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Azafluorenes. Synthesis and conversions

N S Prostakov, A T Soldatenkov, N M Kolyadina, A A Obynochnyi

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Abstract. Data on the chemistry of azafluorenes (indenopyridines) for the last two decades are summarised. Methods of synthesis of all isomeric (as regards the position of the nitrogen atom) azafluorenes are considered. The main reactions of azafluorenes are analysed, their reactivity is determined by the presence and mutual influence of two different conjugated fused rings (benzene and pyridine) and the mode of fusion of the indene and pyridine fragments. The principal conversions of substituents at different positions of the azafluorene system are considered. Evidence is presented on the natural occurrence of azafluorenes, the biological activity of their synthetic derivatives, and on the structure and physicochemical properties of azafluorenes and their derivatives. The bibliography includes 204 references.

I. Introduction

The chemistry of isomeric azafluorenes (indenopyridines) has been discussed in two reviews,[1,2] which summarise the data published mostly before 1975. It should be noted that these reviews dealt mainly with the chemistry of 2-azafluorene, and an extreme scarcity of data on isomeric 1- and 3-azafluorenes has been mentioned (1-azafluorene was first obtained as late as 1975). A large body of evidence has been accumulated in the current literature over the last two decades concerning the development of general methods of synthesis of these tricyclic fused systems together with in-depth analysis and comparison of reactivity of isomeric azafluorenes, and a search for promising biologically active derivatives among newly synthesised compounds. Considerable recent interest in azafluorenes has been stimulated by the discovery in mid-1980s of numerous plant alkaloids having mostly the structure of 4-azafluorenone. Moreover, there is evidence in both scientific and patent literature on the manifestation of antihistamine, neurotropic, antibacterial, antioxidant, and pesticide activities by azafluorene derivatives.

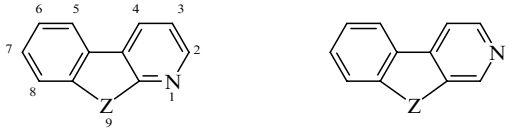
N S Prostakov, A T Soldatenkov, N M Kolyadina, A A Obynochnyi
Russian Peoples' Friendship University, ul. Ordzhonikidze 3,
117198 Moscow, Russian Federation. Fax (7-095) 954 03 36.
Tel. (7-095) 955 07 44 (N S Prostakov),
(7-095) 955 09 32 (A T Soldatenkov)

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This review presents and discusses the data on the strategy of synthesis of azafluorenes and their conversions involving the benzene, pyridine, and cyclopentadiene rings, which constitute the azafluorene system and exert a mutual influence on the chemical properties of these compounds. Data on the natural occurrence of azafluorenes and the biological activity of their synthetic derivatives are also generalised.

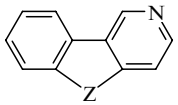
II. Structure and physicochemical properties

All of the isomeric (as regards the position of the nitrogen atom) unsubstituted azafluorenes (**1**–**4**) and azafluorenones (**5**–**8**)[1–4] the structure of which is given below, have now been described:

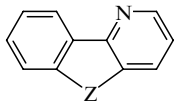


1,5

2,6



3,7



4,8

1–**4**: Z = CH_2; **5**–**8**: Z = C=O.

Quantum-chemical calculations have been performed[5,6] for the distribution of π-electron density and localisation energy of the protonated forms of 1-, 3-, and 4-azafluorenones. According to these calculations, electrophilic substitution must occur at the phenylene ring, presumably, at C(7). The luminescence spectra of unsubstituted azafluorenes, their 9-oxo-derivatives, and 9-arylidene azafluorenes have been studied.[7–9] Thus, the UV spectra of 1- and 4-azafluorenes display a bathochromic shift of the α*-absorption band, a hypsochromic shift of the *p*-band, and an increase in intensity of the α*-band as compared with fluorene. In the case of 2-azafluorene, a hypsochromic shift of these bands is accompanied by a decrease in their intensity and a bathochromic shift of the α-band occurs. It is conclusion that the α*- and *p*-bands for 1- and 4-azafluorenes, like for fluorene, possess fluorescent character, while in the case of 2-azafluorene, this property is inherent in the α-band. Unlike other isomeric azafluorenes, 3-azafluorene is unstable and undergoes rapid photoconversions in the light.

The ^{13}C and ^{1}H NMR spectra of azafluorenes **1**–**4** have been studied.[3, 10–12] The ^{1}H NMR spectra of a series of 9-arylidene-2-azafluorenes were also studied with the use of shift-reagents.[8]

The IR spectra of azafluorenes do not contain specific absorption bands and are mostly used in studies on the synthesis of derivatives of these compounds to confirm the presence and position of substituents. The carbonyl group in the azafluoren-9-ones **5**–**8** absorbs in the characteristic region, i.e., at 1715–1735 cm^{-1}. The IR spectra of 1,4-dihydro-4-azafluorenes,[13] particularly those containing electron-withdrawing substituents at C(3), were studied in more detail.[14, 15]

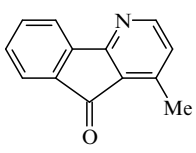
X-Ray analysis of 1,3,9-triphenyl-4-azafluorene have shown that the torsional angles between the planes of the azafluorene and phenyl rings are equal to 8.4°, 55.4°, and 44°, respectively.[16] According to the X-ray data, the azafluorene polycycle of 9-benzylidene-1-azafluorene is not absolutely flat, since the angle between its two six-membered rings is 4.1°.[17] The exocyclic carbon atom, C(10), of the fulvene fragment is above the plane of the five-membered ring, the corresponding torsional angle is 4°. The carbon atom of the phenyl substituent bound to C_{10} deviates from the plane of the five-membered ring even more, the corresponding torsional angle is as much as 8.5°. The phenyl substituent is turned by 65° relative is the mean plane of the azafluorene skeleton, which confirms that through-space charge-transfer complexes can form in the case where the nitrogen atom occupies position 1 in the azafluorene fragment.[18]

There are no quantitative data on the basicity of the pyridine fragment and the CH-acidity of the methylene group of azafluorenes. The quantum-chemical characteristics of alkyl- and nitro-substituted 4-azafluorenones have been considered.[19]

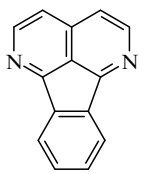
A systematic study of the electron impact-induced mass spectra of azafluorenes and their derivatives has been carried out.[3, 20–28] It has been shown that fragmentation of the unsubstituted azafluorenes **1**–**4** is virtually independent of the position of the nitrogen atom. The mass spectra of these compounds contain molecular ions as the most abundant peaks, while the characteristic pathways of their fragmentation are determined by the mode of elimination of the hydrogen atom and the HCN molecule. Fragmentation of the azafluorenones **5**–**8** is characterised by the elimination of the CO molecule, which is most intense for 1- and 4-azafluorenones. In the case of substituted azafluorenes, the character of fragmentation is determined by the nature of the substituent. Quantum-chemical calculations were used to estimate the probability of electron impact-induced rearrangement of azafluorenes and their derivatives.[27]

III. Occurrence in nature

The first plant alkaloid with the azafluorene structure was isolated in 1976 from the arboreal part of the plant *Onychopetalum amazonicum*.[29] This alkaloid (onychin, **9**) was initially identified as 4-methyl-1-azafluoren-9-one. However, the synthesis of the isomeric ketones[30] has established that onychin is in fact 1-methyl-4-azafluorenone. The ^{1}H and ^{13}C NMR spectra of this alkaloid have been studied in detail.[31]



9, Onychin



10, Eupolauridine

Recent studies of the plants of the Annonaceae genus have revealed 14 alkaloids having the structure of methoxy- and hydroxy-substituted 4-azafluorenones;[32–35] methods for the synthesis of some of these compounds have been proposed.[36–45] Several alkaloids of more complex structure also incorporate azafluorenes as fragments, *cf.*, *e.g.*, eupolauridine (**10**).[46] It should be noted that 4-azafluorene was first isolated from tarry coal coking products;[47] some of its derivatives have been recently identified by chromatographic methods in the atmosphere in the vicinity of coal-tar chemical plants.[48]

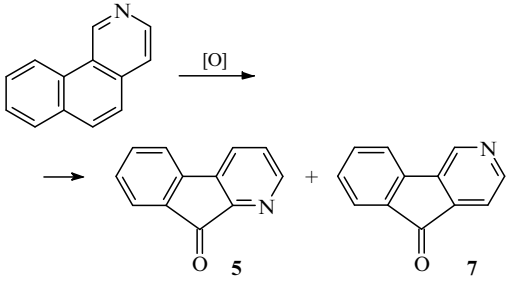
IV. Methods of azafluorene synthesis

The known methods of azafluorene synthesis can be divided into three main groups. The first of them makes use of degradation of nitrogen-containing fused compounds into tricyclic azafluorenes. The principle exploited in the second group is the increase in the number of fused rings by annelation of the heterocycle to the bicyclic system (indene). The strategy of the third group methods entails various reactions of intramolecular cyclocondensation of aryl- or aroyl pyridines with involvement of substituents.

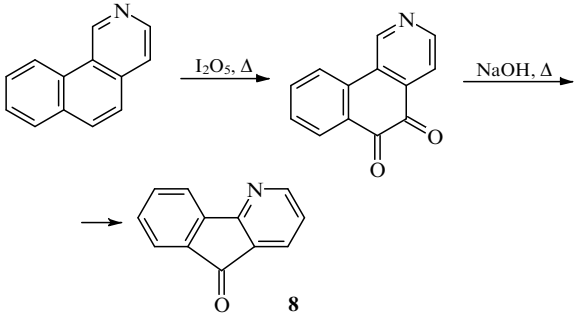
1. Oxidative degradation of azafluoranthenes and azaphenanthrenes

The first 1- and 4-azafluorenone derivatives were obtained by oxidation of substituted azaphenanthrenes with potassium permanganate.[49, 50]

Similarly, several azafluoranthenes were converted with low yields into these azafluorenones.[51, 52] Later,[3] the 1- and 3-azafluorenones **5** and **7** were isolated with a total yield of 12% from the products of oxidation of 2-azaphenanthrene with potassium permanganate.



An effective two-step procedure has been proposed for the synthesis of 1- and 4-azafluorenones by oxidation of the corresponding azaphenanthrenes azaphenanthrenequinones (yields 48%–80%) with iodine pentoxide.[53] They smoothly rearrange into azafluorenones (yields 70%–88%) on heating in aqueous solution of alkali. The limitation of this method is that some of the original azaphenanthrenes are difficult to obtain. For example, 2-azaphenanthrene is obtained from 2-formylnaphthalene in four steps.

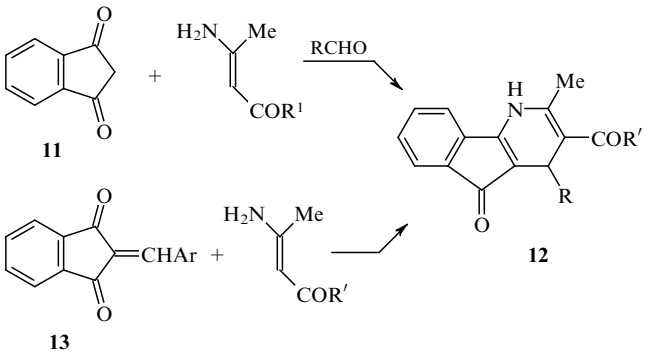


2. Condensations involving indane derivatives

The strategy of formation of azafluorene systems based on the indane derivatives entails several approaches differing in the number of components used, the source of nitrogen needed for the formation of the heterocycle (ammonia, β-aminocrotonates, β-aminoalkanoic acids, amino- or alkylamino-derivatives of indane) and, finally, the type of heterocyclocondensation.

The condensation in a three-component system, indane-1,3-dione (**11**)–aminocrotonate–aldehyde, is the most efficient and

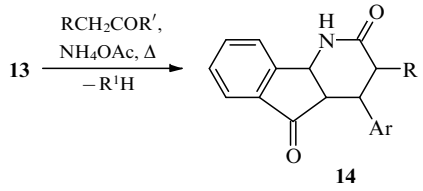
widely used for the synthesis of 1,4-dihydro-4-azafluorenes.[54–59] The resulting dihydroazafluorenes (**12**) can be then easily aromatised with oxidants or, in some cases, under UV irradiation.[60–63]



R = H, Me, Ar; R′ = OMe, OEt, SMe, SEt, SCH_2Ph.

