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The chemistry of indoloindoles †

Sh A Samsoniya, M V Trapaidze

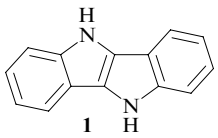
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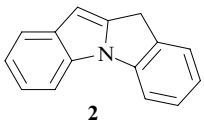
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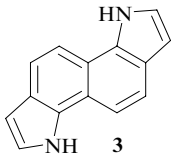
Abstract. Methods for the synthesis of substituted and unsubstituted indoloindoles are considered. Characteristic features of electrophilic substitution in the indoloindole system and some transformations in the side chains are discussed. The bibliography includes 86 references.

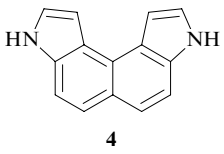
I. Introduction

In recent years, considerable attention has been paid to the study of diverse synthetic analogues of indole, which was stimulated by their potential biological activities.[1, 2] Of particular interest among these compounds are indoloindoles in which indole fragments are fused so as to have in common either carbon atoms of the pyrrole rings {*e.g.*, 5*H*,10*H*-indolo[3,2-*b*]indole (**1**)} or carbon and nitrogen atoms of the pyrrole rings {*e.g.*, 10*H*-indolo[1,2-*a*]indole (**2**)}, or carbon atoms of the benzene rings {*e.g.*, 1*H*,6*H*-indolo[7,6-*g*]indole (**3**), 3*H*,8*H*-indolo[4,5-*e*]indole (**4**), *etc.*}. The last-mentioned compounds are of interest because the reactive pyrrole rings in their molecules remain unsubstituted and capable of various transformations.


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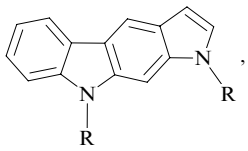

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Natural compounds containing an indoloindole fragment in which the fused indole rings have the carbon atoms of the benzene rings in common have not yet been found.

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The present review generalises data on the synthesis and properties of the above-mentioned indoloindoles and related compounds in which two indole fragments are fused so that three or four carbon atoms of the benzene and pyrrole rings are in common simultaneously. Compounds of the type



in which the pyrrole ring of one indole molecule is fused to the benzene ring of the other molecule are beyond the scope of this review, because in conformity with the IUPAC rules, they are called pyrrolocarbazoles.

Since no reviews on indoloindoles have been published as yet, we did not restrict ourselves to consideration of only recent studies but also included the results of earlier studies.

II. Synthesis and use of indoloindoles with carbon atoms of the pyrrole rings in common

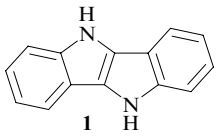
The first reported synthesis of indoloindoles dates back to 1884 when P Golubeva [3] obtained a neutral compound with the molecular formula $C_{14}H_{10}N_2$ by the reduction of *o*,*o*′-dinitrobenzil (formed upon oxidation of dinitrodeoxybenzoin) with tin and hydrochloric acid in ethanol

$$C_{14}H_8(NO_2)_2O_2 + 7\,H_2 \longrightarrow C_{14}H_{10}N_2 + 6\,H_2O.$$

Golubeva [3] suggested that this compound is a tolan derivative and called it 'diiminotolan'.

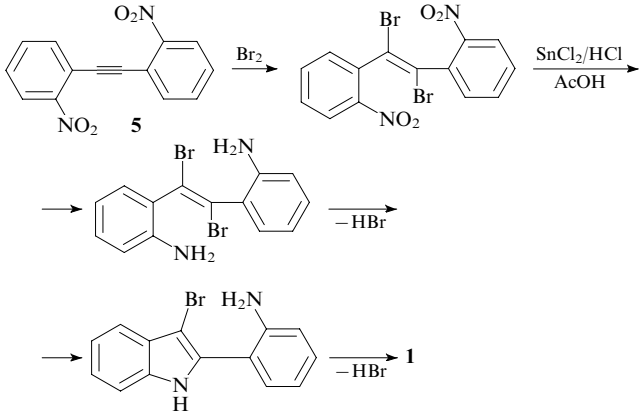
Later, Kliegl and Haas [4] prepared a compound identified as dinitrobenzil, according to elemental composition, by oxidation of *o*,*o*′-dinitrotolan with a mixture of chromic and glacial acetic acids. The reduction of this product with tin gave a compound identical to Golubeva's 'diiminotolan'. They suggested that reduction of dinitrobenzil does not give 'diiminotolan', as Golubeva believed, but is accompanied by ring closure to give compound **1**, which they called 'doubly fused indole'.

† Dedicated to the cherished memory of professor Nikolai Nikolaevich Suvorov.



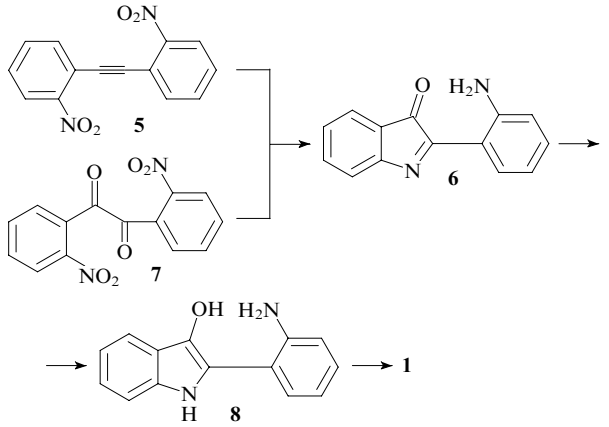
1

The targeted synthesis of 5*H*,10*H*-indolo[3,2-*b*]indole (**1**) was first performed by Ruggli.[5] He used *o*,*o*′-dinitrotolan (**5**), as the starting compound, which was oxidised with bromine to give 1,2-dibromo-1,2-di(*o*-nitrophenyl)ethylene. The reduction of this product with tin(II) chloride ‡ in hydrochloric acid afforded product **1**,



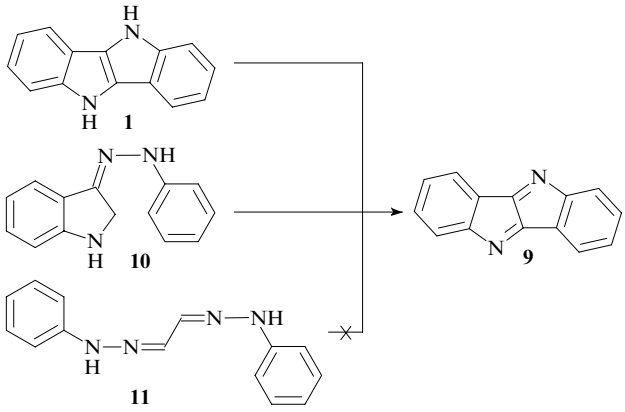
which was almost identical to the 'diiminotolan' obtained by Golubeva in the physicochemical properties.

Later, Ruggli and Zaeslin [7] reported an improvement of the method for the synthesis of indoloindole **1** from *o*,*o*′-dinitrotolan (**5**). They first prepared 2-(*o*-aminophenyl)indolenin-3-one (**6**) by refluxing compound **5** in an aqueous solution of sodium sulfide followed by reduction with tin(II) chloride in a mixture of hydrochloric and glacial acetic acids at 70 °C to give 5*H*,10*H*-indolo[3,2-*b*]indole (**1**) (yield 78%). Compound **1** was formed as colourless crystals poorly soluble in conventional organic solvents. According to Ruggli and Zaeslin,[7] it was not 2-(*o*-aminophenyl)indolenin-3-one (**6**) that cyclised in this reaction but its reduced form, compound **8** formed after acidification.



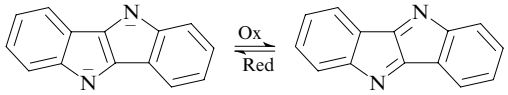
Compound **6** can also be obtained by the reduction of *o*,*o*′-dinitrobenzil **7** in a neutral solution in the presence of Ni.

Dehydrogenation of indoloindole **1** on treatment with chloranil [6] results in a product for which a quinonoid structure and the name dehydroindoloindole were proposed. The structure of 5,10-didehydroindolo[3,2-*b*]indole (**9**) was confirmed by IR and UV spectroscopic data. Oxidative dehydrogenation of indoloindole **1** (in boiling acid) was also carried out by Treibs.[8,9] Subsequently, he attempted to develop a more convenient method for the synthesis of 5,10-didehydroindolo[3,2-*b*]indole (**9**). To this end, he investigated the following reactions:[9]

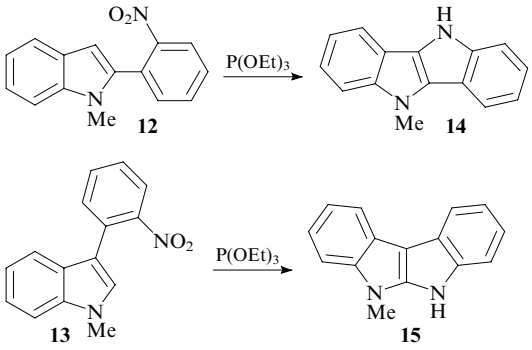


However, it turned out that compound **9** is formed in low yield from indolin-3-one phenylhydrazone (**10**) and is not formed at all from glyoxal diphenylhydrazone (**11**).

