Russian Chemical Reviews **63** (12) 997 – 1018 (1994)
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UDC 547.759.4

The chemistry of isoindoles

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Abstract. Data on the synthesis and the physical and chemical properties of isoindoles published in 1981 – 1992 are considered. The problems of the aromaticity and the reactivity of the isoindole system are discussed. The bibliography includes 169 references.

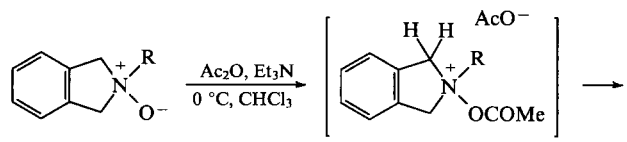
I. Introduction

Several reviews[1,2] and monographs[3] on the chemistry of isoindole have been published in the last decade. However, the interest in this system is not flagging. New isoindoles have been obtained, some of which have been isolated in a pure form and some have been characterised as Diels–Alder adducts. New methods of synthesis of isoindole systems have been discovered. Calculations of the electronic structure have been carried out by methods which had not been applied previously, a new concept of the aromaticity of this system has been put forward, the X-ray diffraction analysis of isoindoles has been achieved, and new reactions have been investigated. Data have been published on the biological activity of isoindole systems.

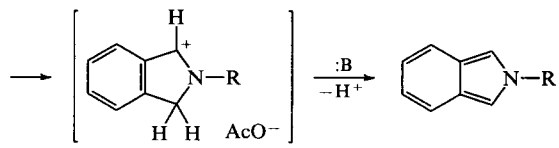
II. Methods of synthesis of isoindoles

1. Elimination reactions with participation of isoindoline *N*-oxides

The possibilities of this method, developed by German workers,[4] have been demonstrated in numerous examples and the method has attracted attention because of the high yields of 2-R-isoindoles. It consists in the treatment of the corresponding isoindoline *N*-oxide at a reduced temperature with acetic anhydride and triethylamine in chloroform and can be followed with the aid of ^{1}H NMR spectra. It has been suggested that the *O*-acetylation of the oxide **1** takes place initially and this is followed by the base-induced regiospecific 1,2-elimination of the elements of acetic acid from the intermediate **2**, and finally by the deprotonation of the intermediate 2-R-1*H*-isoindolium salts **3** with formation of 2-R-isoindoles **4**.

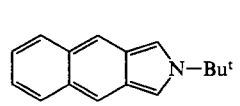


1 **2**

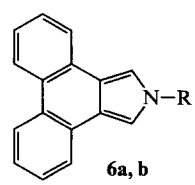


3 **4**

According to the authors,[4] the reaction resembles the Polonovski reaction. The available compounds indicate the possibility of extensive variation of the substituent in the 2-position in the system: the substituent can be an alkyl (10 compounds),[5] allyl,[4] and arylalkyl[6] group or the very frequently employed *tert*-butyl group.[5–12] In all the known examples of the isoindoles obtained by this procedure, the 1- and 3-positions in the system are free while the benzene component of the bicyclic system may contain methyl groups,[12] nitro-groups,[7] chlorine atoms,[12] or it can be condensed with other rings. The isoindoles **5**–**10** have been described in a number of communications.[6,8–10]

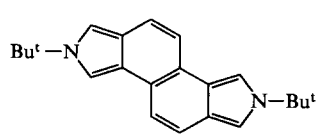


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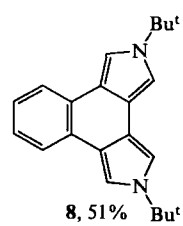


6a, b

6a: R = Bu^t, 80%
6b: R = CH_2Ph, 68%



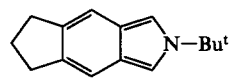
7, 65%



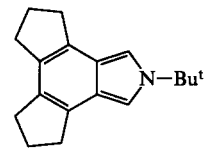
8, 51%

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Received 28 July 1994
Uspekhi Khimii **63** (12) 1064 – 1086; translated by A K Grzybowski