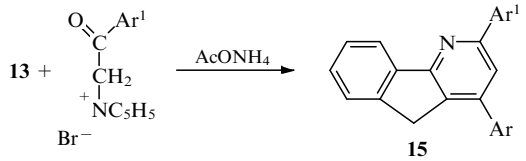
Apparently, the first step is the reaction of the aldehyde with the activated methylene group of the indane-1,3-dione **11** resulting in the intermediate 2-arylidene-(or 2-alkylidene)indanedione. The latter must be then converted into the polycycle **12** as a result of [3 + 3]-cyclocondensation. Indeed, this pathway has been confirmed experimentally [64–69] for the condensation in a two-component system: arylidenediones (**13**) – aminocrotonates.

If ammonia and esters (or amides) containing an activated α-methylene group are used in condensation with arylidenediones, the hexahydro derivatives of 4-azafluorene-3,9-diones (**14**) are formed with yields of up to 80%.

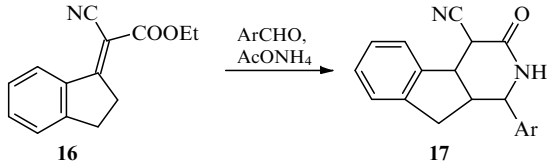


R = CN, COOEt, COOMe, COOPh; R′ = OEt, NH_2;
Ar = Ph, C_6H_4Cl-4, C_6H_4Me-4.

By varying the methylene component, fully aromatised azafluorenes can be obtained in this condensation. Thus, in the reaction of the arylidenedione **13** with 1-phenacylpyridinium bromide the good leaving azinium group favours the formation of the aromatic indenopyridinium structure **15**.[55,70] This procedure was used in the synthesis of many 1,3-diaryl-4-azafluorenes **15**.



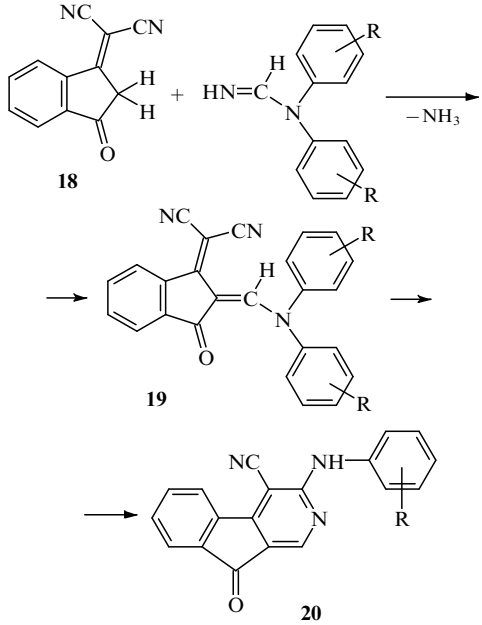
On going from indanones to the indanylidenes **16**, as components of the condensation with aldehydes and ammonia, one can obtain substituted azafluorenes **17**, e.g., cyanohexahydro-2-azafluoren-3-one.[68]



Ar = Ph, $C_6H_4NO_2$-4.

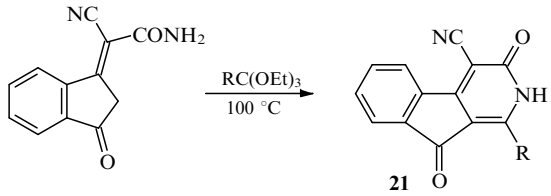
The use of nitrogen-containing components in the form of nitriles, amines, or amides has made it possible to pass to the condensation of two-component systems.

3-Dicyanomethyleneindanone (**18**) possessing an active methylene group forms upon interaction with diarylformamidines the derivatives **19**, which further convert into 3-arylamino-substituted 2-azafluoren-9-ones **20** as a result of cyclisation and Dimroth rearrangement.[71]



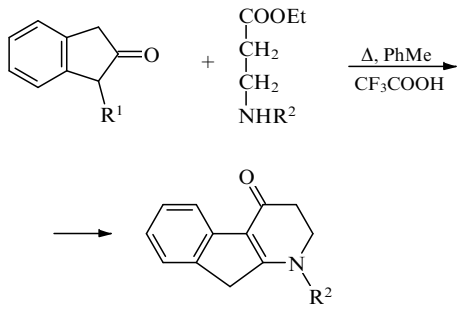
R = H, 2-Me, 2-Cl, 2-Pr, 2-MeO, 4-Me, *etc.*

2,3-Dihydroxy-2-azafluoren-3-one derivatives **21** can be obtained by heating (3-oxoindanylidene) cyanoacetamide with orthoesters.[72] The stage of intramolecular heterocyclisation must be preceded by condensation with the formation of 2-methyleneindanone, with the same substitution pattern.



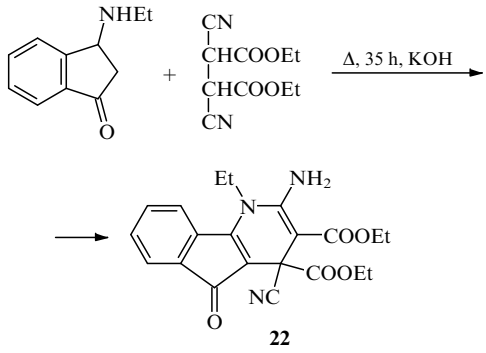
R = H, Me, Ph.

2-Indanones enter into [2 + 4]-cyclocondensation on heating with ethyl 2-benzyl- or 3-methylaminopropionate to give high yields of tetrahydro-1-azafluoren-4-ones.[73,74]



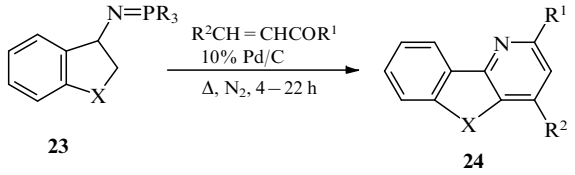
R^1 = H, Ph; R^2 = Me, CH_2Ph.

The amino group initially introduced into the C(3) position of indan-1-one allows the construction of 4-azafluorenes with the dihydropyridine ring (**22**). These indanone derivatives enter into [3 + 3]-cyclocondensation, *e.g.*, with diethyl dicyanosuccinate.[75]



22

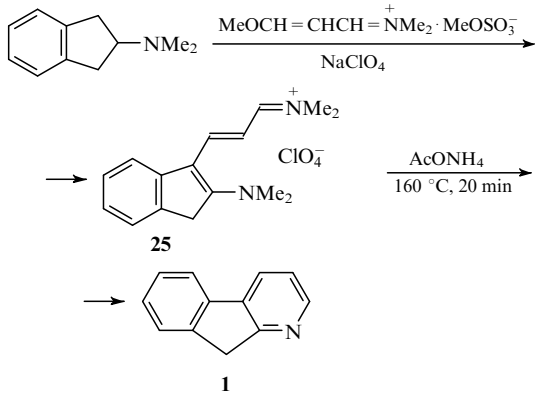
[3 + 3]-Heterocyclisation occurs in the case of iminophosphoranes **23** and α,β-unsaturated ketones or aldehydes. This gives in the aromatic 4-azafluorenes **24**.[76]



23 **24**

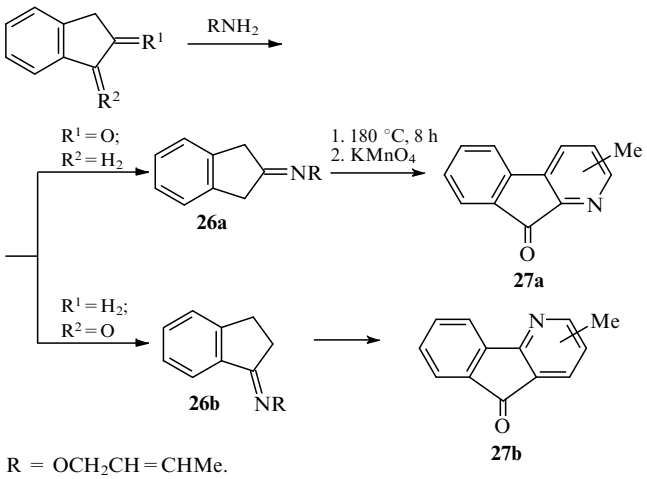
R = Bu^n, Ph; X = CH_2, CO;
R^1, R^2 = H, Me, Ph.

Several intramolecular cyclisations of one-component systems are known. 1-Azafluorene (**1**) was obtained by thermal cyclisation of the polymethinium salt of 2-dimethylaminoindene (**25**) in the presence of ammonium acetate.[4]



25 **1**

The isomers of the alkaloid onychin (**9**), two methyl-substituted 1-azafluorenones and two methyl-substituted 4-azafluorenones, were obtained by oxidative thermolysis of 1(2)-but-2-enyloxyiminoindanes **26**.[30] In the former case, a mixture of

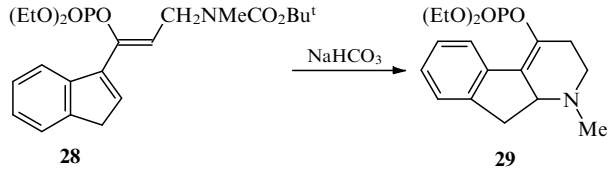


26a **27a** **26b** **27b**

R = $OCH_2CH=CHMe$.

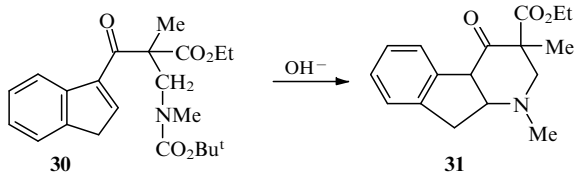
4- and 2-methyl-1-azafluorenes (**27a**) was formed from the 2-substituted derivative **26a** in a 38% yield; in the latter, a mixture of 1- and 3-methyl-4-azafluorenes (**27b**) was formed from the 1-substituted derivative **26b**.

The dienol phosphate **28** is converted into the tetrahydro-1-azafluorene **29** under the action of sodium hydrogencarbonate.[77, 78]



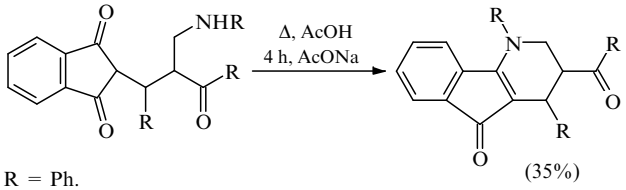
28 **29**

An analogous electrophilic cyclisation was used to convert the β-keto ester **30** into the substituted hexahydro-1-azafluorene (**31**).[79]



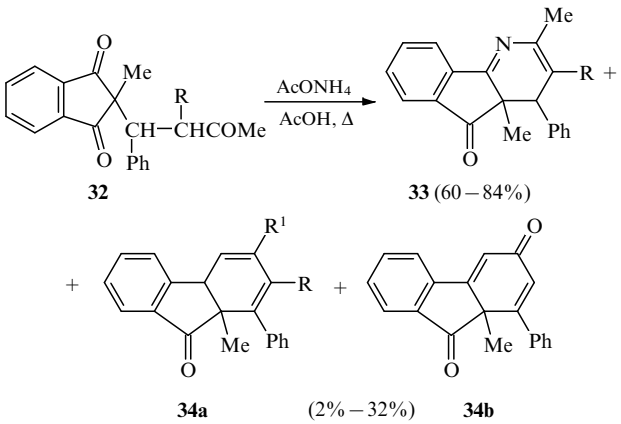
30 **31**

Azafluorene systems can be formed by intramolecular heterocyclisation of indan-1(3)-ones with 3-phenylamino substituents at C(2).[80] This procedure was used to obtain partially hydrogenated 4-azafluorenones from 1-indane-1,3-diones having an α-aminomethyl-substituted fragment of propiophenone at C(2).



R = Ph.

