U.D.C. 547.831/836

Benzoisoquinolines and Azafluorenes

N.S.Prostakov

Methods of preparation, synthetic reactions, and properties are surveyed for the difficultly accessible polyfused nitrogen-containing heterocyclic systems—benzo[*f*] isoquinoline, benzo[*g*] isoquinoline, benzo[*h*] isoquinoline, and azafluorenes in which the position of the nitrogen atom in the pyridine ring varies. A list of 77 references is included.

CONTENTS

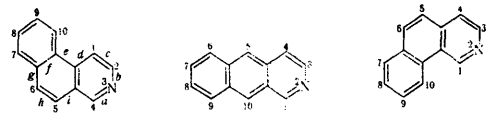
I. Benzoisoquinolines 774
1. Benzo[*f*] isoquinolines 774
2. Benzo[*g*] isoquinolines 774
3. Benzo[*h*] isoquinolines 776
II. Azafluorenes 777

Benzoisoquinolines and azafluorenes, which are tricyclic fused nitrogen-containing systems, still remain a little studied group of compounds. An apt comparison is that the monograph "Heterocyclic Compounds"[1] devotes a long chapter to benzoquinolines, whereas only a few words are said about benzoisoquinolines and azafluorenes. Only one example is given of the synthesis of benzo[*g*]isoquinoline and the isolation of a small quantity of 9-oxo-3-phenyl-4-azafluorene-1-carboxylic acid by the oxidation of 2-phenylbenzo[*h*]quinoline-4-carboxylic acid. The information on this group of compounds to be found in the literature is also limited.

Yet both benzoisoquinolines and azafluorenes are of definite interest. Among compounds of this type have been found quite effective physiologically active substances. Their use for the synthesis of various dyes is also promising. But perhaps the greatest value of these compounds is that they can form portions of systems which closely resemble alkaloids.

I. BENZOISOQUINOLINES

The nomenclature of the benzoisoquinolines is similar to that of the benzoquinolines:



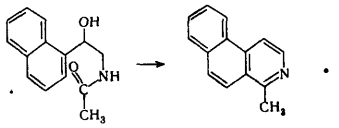
(I) (II) (III)

(I) benzo[*f*]isoquinoline (5,6-benzoisoquinoline, 2-azaphenanthrene)
(II) benzo[*g*]isoquinoline (6,7-benzoisoquinoline, 2-azaanthracene)
(III) benzo[*h*]isoquinoline (7,8-benzoisoquinoline, 3-azaphenanthrene).

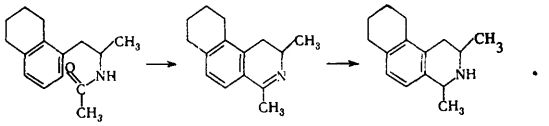
Synthetic routes for building up benzoisoquinoline systems are as yet relatively few, being limited mainly to Bischler–Napiralski[2], Pictet–Gams[3], and Pictet–Spengler[4] condensations and the dehydrocyclisation of *ortho*-substituted benzylpyridinecarboxylic acids, 4-*o*-xylylpyridines, and 4-benzyl-3-methylpyridines. The photochemical cyclisation of stilbazoles has been used in the synthesis of benzoisoquinolines.

1. Benzo[*f*]isoquinolines

4-Methylbenzo[*f*]isoquinoline can be obtained by boiling *N*-(2-hydroxy-2-naphth-1′-ylethyl)acetamide with phosphorus pentoxide in xylene[5]:

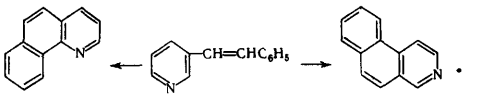


Partly hydrogenated substituted derivatives of benzo[*f*]isoquinolines have been synthesised by the Bischler–Napiralski method from *N*-[1-methyl-2-(5,6,7,8-tetrahydronaphth-1-yl)ethyl]acetamide, cyclisation being accomplished in the presence of phosphoryl chloride[6]:



1,2,7,8,9,10-Hexahydro-2,4-dimethylbenzo[*f*]isoquinoline was converted by catalytic hydrogenation into 1,2,3,4,7,8,9,10-octahydro-2,4-dimethylbenzo[*f*]isoquinoline. Several other partly hydrogenated substituted benzo[*f*]isoquinolines have been obtained by the same scheme of reactions.

The photochemical cyclisation of stilbazoles has been studied. Prolonged ultraviolet irradiation of a solution of 3-styrylpyridine and also of 3-*p*-methylstyrylpyridine in hexane yields a mixture of benzo[*f*]isoquinoline and benzo[*h*]quinoline (or the methyl derivatives of these heterocycles), which has been separated by chromatography on alumina[7,8]:

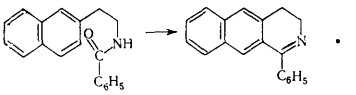


The *trans* and *cis* isomers of 3-styryl- and 3-*p*-methylstyryl-pyridines have been used in these reactions. In the same way 6-cyanobenzo[*f*]isoquinoline has been obtained from *trans*-3-β-cyanostyrylpyridine[9].

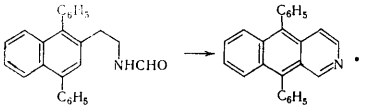
2. Benzo[*g*]isoquinolines

From the point of view of synthesis this benzoisoquinoline system has been studied in greater detail than the benzo[*f*]isoquinoline system. It can be constructed by

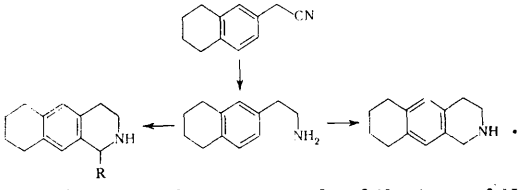
various methods. Several substituted benzo[*g*]isoquinolines have been obtained by the Bischler–Napiralski reaction. 3,4-Dihydro-1-phenylbenzo[*g*]isoquinoline has been isolated[10] by the condensation of *N*-2-naphth-2′-ylethylbenzamide (boiling in toluene with phosphoryl chloride):



3,4-Dihydrobenzoisoquinoline systems are readily converted into benzoisoquinoline systems, even by the action of atmospheric oxygen[11]. Condensation of the *N*-formyl derivative of 2-(1,4-diphenylnaphth-2-yl)ethylamine in the presence of phosphoryl bromide at once yields 5,10-diphenylbenzo[*g*]isoquinoline[12]:



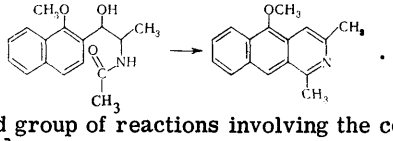
Several hydrogenated benzo[*g*]isoquinolines have been synthesised from 2-cyanomethyl-5,6,7,8-tetrahydronaphthalene[6]. On reduction with lithium tetrahydroaluminate this cyanide was converted into 2-(5,6,7,8-tetrahydronaphth-2-yl)ethylamine, which after acetylation, subsequent Bischler–Napiralski cyclisation, and hydrogenation gave 1,2,3,4,6,7,8,9-octahydro-1-methylbenzo[*g*]isoquinoline. When the same amine was condensed with formaldehyde by the Pictet–Spengler method, 1,2,3,4,6,7,8,9-octahydrobenzo[*g*]isoquinoline was isolated:



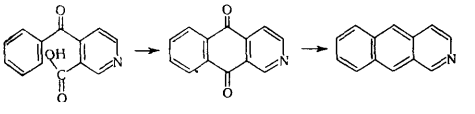
There are indications that compounds of the type of *N*-substituted 1,2,3,4,6,7,8,9-octahydro-3-methylbenzo[*g*]isoquinolines have a strong analgesic effect.