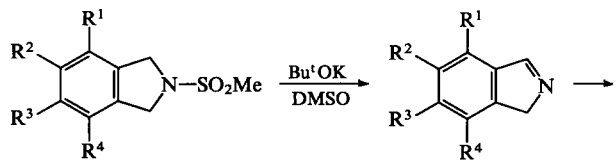
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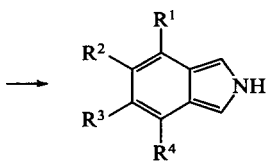
10, 90%

2. Elimination with participation of 2-R-isoindolines

The previously described method of synthesis of 2*H*-isoindoles via the 1,2-elimination of methanesulfinate from *N*-methanesulfinylisoindolines **11** on treatment with potassium *tert*-butoxide in dimethyl sulfoxide (DMSO) (60–65 °C) or ether has been developed further in a number of studies.[13–17] The required isoindolines **11** can be synthesised from the corresponding 1,2-bis(bromomethyl)benzenes and methanesulfonamide.[16] It has been suggested that the 1*H*-isoindole **12** is formed initially and then isomerises to the 2*H*-isoindole **13** as a result of a tautomeric transformation. The isoindoles **13a** (yield 94%) and **13b, c** have been described by Kreher and Kohl[14] and Kreher and Herd[17] respectively.



11 **12**



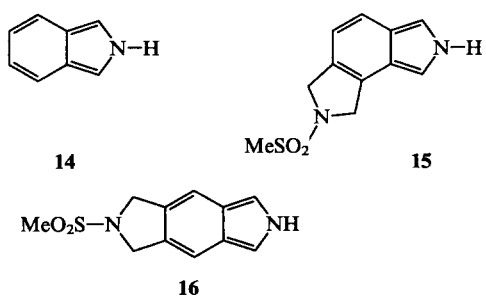
13a–c

13a: $R^1 = R^2 = R^3 = H$; $R^2 = COBu^t$

13b: $R^1 = R^2 = R^3 = R^4 = Cl$

13c: $R^1 = R^2 = R^3 = R^4 = Br$

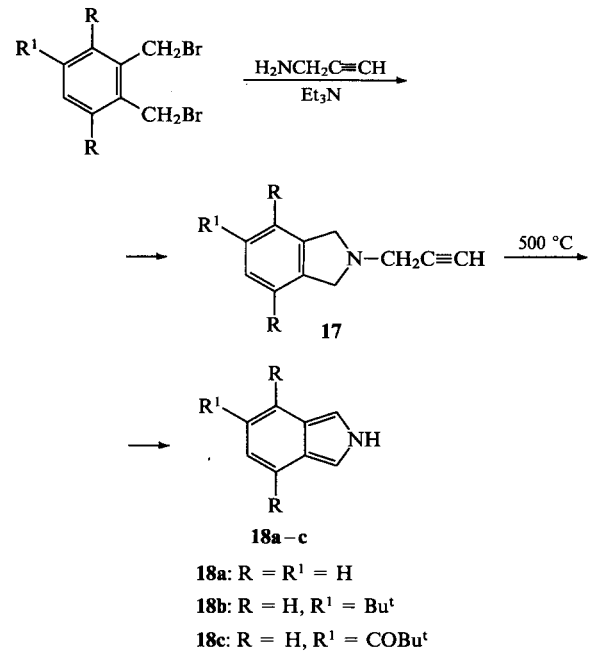
The isomeric compounds **15** and **16** as well as the parent isoindole **14** have been isolated by a similar method.[13] The last compound is obtained as a 0.05 M solution in ether.[15,16] The authors[15] believe that this method is in fact best for the preparation of solutions of the isoindole **14**.



14 **15**

16

The method involving the elimination of propyne from *N*-propargylisoindolines **17** at a high temperature can serve as a general approach to the synthesis of 2*H*-isoindoles **18**.[15,18] The yields of the products are fairly high. The isoindolines required are obtained from *o*-xylylene dibromides and propargylamine.



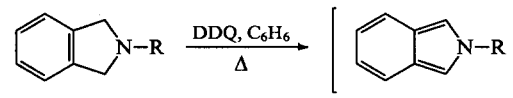
18a–c

18a: $R = R^1 = H$

18b: $R = H$, $R^1 = Bu^t$

18c: $R = H$, $R^1 = COBu^t$

It has been shown[19] that 2-R-isoindoles can be obtained by dehydrogenating *N*-(ethoxycarbonyl)isoindolines **19** in benzene or diglyme with the aid of chloranil or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The isoindoles **20** were not isolated from the reaction mixture but were converted into Diels–Alder adducts with maleimide derivatives.