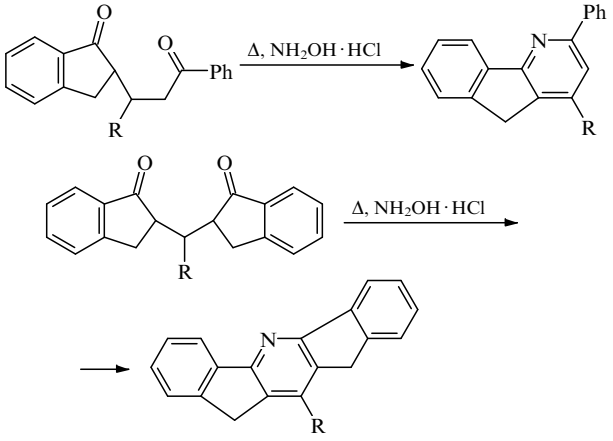
1,5-Diketones smoothly form a pyridine ring in reactions with primary amines; therefore, the principle of heterocyclisation has been successfully applied to the synthesis of azafluorenes. Thus, cyclisation of 2-(3′-oxoalkyl)-substituted indanediones (**32**) has been used to synthesise dihydro derivatives of 4-azafluorenone **33** with yields of up to 84%.[81] In this case, the formation of azafluorenes is accompanied by cyclisation into the substituted dihydrofluorenones **34**, which is suppressed in aprotic solvents. When the methyl group at C(2) of indanone is substituted for bromine, the azafluorene system is not formed at all.



32 **33** (60 – 84%) **34a** (2% – 32%) **34b**

R = CO_2Et, COMe; R^1 = OH, NH_2

Boiling of 2-(3-oxo-3-phenylpropyl)indan-1-one [82,83] or bis-(1-oxoindan-2-yl)methanes in ethanol with a twofold excess of $NH_2OH \cdot HCl$ results in 4-azafluorenes or indene[1,2-*b*]azafluorenes.[82]

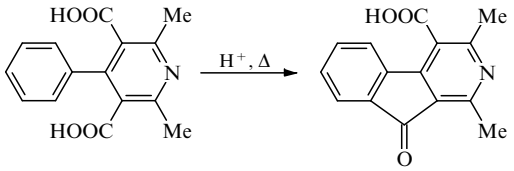


R = H, Me, Ph.

Until now, compounds of the 3-azafluorene series could not be obtained from indanone derivatives. Despite successful application of the approach discussed to the synthesis of some derivatives of 1- and 2-azafluorenes, this procedure seems to be of preparative importance in the synthesis of 4-azafluorene derivatives.

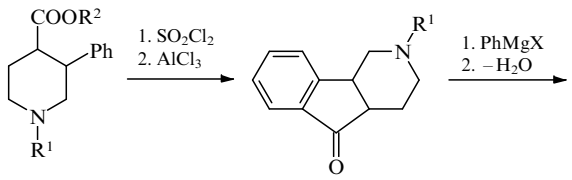
3. Intramolecular condensations of substituted aryl- and benzoylpyridines

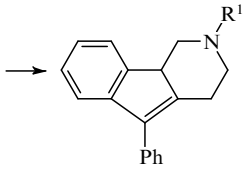
The availability of diverse pyridine derivatives has offered broad possibilities for synthesising all isomeric azafluorenes based on them and varying the nature and position of substituents. The methods considered in this section are mostly based on cyclisation of aryl- or aroylpyridines with benzene or pyridine rings substituted in the ortho-position. The pioneering study of this kind,[84] which was followed by numerous analogous investigations,[45,52,85–87] reported on the acid-catalysed cyclisation of 2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylic acid to the azafluorenone **35**.



35

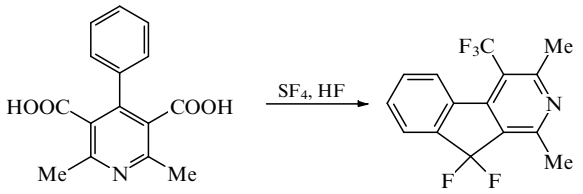
Analogous cyclisation of the corresponding phenylpyridinecarboxylic acids,[85–88] respective acid chlorides,[89] nitriles and esters,[45,46,90–92] resulted in a vast number of 2- and 4-azafluorene derivatives. Sulfuric [84] and polyphosphoric acids,[45,92–94] aluminium chloride,[95] and some other compounds [96] were used as condensing agents. Thus, 3-azafluorene derivatives have been obtained from phenylpiperidinic acids by converting them into acid chlorides followed by cyclisation in the presence of $AlCl_3$.[95]





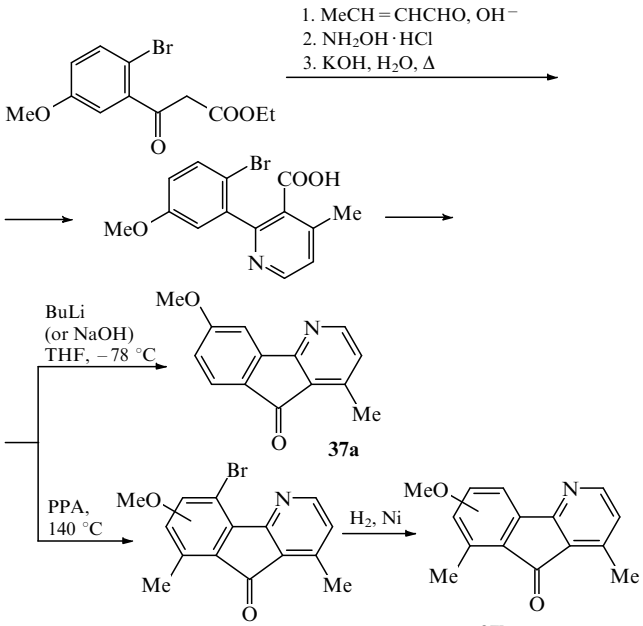
R^1 = Me, CH_2Ph; R^2 = H, Me, Et.

The cyclisation of 4-phenylpyridine-3,5-dicarboxylic acid in the presence of hydrofluoric acid is worth noting.[95] This reaction gives 9,9-difluoro-1,3-dimethyl-4-trifluoromethyl-2-azafluorene **36** instead of the expected azafluoren-9-one with a carboxylic group at C(4).



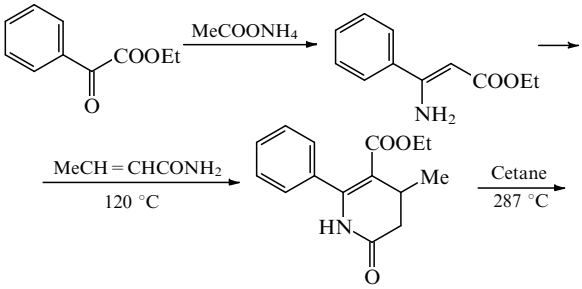
36

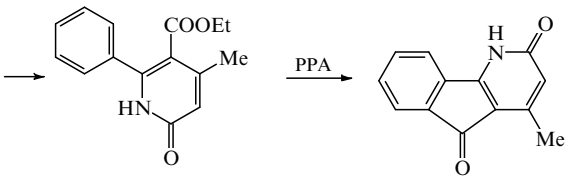
Methods have been proposed for synthesising the azafluorene alkaloids **37a**,**b** [41,45] and **38** [35] by cyclisation of the corresponding pyridine derivatives, which had been prepared from benzoylacetates as shown in the schemes given below. It has been found that the alkaloid **37b** possesses antifungal activity.[93]



37a

37b

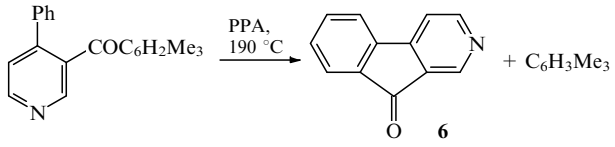




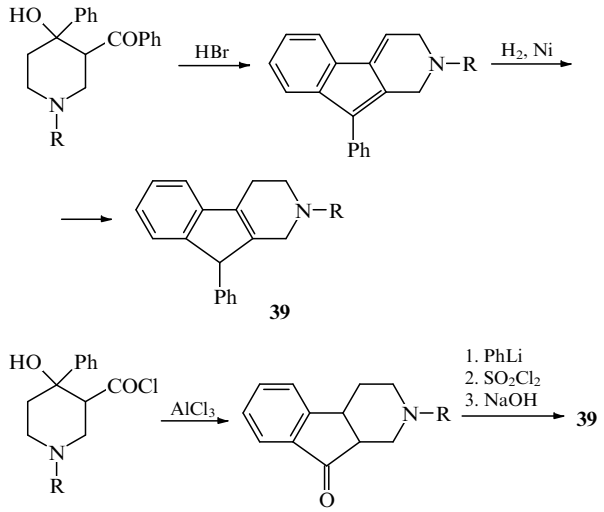
PPA = polyphosphoric acid. **38**

Synthesis of azafluorenes by thermal cyclocondensation of pyridinecarboxylic acids has the following limitations: multi-stage of synthesis of the starting compounds and, in the case of 1- and 3-azafluorenone derivatives (the former has not been prepared by this method thus far), the high probability of a side-process, decarboxylation of derivatives of α- and β-pyridinecarboxylic acids.

Substituted phenylpyridines having an aroyl group in the ortho-position can also be used in the acid-catalysed thermal cyclisation.[3, 96, 97]

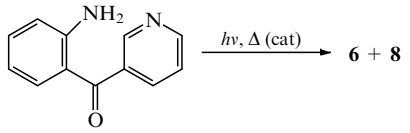


Similar cyclisations occur successfully in the case of piperidine derivatives. For example, a number of 9-phenyl-tetrahydro-2-azafluorenes have been obtained, one of which (**39**, R = Me) is used as an antihistamine drug.[89, 98–101]

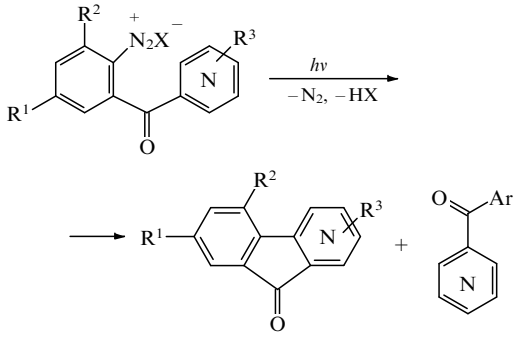


R = Alk, Ph.

The *o*-amino group served as a leaving group in the radical intramolecular cyclisation of 3-benzoylpyridine.[102, 103] UV-irradiation or heating of 3-(2-aminobenzoyl)pyridine in the presence of copper, silver, zinc, or iron gives a mixture of 4- and 2-azafluorenones (**6** and **8**) in approximately equal amounts (total yield 50% – 60%).



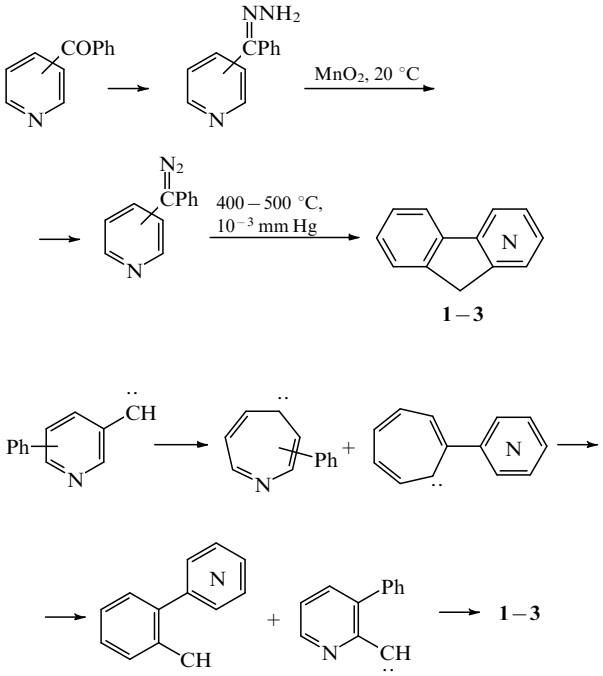
A series of 2-, 3-, and 4-azafluorenones substituted in the benzene or pyridine ring have been synthesised by photochemical decomposition of diazonium salts obtained from *o*-aminobenzoyl derivatives of pyridine.[104]



R[1], R[2], R[3] = H, Me, F, Cl.

The yield of azafluorenones varied from 25% to 74% depending on the nature of substituents, concentration of diazonium ions and reaction sensitisers (2,2′-dipyridyl complexes with ruthenium or copper). With sensitisers, the formation of benzoylketones as by-products decreased sharply. Radical cyclisation to azafluorenones when the diazonium ion is localised in the pyridine ring (particularly, in the α-position), is less effective. This method can be considered as general, although it has a number of disadvantages, such as the multi-stage synthesis of the starting compounds and the non-selectivity of the cyclisation step characteristic of radical processes.