The condensation of *N*-acylated 2-(5,6,7,8-tetrahydronaphth-2-yl)-1-methylethylamines has been accomplished. 1-Benzyl-3,4,6,7,8,9-hexahydrobenzo[*g*]isoquinoline has been obtained by the cyclisation of *N*-β-(6-tetralylethyl)-phenylacetamide[13].

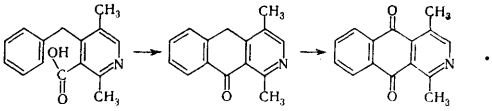
The Pictet–Gams method has been used in syntheses of benzo[*g*]isoquinolines as well as in the preparation of benzo[*f*]isoquinolines. An example is the synthesis of 5-methoxy-1,3-dimethylbenzo[*g*]isoquinoline[14]:



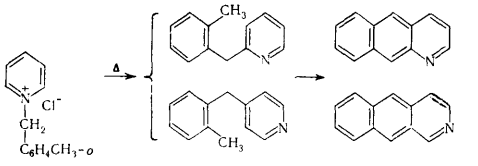
In a second group of reactions involving the construction of the benzo[*g*]isoquinoline system use is made of a preformed pyridine ring. Benzo[*g*]isoquinoline is obtained from 4-benzoylpyridine-3-carboxylic acid, which was converted by intramolecular condensation (with sulphuric acid at 175°C) into 2-aza-anthraquinone, from which benzo[*g*]-isoquinoline was obtained by reduction with zinc dust in aqueous ammonia[15]:



The cyclisation of 4-benzyl-2,5-dimethylpyridine-3-carboxylic acid by means of polyphosphoric acid yields the corresponding 2-aza-anthrone (in 85% yield), which is readily oxidised by atmospheric oxygen to 1,4-dimethyl-2-aza-anthraquinone[16]:



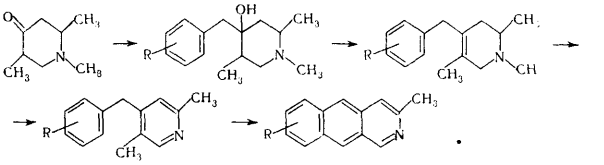
Similarly to the dehydrocyclisation of *o*-benzyltoluene to anthracene, benzo[*g*]isoquinoline has been obtained from 4-*o*-xylylpyridine. The initial substituted benzylpyridines are synthesised by Ladenburg's method, which was first developed in detail for these purposes by Chichibabin[17,18]. When *o*-xylyl chloride is heated (to 250°C) with pyridine in the presence of copper, a mixture of 2- and 4-*o*-xylylpyridine is formed, in which the latter isomer predominates. When the mixture of these substituted pyridines is passed over copper turnings or over pumice impregnated with lead oxide at 580–590°C, dehydrocyclisation takes place, with the formation of benzo[*g*]quinoline and benzo[*g*]-isoquinoline, the latter being comparatively easily isolated from the mixture because of its sparing solubility[19]:



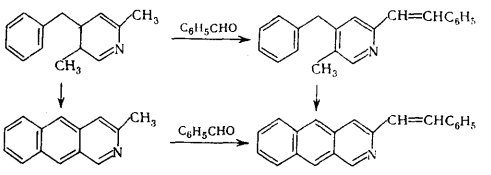
8-Methylbenzo[*g*]isoquinoline has been obtained in the same way from *o*- and *p*-dimethylbenzylpyridinium chloride.

A method has been worked out for obtaining benzo[*g*]-isoquinoline systems by the dehydrocyclisation of 4-benzyl-3-methylpyridines. The latter are synthesised from 4-oxopiperidines. The tertiary alcohols obtained from the oxopiperidines are converted by dehydration followed by catalytic dehydrogenation and *N*-dealkylation into quite high yields of substituted pyridine bases[20–22]. The dehydrocyclisation of 4-benzyl(alkylbenzyl)pyridines containing a 3-methyl group in the pyridine ring is accomplished at 500–510°C on the same dehydrogenation catalysts as are used at the stage of synthesis of 4-benzylpyridines.

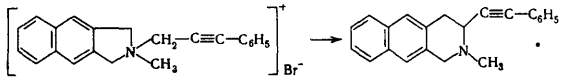
The reaction scheme given below is for the synthesis of 3-methylbenzo[*g*]isoquinoline[23] and its homologues from 1,2,5-trimethyl-4-oxopiperidine[24]:



3-Styrylbenzo[*g*]isoquinoline can be synthesised in two ways—by the direct condensation of 3-methylbenzo[*g*]isoquinoline with benzaldehyde and by the dehydrocyclisation of 4-benzyl-5-methyl-2-styrylpyridine:



The partly hydrogenated substituted derivative 1,2,3,4-tetrahydro-2-methyl-3-2′-phenylethynylbenzo[*g*]isoquinoline is formed on heating 2-(3-phenylprop-2-ynyl)benzo[*f*]-isoindolinium bromide in the presence of anhydrous caustic soda in benzene, the starting material being obtained from 2-methylbenzo[*f*]isoindoline and 3-phenylprop-2-ynyl bromide. These transformations are based on the rearrangement of derivatives of prop-2-ynylammonium halides:



The structure of the heterocyclic compound obtained was proved by means of its ultraviolet and nuclear magnetic resonance spectra[25].

Benzo[*g*]isoquinoline[3] are high-melting, usually sparingly soluble substances, which sublime in a high vacuum. In some solvents they fluoresce. They resemble anthracene in electronic structure. Their ultraviolet spectra are very alike[12,26,27]. Benzo[*g*]isoquinolines, like anthracene, exhibit two systems of absorption bands—a Y-band (2500 Å), due to vibrations of π-electrons in the plane of the rings, and an X-band (3000–3500 Å), due to vibrations of excited π-electrons perpendicular to the plane of the rings.

Comparison of the ultraviolet spectra of unsubstituted benzo[*g*]quinoline and benzo[*g*]isoquinoline with that of anthracene reveals a slight (10 Å or 140 cm^{-1}) bathochromic shift in the Y-band in the former, and a slight (20 Å or 350 cm^{-1}) hypsochromic shift in the same band in the latter. The X-system of bands exhibits a bathochromic displacement of the long-wavelength boundary of the region by 90 and 160 Å (625 and 1000 cm^{-1}) respectively in benzo[*g*]-quinoline and benzo[*g*]isoquinoline, and a decrease in intensity of absorption in the X-region (by a factor of about 1.5).