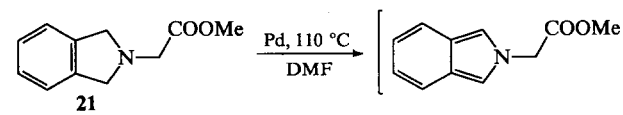


19 **20a, b**

20a: R = COOEt

20b: R = Tos

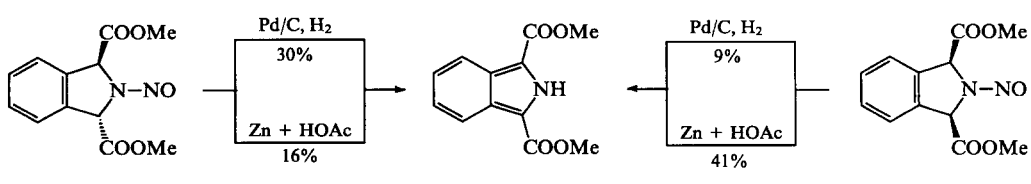
The dehydrogenation of the methyl ester of isoindoline-2-acetic acid **21** takes place in dimethylformamide (DMF) over palladium black at 110 °C and leads to the corresponding isoindole, which has also been characterised as the Diels–Alder adduct.[20]



21

The reduction of the stereoisomeric forms of *N*-nitrosoindoles (*E* and *Z*) leads to 1,3-dimethoxycarbonyl-2*H*-isoindole **22** in low yields (Scheme 1).[21]

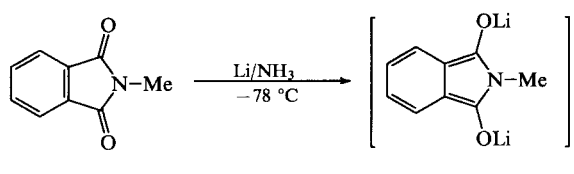
Scheme 1



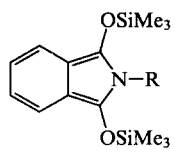
dl-*E* **22** meso-*Z*

3. Synthesis of isoindoles from phthalimides

Flynn[22] was the first to demonstrate that the dianion of *N*-methylphthalimide has the *o*-quinonoid electronic structure **23**. The reduction of *N*-methylphthalimide dissolved in tetrahydrofuran (THF) by metallic lithium (2.1 equivalents) in liquid ammonia leads to a dark-red solution containing the dianion, the structure of which can be demonstrated by chemical reactions. The electrochemical reduction of *N*-methyl- and *N*-phenyl-phthalimides in anhydrous acetonitrile using a mercury cathode in the presence of tetraethylammonium chloride and an excess of trimethylsilyl chloride leads to the corresponding isoindoles **24a, b** via the dianion in **23**. When equivalent amounts of trimethylsilyl chloride are used, other products are formed.[23,24] The attempts to obtain the isoindoles **24c, d** from the corresponding phthalimides must be regarded as a development of this method. Under similar conditions, the electrochemical reductive silylation of *N*-alkoxyphthalimides leads to 2-alkoxy-1,3-bis(trimethylsiloxy)isoindoles.[25] All the isoindoles **24a–d** have been identified through the corresponding Diels–Alder adducts.



23

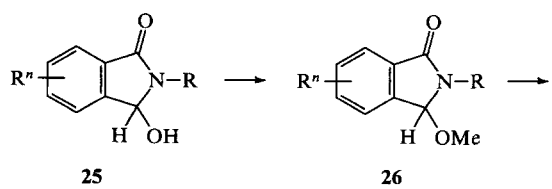


24a–d

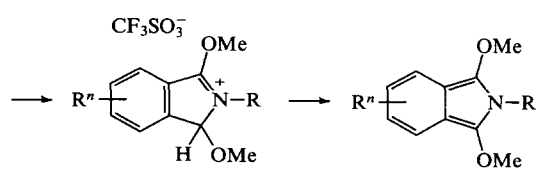
R = Me (**a**), Ph (**b**), OMe (**c**), OCH_2Ph (**d**)

The reduction of *N*-methyl- and *N*-phenyl-phthalimides at room temperature with zinc powder in 2,6-lutidine in the presence of THF and an excess of trimethylsilyl chloride has been investigated.[26] The reaction mixture was treated with ultrasound. The authors believe that the silylated isoindoles **24a, b** are also intermediates in this reaction.