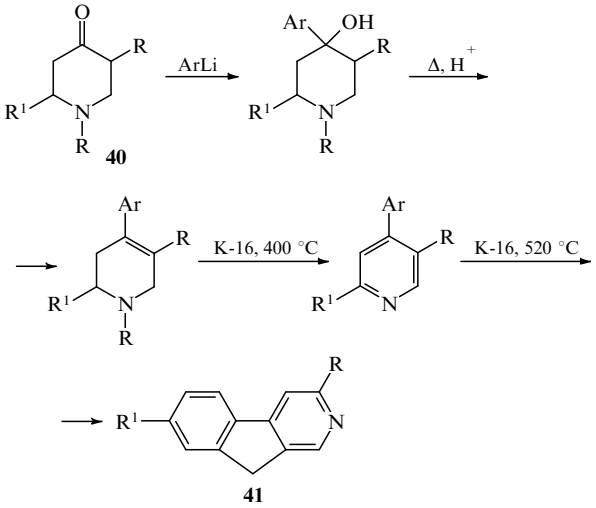
Wentrup *et al.*[3, 105] have carried out an original conversion of 3- and 4-benzoylpyridines into azafluorenes via hydrazones and diazomethanes, which were subjected to thermolysis *in vacuo*. Under pyrolysis conditions, as was demonstrated in experiments with radiolabelled carbon atoms,[3, 106] the carbenes formed result in expansion of the benzene and/or pyridine ring with subsequent cyclisation to azafluorenes.



In the case of phenyl-3-pyridyldiazomethane, a 1.3 : 1.0 mixture of 1- and 3-azafluorenes is formed in a total yield of 42%, while the pyrolysis of 4-pyridyl-substituted diazomethane gives only 2-azafluorene (68% yield). 4-Azafluorene cannot be obtained by this route.

Serious drawbacks of this method (multi-stage synthesis, the formation of mixtures of azafluorenes, and the necessity to perform pyrolysis in high vacuum) do not allow its use for preparative purposes.

A general procedure for the preparative synthesis of all isomeric azafluorenes (including alkyl- and aryl-substituted ones) has been developed in our laboratory.[107–115] The number of stages in this method depends on the procedure used for obtaining the synthon with a predetermined position of substituents.[109–118] At the final stage, the azafluorene precursor, viz., the alkyl-substituted phenylpyridine, is subjected to vapour-phase heterocyclisation at 520–540 °C on an industrial catalyst K-16 (a mixture of metal oxides). With 1,2,5-trimethyl-4-piperidone **40** as the starting material, 3-methyl-2-azafluorene **41** was obtained by this method;[108] some other 2-, 3- and 4-azafluorenes with different positions of methyl and phenyl substituents were also obtained.[109,112–115]

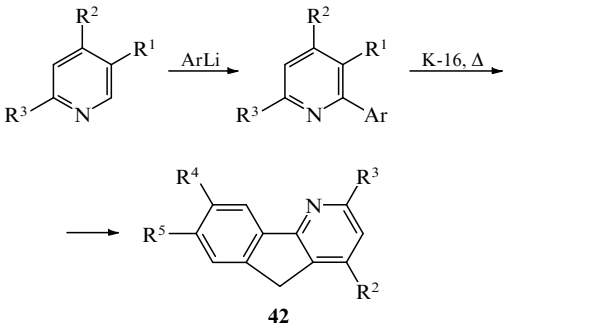


40 **41**

R = Me; R^1 = H, Me; Ar = Ph, C_6H_4Me-4, $C_6H_3Me_2$-2,4.

However, the attempts to obtain 1-azafluorene derivatives from the corresponding γ-piperidones have so far been unsuccessful.

A two-stage synthesis of 4-azafluorene derivatives **42** consisting in nucleophilic arylation of pyridine, 3-picoline, and lutidines with subsequent heterocatalytic dehydrocyclisation of alkylphenylpyridines is highly efficient.[109,116]

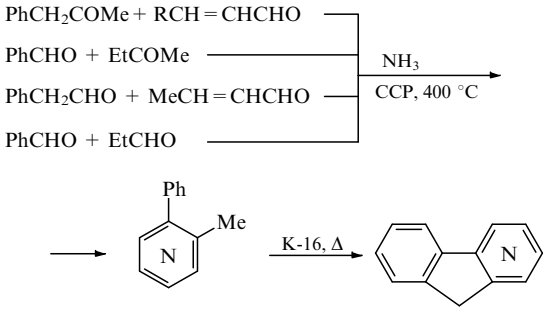


42

R^1–R^5 = H, Me; Ar = Ph, C_6H_4Me-2, C_6H_4Me-4, $C_6H_3Me_2$-3,4.

Dehydrocyclisation of 3-methyl-2-phenylpyridine or 2-*o*-tolylpyridine gives 4-azafluorene with equal yields (~20%) irrespective of what ring, pyridine or benzene, is involved in ring closure with involvement of the methyl group. However, this two-stage modification does not permit one to obtain azafluorenes with any other position of the nitrogen atom.

The most common approach is the one, in which all the necessary methyl(phenyl)-substituted pyridines are synthesised by the Chichibabin method (with yields of up to 55%) using vapour-phase heterocatalytic cyclisation of carbonyl compounds with ammonia on a cadmium-calcium phosphate catalyst (CCP).[111,117–120] These pyridines are then subjected to dehydrocyclisation on oxide catalysts into all kinds of isomeric azafluorenes **1**–**4** and their alkyl-substituted in pyridine ring homologues.



R = H, Me. **1–4**

Thus, comparison of the known methods used to synthesise azafluorenes reveals that the most effective (particularly, for preparing 1- and 3-azafluorenes) is the two-stage procedure based on the synthesis of phenylpyridines by Chichibabin's reaction and their subsequent dehydrocyclisation. The low yields of azafluorenes (20%–40%) at the stage of dehydrocyclisation are compensated for by the high selectivity of the process, and recycling of unconsumed phenylpyridine allows one to obtain azafluorenes in quantitative yields.

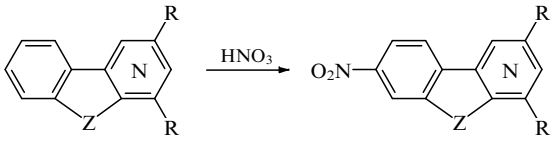
V. Transformations of azafluorenes

The chemical properties of azafluorenes and their derivatives are determined by the following factors: (1) the presence of two conjugated, fused cycles of different nature (benzene and pyridine) in one molecule; (2) the order of fusion of the indene and pyridine fragments; (3) the position and nature of functional groups in the case of substituted azafluorenes.

1. Reactions at the benzene nucleus

a. Electrophilic substitution

Among the reactions of electrophilic substitution, only nitration and bromination have been studied. In the nitration of unsubstituted azafluorenes,[25,97,121] azafluorenones,[6,25,97] and 4-azafluorenone *N*-oxide [122] the 7-nitro derivatives **43** are always isolated as the main product irrespective of the position of the nitrogen atom in the original polycycle. These experimental results confirm the preferential orientation of electrophilic substitution inferred from quantum-chemical calculations for 1-, 3-, and 4-azafluorenones.[5,6]

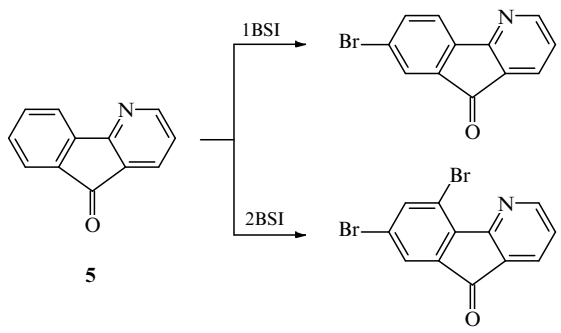


43

R = H, Me; Z = CH_2, CO, CHNHAc.

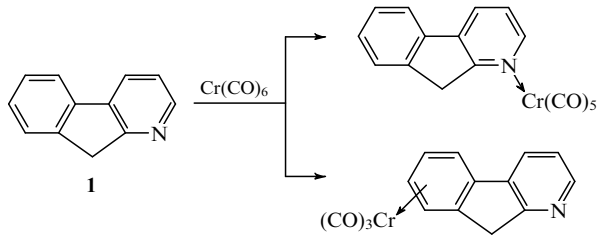
The nitro group is readily reduced (with Zn·Hg or $SnCl_2$ in HCl) into the amino group.[90] Carbonylation of 7-nitro-1-azafluorene in the presence of selenourea gives a mixture of 7-amino- and 7-carbamoyl-1-azafluorenes.[123]

Bromination of 1- and 4-azafluorenones **5** and **8** in the benzene ring has been performed with bromosuccinimide (BSI) in 70% H_2SO_4 at 50 °C. This reaction gives 7-bromo-, 5,7-dibromo-, and 5,6,7-tribromo derivatives, which is in a good agreement with the calculated reactivity indices.[5] The use of molecular bromine requires more drastic conditions: 100% H_2SO_4, 150–170 °C, autoclave.[5]



b. π-Complex formation

Nesmeyanov *et al.*[124, 125] have studied the interaction of azafluorenes with chromium, molybdenum, and tungsten carbonyls. It has been found that only 4-azafluorene forms arenechromotricarbonyl π-complexes with the benzene ring, whereas 1-azafluorene forms mixtures of π- and *n*-complexes (yields 5% – 30%).



2. Reactions at the pyridine nucleus

a. Quaternisation and complex formation

The reactivity of the pyridine fragment in azafluorenes is typical of pyridine itself. Azafluorenes easily quaternise to give *N*-alkyl halides, picrates, *N*-phenacyl halides, and complexes with BF_3.[126 – 140] They also form *N*-donor complexes with copper and silver salts.[131] With metal carbonyls [124, 125] 2- and 3-azafluorenes form only *n*-complexes. In the case of azafluorenones, the yields of quaternary salts decrease,[6, 126 – 128] apparently, due to the lower basicity of the pyridine fragment.

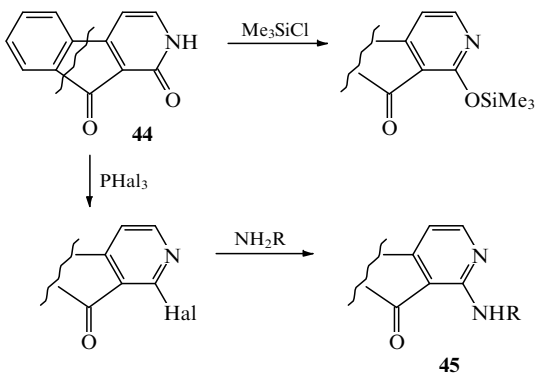
b. Deprotonation of azafluorenium salts

Quaternised azafluorenes contain in their five-membered ring the methylene group with high CH-acidity, which is readily deprotonated by basic reagents. For this reason, deprotonation of azafluorenium salts is used to obtain indenopyridine anhydrobases containing cyclopentanpyridine fragments. The latter comprise a 10π-electron nonbenzoid aromatic system and belong to the pseudoazulene series, the isoelectronic analogues of azulene. A comprehensive reveiw on the methods of synthesis of these azafluorene derivatives and their reactivity has been published recently.[132]

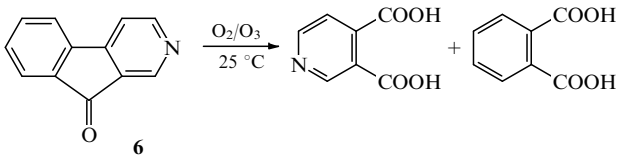
c. Oxidation

Interaction of azafluorenes and azafluorenones with hydrogen peroxide results in *N*-oxides,[52, 109, 126, 133] which can be easily deoxygenated to free bases on heating with PBr_3.[122]

Oxidation of quaternary indenopyridinium salts with air or potassium ferricyanide in alkaline media gives indenopyridones.[134, 135] The oxogroup in the α-pyridone fragment of the azafluorenediones **44** is converted into the ether group under the action of trialkylchlorosilanes and can be substituted for the halogen.[93] The latter is substituted for amino groups with amines under pressure.[45] The amino derivatives **45** can also be obtained from carbamoylazafluorenes by Hoffmann rearrangement.