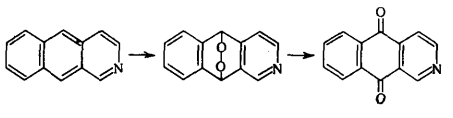
The effect of the nitrogen atom in these systems is analogous to that of such non-chromophoric substituents in the anthracene molecule as chloro and alkyl.

meso-Disubstituted benzo[*g*]isoquinolines show an additional absorption peak in the region of 3000 Å. It is assumed[26] that the pyridine ring, and also phenyl rings in *meso*-positions in substituted benzo[*g*]isoquinolines, do not lie in the plane of the naphthalene ring system.

Several papers present results of quantum-mechanical calculations on benzo[*g*]isoquinoline systems[28–32].

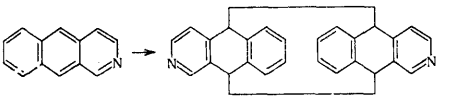
Benzo[*g*]isoquinoline forms an adduct with maleimide[12].

Like aromatic linear fused tricyclic systems, benzo[*g*]-isoquinolines undergo photochemical reactions[33,34]. When a solution of benzo[*g*]isoquinoline in carbon disulphide is exposed to sunlight, an unstable photo-oxide is formed, which is oxidised in the air to 2-aza-anthraquinone (3,4-phthaloylpyridine):



Exposure of a solution of 5,10-diphenylbenzo[*g*]isoquinoline in carbon disulphide gave a 20% yield of its photo-oxide (colourless), and this decomposes at 145–165°C, evolving up to 80% of the combined oxygen[12,35].

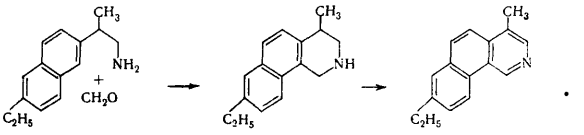
As with anthracene, illumination of solutions of benzo-[*g*]isoquinoline in alcohol, acetone, benzene, or ether in the absence of air yields greenish crystals of a "photo-dimer", which does not melt, but on being heated regenerates the monomer[34]:



The ultraviolet spectrum of the "photodimer" contains maxima characteristic of pyridine and benzene, the reason for this being the "disengagement" of these rings.

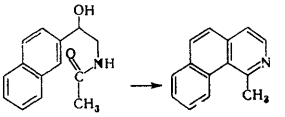
3. Benzo[*h*]isoquinolines

The usual methods for building up isoquinoline systems are employed in the synthesis of benzo[*h*]isoquinolines. Application of the Pictet–Spengler method for the condensation of 2-(6-ethylnaphth-2-yl)propylamine with formaldehyde gives 8-ethyl-1,2,3,4-tetrahydro-4-methylbenzo[*h*]isoquinoline, which on dehydrogenation by means of selenium (at 340°C) is converted into 8-ethyl-4-methylbenzo[*h*]isoquinoline[36]:

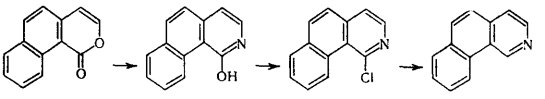


1,2,3,4-Tetrahydrobenzo[*h*]isoquinoline has been synthesised by the same method—by condensing 2-naphth-2′-ylethylamine with formaldehyde[37].

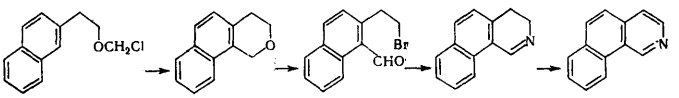
The Pictet–Gams method has been used to obtain 1-methylbenzo[*h*]isoquinoline from *N*-(2-hydroxy-2-naphth-2′-ylethyl)acetamide[38]:



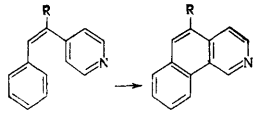
Several preparations of benzo[*h*]isoquinolines start from oxygen-containing fused tricyclic heterocycles. When 7,8-benzoisocoumarin is heated with an alcoholic solution of ammonia, 1-hydroxybenzo[*h*]isoquinoline is formed. Replacement of the hydroxyl by chlorine and subsequent removal of the latter by hydrogenation (palladium on charcoal, alcoholic caustic soda solution) converted it into benzo[*h*]isoquinoline[38]:



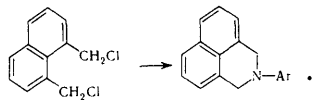
2-2′-Chloromethoxyethylnaphthalene on treatment with aluminium chloride in carbon disulphide is converted into 7,8-benzoisochroman, subsequent bromination of which with cleavage of the oxygen ring leads to 2-2′-bromoethyl-naphthal-1-aldehyde. Heating this δ-halogenated aldehyde with ammonia, by the well known method used in the synthesis of isoquinolines[39], gave 3,4-dihydrobenzo[*h*]isoquinoline, which on dehydrogenation over platinum black was converted into benzo[*h*]isoquinoline[40]:



Benzo[*h*]isoquinolines are formed by the photocyclisation of γ-stilbazoles. *trans*-4-Styrylpyridine and *trans*-4-α-methylstyrylpyridine yield respectively benzo[*h*]isoquinoline and 5-methylbenzo[*h*]isoquinoline[9]:

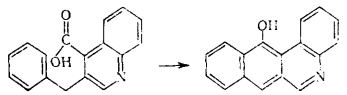


The synthesis of a partly hydrogenated benzo[*de*]isoquinoline system has been described. Several 2-aryl-2,3-dihydro-1*H*-benzo[*de*]isoquinolines have been obtained from 1,8-bischloromethylnaphthalene and primary amines in the presence of triethylamine (boiling in toluene):



Compounds of this type do not form peroxy-compounds when treated in chloroform or benzene solution with oxygen in the light at 60°C.[41]

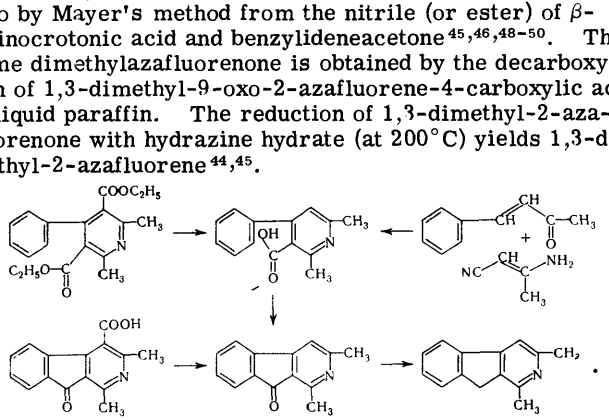
Information on the synthesis of dibenzoisoquinolines is extremely limited. An example is 5-hydroxy-3,4:6,7-dibenzoisoquinoline, which is obtained by the intramolecular condensation of 3-benzylcinchoninic acid in the presence of aluminium chloride:



Similarly 5-hydroxy-1-phenyl-3,4:6,7-dibenzoisoquinoline has been synthesised from 3-benzyl-2-phenylcinchoninic acid (obtained from ω-benzylacetophenone and isatinic acid)[42,43].