A novel method of synthesis of 1,3-dimethoxy-2-R-isoindoles has been proposed.[27] It consists in the reduction of phthalimides by magnesium to 3-hydroxyphthalimidine **25**, which is converted into 3-methoxyphthalimidine **26**. The *O*-alkylation of the latter with CF_3SO_2OMe affords 1,3-dimethoxy-2-R-1*H*-isoindolium trifluoromethanesulfonate **27**, the deprotonation of which with the aid of lithium diisopropylamide leads to the relatively unstable 1,3-dimethoxy-2-R-isoindoles **28**, which have been identified via Diels–Alder adducts.



25 **26**

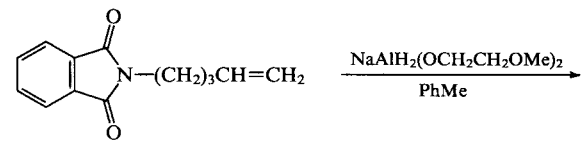


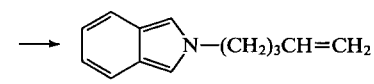
27 **28**

R = H, Me

R^n = H; 5,6-Me, 4,7-Me; 5,6-Cl

The method involving the chemical reduction of phthalimide has been used in the synthesis of the isoindole **29**. The target product was isolated in a moderate yield from a mixture with an isoindoline and phthalimidine.[28]

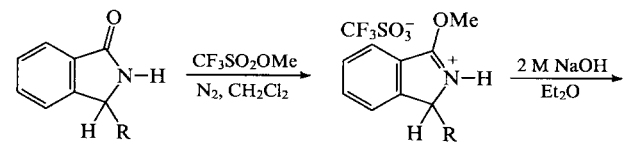




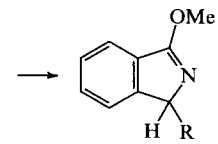
29

4. Synthesis of isoindoles from phthalimidines

The study of the alkylation of various phthalimidines with the aid of the Meerwein reagent or methyl trifluoromethanesulfonate was continued during the period analysed.[29–32] Thus a series of 1-R-3-methoxy-1*H*-isoindoles **31** have been obtained by alkylating 1-R-3-oxo-1,2-dihydroisoindoles.[29,33] The regioselective *O*-alkylation in the first stage results in the formation of 1-R-3-methoxy-1*H*-isoindolium triflates **30** (the yields expressed in % are as follows for different R: 91 for Me, 72–89 for Ph, 4-MePh, and 4-ClPh, and 50 for 4-MeOPh), which are treated with a base in the presence of ether in the second stage. This method makes it possible to extract immediately the deprotonated products into the organic phase and to isolate 1-R-3-methoxy-1*H*-isoindoles **31** in 74%–93% yield.[29]