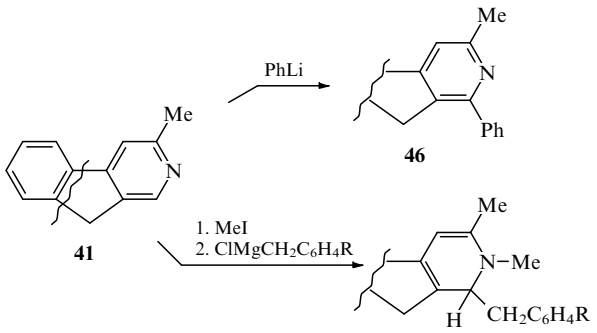


Deep oxidation of the 2-azafluorenone **6** by ozonolysis with subsequent treatment with hydrogen peroxide results in the oxidative cleavage of the tricyclic azine with the formation of cinchomeronic and phthalic acids.[3]



d. Arylation and benzylation

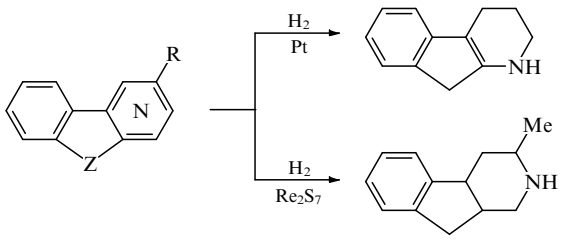
Arylation of the 2-azafluorene **41** with phenyllithium [109] gives its 1-phenyl derivative **46** in low yield. The efficiency of nucleophilic substitution increases when the azafluorene *N*-oxide is used. Benzylation of the azafluorene *N*-oxide or methiodide with benzylmagnesium halides also occurs at the free α-position of the pyridine ring.[109, 136]



R = H, 4-OMe.

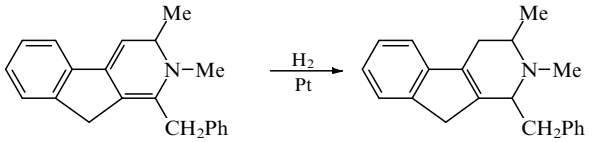
e. Hydrogenation

Catalytic hydrogenation of azafluorenes with platinum,[110] nickel, and rhenium heptasulfide [137] is carried out at high pressure and is accompanied by partial or complete reduction of the pyridine ring.



R = H, Me; Z = CH_2, CHOH, CO.

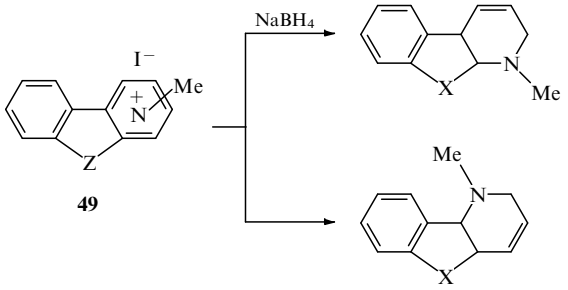
In the case of rhenium heptasulfide, *N*-alkylation may occur if the hydrogenation is performed in an alcohol. The dihydro derivatives of 2-azafluorene **48** are reduced on platinum, nickel, or palladium into tetra- and hexahydro derivatives at atmospheric pressure.[98–100, 136]



48

2-Azafluorenes are reduced with sodium in ethanol to indanopiperidines.[110, 138] The stereochemistry of these hexahydro derivatives has been studied by ^{1}H NMR.[138–140]

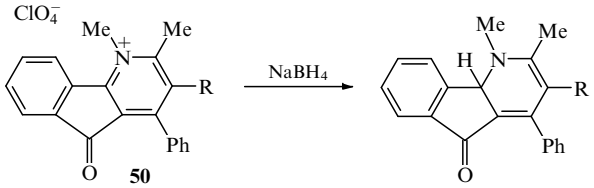
The azafluorene methiodides **49** are smoothly reduced with sodium borohydride to tetrahydro derivatives.[6, 141–143] The residual double bond is usually localised in the β,γ-position relative to the nitrogen atom irrespective of the mode of fusion of the pyridine fragment with the cyclopentadiene ring.



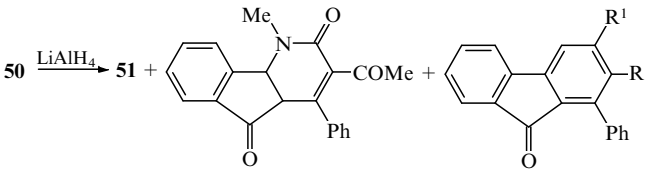
49

Z = CO, CH_2; X = CH_2, CHOH.

Reduction of the 4-azafluorenonium perchlorate (**50**) with sodium borohydride gives 4,4*a*-dihydroxy derivatives (**51**). However, when lithium aluminium hydride is used, products of nucleophilic recyclisation of the pyridine ring are formed along with the derivative **51**.[143]



50 **51**

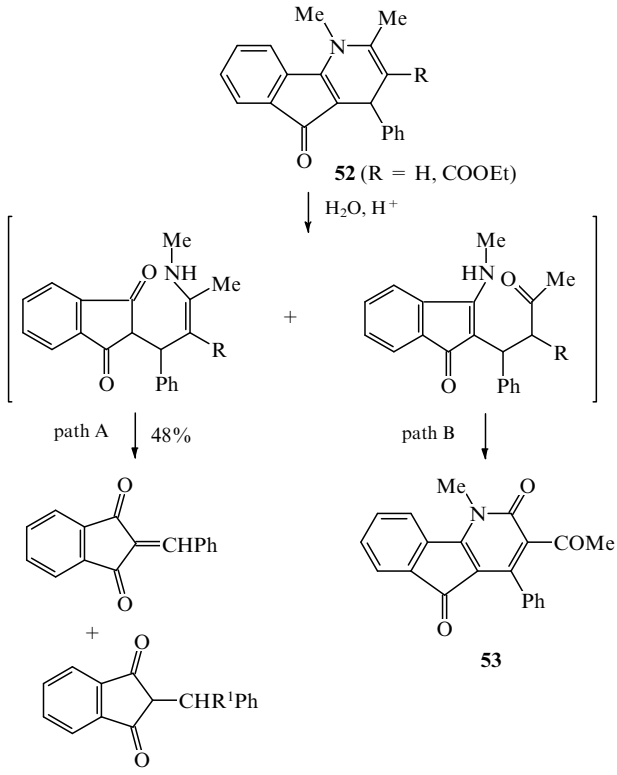


R = COOEt; R^1 = OH, NHMe.

Reduction of azafluorenium cations with sodium hydrosulfite results in indanopiperidine.[142]

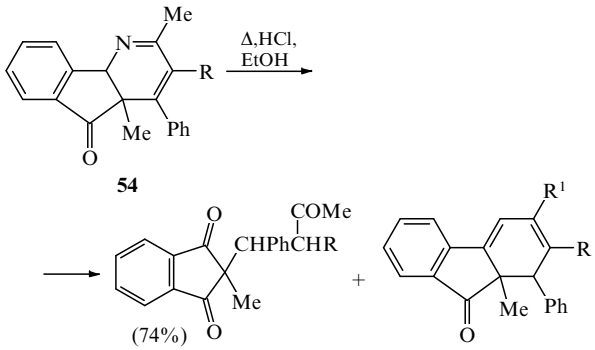
f. Hydrolysis of 1,4-dihydro-4-azafluorenes

These compounds are decyclised upon acid hydrolysis with the cleavage of the N–C bond in two directions followed by elimination of the amine fragment (route A) or recyclisation into indenopyridones **53** (route B).[81, 144–150]



R^1 = H (27% yield), CHRCOMe (18% yield).

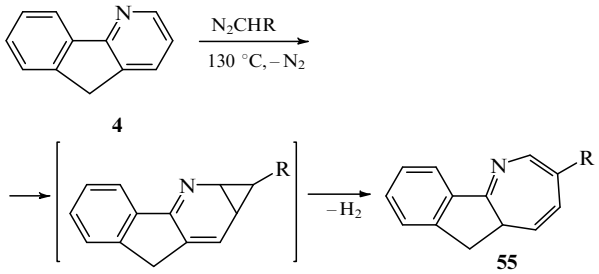
The cleavage of the N–C(4*a*) bond occurs more easily. Similar hydrolysis of 1,9*a*-dihydro-4-azafluorenone **54** gives 1,9*a*-dihydrofluorenone and substituted indanedione.[81, 114, 146]



R = CO_2Et; R^1 = OH (10% yield), NH_2 (12% yield).

g. Other reactions

The thermal reaction of 4-azafluorene with ethyl diazoacetate results in indenoazepine (**55**).[151] Apparently, the initial addition of the carbene to the double bond of the pyridine ring is followed by its expansion and dehydrogenation.[152]



R = COOEt.

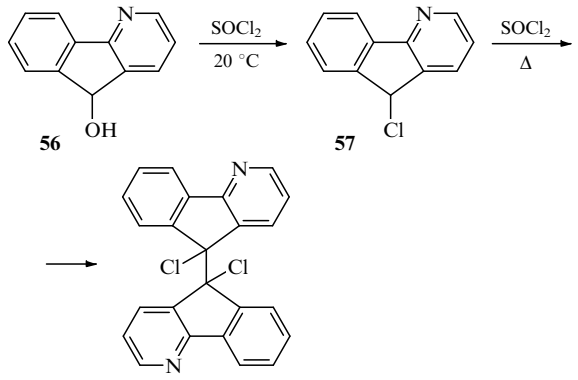
3. Syntheses involving the methylene group

a. Oxidation

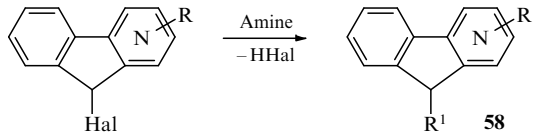
The azafluorenes **1**–**4** are readily oxidised to the azafluoren-9-ones **5**–**8** with $KMnO_4$ or $Na_2Cr_2O_7$ in CH_3COOH (yields 40%–60%).[112, 116, 153] The oxidation with oxygen in the presence of the Rodionov catalyst [154] or an alkali in DMSO [117] increases the yield of ketone up to 80%–90%. An exceptional tendency of 3-azafluorene to oxidation (unlike that of its isomers) has been exemplified by its quantitative conversion into a stable 9-oxo derivative by mere bubbling of air through its hexane solution.[6] Methyl- and styryl-substituted azafluorenes are oxidised to azafluoren-9-one carboxylic acids with $KMnO_4$ or SeO_2.[108, 155] The thermal (180–220 °C) decarboxylation of these acids has been studied.[50, 51, 64, 84]

b. Halogenation

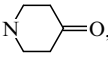
Hydrogen atoms and the hydroxyl group at C(9) of azafluorene (**56**) are readily substituted for halogen on treatment with BSI, carbon tetrachloride (in aqueous alkali in the presence of triethylbenzylammonium salt), thionyl chloride, and hydrogen halide.[89, 153, 156–160] It is remarkarble that under halogenation conditions, 9-chloro azafluorenes (**57**) dimerise on heating.[156]



9,9-Diiodo-1-azafluorene is formed as the sole product on attempted carbonylation of 1-azafluoren-9-ol in the presence of hydrogen iodide and rhodium iodide.[123] Halogen derivatives are readily reduced with zinc in ethanol [161] and halogen atoms are smoothly substituted by nucleophiles. Thus, the interaction of 9-bromo-4-azafluorene with NH_3 and amines gives the corresponding 9-aminoazafluorenes **58**.[157, 162] Some of them are promising as inhibitors of lipid peroxidation.

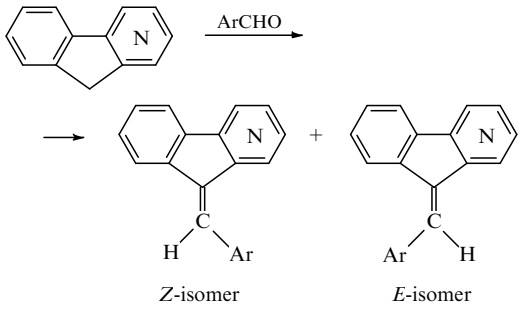


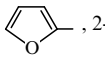
Hal = Cl, Br; R = H, Me;

R^1 = NH_2, , , $N(CH_2CH_2R^2)_2$, where R^2 = OH, OCOEt, $OCONH_2$.

c. Condensation with aldehydes and ketones

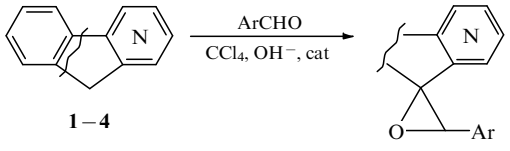
Aromatic and heteroaromatic aldehydes easily couple with azafluorenes at the methylene group in the presence of bases to give 9-arylidene derivatives.[117, 153, 163–170] In some cases, the geometric isomers of these benzopyridofulvenes could be separated chromatographically which made it possible to establish their molecular structure (using X-ray structural analysis) and to relate their physical and spectral characteristics with their (*Z*)- or (*E*)-form.[8, 17, 18, 168]



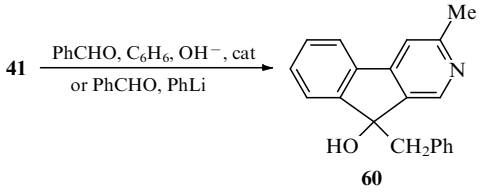
Ar = Ph, C_6H_4R (where R = Br, Cl, OMe, OH, NO_2, NMe_2), , 2-, 3- and 4-Py, 3-Py·MeI.