Compound **9** and some derivatives of indoloindole **1** were synthesized by Hünig and Steinmetzer [10–13] in a study of various redox systems, in particular, the system

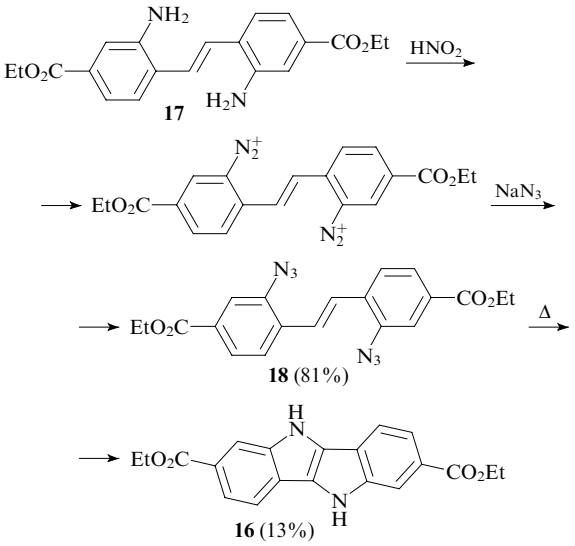


Cadogan *et al.*[14] proposed a new method for the synthesis of carbazoles, indoles, indazoles and related compounds, which involved the reduction of appropriate nitro compounds with triethyl phosphite. It was found that reduction of mononitro derivatives gives products in high yields, while in the case of dinitro compounds, the yields are moderate. Thus *o*,*o*′-dinitrostilbene was converted into indoloindole **1** in a very low yield (2%), whereas treatment of 1-methyl-2-(*o*-nitrophenyl)indole (**12**) and its 3-isomer **13** with triethyl phosphite in cumene at 160 °C resulted in the formation of 10-methyl-5*H*-indolo[3,2-*b*]indole (**14**) and 6-methyl-5*H*-indolo[2,3-*b*]indole (**15**), respectively, in good yields.[15]

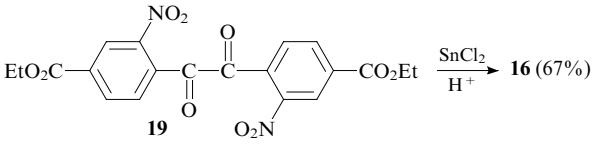


Kaszynski and Dougherty [16] prepared diethyl 5*H*,10*H*-indolo[3,2-*b*]indole-2,7-dicarboxylate (**16**) from diethyl 2,2′-diaminostilbene-4,4′-dicarboxylate (**17**) according to the following scheme:

‡ Heller [6] proposed the use of zinc dust in acetic acid for the reduction of *o*,*o*′-dinitrobenzil.

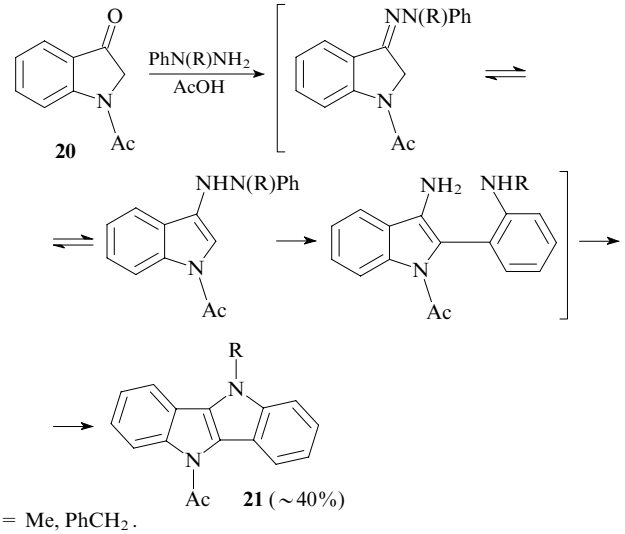


The cyclisation of diazide **18** took place in *o*,*o*′-dichlorobenzil at 155 °C. In this reaction, indolo[1,2-*b*]indazole derivatives were obtained as by-products. Diester **16** can also be obtained by simultaneous reduction ($SnCl_2$) and cyclisation of compound **19** in a mixture of hydrochloric and acetic acids.



Kaszynski and Dougherty[16] also synthesised the *N*,*N*′-dimethyl derivative of compound **16** and studied its electrochemical oxidation in CH_2Cl_2 in the presence of $Bu_4N^+ClO_4^-$ to give stable radical cation $\mathbf{16}^{+\bullet}$. It was assumed that the indoloindole obtained could find use in the synthesis of polaronic ferromagnets.

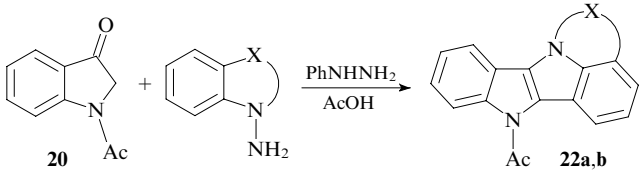
A new synthetic route to indolo[3,2-*b*]indole derivatives based on *N*-substituted indoxyls and phenylhydrazines has been proposed.[17] Refluxing of 1-acetylindolin-3-one (**20**) with substituted phenylhydrazines in acetic acid for 10 min gave the corresponding indolo[3,2-*b*]indoles (**21**).



R = Me, $PhCH_2$.

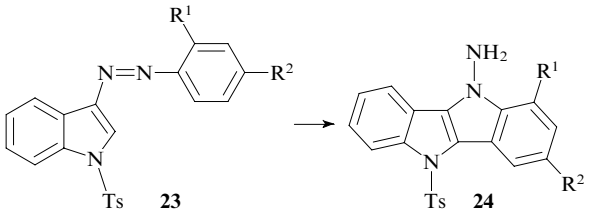
The process involves the formation of hydrazones, which then undergo the Fischer reaction to be converted into the corresponding indoloindoles. The acetyl derivative **20** may be replaced by the tosyl derivative;[18] in this case, the yield of indolo[3,2-*b*]indole is 50%.

The Fischer method has found use in the synthesis of diverse fused heterocycles. In particular, this approach was employed to prepare indolo[3,2-*b*]indolo[1,7*a*,7-*ab*]tetrahydropyridine (**22a**) and indolo[3,2-*b*]indolo[1,7*a*,7-*ab*]diazepinone (**22b**).[19]



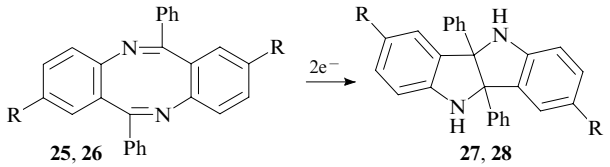
X = $(CH_2)_3$ (**22a**), $NHC(O)(CH_2)_2$ (**22b**).

Cyclisation of phenylazoindoles **23** in acetic acid at 60–70 °C in the presence of $Na_2S_2O_4$ gave 10-amino-5-tosylindolo[3,2-*b*]indoles **24**.[20]



R^1, R^2 = H, Hal, Alk.

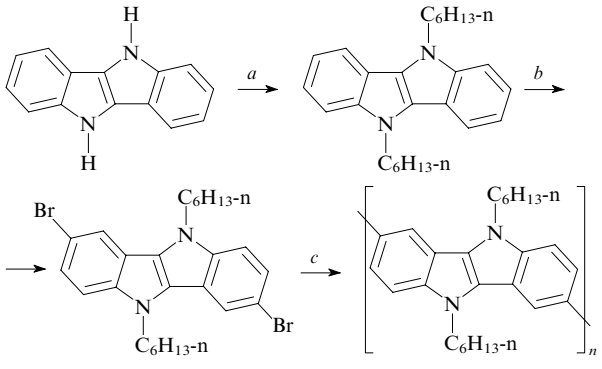
Yet another route to indolo[3,2-*b*]indole derivatives is electrochemical reduction of bis-Schiff bases.[21] The reduction of 6,12-diphenyldibenzo[*b*,*f*][1,5]diazocine (**25**) and its 2,8-dichloro derivative **26** gives 4*b*,9*b*-diphenyl-4*b*,5,9*b*,10-tetrahydroindolo[3,2-*b*]indole (**27**) and its 3,8-dichloro derivative (**28**) in 94% and 69% yields, respectively.[22]



R = H (**25**, **27**), Cl (**26**, **28**).

Previously, compounds **27** and **28** were obtained in relatively low yields[23–25] by the reduction of compounds **25** and **26** with zinc in acetic acid or by platinum oxide-catalysed reduction.

Recent publications describe the use of indolo[3,2-*b*]indoles in the synthesis of high-spin polymeric materials for light emitting diodes. Thus the synthesis and electroluminescent properties of a high-spin polymer, poly(5,10-dihexylindolo[3,2-*b*]indole-2,7-diyl) (**29**), have been reported.[26] This



(*a*) n-$C_6H_{13}Br$, NaH, THF; (*b*) Br_2, pyridine, CCl_4; (*c*) $Ni(COD)_2$, COD, 2,2′-bipyridine.

polymer possessed good optical and electroluminescent properties, but unfortunately had a low molecular mass and formed poor-quality polymeric films.

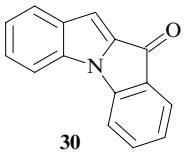
Earlier, high-spin polymers with a similar structure containing an indolo[3,2-*b*]indole fragment in the monomer unit were prepared by Murray *et al.*,[27] who have called them the prototypes of polaronic ferromagnets.

A study of the hole conduction of various heterocyclic systems related to the class of 5,10-dihetera-5,10-dihydroindeno[3,2-*b*]indenes[28] has shown that 5,10-dihydroindolo-[3,2-*b*]indole possesses the best characteristics (luminescent properties and the lifetime).

Dobrin and co-workers[29–32] studied the photophysical properties of 5*H*,10*H*-indolo[3,2-*b*]indole (**1**) and its derivatives (in particular, 5,10-dimethylindolo[3,2-*b*]indole and its 2,7-diethoxycarbonyl derivative) using the spectral and quantum-chemical methods. These compounds can be considered to be stilbene analogues, as they contain a stilbene chromophore as a part of a tetracyclic system.