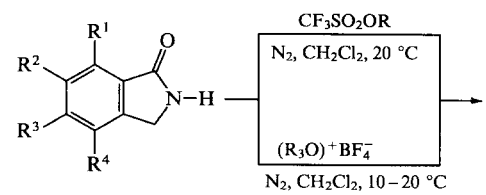


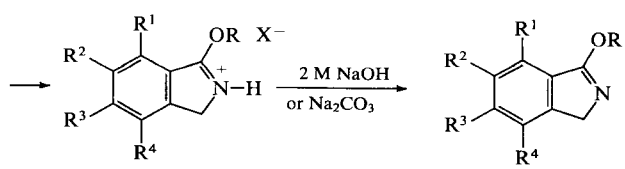
30



31

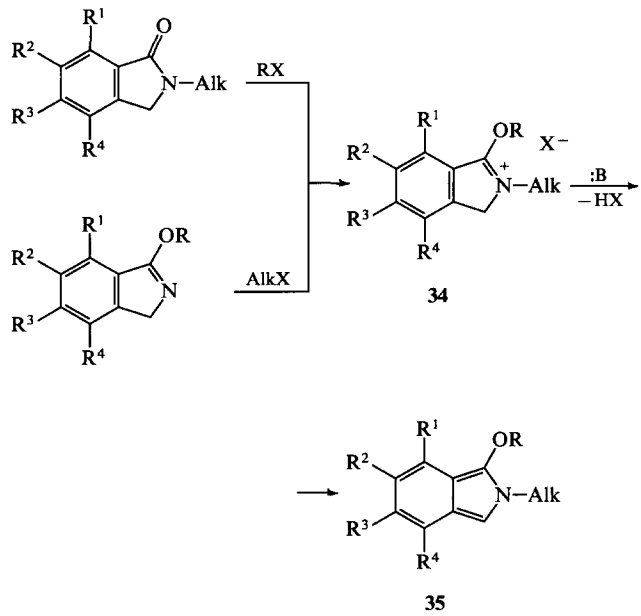
A series of 3-alkoxy-1*H*-isoindoles **33** (13 compounds), containing substituents of different electronic nature in the benzene part of the bicyclic compound, have been obtained by similar procedures.[30]





32 **33**

The preparation of the corresponding 3-ethoxy-1*H*-isoindole from 5,6-dimethoxyphthalimidine in 81% yield has been described.[34] The alkylation was carried out with triethyloxonium tetrafluoroborate. The study of the spectroscopic characteristics of compounds of type **31** and **33** showed that they exist exclusively in the isoindolenine form and do not exhibit a tendency towards conversion into the isoindole form.[29,30] If the isoindolenines **31** and **33** are alkylated with methyl trifluoromethanesulfonate, then the quaternary salts **34** are formed. These are the products of the regioselective *N*-alkylation which are readily deprotonated after treatment with bases (2 M NaOH or lithium diisopropylamide) and are converted into 1-alkoxy-2-methylisoindoles **35**.[31,32] The salts **34** can be obtained also by the direct *O*-alkylation of *N*-methylphthalimidines with the aid of the same alkylating agents, although such alkylation does not occur if the bicyclic system has been deactivated by substituents in the benzene component. This has been observed when attempts were made to alkylate 4,5,6,7-tetrachloro-*N*-methylphthalimidine with methyl trifluoromethanesulfonate.[31]



34

35

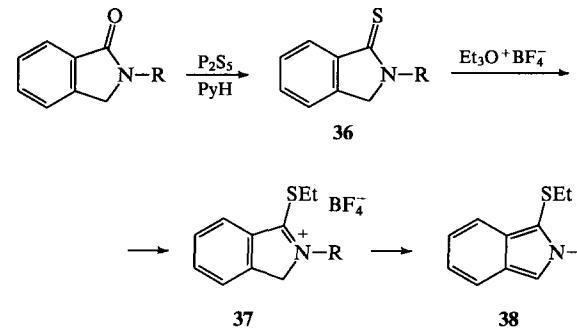
R = Me, Et

The alkoxyisoindoles **35** are unstable. They have been identified via Diels–Alder adducts, some of them being also investigated by the ^{1}H NMR method.

It was found that the stability of the compounds in solution depends on the type of the alkyl substituent at *N*(2). It it is a methyl group, then the ^{1}H NMR spectrum, recorded after brief drying of the organic layer, reveals the presence of a mixture consisting of the isoindole and the corresponding isoindolinone (for example, their ratios are 1 : 1.25 for R = Me and 1 : 1.5 for R = Et). The ratio for 2-*tert*-butyl-1-methoxy-2*H*-isoindole is more favourable (8 : 1).[32]

1-Ethylthio-2-R-isoindoles are obtained from the corresponding phthalimidines via their successive conversion initially into the thiophthalimidines **36** and then, by the regioselective *S*-alkylation of the latter, into 3-ethylthio-2-R-1*H*-isoindolium tetrafluoroborates **37**. The reaction chain is completed by the deprotonation of the above salts with formation of the isoindoles **38**.[35]