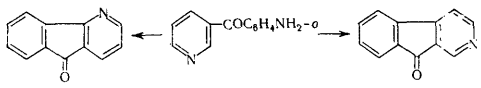
II. AZAFLUORENES

Among this group of compounds the 2-azafluorenes have been the most thoroughly studied. A usual method of synthesising 2-azafluorenes and their derivatives consists in the cyclisation of substituted pyridinecarboxylic acids. 1,3-Dimethyl-2-azafluorenone is obtained in ~90% yield from 2,6-dimethyl-4-phenylpyridine-3-carboxylic acid (by heating with sulphuric acid at 100°C) and in lower yield from the chloride of this acid (by treatment with aluminium chloride)[44-46]. The initial 2,6-dimethyl-4-phenylpyridine-3-carboxylic acid is obtained by the partial hydrolysis of diethyl 2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate with subsequent decarboxylation of the 5-ethoxycarbonyl-2,6-dimethyl-4-phenylpyridine-3-carboxylic acid[47], and also by Mayer's method from the nitrile (or ester) of β-aminocrotonic acid and benzylideneacetone[45,46,48-50]. The same dimethylazafluorenone is obtained by the decarboxylation of 1,3-dimethyl-9-oxo-2-azafluorene-4-carboxylic acid in liquid paraffin. The reduction of 1,3-dimethyl-2-azafluorenone with hydrazine hydrate (at 200°C) yields 1,3-dimethyl-2-azafluorene[44,45].



Dehydrocyclisation of the appropriate substituted pyridine-3-carboxylic acids yields 9-oxo-2-azafluorene-1-carboxylic acid and 7-methoxy(or hydroxy)-1,3-dimethyl-2-azafluorenone[44,51,52]. 2-Azafluorene itself (pyridofluorene) can be isolated by the decarboxylation of 2-azafluorene-1,3,4-tricarboxylic acid in the presence of soda-lime[51]. Condensation with conversion to the corresponding 2-azafluorenone could not be achieved with 2,6-dimethyl-4-*p*(or *m*)-nitrophenylpyridine-3-carboxylic acid. The condensation of 4-*o*-methoxyphenyl-2,6-dimethylpyridine-3-carboxylic acid yields 9,10-dihydro-1,3-dimethyl-10-oxo-9-oxa-2-azaphenanthrene[44,51,52].

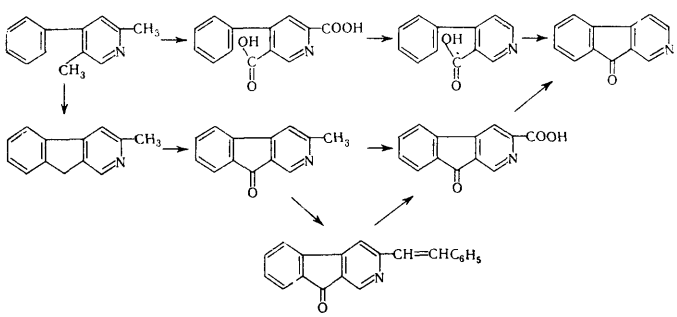
The cyclisation of 3-*o*-aminobenzoylpyridine has been accomplished in investigations of the mechanism of the Pschorr reaction. Ultraviolet irradiation in acid solution was used, the products being 2-azafluorenone (26.2%) and 4-azafluorenone (36.8%)[53]:



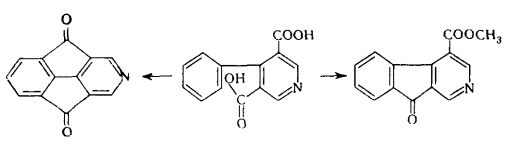
3-Mesitoyl(or duroyl)pyridine reacts with phenylmagnesium bromide to form compounds corresponding to dihydrophenylated 3-mesitoyl(or duroyl)pyridine. On dehydrogenation they yield 3-mesitoyl(or duroyl)-4-phenylpyridine, which when heated (185–200°C at 25 mm) is converted into 2-azafluorenone in 50% yield[54].

4-Aryldimethylpyridines have also been used in the synthesis of substituted 2-azafluorenes. Such systems can be obtained in two ways from 2,5-dimethyl-4-phenylpyridine. Oxidation of the pyridine base and partial decarboxylation of the resulting 4-phenylpyridine-2,5-dicarboxylic acid led to the preparation of 4-phenylpyridine-3-carboxylic acid, cyclisation of which yielded 2-azafluorenone[23].

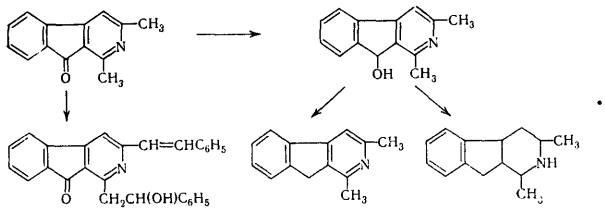
The second route consists in the dehydrocyclisation of 4-aryl-2,5-dimethylpyridines on dehydrogenation catalysts at 500–520°C. The 3-methyl-2-azafluorene obtained from 2,5-dimethyl-4-phenylpyridine in this way was converted into 3-methyl-2-azafluorenone, into 9-oxo-2-azafluorene-3-carboxylic acid, and into 2-azafluorenone[55]:



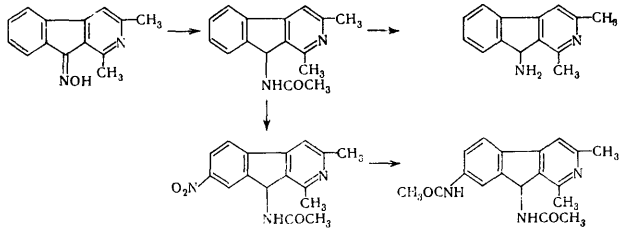
The dehydrocyclisation of 2,5-dimethyl-4-*p*-tolylpyridine yields 3,7-dimethyl-2-azafluorene, which has been converted into 3,7-dimethyl-2-azafluorenone[56]. When 4-phenylpyridine-3,5-dicarboxylic acid undergoes dehydrocyclisation, methyl 9-oxo-2-azafluorene-4-carboxylate is obtained together with a small quantity of 3-azatetracyclo-[9,2,1,$0^{5,13}$,$0^{7,12}$]tetradeca-2,4,7,9,11,13-hexaene-6,14-dione[57]:



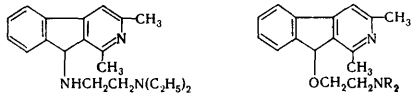
There are indications that derivatives of 1,3-dimethyl-2-azafluorene exert a spasmolytic action. 1,3-Dimethyl-2-azafluorenone has been subjected to several chemical transformations in order to obtain physiologically active substances. Its reduction with zinc dust in an aqueous-alcoholic solution of ammonia gave 1,3-dimethyl-2-azafluorenol (identified as the picrate), which on further reduction with sodium in alcohol was converted into hexahydro-1,3-dimethyl-2-azafluorene and 1,3-dimethyl-2-azafluorene. Condensation of 1,3-dimethyl-2-azafluorenone with benzaldehyde in the presence of zinc chloride gives 1-2′-hydroxyphenethyl-3-styryl-2-azafluorenone:



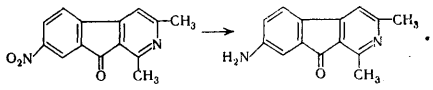
1,3-Dimethyl-2-azafluorenone oxime is reduced by zinc dust in acetic acid or anhydride to 1,3-dimethyl-2-azafluorene and 9-acetamido-1,3-dimethyl-2-azafluorene. The latter could be hydrolysed by treatment with phosphoric acid at 200°C. The resulting 9-amino-1,3-dimethyl-2-azafluorene is a strong base, which actively absorbs carbon dioxide from the air. 9-Acetamido-1,3-dimethyl-2-azafluorene can be nitrated, the nitro-derivative obtained in quantitative yield being assumed to have the structure 9-acetamido-1,3-dimethyl-7-nitro-2-azafluorene. Reduction of this product with zinc dust in acetic anhydride yields (presumably) 7,9-diacetamido-1,3-dimethyl-2-azafluorene[44,51].