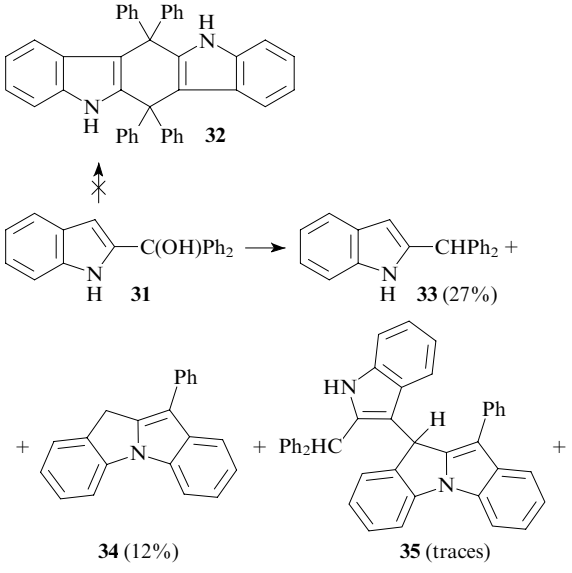
III. Indoloindoles with carbon and nitrogen atoms of the pyrrole rings in common

The interest in indoloindoles with carbon and nitrogen atoms of the pyrrole rings in common is due to their biological activities. The first derivative with this type of fusion, namely, 10*H*-indolo[1,2-*a*]indol-10-one (**30**), was prepared in 40% yield back in 1953 by Shirley and Roussel[33] upon treatment of *N*-phenylindole with excess n-butyllithium and saturation with carbon dioxide. The oxime of compound **30** was also prepared. It was suggested that indoloindole **30** is formed upon the reaction of 2,2′-dilithiated *N*-phenylindole with CO_2.



30

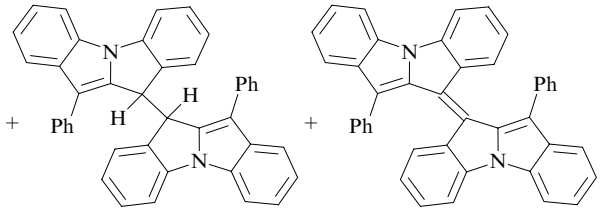
Thermolysis of dilute solutions of 2-(hydroxydiphenylmethyl)indole (**31**) in boiling bromobenzene did not give the expected dimer **32**, but afforded instead a mixture of products **33**–**37** comprising 11-phenyl-10*H*-indolo-[1,2-*a*]indole (**34**) and its derivatives **35**–**37**.[34] The structures of compounds **34**–**37** were proposed based on the data from IR and UV spectroscopy.



32

31 **33** (27%)

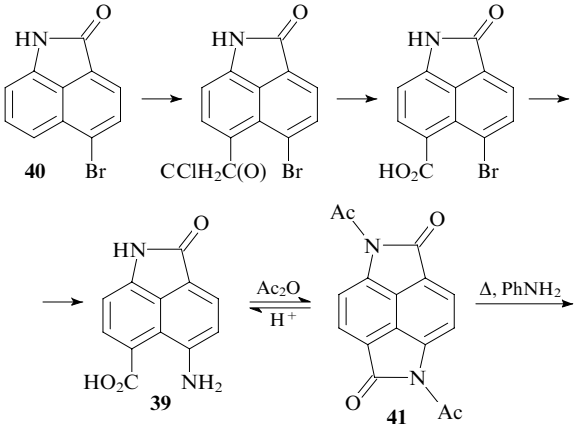
34 (12%) **35** (traces)



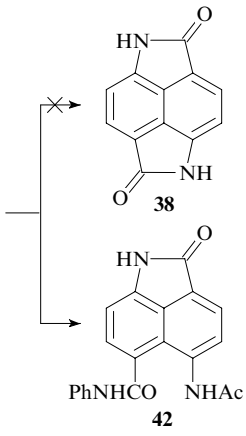
36 (42%) **37** (traces)

IV. Indoloindoles with carbon atoms of the benzene and pyrrole rings in common

In order to study the possibility of preparing fused heterocyclic compounds with two pyrrole rings upon cyclisation of substituents located in the *peri*-position of the naphthalene nucleus, an attempt was made to synthesise indolo[5,4,3*a*,3-*cde*]indole-2,6-dione (**38**).[35] 5-Amino-2-oxobenzo[*c*,*d*]indoline-6-carboxylic acid (**39**), which was obtained from 5-bromobenzo[*c*,*d*]indolin-2-one (**40**), was subjected to the cyclisation.



40 **39** **41**

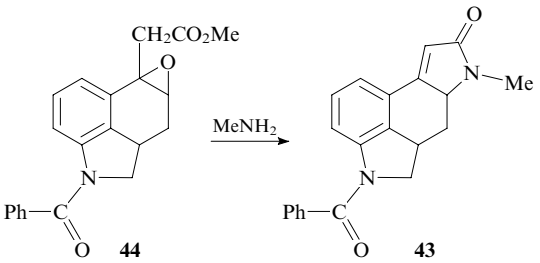


38 **42**

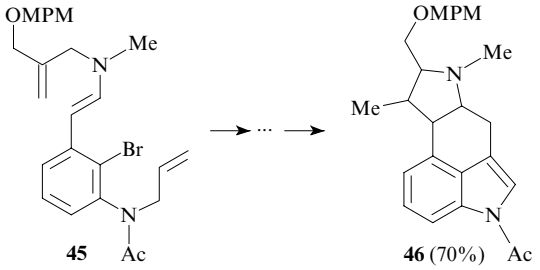
Lactam ring closure in the *peri*-positions of the naphthalene nucleus was attained only by refluxing compound **39** in acetic anhydride. This gave 1,5-diacetyl-1,5-dihydroindolo-[5,4,3*a*,3-*cde*]indole-2,6-dione (**41**) in 59% yield. This amide proved unstable; in an acidic medium it was converted into the starting compound **39**. Heating of compound **41** in aniline did not give unsubstituted indolo[5,4,3*a*,3-*cde*]indole-2,6-dione (**38**); instead, opening of one lactam ring took place to give compound **42**.

Yet another indoloindole fused so as to have the carbon atoms of the benzene and pyrrole rings in common, namely, 4-benzoyl-7-methyl-5,5*a*,6,6*a*-tetrahydroindolo[6,5,4-*cd*]indol-8-one (**43**), was isolated at a stage of synthesis of lysergic acid[36] by the reaction of 1-benzoyl-5-methoxycarbonylmethyl-

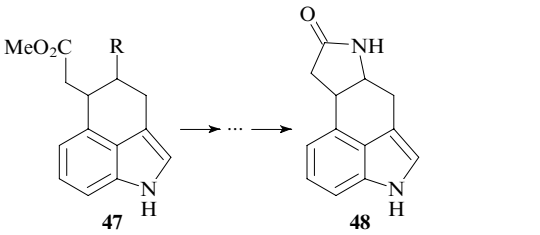
4,5-epoxy-1,2,2*a*,3,4,5-hexahydrobenz[*c*,*d*]indole (**44**) with a large excess of methylamine in an autoclave (100 °C, 6 h).



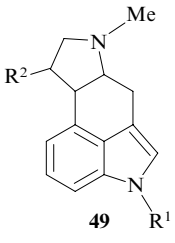
An attempted synthesis of lysergic acid from enamine **45** resulted in indolo[6,5,4-*cd*]indole **46** as one of the products.[37]



Japanese researchers [38–40] prepared indolo[6,5,4-*cd*]indole derivatives and used them as prolactin secretion inhibitors and intermediate compounds in the synthesis of drugs. In one study,[40] they used tetrahydrobenzo[*c*,*d*]indole **47** (R = NO_2) as the starting compound; refluxing of compound **47** with zinc amalgam in 2 M HCl gave the corresponding amine (R = NH_2). Cyclisation of this product in aqueous methanol containing $NaHCO_3$ resulted in indolo[6,5,4-*cd*]indole **48** in high yield (87%).



A patent [41] describes the preparation of a large group of substituted hexahydro-4*H*-indolo[6,5,4-*cd*]indoles **49** from agroclavine and ergoline derivatives.



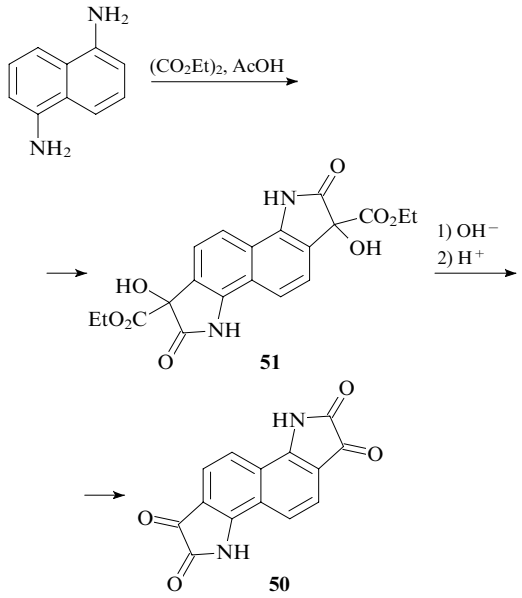
R^1 = H, $PhSO_2$;
R^2 = Ac, CO_2H, CN, NH_2, AlkOC(O), $Alk_2NC(O)$, *etc.*

The synthesis of a series of tetracyclic indole derivatives, in particular indolo[3,2,1-*hi*]indoles, using the Fischer reaction has been described; their anticonvulsant activities have been studied.[42]

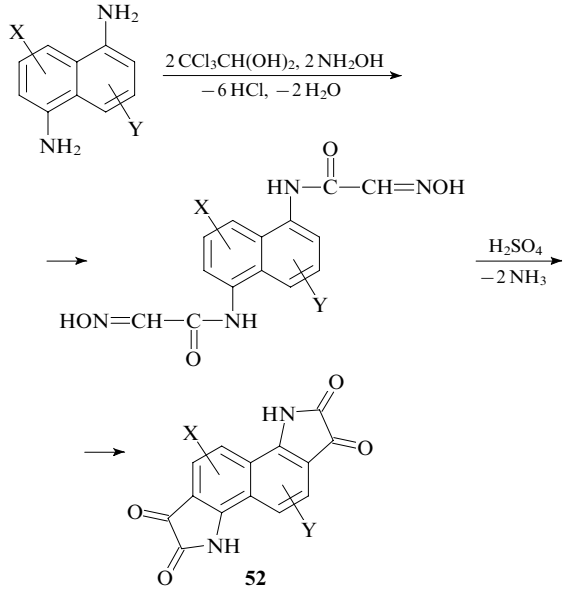
V. Indoloindoles with carbon atoms of the benzene rings in common

1. Synthesis of substituted indoloindoles

The first indolo[7,6-*g*]indole derivatives, namely, 1*H*,6*H*,2,3,7,8-tetrahydroindolo[7,6-*g*]indole-2,3,7,8-tetraone (**50**) and its monophenyl- and diphenylhydrazones, were prepared in 1922.[43] Compound **50** is formed on heating 1,5-naphthylenediamine with diethyl oxalate in acetic acid followed by hydrolysis of diester **51** with potassium hydroxide and neutralisation with HCl.