The influence of the position of the nitrogen atom in the pyridine fragment and the structure of the aromatic aldehyde on the ratio of (*Z*)- and (*E*)-isomers of 9-arylideneazafluorenes has been investigated. A possibility has been established of intramolecular through-space interaction (of the charge-transfer complex type) between the arylidene fragment and the unshared electron pair of the nitrogen atom, which can occur only in the case of 1-azafluorene derivatives.[8, 168] 9-Alkylidene-azafluorene derivatives have been prepared.[167] Ketones (e.g. benzophenone) also interact with azafluorenes.[163] If these condensations are carried out in the presence of air, considerable amounts of azafluorenes and 1,2-di(azafluorenylidene)ethanes are formed.[161, 166] The methyl groups at the α- and γ-positions of the pyridine ring of azafluorene are also active as regards condensation with aromatic aldehydes, which allows synthesis of compounds of the stilbene type.[108, 155, 163] In some cases, arylazafluorenylethyl alcohols [166] and cyclisation products of α-styryl derivatives, 3-azafluoranthenes were isolated.[114] A series of carbocyanine dyes have been synthesised with involvement of the 3-methyl group of 2-azafluorene.[169]

Under conditions of phase-transfer catalysis, the azafluorenes **1**–**4** couple with aromatic aldehydes (NaOH, CCl_4) with the formation of (*Z*)- and (*E*)-isomeric spiro(azafluoren-9,2′-oxiranes) **59**.[161]



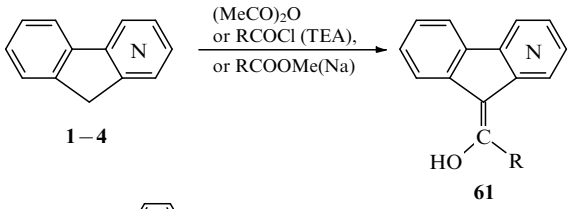
The side products of this reaction are 9,9-dichloro- and 9-benzylideneazafluorenes as well as bi(azafluorenylidenes-9). The latter are easily formed in the alkaline dehalogenation of 9,9-dihalogenoazafluorenes.[146, 153] The use of benzene as the organic phase results in phenyl(azafluorenyl-9)methanol (**60**), which can be also obtained by the reaction of benzaldehyde with azafluorene in the presence of phenyllithium.[170]



d. Acylation and alkylation

The azafluorenes **1**–**4**, like fluorene, are acylated at C(9) with acetic anhydride,[171] acyl chlorides,[130, 183] and alkylcarboxylic acid esters in the presence of alkali metals.[170, 172] However, unlike 9-acylfluorenes, acyl derivatives of azafluorenes occur as enols

61, which seems to be assignable to the higher CH-acidity of azafluorenes.

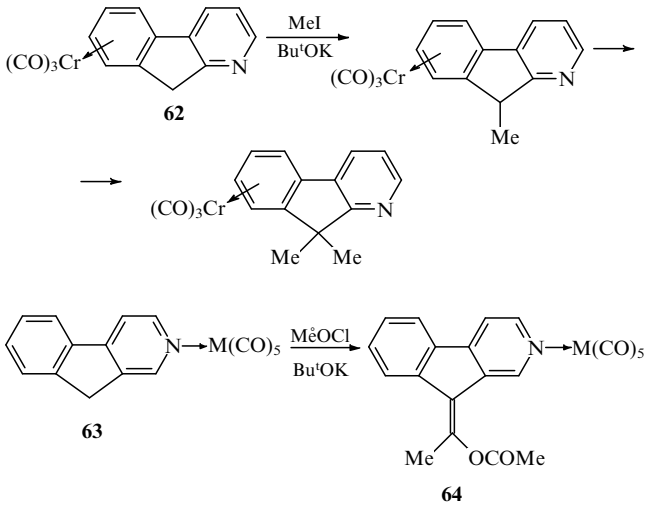


1–4 **61**

R = Me, Et, Ph, , PhCH=CH, $PhOCH_2$.

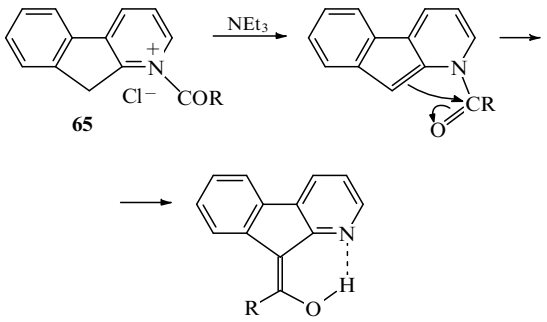
Spectroscopic studies have shown that in the crystalline state as well as in polar and aprotic solvents 9-formyl-4-azafluorene exists in the enolic form, whereas in nonpolar and protic solvents, it is a mixture of aldehyde and enolic forms.[173]

Reactions of alkyl halides and acid chlorides with arenochromotricarbonylazafluorenes under deprotonation conditions have been studied.[124, 125] It has been shown that π-complexes **62** are alkylated at C(9) and *N*-donor complexes **63** are acylated analogously, with the formation of enol acetates **64**.



62 **63** **64**

Treatment of 1-acyl-1-azafluorenium chlorides (**65**) with bases in benzene is accompanied by the formation of unstable, deep-coloured 1-acyl-1*H*-indenopyridines. Under the action of BF_3 they undergo a 1 → 3 acyl shift and are quantitatively converted into 9-acylindenopyridines, which exist in the enolic form stabilised by an intramolecular hydrogen bond.[130] No acyl shift occurs in the case of isomeric azafluorenes.

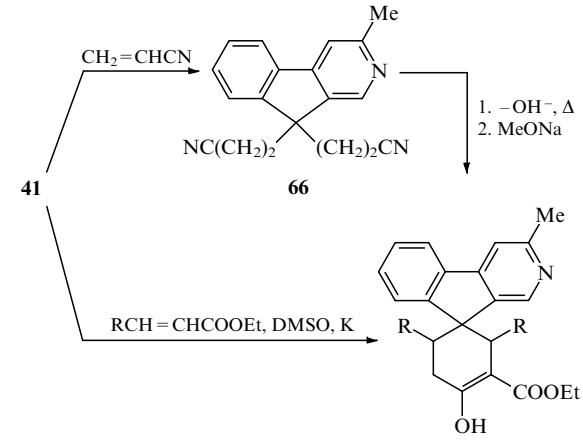


65

R = Me, Ph, $C_6H_4NO_2$-4.

Aralkylation of 4-azafluorene has been carried out at C(9) using a mixture of veratryl alcohol and veratraldehyde in the presence of KOH.[165]

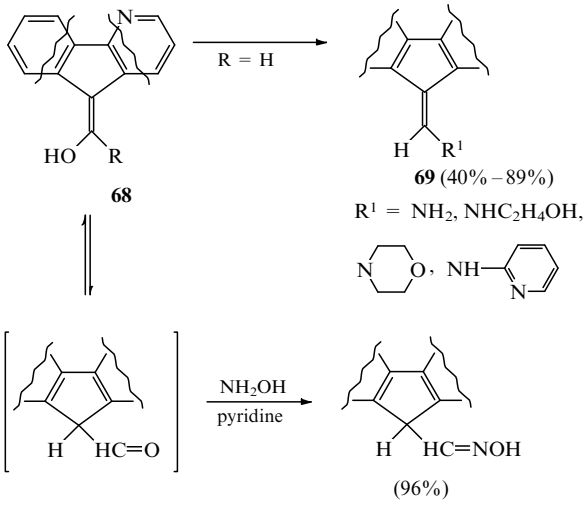
2- And 4-azafluorenes are readily alkylated under conditions of the Michael reaction [21] and are cyanoethylated with acrylonitrile in the presence of the Rodionov catalyst.[114, 154, 174, 175] The 9,9-bis(cyanoethyl)azafluorenes (**66**) obtained are then hydrolysed to dibasic acids thus which give after esterification entered into the Dieckmann condensation to spiro(azafluorene-9,1′-cyclohex-3-enes) (**67**). Analogous spiro-compounds are formed in one step with 20% – 54% yields when esters of α,β-unsaturated acids react with azafluorene in the presence of potassium.[176]



67

e. Reactions of 9-methylene derivatives of azafluorenes

9-Hydroxymethyleneazafluorenes (**68**) are converted by nucleophiles (ammonia or amines) into 9-aminomethylene derivatives (**69**), whereas with hydroxylamine, they form a stable 9-formylazafluorene oxime.[172]

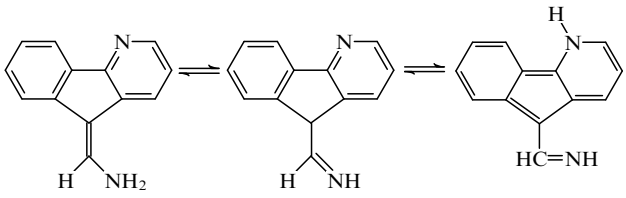


68 **69** (40% – 89%)

R^1 = NH_2, NHC_2H_4OH,

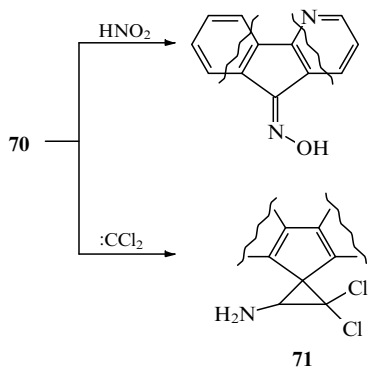
(96%)

9-Aminomethylene-4-azafluorene **70** exists as enamine and two tautomeric imines. Quantum-chemical calculations as well as UV and IR spectral data indicate that this compound has the enamine structure.[177]



70

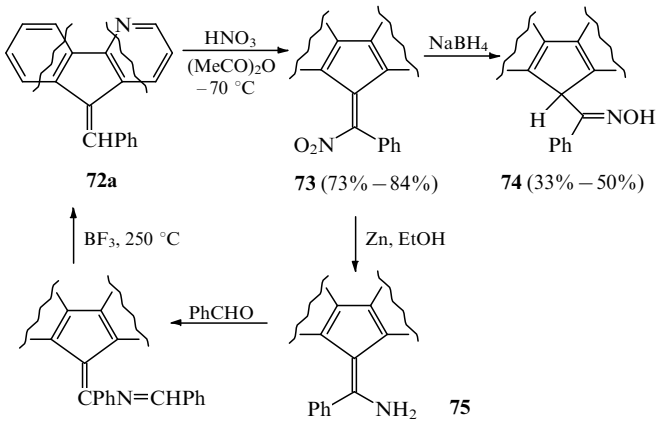
Its nitrosation gives the 2-azafluorenone oxime. Dichlorocarbene adds to the exocyclic C=C bond of the compound **70** to give the spirocyclopropane derivative **71**.



71

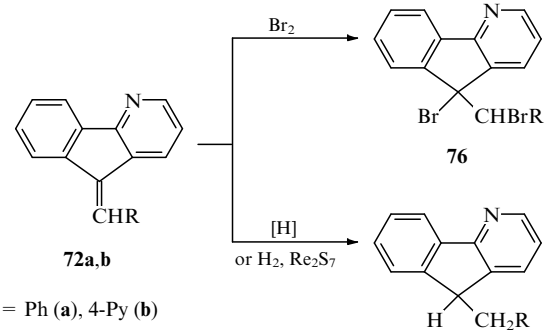
Acylation of the enamine **70** gives normal mono- or diacetyl derivatives.

Nitration of benzylindeneazafluorene (**72a**) with acetyl nitrate results in the substitution of hydrogen at C(10) with the formation of 9-α-nitrobenzylideneazafluorenes (**73**) as (*Z*)- and (*E*)-isomers in a ratio of 1 : 2.5; these compounds can be reduced the oxime **74** or amine **75**.[172] Condensation of the latter with aldehydes smoothly gives Schiff's bases with the *S-trans*-configuration of the azadiene fragment.[178] Thermolysis of these imines in the presence of BF_3 gives the original compound, **72a**.