9-2′-Diethylaminoethylamino-1,3-dimethyl-2-azafluorene, obtained from 9-amino-1,3-dimethyl-2-azafluorene and 2-diethylaminoethyl chloride, is similar in structure to Antergan[58]. Other derivatives of 2-azafluorene, the 9-2′-dialkylaminoethoxy-1,3-dimethyl-2-azafluorenes, resemble Dimedrol, and have been prepared from 1,3-dimethyl-2-azafluorenol and the corresponding dialkylaminoethyl chlorides (by heating with sodamide in benzene):



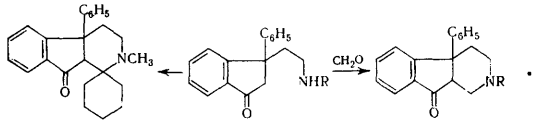
The nitration of 9-acetamidofluorene with fuming nitric acid yields two nitro-derivatives—9-acetamido-2,7(and 2,5)-dinitrofluorenes—which have been oxidised to the corresponding dinitrofluorenones[59]. The nitration of 1,3-dimethyl-2-azafluorenone gives a good yield of a mononitro-derivative, which by analogy with the nitro-derivative formed by the nitration of fluorenone itself under similar conditions, is assumed to be 1,3-dimethyl-7-nitro-2-azafluorenone. This nitro-derivative is reduced to 7-amino-1,3-dimethyl-2-azafluorenone, in which the amino-group exhibits an imino-character[48]:



The isomeric 4-amino-1,3-dimethyl-2-azafluorenone is obtained by Hofmann's reaction from 4-carbamoyl-1,3-dimethyl-2-azafluorenone. It did not prove possible to effect the conversion from ethyl 5-amino-2,6-dimethyl-4-phenylpyridine-3-carboxylate, through the 5-diacetylamino- and 5-benzamido-2,6-dimethyl-4-phenylpyridine-3-carboxylic acid (cyclisation in the presence of sulphuric acid), to a 4-amino-1,3-dimethyl-2-azafluorenone substituted in the amino-group[48].

When 3-benzoyl-1,2,5,6-tetrahydro-1-methyl-4-phenylpyridine is treated with hydrazine hydrate in the presence of sodium methoxide (in triethylene glycol at 190°C), 3-benzyl-1,2,5,6-tetrahydro-1-methyl-4-phenylpyridine is formed, and in the form of its hydrochloride has been subjected to cyclisation (with polyphosphoric acid at 130°C). Chromatographic separation of the reaction products on aluminium oxide led to the isolation of a partly hydrogenated substituted 2-azafluorene—racemic 1,2,3,4,4a,9a-hexahydro-2-methyl-4a-phenyl-4*H*-indeno[2,1-*c*]pyridine.

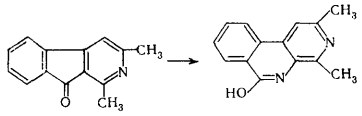
Analogous partly hydrogenated 2-azafluorene systems have been obtained by the Wolff–Kishner reduction of 1,2,3,4,4a,9a-hexahydro-6-methoxy-2-methyl-9-oxo-4a-phenylindeno[2,1-*c*]pyridine and by reducing 1,2,3,4,4a,9a-hexahydro-9-oxo-4a-phenyl-2-propyl(or cyclopropyl)-indeno[2,1-*c*]pyridine with zinc. In one of the procedures the initial oxo-derivatives are obtained by condensing *N*-methyl(propyl, or cyclopropyl)-2-(3-oxo-1-phenylindan-1-yl)ethylamine with formaldehyde in acid medium:



When a mixture of *N*-methyl-2-(3-oxo-1-phenylindan-1-yl)-ethylamine and cyclohexanone is treated with aluminium isopropoxide in toluene, spirocyclohexane-1,1′-1,2,3,4,4a,9a-hexahydro-2-methyl-9-oxo-4a-phenylindeno[2,1-*c*]pyridine is obtained, and the spirocycloheptane analogue is obtained in the same way[60].

Among compounds containing a partly hydrogenated 2-azafluorene system, 2,3,4,9-tetrahydro-2-methyl-9-phenyl-1*H*-indeno[2,1-*c*]pyridine (Phenindamine, Tephorin) has been proposed as an antihistamine preparation[61].

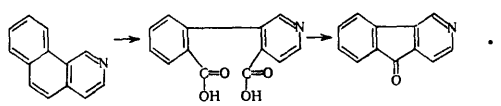
The possibility has been studied of passing from the 2-azafluorene to the diazaphenanthrene system. Beckmann expansion of the ring, with 1,3-dimethyl-2-azafluorenone oxime as starting material, could not be accomplished. Application of the Schmidt reaction to the ketone gave 9-hydroxy-1,3-dimethyl-2,10-diazaphenanthrene, the structure of which was proved by comparison with the analogous substance formed by the oxidation of 1,3,9-trimethyl-2,10-diazaphenanthrene with chromic acid[48]:



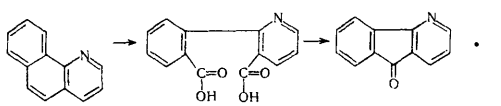
Ethyl 1,3-dimethyl-9-oxo-2-azafluorene-4-carboxylate has been converted by the Schmidt rearrangement into a

35% yield of ethyl 9-hydroxy-1,3-dimethyl-2,10-diazaphenanthrene-4-carboxylate, some of whose reactions and whose structure have been studied.

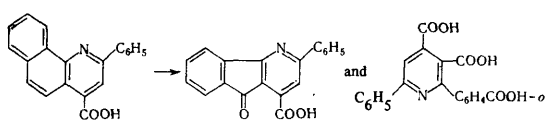
There are indications that compounds of the 3-azafluorene series possess sedative, neuroleptic, and adrenolytic activity[62]. However, very little work has been done on 3- and 4-azafluorenes. Benzo[*h*]isoquinoline has been used to obtain 3-azafluorenone itself. 3-Phenylpyridine-4,*o*-dicarboxylic acid was isolated from its oxidation, and thermal condensation of this compound led to 3-azafluorenone[38]:



4-Azafluorenone has been obtained in a similar way from 2-phenylpyridine-3,*o*-dicarboxylic acid, which was isolated from the oxidation of benzo[*h*]quinoline:

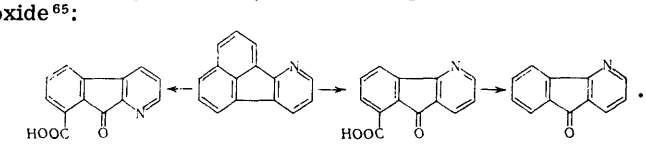


A small quantity of 9-oxo-3-phenyl-4-azafluorene-1-carboxylic acid is formed together with 2,6-diphenylpyridine-3,4,*o*(2)-tricarboxylic acid by the oxidation of 2-phenylbenzo[*h*]quinoline-4-carboxylic acid[63]:

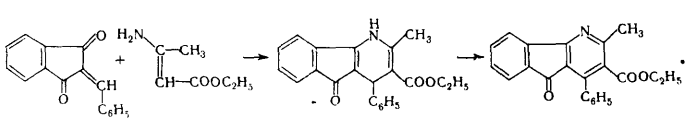


In a similar manner 9-oxo-4-azafluorene-1,3-dicarboxylic acid has been obtained from benzo[*h*]quinoline-2,4-dicarboxylic acid, and 9-oxo-1-azafluorene-2,4-dicarboxylic acid from benzo[*f*]quinoline-1,3-dicarboxylic acid[64].