Subsequently, indolo[7,6-*g*]indole tetraoxo derivatives **52** substituted in the benzene ring were prepared [44] using the classical Sandmeyer synthesis of isatins from diaminonaphthalene as shown below.

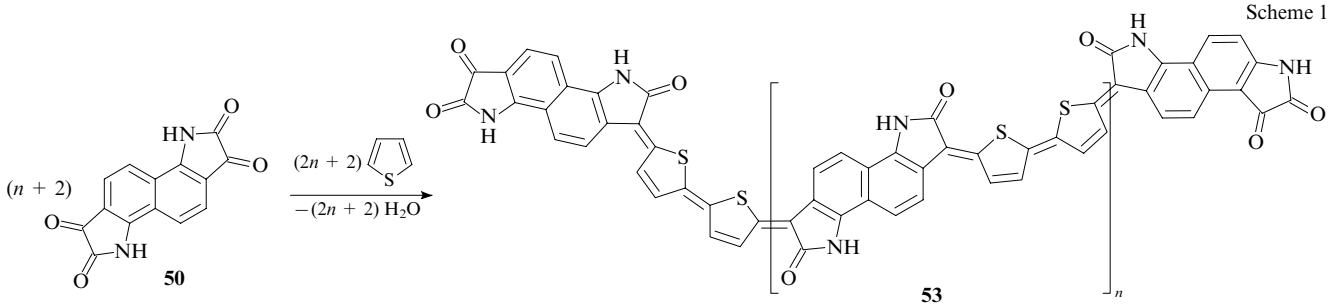


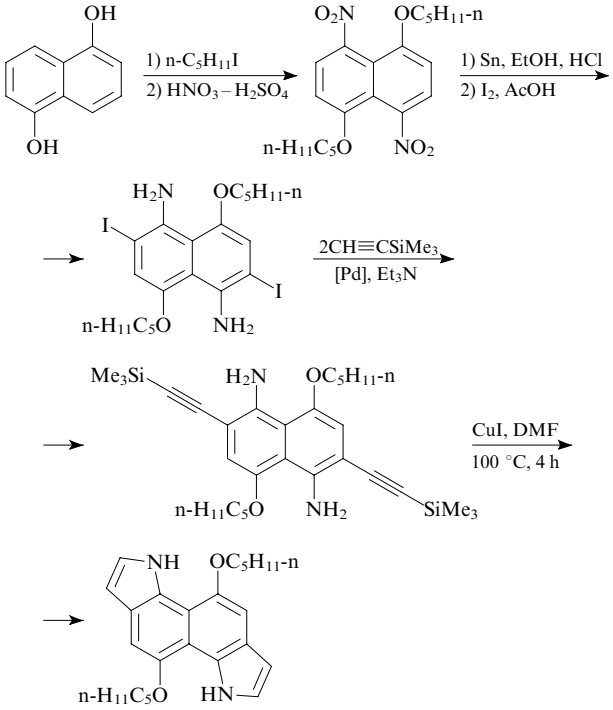
X, Y = H, Hal, Alk, AlkO, NO_2, CN.

Kossmehl and Manecke [45] prepared indolo[7,6-*g*]indoletetraone **50** in the same way and then converted this product into polymer **53** containing fragments of this indoloindole. Compound **50** was coupled with thiophene in a mixture of glacial acetic and concentrated sulfuric acids. Polymer **53** was obtained in 84% yield as a dark purple powder, which did not melt up to 600 °C and was insoluble in conventional organic solvents (Scheme 1).

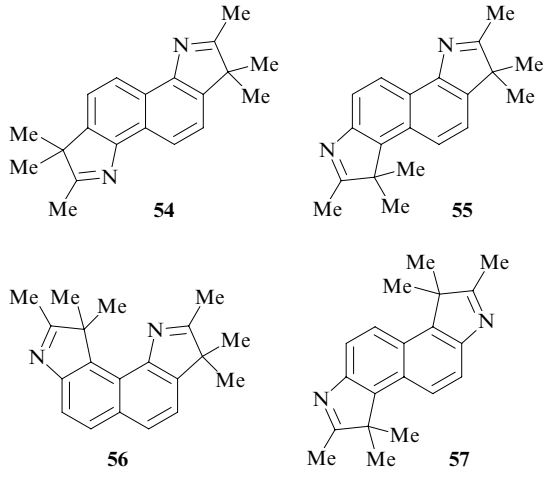
A new approach to the synthesis of substituted indolo[7,6-*g*]indoles using readily available 1,5-dihydroxynaphthalenes as the starting compounds has been proposed.[46]

Scheme 1

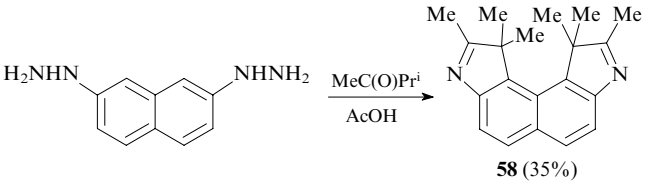




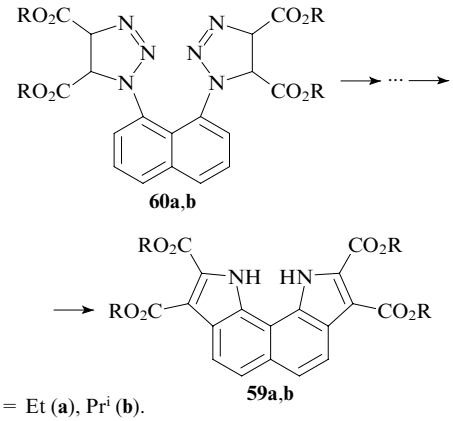
The Fischer cyclisation of isopropyl methyl ketone 1,5-, 1,6-, 1,7- and 2,6-naphthylenedihydrazones gave isomeric hexamethylindoloindoles: 2,3,3,7,8,8-hexamethyl-3*H*,8*H*-indolo[7,6-*g*]indole (**54**), 2,3,3,6,6,7-hexamethyl-3*H*,6*H*-indolo[6,7-*e*]indole (**55**), 2,3,3,9,10,10-hexamethyl-3*H*,10*H*-indolo[7,6-*e*]indole (**56**) and 1,1,2,6,6,7-hexamethyl-1*H*,6*H*-indolo[5,4-*e*]indole (**57**), which were used as hetero residues in the synthesis of carbocyanine dyes.[47]



The researchers cited [47] were unable to prepare hexamethylindoloindoles from isopropyl methyl ketone 2,7-napthylenedihydrazone, because only one pyrrole ring was closed in this case due to steric hindrance. Only recently,[48] was 1,1,2,9,10,10-hexamethyl-1,10-dihydroindolo[4,5-*e*]indole (**58**) synthesised in 35% yield by the Fischer reaction of 2,7-napthylenedihydrazine and isopropyl methyl ketone in acetic acid without isolation of the dihydrazone.



Substituted indolo[6,7-*g*]indoles **59a**,**b** were prepared using photolysis of 1,1′-(1,8-napththylene)bis(1*H*-1,2,3-triazoles) (**60a**,**b**) (450 W, high-pressure Hg lamp, quartz, 20 °C).[49] The reaction occurs in two steps, one pyrrole ring being closed first followed by closure of the other ring.



R = Et (**a**), Pr^i (**b**).

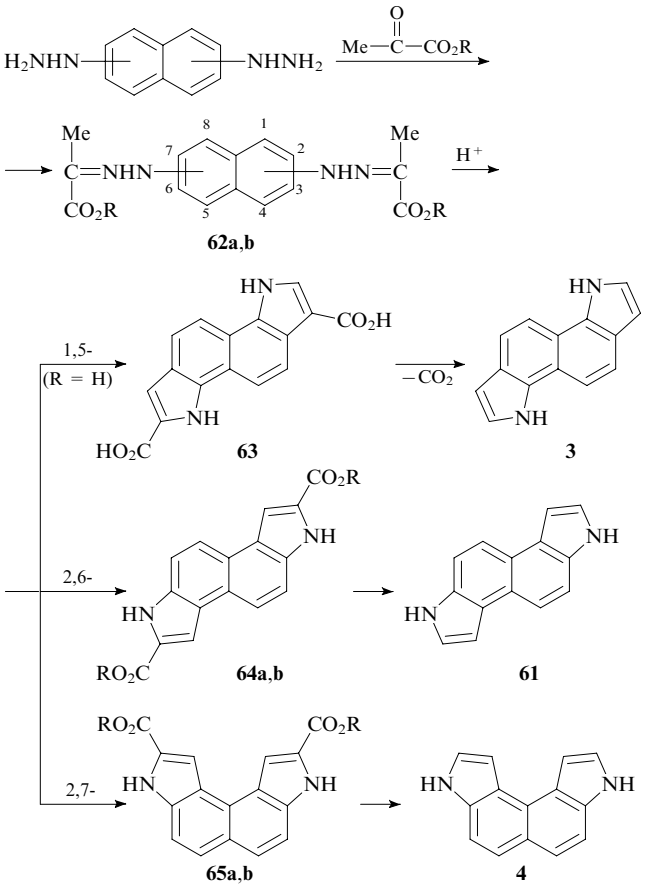
The structure of compound **59a** was confirmed by X-ray diffraction analysis.[50]

2. Synthesis of unsubstituted indoloindoles

The systematic investigation into the synthesis of unsubstituted indoloindoles in which the indole fragments have the carbon atoms of the benzene rings in common was started in 1977 simultaneously at the Chairs of Organic Chemistry of the D I Mendeleev Russian University of Chemical Technology and the I Javakhishvili Tbilisi State University.