72a **73** (73% – 84%) **74** (33% – 50%) **75**

The exocyclic double bond of benzopyridofulvenes of the **72a**,**b** type is readily reduced with lithium aluminium hydride[163] or a mixture of benzyl alcohol with KOH at 200 °C.[165] In the case of pyridylmethyleneazafluorene, catalytic hydrogenation over Re_2S_7 also occured at this bond and did not affect the pyridine rings.[179]



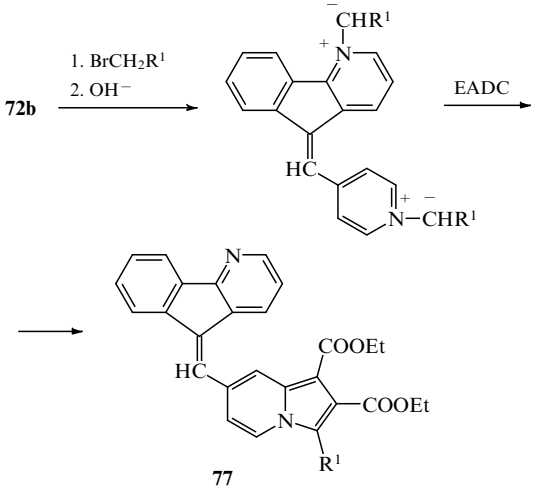
76

72a,**b**

R = Ph (**a**), 4-Py (**b**)

The latter finding suggests that the substrate is coordinated at the acidic centres of rhenium heptasulfide through the π-excessive fulvene fragment rather than through the pair of unshared electrons of the nitrogen atom. Calculations on this type of fulvene system provide support for the localisation of the negative charge at the carbon atoms of the exocyclic double bond.[8,17] The bromine molecule readily adds at this double bond in the compounds **72a**,**b** to give dibromo derivatives **76**.

The pyridylmethyleneazafluorene **72b** forms a double salt with bromoacetophenone, which generates a double ylide under the action of bases. This ylide adds only one molecule of ethylacetylenedicarboxylic acid (EADC) and only at the pyridyl radical to form the adduct **77**; the phenacyl substituent at N_4 of the azafluorene skeleton is split off in the process.[17]

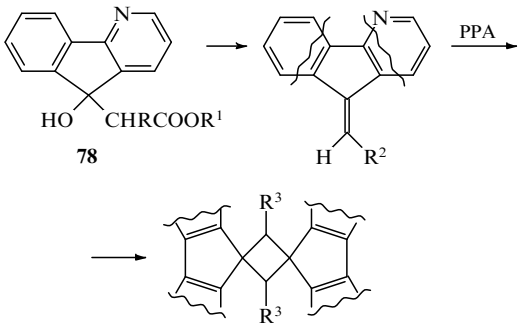


77

R^1 = COPh.

The Wagner hydroxylation of the exocylic C=C bond results in the glycol.[180,181]

2-(9-Hydroxyazafluoren-9-yl)propionic and (9-hydroxyazafluoren-9-yl)acetic acids or their esters **78** were converted via 9-methylene derivatives into dispirobis(4-azafluorene)-9-1′,3′-cyclobutanes **79**.[161,182]



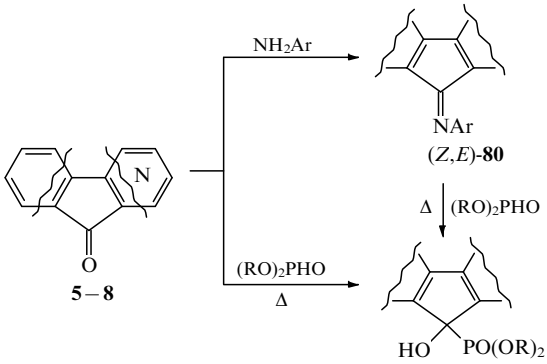
78 **79**

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

4. Syntheses involving the carbonyl group of azafluoren-9-ones

a. Condensation with amines and CH-active compounds

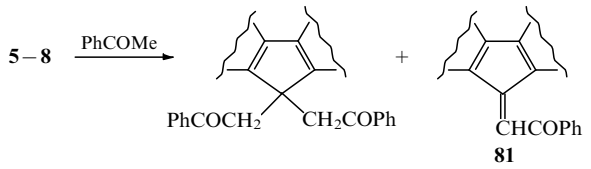
The azafluorenones **5**–**8** give oximes, hydrazones, semicarbazones,[2,6,45,183] and Schiff's bases **80**.[116,184]



Higher yields of the latter compounds have been achieved with the use of BF_3 as the catalyst. The dependence of the ratio of the configurational *Z*,*E*-isomers of the ketimines **80** on the nature of the amine component used for condensation was studied by ^{1}H NMR. An alternative synthesis of arylazomethines of the type **80** has been carried out by condensation of azafluorenes with *p*-nitrosoanilines followed by reduction of the intermediate nitrones with zinc in ethanol.[158, 184]

The Schiff's bases **80**, like the original azafluorenones, add dialkyl phosphites to give the corresponding 9-azafluorenylphosphonates.[185] 9-Iminoazafluorenes were converted into 9-amino derivatives with Zn(Fe) in AcOH or Ac_2O,[19, 45] NH_2-NH_2 (Raney Ni)[183] or $LiAlH_4$.[184]

Under alkaline conditions, azafluorenones condense with acetophenone to give 9,9-bis(phenacyl)- and 9-phenacylidene derivatives **81**.[180, 181]



81

b. Reduction

Heating of azafluorenones with hydrazine hydrate in an autoclave results in the reduction of the oxo-group to the methylene group in high yield.[3, 92, 186] In lower yields azafluorenes are formed on reduction with zinc amalgam in hydrochloric acid.[3] Sodium borohydride reduces azafluorenes only to alcohols[142–144] which are smoothly esterified with acid anhydrides[187] and acid chlorides.[141]

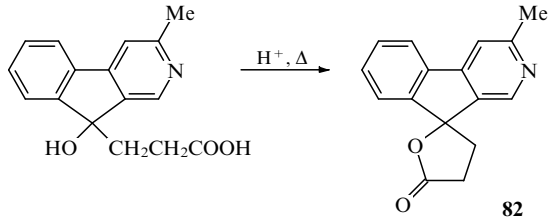
c. Interaction with organometallic compounds

Azafluorenones react with phenyl- and methyllithium and with benzylmagnesium chloride to give the ordinary products of nucleophilic addition, i.e., the corresponding tertiary alcohols.[187] The yield of alcohols depends on the position of the nitrogen atom and the presence of substituents.[141, 142] These alcohols are easily dehydrated in acid media or in the presence of P_2O_5.[165, 167, 187] In the presence of zinc, the esters of α-bromocarboxylic acids add to the C=O group of azafluoren-9-ones to give the corresponding 9-substituted azafluoren-9-ols.[161]

5. Cyclisation reactions involving substituents

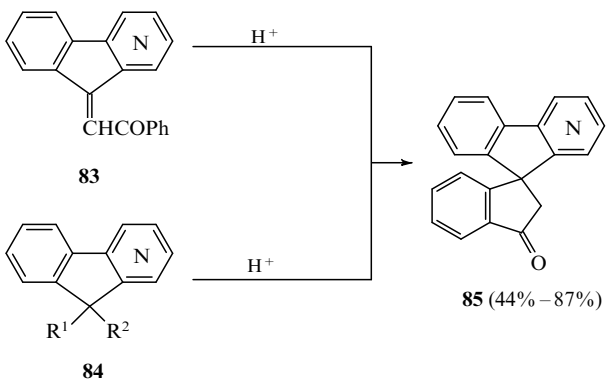
a. Synthesis of spiro-coupled derivatives

Heating of β-(9-hydroxy-2-azafluoren-9-yl)propionic acid in acid media results in cyclisation to the spirolactone **82**.[154]



82

9-Phenacylideneazafluorenes **83** and 9-hydroxy-9-phenylethynylazafluorenes **84** also enter into acid-catalysed cyclocondensation to give spirocompounds of the type **85** with indanone fragments.[180, 181] Condensation of the phenacylidene derivative **83** with hydrazine gives a spiro-fused pyrazoline **86** in quantitative yield.[180]



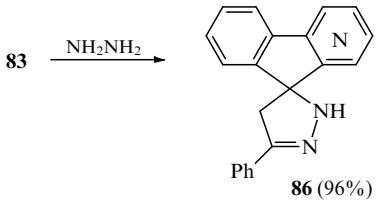
83

85 (44% – 87%)

84

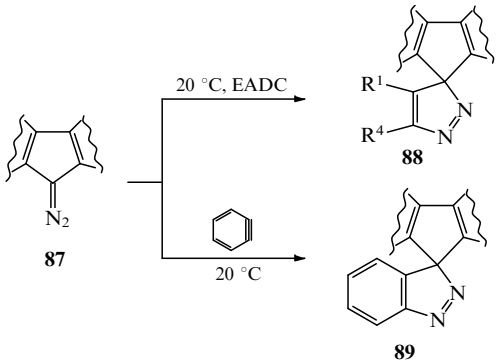
R^1 = OH, R^2 = PhC≡C

R^1 = R^2 = CH_2COPh



86 (96%)

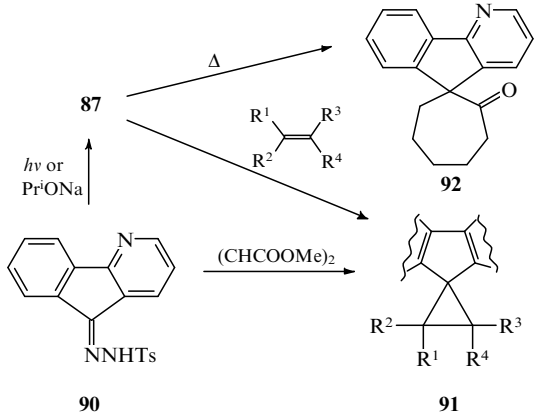
9-Diazo-4-azafluorene (**87**) gives spiro(4-azafluorene-9,3′-3*H*-pyrazole) (**88**),[188] the product of cycloaddition of EADC, and an analogous spiro-compound **89** with dehydroxybenzene.[189] Dimethyl fumarate reacts with tosylhydrazone **90** on boiling in benzene in the presence of sodium alkoxide to give spiro(4-azafluorene-9,3′-cyclopropane) (**91**).[188]



87

88

89



92

90

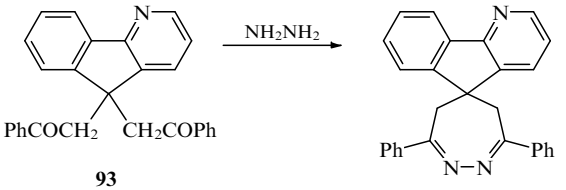
91

R^1 = COOMe, Ph, CHO, $SiMe_3$, CN;

R^2, R^3 = H; R^4 = COOMe.

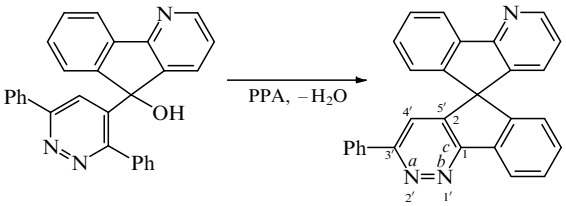
Similar compounds were obtained upon interaction of the derivative **87** with certain unsaturated compounds.[190] In the case of cyclohexanone, spiro(4-azafluorene-9,2′-cycloheptanone) (**92**) was isolated.