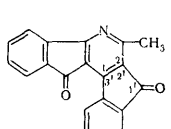
The oxidation with potassium permanganate of 10-azafluoranthene, isolated by the fractional distillation of coal-tar pitch, yields a mixture of 9-oxo-1(and 4)-azafluorene-8-carboxylic acids, from the latter of which 4-azafluorenone is obtained by decarboxylation in the presence of calcium oxide[65]:



Condensation of 2-benzylideneindane-1,3-dione with ethyl β-aminocrotonate produces ethyl 1,4-dihydro-3-methyl-9-oxo-1-phenyl-4-azafluorene-2-carboxylate, which after oxidation with chromic acid in acetic acid is converted into ethyl 3-methyl-9-oxo-1-phenyl-4-azafluorene-2-carboxylate:



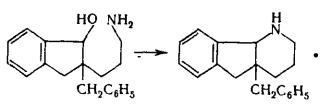
Hydrolysis of this ester (by heating it with concentrated sulphuric acid) leads to further condensation, with the formation of 3-methyl-4-azaindeno(3′,2′ : 1,2)fluorene-1′,9-dione



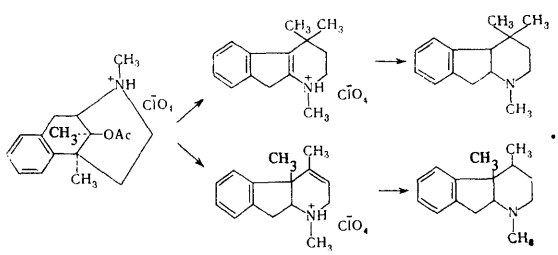
Various substituted 1-aryl-4-azafluorenones have been obtained by the method used to synthesise ethyl 3-methyl-9-oxo-1-phenyl-4-azafluorene-2-carboxylate. The oxime of this ester has been converted into the 9-diacetylamino- and 9-acetamido-derivatives[66]. 2-Aminopropenyl methyl and phenyl ketones and β-aminocinnamonitrile have also been used for condensation with benzylideneindane-1,3-dione, the products being respectively 2-acetyl- and 2-benzoyl-3-methyl-1-phenyl-4-azafluorenones and 2-cyano-1,3-diphenyl-4-azafluorenone. An attempt to prepare 1-alkyl-4-azafluorenones in a similar manner was unsuccessful.

α-(1,3-Dioxoindan-2-yl)benzylmalonamide has been cyclised to 1,2,4-trihydro-3,9-dioxo-1-phenyl-4-azafluorene-2-carboxyamide, from which saponification followed by decarboxylation yielded 1,2,3,4-tetrahydro-1-phenyl-4-azafluorene-3,9-dione[67].

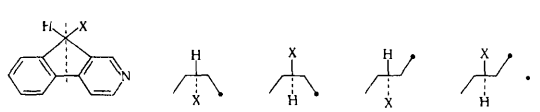
A partly hydrogenated substituted 4-azafluorene system, 4a-benzyl-1,2,3,4-tetrahydro-5*H*-indeno[1,2-*b*]pyridine, has been isolated by the condensation of 2-2′-aminopropyl-2-benzylindan-1-ol, this being obtained by the hydrogenation of 2-benzyl-2-2′-cyanoethylindan-1-one:



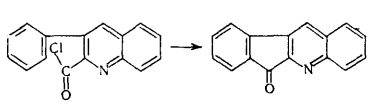
Information on the preparation of 1-azafluorene derivatives is extremely sparse. A partly hydrogenated substituted 1-azafluorene is obtained by the pyrolysis of the perchlorate of 9-acetoxy-2,5,9-trimethyl-6,7-benzomorphan. The perchlorates of 1,2,3,4-tetrahydro-1,4,4-trimethyl-9*H*-indeno[2,1-*b*]pyridine and 1,2,4a,9a-tetrahydro-1,4,4a-trimethyl-9*H*-indeno[2,1-*b*]pyridine were isolated, and were then hydrogenated in the nitrogen-containing ring[68,69]:



Papers on the stereochemistry of substituted azafluorenes are almost completely lacking. It has been suggested[52] that 9-substituted azafluorenes may have four geometrical isomers owing to a non-planar structure:

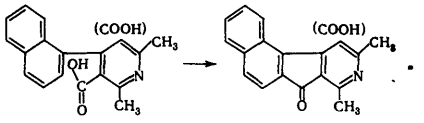


Intramolecular cyclisation is the principal method employed in the synthesis of azabenzofluorene structures. Application of the Friedel–Crafts reaction to 3-phenylquinoline-2-carbonyl chloride (in nitrobenzene) yields 1-aza-2,3-benzofluorenone[70]:

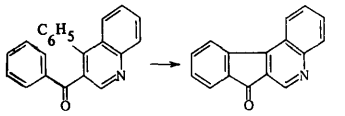


1,3-Dimethyl-2-aza-5,6-benzofluorenone has been obtained from 2,6-dimethyl-4-naphth-1′-ylpyridine-3-carbonyl

chloride and also from 2,6-dimethyl-4-naphth-1′-ylpyridine-3,5-dicarboxylic acid, 1,3-dimethyl-9-oxo-2-aza-5,6-benzofluorene-4-carboxylic acid also being isolated in the latter case[44]:

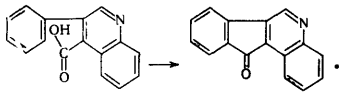


3-Benzoyl-4-phenylquinoline and also 3-mesitoyl-4-phenylquinoline are cyclised under the influence of polyphosphoric acid to 2-aza-3,4-benzofluorenone[54]:

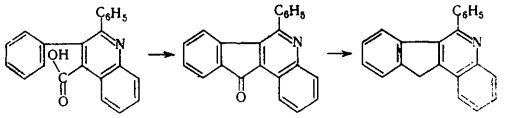


The same azafluorenone is obtained by the cyclisation of 4-phenylquinoline-3-carboxylic acid[71].