Isomeric unsubstituted indoloindoles **3**, **4** and **61** were obtained by cyclisation of pyruvic acid or ethyl pyruvate 1,5-, 2,6- and 2,7-napthylenedihydrazones (**62a**,**b**), which were prepared from the corresponding napthylenedihydrazines under conditions of the Fischer reaction (Scheme 2).[51–53]

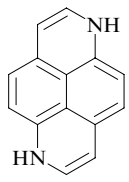
Scheme 2



R = H (**a**), Et (**b**).

The cyclisation of pyruvic acid napththylenedihydrazones **62a** was carried out in a mixture of concentrated sulfuric and glacial acetic acids, while the cyclisation of ethyl pyruvate dihydrazones **62b** was performed in a mixture of esters of polyphosphoric acid. The subsequent thermal decarboxylation of diacids **63**, **64a** and **65a** yielded unsubstituted 1*H*,6*H*-indolo[7,6-*g*]indole (**3**), 3*H*,8*H*-indolo[5,4-*e*]indole (**61**) and 3*H*,8*H*-indolo[4,5-*e*]indole (**4**).

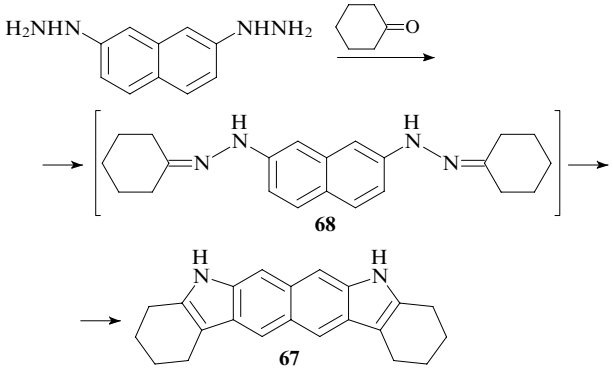
Theoretically, one could suggest that cyclisation of pyruvic acid 1,5-napththylenedihydrazone followed by decarboxylation would give compound **66** with four six-membered rings; however, ^{1}H NMR spectroscopic data attest to a structure in which protons occur in six- and five-membered rings, which is consistent with structure **3**.[54]



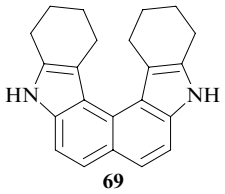
66

The cyclisation of 2,6- and 2,7-napththylenedihydrazones may give six isomeric indoloindoles, four symmetrical (two linear and two angular) and two asymmetric ones. Chromatographic monitoring of the cyclisation of dihydrazones showed the presence of several products; however, only one isomer was isolated in each case (namely, compounds **64** and **65**), *i.e.*, in both cases, cyclisation involved more reactive α-positions of the naphthalene nucleus.[52]

As an attempt to obtain linear indoloindoles, cyclisation of cyclohexanone 2,7-napththylenedihydrazone was carried out.[55, 56] In this case, due to the steric influence of the cyclohexane ring, cyclisation of the dihydrazone to give linear structure **67** seemed more likely. Indeed, one-pot reaction carried out in a mixture of concentrated acetic and sulfuric acids gave this compound without isolation of the extremely unstable dihydrazone **68**.

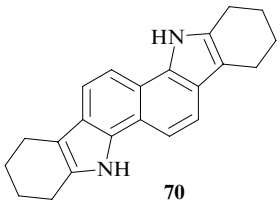


Angular isomer **69** was formed in this reaction as an admixture, which was proved by ^{1}H NMR spectroscopy.



69

Similarly, compound **70** was prepared from 1,5-naphthylenedihydrazine and cyclohexanone.[57]



70

3. Quantum-chemical calculations for unsubstituted indoloindoles

The molecules of indoloindoles **3**, **4** and **61** are tetracyclic fused conjugated hetero systems. According to Albert's classification,[58] indoloindoles are π-excessive heterocycles, as the number of π-electrons in their aromatic system exceeds the number of atoms in the rings. In this respect, they resemble indoles and benzindoles, but differ from them by the presence of the second heteroatom. Pozharskii[59] classified these fused π-excessive heterocycles as a separate group, as in these cases, the benzene rings also become π-excessive due to the shift of the π-electron density in the heterocycle. In the molecules of indoloindoles **3**, **4** and **61**, the π-excessive character extends to the naphthalene nucleus.

Quantum-chemical calculations for the molecules of 1*H*,6*H*-indolo[7,6-*g*]indole (**3**),[60] 3*H*,8*H*-indolo[4,5-*e*]indole (**4**)[61] and 3*H*,8*H*-indolo[5,4-*e*]indole (**61**)[62] were carried out. The electronic structure of the indoloindole molecule **3** was calculated by the CNDO MO and those of molecules **4** and **61** were determined using the SCF MO method in the CNDO/2 approximation.[63] The calculations for molecules **3** and **4** were carried out using the Maslov programme,[64] those for molecule

61, using software developed at the Department of Chemistry of the Moscow State University (Ref. 65).§

It can be seen from the molecular diagrams of indoloindoles **3**, **4** and **61** (Figs 1–3) that the introduction of an additional pyrrole ring into the [4,5]- and [6,7]-benzindole molecules results in a more pronounced electron delocalisation. The charge density and the overall ($\sigma+\pi$) charges are maximum for the atoms located at the β-positions of the pyrrole rings; the electron density is also increased at positions 5,10 (compound **3**), 4,9 (compound **61**) and 4,7 (compound **4**) of the naphthalene nucleus.

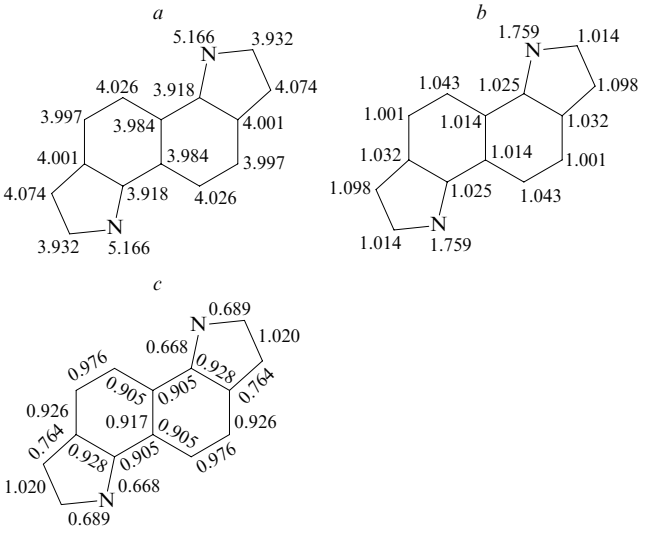


Figure 1. Molecular diagram of indoloindole **3**.
(*a*) Overall ($\sigma+\pi$) charges, (*b*) π-electron densities, (*c*) bond orders.

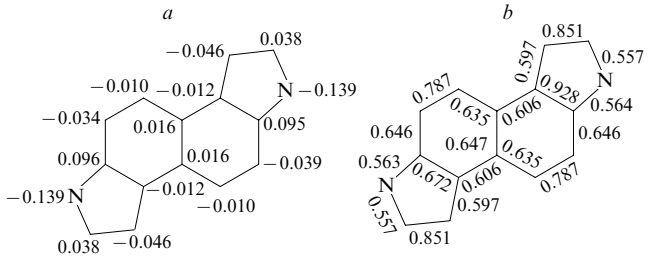


Figure 2. Molecular diagram of indoloindole **61**.
(*a*) Charge density on the atoms, (*b*) Wiberg indices.

Unlike indole, pyrroloindole [66] or other indoloindole isomers, in the molecule of indoloindole **4**, the highest π-electron densities occur on the α-carbon atoms of the pyrrole rings,[67] which is abnormal for the indole ring.

4. Reactions of indoloindoles with the carbon atoms of the benzene rings in common

a. Cycloaddition and cyclocondensation

The reactions of indoloindoles **58** and **54** with 2′,3′-dimethoxycarbonylspirofluorenecyclopropene yielded dispiropoly-

§ A programme package Viking was designed at the NMR laboratory of the Department of Chemistry of the Moscow State University for the calculation of physicochemical properties of molecules by semiempirical quantum-chemical methods including CNDO/2.

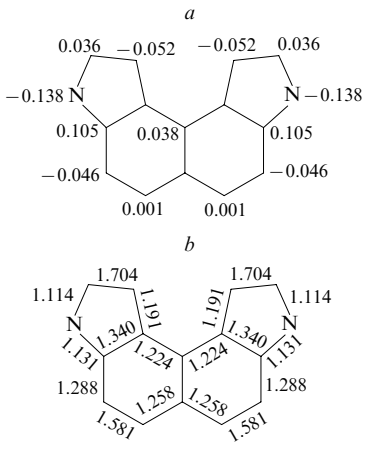
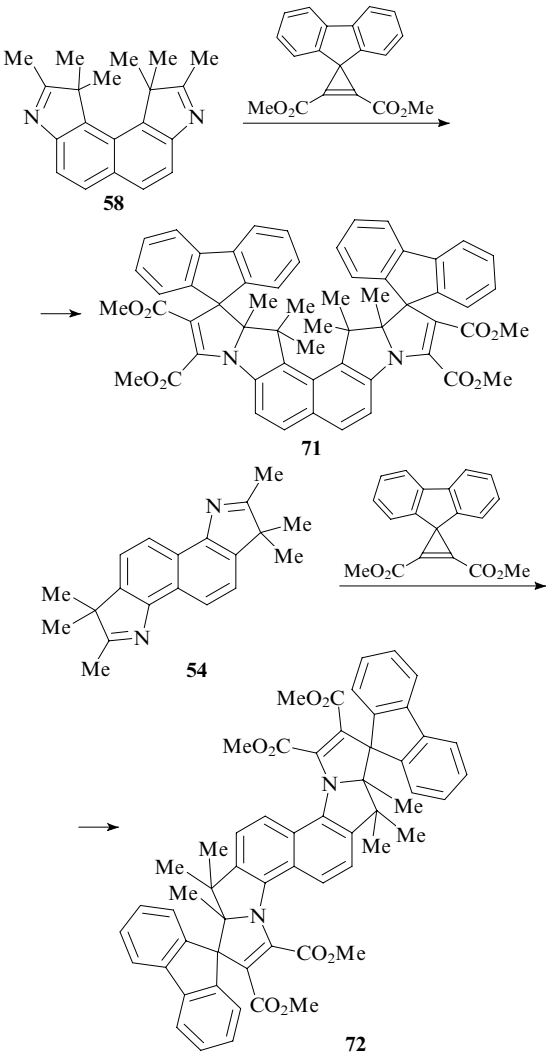


