. S. V. Kessar, T. Singh, and R. Vohra, *Tetrahedron Lett.*, **28**, 5323 (1987).
44. S. V. Kessar, T. Singh, and R. Vohra, *Ind. J. Chem.*, **30B**, 99 (1991).
45. F. G. Fang and S. J. Danishefsky, *Tetrahedron Lett.*, **30**, 2747 (1989).
46. S. Ruchirawat and P. Sahakitpichan, *Tetrahedron Lett.*, **41**, 8007 (2000).
47. W. Klötzer, S. Teitel, J. F. Blount, and A. Brossi, *J. Am. Chem. Soc.*, **93**, 4321 (1971).
48. W. Klötzer, S. Teitel, and A. Brossi, *Helv. Chim. Acta*, **54**, 2057 (1971).
49. R. Hohlbrugger, W. Klötzer, *Chem. Ber.*, **107**, 3457 (1974).
50. S. Teitel, W. Klötzer, J. Borgese, and A. Brossi, *Can. J. Chem.*, **50**, 2022 (1972).
51. C. J. Moody and G. J. Warrellow, *J. Chem. Soc., Perkin Trans. 1*, 2929 (1990).
52. C. J. Moody and G. J. Warrellow, *Tetrahedron Lett.*, **28**, 6089 (1987).
53. S. Yasuda, Y.-I. Sugimoto, C. Mukai, and M. Hanaoka, *Heterocycles*, **30**, 335 (1990).
54. J. R. Fuchs and R. L. Funk, *Org. Lett.*, **3**, 3923 (2001).
55. D. Walterova and F. Santava, *Collect. Czech. Chem. Commun.*, **35**, 1623 (1968).
56. M. Shamma, *The Isoquinoline Alkaloids*, Academic Press, New York (1972).
57. J. L. Moniot, D. M. Hindenlang, and M. Shamma, *J. Org. Chem.*, **44**, 4343 (1979).
58. G. Manikumar and M. Shamma, *Heterocycles*, **14**, 827 (1980).
59. C. K. Dorn, F. J. Koszyk, and G. R. Lenz, *J. Org. Chem.*, **49**, 2642 (1984).
60. J. L. Moniot, D. M. Hindenlang, and M. Shamma, *J. Org. Chem.*, **44**, 4347 (1979).
61. M. Shamma, J. L. Moniot, and D. M. Hindenlang, *Tetrahedron Lett.*, 4273 (1977).
62. V. Elango and M. Shamma, *J. Org. Chem.*, **48**, 4879 (1983).
63. C. Lamas, C. Saa, L. Castedo, and D. Domknguez, *Tetrahedron Lett.*, **33**, 5653 (1992).
64. G. Rodrkguez, L. Castedo, D. Domknguez, and C. Sai, *Tetrahedron Lett.*, **39**, 6551 (1998).
65. G. Rodrkguez, L. Castedo, D. Domknguez, C. Sai, W. Adam, and C. R. Saha-Möller, *J. Org. Chem.*, **64**, 877 (1999).
66. A. Padwa, L. S. Beall, C. K. Eidell, and K. J. Worsencroft, *J. Org. Chem.*, **66**, 2414 (2001).
67. Y. Koseki, S. Kusano, H. Sakata, and T. Nagasaka, *Tetrahedron Lett.*, **40**, 2169 (1999).
68. Y. Koseki, S. Katsura, S. Kusano, H. Sakata, H. Sato, Y. Monzene, and T. Nagasaka, *Heterocycles*, **59**, 527 (2003).
69. H. Heaney and K. F. Shuhaibar, *Tetrahedron Lett.*, **35**, 2751 (1994).
70. F. I. Zubkov, E. V. Boltukhina, A. P. Krapivko, and A. V. Varlamov, *Khim. Geterotsikl. Soedin.*, 1737 (2003). [*Chem. Heterocycl. Compd.*, **39**, 1534 (2003)]
71. F. I. Zubkov, E. V. Boltukhina, K. F. Turchin, and A. V. Varlamov, *Tetrahedron*, **60**, 8455 (2004).
72. E. Valencia, V. Fajardo, A. J. Freyer, and M. Shamma, *Tetrahedron Lett.*, **26**, 993 (1985).
73. M. Shamma and M. Rahimizadeh, *J. Nat. Prod.*, **49**, 398 (1986).
74. R. Yoneda, Y. Sakamoto, Y. Oketo, K. Minami, S. Harusawa, and T. Kurihara, *Tetrahedron Lett.*, **35**, 3749 (1994).