3-Aza-1,2-benzofluorenone can be synthesised by the condensation of 3-phenylcinchoninic acid by means of sulphuric acid[70]:

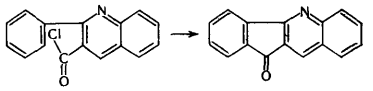


Analogous 4-alkylated (or 4-phenylated) azabenzofluorenones are obtained from 2-substituted 3-phenylcinchoninoyl chlorides by the Friedel–Crafts reaction and also from the acids themselves[43,71]. An example is the synthesis of 4-phenyl-3-aza-1,2-benzofluorenone from 2,3-diphenylcinchoninic acid:

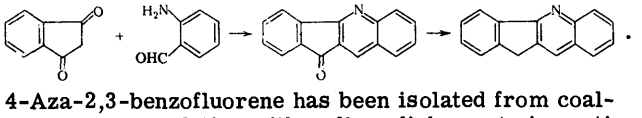


Conversion to azafluorene structures is accomplished by means of hydrazine hydrate or by reduction with tin in a mixture of acetic and hydrochloric acids.

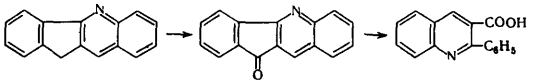
2-Phenylquinoline-3-carboxylic acid and also its chlorides are used in the synthesis of 4-aza-2,3-benzofluorenone[71]:



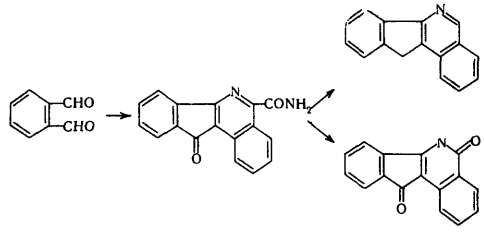
4-Aza-2,3-benzofluorenone is also obtained by condensing *o*-aminobenzaldehyde with indane-1,3-dione, and is then reduced with zinc dust to 4-aza-2,3-benzofluorene[72]:



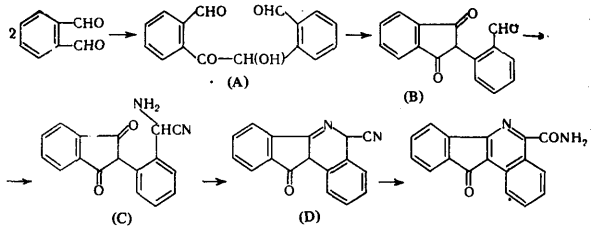
4-Aza-2,3-benzofluorene has been isolated from coal-tar pitch. Its oxidation with sodium dichromate in acetic acid yielded 4-aza-2,3-benzofluorenone. In molten caustic potash the latter is converted into 2-phenylquinoline-3-carboxylic acid[65]:



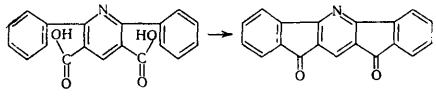
Treatment of phthalaldehyde with sodium cyanide gives a low yield of 9-oxo-4-aza-1,2-benzofluorene-3-carboxyamide. Hydrolysis of the latter with hydrochloric acid, followed by reduction with zinc in acetic acid, led to 4-aza-1,2-benzofluorene, oxidation of which with copper sulphate in pyridine yielded 11-oxoindeno[1,2-*c*]isocarbostyryl[73]:



The mechanism suggested for this reaction is that treatment of phthalaldehyde with sodium cyanide involves initially a normal benzoin condensation (A). Intramolecular condensation then yields an indanedione structure (B), the free aldehyde group of which is attacked by cyanide and ammonia with conversion into an amino-nitrile grouping (C). This latter undergoes cyclisation with formation of the dihydroisoquinoline system (D). On oxidation with atmospheric oxygen hydrolysis takes place, with formation of the final product—9-oxo-4-aza-2,3-benzofluorene-3-carboxyamide (1-carbamoyl-11-oxoindeno[1,2-*c*]isoquinoline).

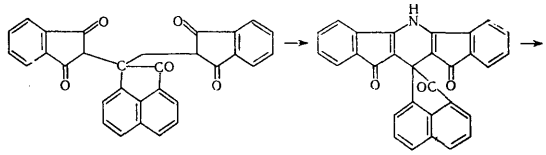


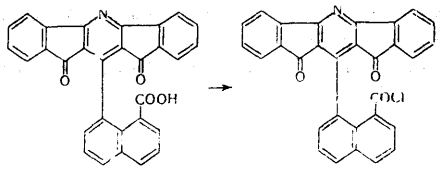
Pentacyclic fused ring systems containing nitrogen, belonging to azafluorene systems, have been obtained by the intramolecular condensation (double cyclisation) of diphenylated 3,5-dicarboxylic acids. Thus 2,6-diphenylpyridine-3,5-dicarboxylic acid yields 2,3 : 5,6-dibenzoylenepyridine[45]:



Similarly, 6-methyl-2,3 : 4,5-dibenzoylenepyridine has been synthesised from 6-methyl-2,4-diphenylpyridine-3,5-dicarboxylic acid[49,66].

An azafluorene compound of this type is a preparation termed Dibepyne, which is 8-(2,3(CO) : 6,5(CO)-dibenzoylenepyrid-4-yl)naphth-1-oyl chloride. Dibepyne is an analytical reagent for primary amines. The starting material in its synthesis is 2,2-di-indanedionylacenaphthen-1-one. When this interacts with ammonium acetate the nitrogen-containing ring closes, with the formation of acenaphthen-1-onespiro(2,4′)-2′,3′(CO) : 6′,5′(CO)-dibenzoylene-1′,4′-dihydropyridine. Subsequent treatment of this compound with hydrogen peroxide, followed by thionyl chloride, leads to the formation of Dibepyne[74–76]:





Several compounds have been synthesised which are analogous in structure to Dibepyne[77].