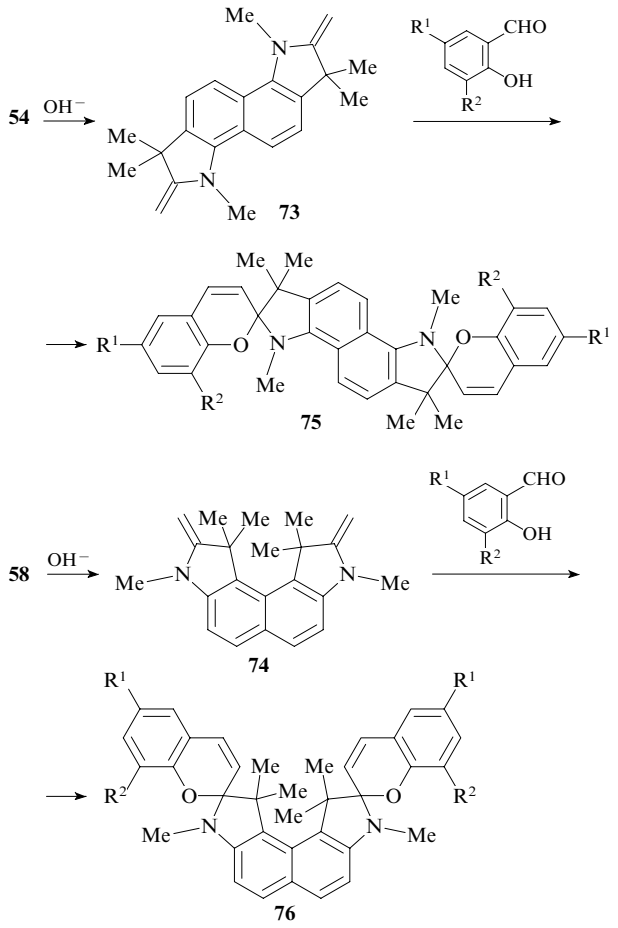
Figure 3. Molecular diagram of indoloindole **4**.
(*a*) Charge density on the atoms, (*b*) Wiberg indices.

cyclic photochromic systems, namely, compounds **71** and **72**.[48, 68, 69]



Yet another method for the preparation of spirocyclic compounds based on indolo[7,6-*g*]- and indolo[4,5-*e*]indoles is the condensation of indoloindoles with substituted salicylaldehydes.[70, 71] To this end, isomeric hexamethyldihydroindo-

loindoles **54**, **58** were first converted into bis-quaternary salts, which were then treated with a warm solution of alkali to obtain the Fischer bases, *viz*., 1,3,3,6,8,8-hexamethyl-2,7-dimethylideneindolino[7,6-*g*]indoline (**73**) and 1,1,3,8,10,10-hexamethyl-2,9-dimethylideneindolino[4,5-*e*]indoline (**74**). The latter compound was condensed with 5-nitro-, 3,5-dinitro- or 3,5-dibromosalicylaldehyde to be converted into spiro compounds **75** and **76** substituted at the pyran fragment.

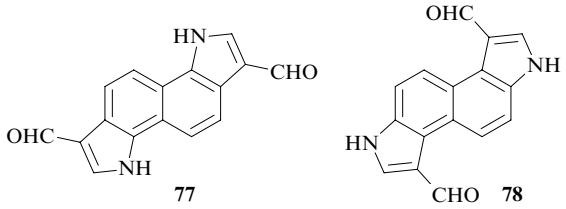


R^1 = NO_2, Br; R^2 = H, NO_2, Br.

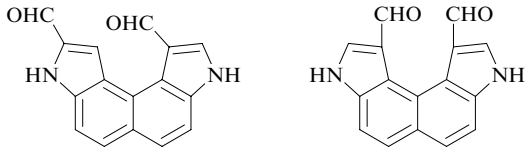
b. Electrophilic substitution in the pyrrole ring

In a study of the chemical properties of indoloindoles with the carbon atoms of the benzene rings in common, it was of interest to elucidate the influence of the mode of fusion of the indole rings on the specific features of various reactions, in particular, electrophilic substitution. It follows from the molecular diagrams of indoloindoles **3**, **4** and **61** that the molecules of these compounds contain two reactive sites most favourable for the electrophilic attack, namely, the β-positions of the pyrrole rings. Since the molecules are symmetrical, these positions are equivalent from both the electronic and steric standpoints. Therefore, it is of interest to find the conditions for selective formation of mono- or disubstituted derivatives and determine the ratios of the yields of mono- and disubstituted products when they are formed simultaneously. One should also take into account the possibility of competitive substitution in the α-positions of the pyrrole rings or in the naphthalene nucleus.

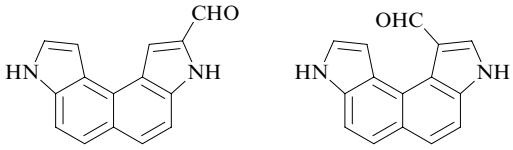
The Vilsmeier reaction. Among numerous methods of formylation of organic compounds, the Vilsmeier – Haack reaction is one of the most synthetically important methods. Indoloindoles **3**, **4** and **61** were formylated using different molar ratios of these compounds to formamide complexes with $POCl_3$ (Vilsmeier complexes, VC). On treatment of indoloindoles **3** and **61** with a threefold excess of VC, symmetrical dialdehydes, *viz*., 3,8-diformyl-1*H*,6*H*-indolo-[7,6-*g*]indole (**77**) and 1,6-diformyl-3*H*,8*H*-indolo[5,4-*e*]indole (**78**), respectively, were formed in high yields.[61,72] Note that dialdehyde **77** was obtained in highly pure state under these conditions and did not require additional treatment for the use in subsequent transformations.[54]



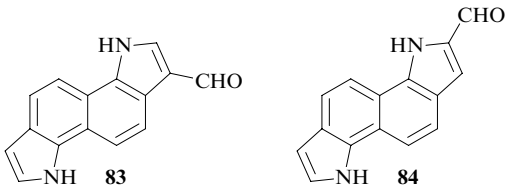
At the same time, indoloindole **4** was converted into a mixture of 1,9- (**79**) and 1,10-diformyl-3*H*,8*H*-indolo[4,5-*e*]indoles (**80**).[72]



With equimolar amount of VC, indoloindole **4** is converted into α- (**81**) and β-monoaldehydes (**82**). Chromatographic monitoring of the formylation showed also the presence of diformyl derivatives **79** and **80** among the reaction products.[61,72]



Indoloindole **3** is converted under the same conditions into a 1 : 1 mixture of 3-formyl- (**83**) and 3,8-diformyl-1*H*,6*H*-indolo[7,6-g]indoles (**77**). An attempt has been made[60] to obtain monoformyl derivative **83**. To this end, the formylation temperature was reduced to 55 – 60 °C and the reactants were taken in a 1 : 1 ratio. Under these conditions, the yield of aldehyde **83** was 43%, 2-formyl-1*H*,6*H*-indolo[7,6-*g*]indole (**84**) being formed as a by-product.

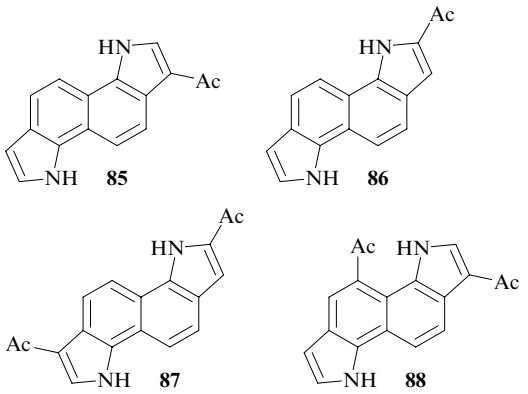


Indolo[7,6-*g*]indole (**3**) does not react with *N*,*N*-dimethylacetamide at 70 – 100 °C. An increase in temperature results in the resinification of the starting compound, no acetylation products being detected in the reaction mixture.[72]

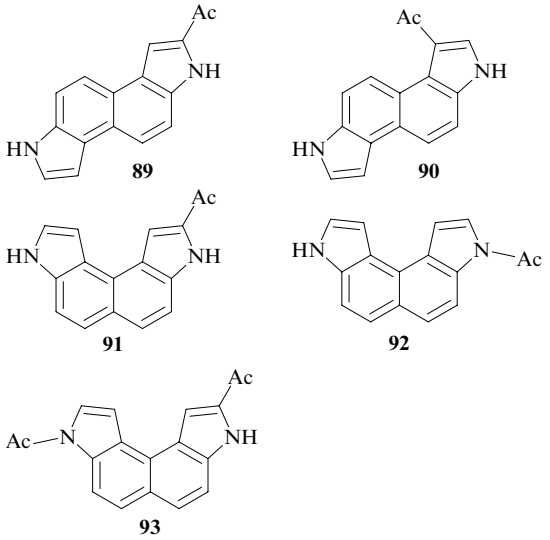
The presented data show that indoloindoles undergo the Vilsmeier – Haack reaction more readily than indole, as indicated by the formation of α-substituted aldehydes in addition to β-substituted products. This is due to the rather high π-electron density on the carbon atoms of the pyrrole ring.

Acetylation. Acetylation of indoloindoles **3**, **4** and **61**[61,72] with acetic anhydride in the presence of acetic acid affords mixtures of acetyl derivatives in low yield. In the case of

acetylation of indolo[7,6-*g*]indole (**3**), both mono- (**85** and **86**) and disubstituted (**87** and **88**) derivatives were isolated from the reaction mixture by column chromatography.