Treatment of the diketone **93** with hydrazine results in spiro(4-azafluorene-9,5′-diazepine) **94**.[191]



93 **94**

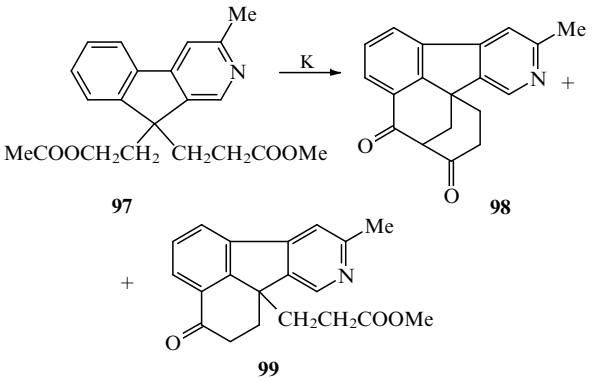
Intramolecular cyclodehydration of 9-(pyridazin-4-yl)aza-fluorenol (**95**) gives spiro{4-azafluorene-9,5′-indeno[1,2-*c*]-pyridazine} (**96**).[191]



95 **96**

b. Annelation of the benzene ring

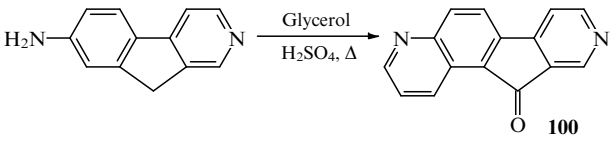
In the presence of potassium the diester of a dibasic acid of the azafluorene series **97** gives two cyclocondensation products, *viz*., **98** and **99**.[162]



97 **98**

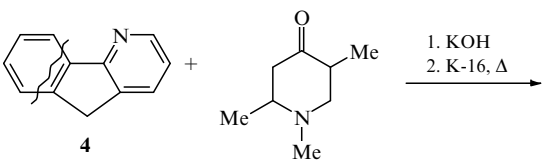
99

Only one cyclisation product **100** has been obtained in low yield from 7-amino-2-azafluorene by the Skraup reaction.[164]

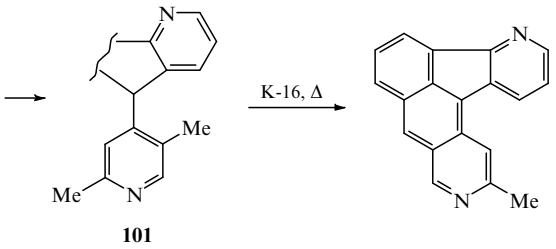


100

4-Azafluorene condenses with 1,2,5-trimethyl-4-piperidone in the presence of KOH to give an unstable product, which was dehydrogenated without isolation into 9-pirydyl-4-azafluorene **101**.[157] The latter was converted into pyridoazafluoranthene by catalytic dehydrocyclisation.



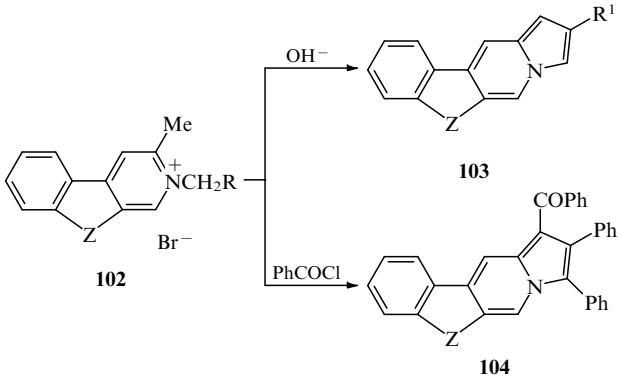
4



101

c. Annelation of the pyridine ring

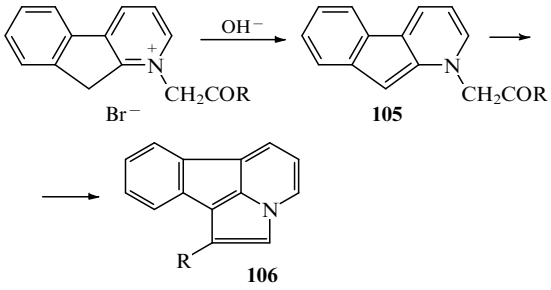
3-Methyl-*N*-phenacyl-2-azafluorenium bromides (**102**) cyclise under condition of the Chichibabin reaction into indenoindolizines (**103**, **104**).[127, 128]



102 **103** **104**

R = COMe, COPh; R^1 = Me, Ph; Z = CH_2, CO, C(OH)Ph.

However, in the case of the 1-azafluorenium this reaction does not take place, and stable anhydro bases **105** are formed instead.[121, 130]

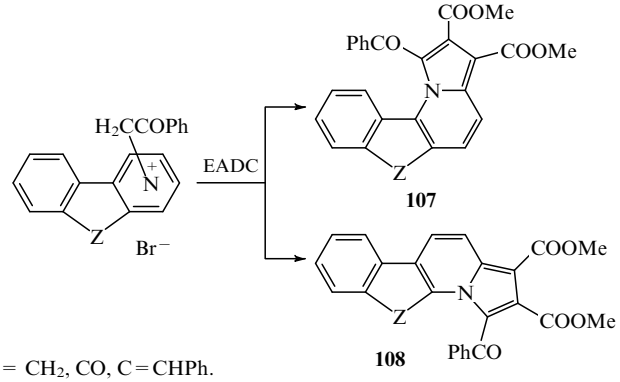


105 **106**

R = Ph, $C_6H_4NO_2$-4.

Nevertheless, the latter were successfully converted into indenoindolizines **106** by thermolysis *in vacuo*.

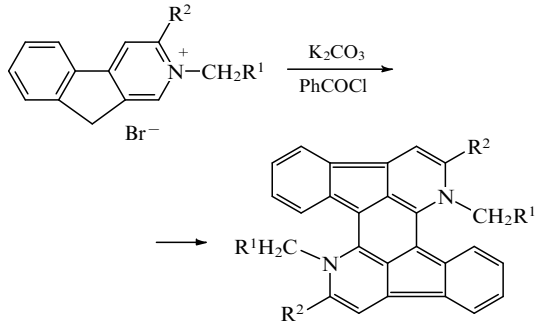
Isomer-*N*-phenacylic azafluorenium bromides enter into 1,3-dipolar cycloaddition reactions with EADC to give indenoindolizines **107** and **108** with different fusion of the rings.[6, 127, 128]



107 **108**

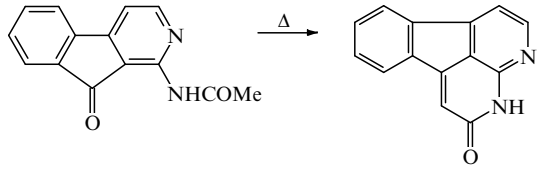
Z = CH_2, CO, C=CHPh.

The quaternary salts of 2- and 4-azafluorenium are deprotonated in the presence of benzoyl chloride to give dimers (in low yields) in the form of *NH*-diazafluoranthenes **109**.[128]

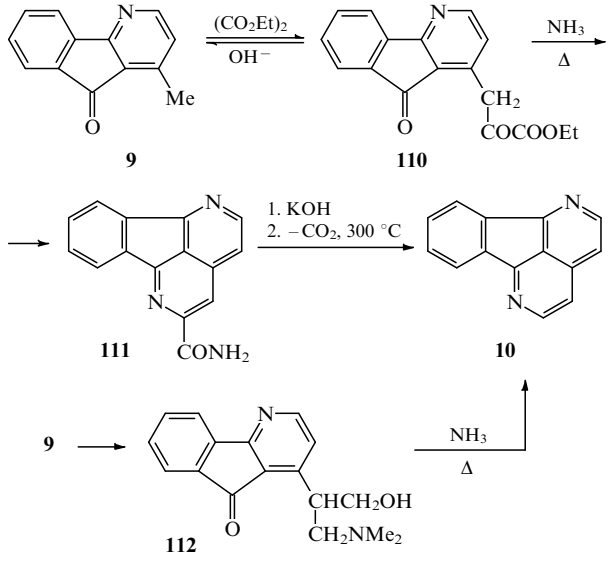


R^1 = COPh; R^2 = H, Me.

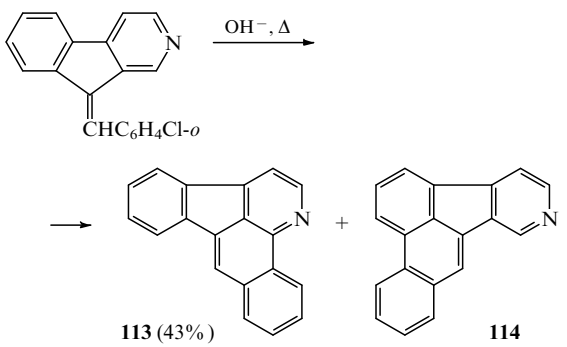
1-Acetylamino-2-azafluorenone was converted into 3*H*-3,4-diazafluoranthen-2-one on heating in DMF in the presence of potassium alkoxide.[45]



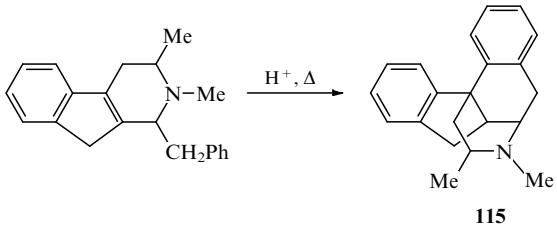
Condensation of diethyl oxalate with the alkaloid onychin (**9**) gives ethyl(9-oxo-4-azafluorenyl)pyruvate (**110**).[45] Its heating with ammonia results in 1,6-diazafluoranthene-2-carboxamide (**111**). The latter was converted by a two-step procedure into the alkaloid eupolauridine (**10**); it could also be obtained by an independent synthesis from the compound **112**, the product of condensation of onychin (**9**) with formaldehyde and dimethylamine.



Polycyclic heterocycles **113** and **114** were obtained on heating of 9-(2-chlorobenzylidene)-2-azafluorene in the presence of alkali.[164]



Cyclisation of 1-benzyl-1,2,3,4-tetrahydro-2-azafluorene in orthophosphoric acid resulted in a structural analogue of morphine **115** in a low yield.[136]

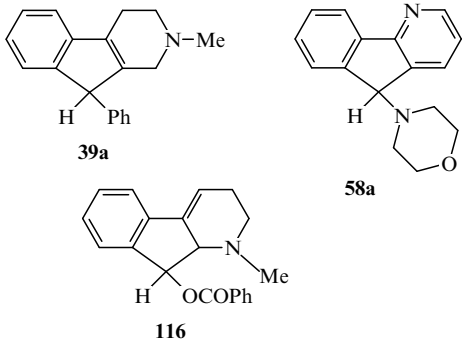


VI. Biological activity of azafluorene derivatives

Azafluorene derivatives display a broad spectrum of biological activities which gives a strong impetus to the synthesis and further biotesting new compounds of this series. 2-Methyl-9-phenyl-1,2,3,4-tetrahydroxy-2-azafluorene (**39a**) has been introduced into clinical practice as an antiallergic drug.[100, 192] Some of its analogues manifest potent spasmolytic, adrenolytic, anaesthetic, and antihistamine activity.[2, 193]

Dihydro- and hexahydro-derivatives of 2-alkylaminoalkyl-9-phenyl-2-azafluorene possess antiarrhythmic and bactericidal activities.[101]

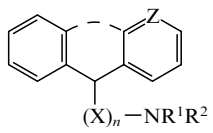
4-Azafluorene-*N*-oxide inhibits the effects of adrenaline and secretion of gastric juice.[133] 1,4-Dihydro-derivatives and 9-amino-derivatives of 4-azafluorene **58a** exhibit a vasodilator activity and manifest the properties of peroxidation inhibitors.[194–196]



As follows from the review of antiviral preparations,[197] alkyl-, carboxy-, and cyano-derivatives of 1-azafluorene have been recommended as antiinfluenza drugs. Derivatives of 1,2,4,9*a*-tetrahydro-1-azafluorene-3-carboxylic acid are considered as simple analogues of ergot alkaloids.[73, 74, 198, 199] 1-Azafluorene and its 9-hydroxy-derivative methiodides display a broad spectrum of antibacterial activities.[126] Several tetrahydro-2–azafluorenes **116** [141] and 9-substituted 1-azafluorenes (semicarbazones, tosylhydrazone, and arylidene- derivatives) are characterised by neurotropic activity and low toxicity.[200] The results of antitumour assay of certain azafluorenones have been documented.[201, 202]

Azafluorene derivatives exhibit a pesticide activity and regulate plant growth and development.[17, 203, 204] An extensive body of evidence concerning the diverse biological activities of these compounds has also been accumulated in the patent literature over the recent years; these data are not considered in the present review.

It should be emphasised that 9-substituted azafluorenes incorporate a fragment of a potentially pharmacophore ('magic') group **117**, which is present in the molecules of numerous drugs affecting biological systems via cholinergic, adrenergic, and histamine receptors.[202]



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It may therefore be expected that a search among these azafluorene derivatives for compounds endowed with a high biological activity is a very promising approach.

In conclusion, the authors express the hope that the review presented will provide further impetus to the expansion and intensification of studies into the chemistry of azafluorenes and will generate professional interest among scientists in related fields (pharmacologists, biochemists, etc.) in this group of heterocyclic compounds, which has currently become chemically available.

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