REFERENCES

1. L.P.Walls, in "Heterocyclic Compounds" (Edited by R.C.Elderfield) (Translated into Russian), Inostr. Lit., Moscow, 1955, Vol.4, p.486.
2. A.Bischler and B.Napiralski, Ber., 26, 1903 (1893).
3. A.Pictet and A.Gams, Ber., 42, 2943 (1909).
4. A.Pictet and T.Spengler, Ber., 44, 2030 (1911).
5. A.Pictet and B.Manevitch, Arch.Sci.phys.nat. Geneve, [4], 35, 40, 15/1; C., I, 1032 (1913).
6. R.Urban and O.Schnider, Montash., 96, 9 (1965).
7. C.E.Loader, M.V.Sargent, and C.J.Timmons, Coll. Czech.Chem.Comm., 30, 127 (1965).
8. G.Galiazzo, P.Bortolus, and G.Cauzzo, Tetrahedron Letters, 3717 (1966).
9. C.E.Loader and C.J.Timmons, J.Chem.Soc., 1078 (1966).
10. K.Kindler, W.Peschke, and G.Plüddemann, Arch. Pharm., 227, 25 (1939).
11. E.Spath, F.Berger, and W.Kuntara, Ber., 63, 134 (1930).
12. J.Robert, Ann.Chim. (France), 7, 722 (1952).
13. E.M.Schultz and R.T.Arnold, J.Amer.Chem.Soc., 71, 1911 (1949).
14. T.R.Govindachari and B.R.Pai, J.Org.Chem., 18, 1253 (1953).
15. A.Philips, Ber., 27, 1925 (1894); 28, 1658 (1895).
16. J.Berger, G.Wolniczak, and M.G.Muelstaedt, Z. Chem., 2, 274 (1962).
17. A.E.Chichibabin, Zhur.Russ.Fiz.-khim.Obshch., 33, 249 (1901).
18. A.E.Chichibabin and P.F.Ryumshin, Zhur.Russ.Fiz.-khim.Obshch., 47, 1297 (1915).
19. J.Braun and J.Nells, Ber., 70, 1760 (1937).
20. N.S.Prostakov and N.N.Mikheeva, Med.Prom., No.2, 11 (1960).
21. N.S.Prostakov and L.A.Gaivoronskaya, Zhur.Obshch. Khim., 32, 76 (1962).
22. N.S.Prostakov, L.A.Gaivoronskaya, N.M.Mikhailova, and L.M.Kirillova, Zhur.Obshch.Khim., 33, 2573 (1963).
23. N.S.Prostakov, L.M.Kirillova, Dkharvar Pkhal'-gumani, L.A.Shakhparonova, and V.P.Zvolinskii, Khim.Geterotsikl.Soed., 1068 (1967).
24. I.N.Nazarov and V.A.Rudenko, Izv.Akad.Nauk SSSR, Otd.Khim.Nauk, 610 (1948).
25. Issei Iwai and Tetsuo Hiraoka, Chem.Pharm.Bull. (Japan), 11, 1556 (1963).
26. A.Etienne and M.Legrand, Bull.Soc.chim.France, 108 (1953).
27. G.Badger, R.S.Pearce, and R.Pettit, J.Chem.Soc., 3199 (1951).
28. I.Samuel, Compt.Rend., 231, 1146 (1950).
29. R.Zahradnik and C.Parkanyi, Coll.Czech.Chem. Comm., 30, 365 (1965).
30. J.Nasielski and E.V.Donckt, Bull.Soc.chim.belges, 72, 725 (1963).
31. J.Koutecky and R.Zahradnik, Coll.Czech.Chem. Comm., 28, 20891 (1963).
32. O.Chalvet, Compt.rend., 244, 1043 (1957).
33. C.Dufraisse and R.Priou, Bull.Soc.chim.France, 6, 1049 (1939).
34. A.Etienne, Compt.rend., 218, 841 (1944).
35. A.Etienne and J.Robert, Compt.rend.,223,331 (1946).
36. K.Wiesner, Chem.and Ind., No.19, 542 (1954).
37. F.Mayer and O.Schnecko, Ber., 56, 1408 (1923).
38. J.N.Chatterjea and K.Prasad, J.Indian Chem.Soc., 37, 357 (1960).
39. E.Schmitz, Chem.Ber., 91, 1133 (1958).
40. G.Coppens, Bull.Soc.chim.belges, 69, 413 (1960).
41. E.Höff, A.Rieche, and H.Schultze, Annalen, 697, 181 (1966).
42. W.Borsche and W.Noll, Annalen, 532, 131 (1937).
43. W.Borsche and O.Vorbach, Annalen, 537, 22 (1939).
44. H.Kahn, V.Petrow, E.L.Rewald, and B.Sturgeon, J.Chem.Soc., 2128 (1949).
45. W.Borsche and H.Hahn, Annalen, 537, 219 (1939).
46. J.N.Chatterjea, J.Indian Chem.Soc., 29, 323 (1952).
47. A.Hantzsch, Ber., 17, 2910 (1884).
48. V.A.Petrow, J.Chem.Soc., 200, 888 (1946).
49. N.Palit and J.N.Chatterjea, J.Indian Chem.Soc., 27, 71, 667 (1950).
50. L.E.Hinkel and H.W.Cremer, J.Chem.Soc., 137 (1920).
51. W.H.Mills, W.H.Palmer, and M.G.Tomkinson, J. Chem.Soc., 2365 (1924).
52. C.F.Koelsch and A.F.Steinhauer, J.Org.Chem., 18, 1516 (1953).
53. R.A.Abramovitch and G.Tetzakin, Tetrahedron Letters, 1511 (1963).
54. R.C.Fuson and J.J.Miller, J.Amer.Chem.Soc., 79, 3477 (1957).
55. N.S.Prostakov, K.Dzhon Mat'yu, and V.A.Kurichev, Khim.Geterotsikl.Soed., 876 (1967).
56. N.S.Prostakov, K.Dzhon Mat'yu, and E.N.Sedykh, Khim.Geterotsikl.Soed., 1072 (1967).
57. N.S.Prostakov, O.I.Sorokin, and A.Ya.Ismailov, Khim.Geterotsikl.Soed., 674 (1967).
58. B.N.Feitelson and V.A.Petrow, J.Chem.Soc., 228 (1952).
59. C.W.Bennet, W.G.Jewsbury, and J.P.Dupuis, J. Amer.Chem.Soc., 68, 2489 (1946).
60. M.D.Draper, U.S.P. 3 274 201 (1966); C.A., 65, 20 106 (1966); U.S.P. 3 282 948 (1966); C.A., 66, 1805 (1967); U.S.P. 3 301 866 (1967).
61. M.V.Rajapurkar, M.L.Sharma, N.K.Joshi, and P.G.Dashputra, Indian J.Med.Res., 52, 502 (1964).
62. Neth.P. 6 500 312 (1966); C.A., 64, 3501 (1966).
63. O.Doebner and P.Kuntze, Annalen, 249, 109 (1888).
64. O.Doebner and J.Peters, Ber., 23, 1228 (1890).
65. R.Oberkobusch, Chem.Ber., 86, 975 (1953).
66. V.Petrow, J.Saper, and B.Sturgeon, J.Chem.Soc., 2134 (1949).
67. Zh.Peltseus, Zh.Freimanis, and G.Vanag, Khim. Geterotsikl.Soed., 374 (1967).
68. R.T.Partitt, E.M.Fry, and E.L.May, J.Org.Chem., 31, 903 (1966).
69. R.T.Partitt, M.Takeda, and I.Kugita, J.Org.Chem., 32, 419 (1967).
70. W.Borsche, Annalen, 532, 127 (1937).
71. W.Borsche and F.Sinn, Annalen, 532, 146 (1937); 538, 283 (1939).
72. E.Noelting and H.Blum, Ber., 34, 2467 (1901).
73. S.Wawzonek, J.K.Stowell, and R.E.Karl, J.Org. Chem., 31, 1004 (1966).

74. G. Ya. Vanag and G. Ya. Dubur, Zhur. Obshch. Khim., 30, 1898 (1960).
75. G. Ya. Dubur and G. Ya. Vanag, Collected Papers, "Metody Polucheniya Khimicheskikh Reaktivov i Preparatov" (Methods of Production of Chemical Reagents and Preparations), Moscow, 1966, Vol. 14, p. 12.
76. G. Ya. Dubur, G. Ya. Vanag, and Ya. R. Uldrikis, Collected Papers, "Metody Polucheniya Khimicheskikh Reaktivov i Preparatov" (Methods of Production of Chemical Reagents and Preparations), Moscow, 1966, Vol. 14, p. 30.
77. G. Ya. Dubur and G. Ya. Vanag, Khim. Geterotsikl. Soed., 170 (1968).

Department of Organic Chemistry,
Lumumba University of International
Friendship, Moscow