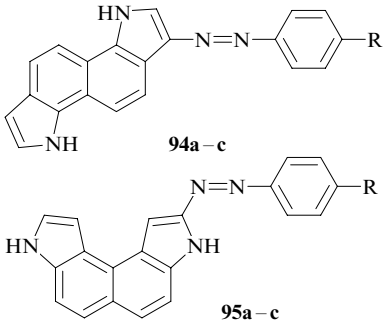
The acetylation of indolo[5,4-*e*]indole (**61**) with acetyl chloride in the presence of $AlCl_3$ yields only monosubstituted α- and β-acetyl derivatives **89** and **90**, while acetylation of indolo[4,5-*e*]indole (**4**) under the same conditions affords only α-acetyl derivatives **91**. In the latter case, minor amounts of *N*-acetyl derivatives **92** and **93** are also formed.



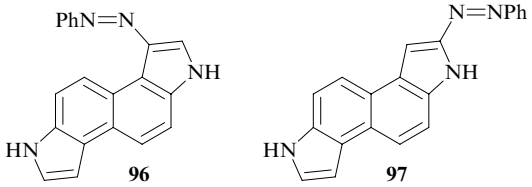
The acetylation of compound **4** at the β-position of the pyrrole ring does not take place, unlike acetylation of indoloindoles **3** and **61**. This is apparently due to steric hindrance created by the closely arranged pyrrole rings in compound **4**. In all cases, the yield of monoacetylated derivatives was substantially higher than the yield of diacetylated products.

The formation of product substituted in the naphthalene nucleus (compound **88**) upon the acetylation of compound **3** is attributable to an increase in the π-electron density and an additional activation of the naphthalene α-position due to the electronic influence of the pyrrole ring.

Azo coupling. Azo coupling tends to be highly selective. Studies of azo coupling of indoloindoles **3**, **4** and **61** with different diazo components in a neutral medium at a 1 : 3 molar ratio of the substrate to the diazonium salt have been reported.[61, 72] Under these conditions, indoloindole **3** is converted into the expected monosubstituted β-phenylazo derivatives **94a**–**c**, while azo coupling of indoloindole **4** follows an abnormal route with a predominant formation of monosubstituted α-phenylazo derivatives **95a**–**c**. The reaction of indoloindole **61** with phenyldiazonium chloride furnishes 1-phenylazo- (**96**) and 2-phenylazo-3*H*,8*H*-indolo[5,4-*e*]indoles (**97**) in a 1 : 4.5 ratio; the reaction with *p*-nitrophenyldiazonium chloride results in polymeric products.

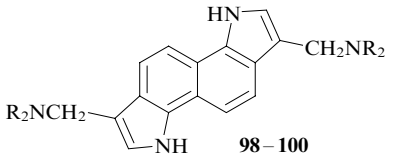


R = H (**a**), Cl (**b**), NO_2 (**c**).



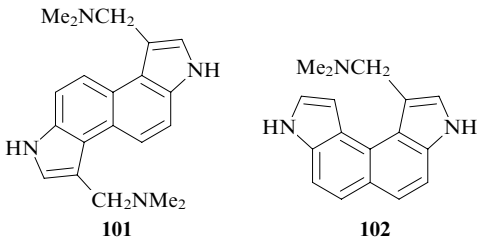
The predominant formation of monosubstituted derivatives in azo coupling may be caused by low electrophilicity of the ArN_2^+ ion, which is insufficient for the subsequent interaction with the monosubstituted phenylazo derivatives formed, in which the electron density of the aromatic system has been reduced by the introduction of the first phenylazo group. The formation of 2-substituted derivatives from compounds **61** and **4** may be due to the steric influence of the pyrrole ring and naphthalene nucleus.

The Mannich reaction. Indoloindole **3** undergoes the Mannich reaction with formaldehyde and amines (dimethylamine, piperidine and morpholine) to give the corresponding disubstituted derivatives **98**–**100** in high yields.[73, 74] The reaction is carried out in acetic acid at 60 °C.



NR_2 = NMe_2 (**98**),  (**99**),  (**100**).

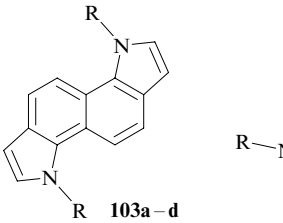
Indoloindoles **61** and **4** are converted into 1,6-bis(dimethylaminomethyl)-3*H*,8*H*-indolo[5,4-*e*]indole (**101**) and 1-dimethylaminomethyl-3*H*,8*H*-indolo[4,5-*e*]indole (**102**), respectively, with the same ease and in high yields.[61]



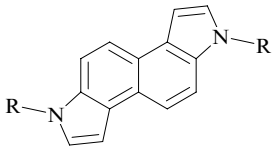
In order to study the probable biological activities, salts of gramine analogues were prepared, namely, 3,8-bis(dimethylaminomethyl)-1*H*,6*H*-indolo[7,6-*g*]indole dihydrochloride, dimethosulfate, dimethiodide and diethiodide,[73, 74] 1-dimethylaminomethyl-3*H*,8*H*-indolo[4,5-*e*]indole methiodide and

1,6-bis(dimethylaminomethyl)-3*H*,8*H*-indolo[5,4-*e*]indole dimethiodide.

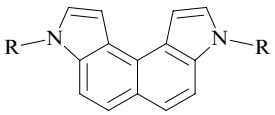
Alkylation. The alkylation of indoloindoles **3**, **4** and **61** was carried out using alkyl halides.[75] In non-polar solvents (for example, under conditions of phase transfer catalysis in a 50% aqueous solution of NaOH), the reactions proceed slowly (~12 h) despite vigorous stirring at a temperature of 60–65 °C. Probably, this is caused by poor solubility of indoloindoles in non-polar solvents. The alkylation of compounds **3**, **4** and **61** in 1,2-dichloroethane at a catalyst (tetrabutylammonium bromide) : substrate molar ratio of 1 : 5 at 40–45 °C yields mainly *N*,*N*′-dialkylindoloindoles.[75] Indolo[4,5-*e*]indole **4** undergoes *N*,*N*′-dialkylation more easily than compounds **3** and **61**, which is due to its better solubility in 1,2-dichloroethane. Compounds **103**–**105** were synthesised by alkylation.[75–77]



103a–d



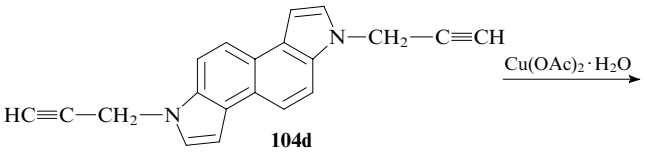
104a–d



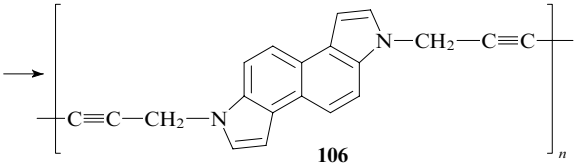
105a–d

R = Et (**a**), Bn (**b**), $CH_2{=}CHCH_2$ (**c**), $CH{\equiv}CCH_2$ (**d**).

Apart from the purely theoretical interest, compounds **103**–**105** are of considerable practical value because of their probable biological activities and the use for preparation of polymers. For example, 3,8-dipropargylindolo[5,4-*e*]indole (**104d**) was used as an example in the Glaser–Eglinton reaction to give polyacetylenes **106** containing fused indoloindole fragments in the monomeric unit,[78] whereas in the case of 3-propargylindole, symmetrical diacetylene was isolated.[79]

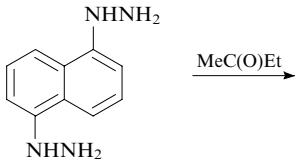


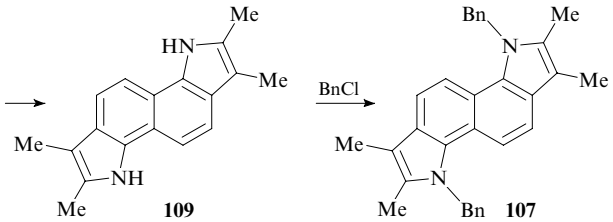
104d



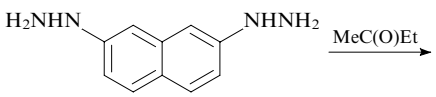
106

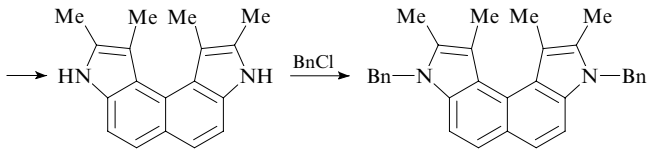
N,*N*′-Dibenzyl-substituted indoloindoles **107** and **108** were obtained by direct Fischer cyclisation of the corresponding napththylenedihydrazines and alkyl ketones followed by benzylation of the cyclisation products **109** and **110**.[57, 68, 80]





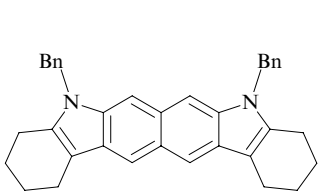
109 **107**



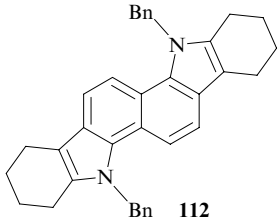


110 **108**

The same publications describe the synthesis of *N*,*N*′-dibenzyl derivatives **111** and **112** from compounds **67** and **70**.



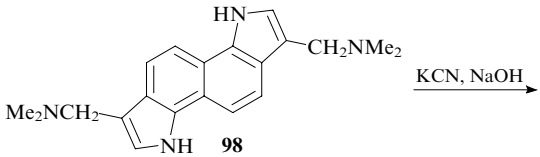
111



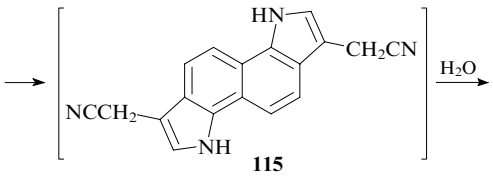
112

c. Transformations in side chains

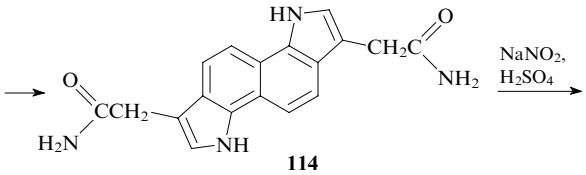
Synthesis of heteroauxin analogue. The synthesis of a heteroauxin analogue, *viz*., 3,8-bis(carboxymethyl)-1*H*,6*H*-indolo[7,6-*g*]indole (**113**), has been reported.[73] 3,8-Bis(dimethylaminomethyl)-1*H*,6*H*-indolo[7,6-*g*]indole (**98**) was used as the starting compound.



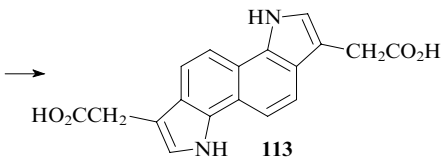
98



115



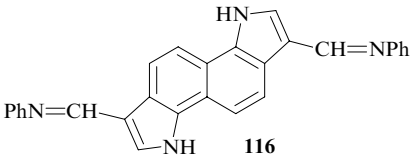
114



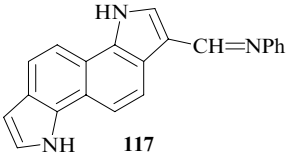
113

After refluxing of an ethanolic solution of compound **98** in the presence of KCN for 17 h, 3,8-bis(carbamoylmethyl)-1*H*,6*H*-indolo[7,6-*g*]indole (**114**) resulting from partial hydrolysis of the intermediate dinitrile **115** precipitates from the reaction mixture. Due to the poor solubility in an alkaline medium, compound **114** does not undergo further hydrolysis; however, in an acidic medium, the Bouveault reaction of amide **114** yields an oily product in which diacid **113** was detected by chromatography.

Condensation involving indolo[7,6-g]indole aldehydes. Aldehydes **77** and **83** are readily coupled with primary amines to give Schiff bases. The reactions of compounds **77** and **83** with aniline resulted in 3,8-diformyl-1*H*,6*H*-indolo[7,6-*g*]indole dianil (**116**) and 3-formyl-1*H*,6*H*-indolo[7,6-*g*]indole anil (**117**), respectively, in high yields.[60] The reaction proceeds without a catalyst.

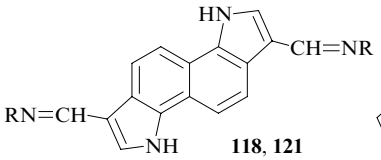


116

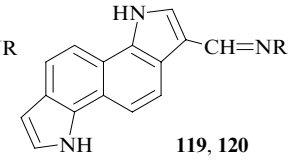


117

The condensation of compounds **77** and **83** with thiosemicarbazide in the presence of a catalytic amount of an ethanolic solution of HCl (pH 4 – 5) occurs equally smoothly giving rise to thiosemicarbazones **118** and **119**.



118, **121**

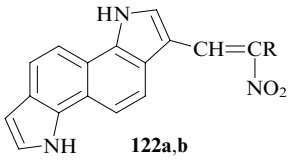


119, **120**

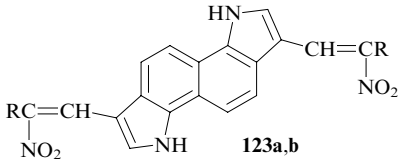
R = NHC(S)NH$_2$ (**118**, **119**), OH (**120**, **121**).

The reaction of monoaldehyde **83** with hydroxylamine proceeds smoothly to yield a mixture of 3-formyl-1*H*,6*H*-indolo[7,6-*g*]indole oxime (**120**) isomers, which could not be separated.[60] The reaction is carried out in ethanol in the presence of sodium hydrogencarbonate. The condensation of dialdehyde **77** takes place only with a strong oximating reagent, *viz*., a mixture of hydroxylamine hydrochloride with pyridine. The reaction yields geometric isomers of 3,8-diformyl-1*H*,6*H*-indolo[7,6-*g*]indole dioxime (**121**); both isomers were isolated by chromatography. According to NMR spectroscopy, these isomers had *syn*,*syn*- and *anti*,*anti*-configurations and existed in the cisoid conformation,[60] which is sterically more favourable than the transoid conformation of the aldoxime groups.

The condensation of monoaldehyde **83** with excess nitromethane (or nitroethane) proceeds in the presence of a catalytic amount of ammonium acetate yielding 3-(2-nitrovinyl)- (**122a**) or 3-(2-nitroprop-1-enyl)indolo[7,6-*g*]indole (**122b**) (the nitroalkane serves as the solvent).[81,82] The reactions of dialdehyde **77** with these nitroalkanes follow different routes depending on the amount of the nitroalkane. When a stoichiometric amount of nitroalkane is used and the reaction is carried out in DMF in the presence of ammonium acetate, disubstituted derivatives **123a**,**b** are formed.



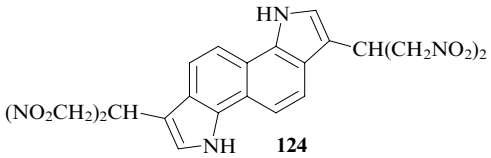
122a,**b**



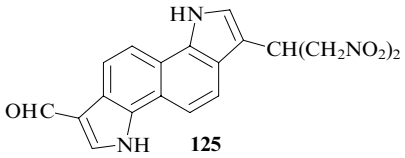
123a,**b**

R = H (**a**), Me (**b**).

With a large excess of nitromethane and a 50% solution of NaOH as the catalyst, the reaction of dialdehyde **77** with nitromethane does not stop after the formation of compound **123a**, but proceeds further to give small amounts (isolated yields 5% – 8%) of the addition products of nitromethane to compound **123a**, namely, 3,8-bis(1,3-dinitroisopropyl)-1*H*,6*H*-indolo[7,6-*g*]indole (**124**) and 3-(1,3-dinitroisopropyl)-8-formyl-1*H*,6*H*-indolo[7,6-*g*]indole (**125**), as followed from their elemental composition and spectroscopic data. The addition of nitromethane to 3-(2-nitrovinyl)indole follows a similar route.[83]

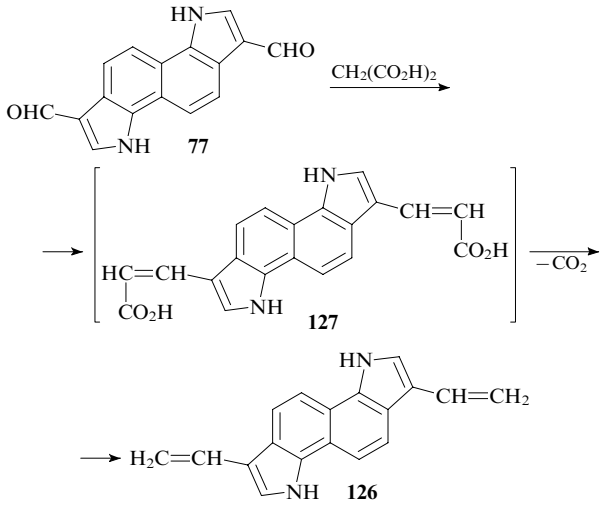


124



125

The condensation of dialdehyde **77** with malonic acid in pyridine in the presence of piperidine affords 3,8-divinyl-1*H*,6*H*-indolo[7,6-*g*]indole (**126**), which is the key compound in the synthesis of various monomeric and polymeric products.[84] Presumably, the condensation gives diacid **127**, which is decarboxylated under the reaction conditions to give compound **126**.

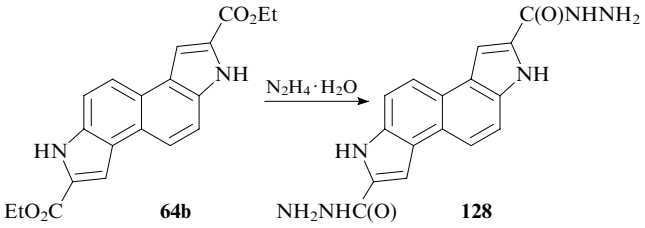


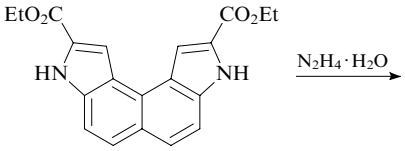
77

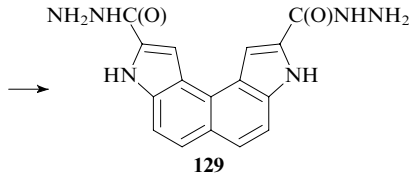
127

126

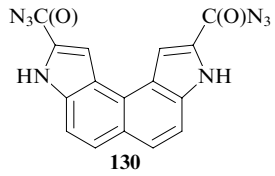
Synthesis and transformations of indoloindole dihydrazides. Refluxing of diesters **64b** and **65b** with hydrazine hydrate in propan-2-ol yielded 2,7-di(hydrazinocarbonyl)-3*H*,8*H*-indolo[5,4-*e*]indole (**128**) and 2,9-di(hydrazinocarbonyl)-3*H*,8*H*-indolo[4,5-*e*]indole (**129**).[85, 86]

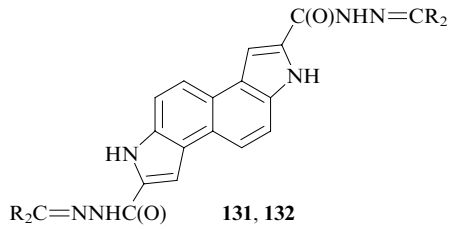






Nitrosation of dihydrazide **129** using sodium nitrite and concentrated HCl gives 2,9-di(azidocarbonyl)-3*H*,8*H*-indolo[4,5-*e*]indole (**130**).[85] Treatment of dihydrazide **128** with ethyl methyl ketone or hexanone resulted in dihydrazones **131** and **132**, respectively.





N=CR$_2$ = N=CMeEt (**131**), N= (**132**).

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