The isoindoles **38** are obtained as a result of the vacuum distillation of a thoroughly ground mixture of the salt **37** with an excess of solid alkali. The ^{1}H NMR spectra have been recorded for some of them. They can be identified as Diels–Alder adducts.[35]



36

37 38

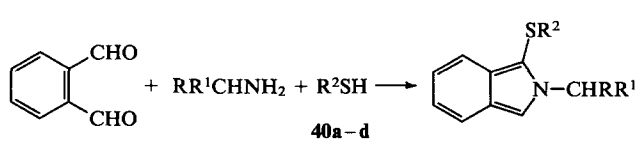
R = Me, Ar

The reduction of phthalimidines with lithium tetrahydroaluminate was proposed a long time ago by Wittig and coworkers (quoted after Babichev and Kovtunenko[3]) as a method of synthesis of the isoindoles **4**. However, according to the data of Kovtunenko et al.,[36] the main product of the reactions of a series of *N*-substituted phthalimidines is the corresponding isoindoline and the formation of traces of isoindoles can be detected only chromatographically. An effective method of synthesis of 2-R-isoindoles from phthalimidines involves the reduction of the latter with lithium bis(2-methoxyethoxy)dihydroaluminate in benzene or toluene. The corresponding isoindoline is as a rule formed as a side product (its yields vary from 5% to 10%). The pure isoindole can be obtained by employing the higher solubility of isoindolines in cold ether. The yields of the isoindoles **4** then amount to 70%–80%.[36]

5. *o*-Phthalic dialdehyde in the synthesis of isoindoles

The study of the fluorescence method for the determination of the terminal amino-groups in aminoacids, proteins, primary amines, etc. via their conversion into 1-alkylthio-2-R-isoindoles **41** continued in the 1980s.[37–44] The review by Garcia Alvarez-Coque et al.[45] covers more than 50 sources in which this reaction has been investigated. It has been shown that *o*-phthalic dialdehyde (OPD) **39** reacts with propylamine in the presence of ethanethiol or mercaptoethanol (ME) (compounds **40a, b**) to form the isoindoles **41a, b**, which have been investigated spectroscopically and identified via adducts with dimethyl ethynedicarboxylate.[39] The fluorescent products obtained by this reaction have been investigated[41] by the stopped flow method. It has been established that, in the presence of an excess of the OPD–ME adduct formed initially, the interaction of the latter with primary amines is pseudo-first order at rates consistent with overall second-order kinetics. It has been shown that the rate of the reaction of the OPD–ME adduct with various aminoacids follows second-order kinetics when OPD : ME : aminoacid ratios of 1 : 1.24 : 1 are maintained. It has been established that the rate of the reaction of the OPD–ME adduct with alanine is a maximum at pH 10.5–11.0, while a large excess of mercaptoethanol slows down the reaction. A decrease in the rate was also observed when mercaptoethanol was replaced by dithiothreitol or propanethiol.[37] An improved method for the preparation of the aminoacid mixture to be subsequently separated with the aid of high-performance liquid chromatography (HPLC) has been proposed.[38] It consists in the conversion of the aminoacid into type **41** isoindoles as a result of treatment with OPD and ME. The identification of the type **41** isoindoles obtained from the aminoacids, carried out after the HPLC with the aid of an electrochemical detector operating under oxidation conditions, has been described.[46] The products formed from a mixture of alkylamines with OPD during the post-column derivatisation (HPLC) have been investigated by chromatograph-linked mass-spectrometry. It has been shown[40] that, when the derivatisation is carried out in the presence of ethanethiol **40a**, the products determined are type **41** isoindoles.

Six β-aminothiols (of the L-cysteine type) have been investigated in the reaction with OPD. It was shown that fluorescent products are formed in such cases without introducing thiols from outside. On the basis of the study of these products and model type **41** isoindoles by combined HPLC (reversed phase) and chromatograph-linked mass spectrometry with subsequent fluorescence detection, it has been suggested that type **41** isoindoles are responsible for the fluorescence in this case also.[47] Comparison of three methods for the determination of traces of aliphatic amines with the aid of HPLC and by means of fluorescence detection showed that the derivatisation method via the corresponding isoindoles **41** has the lowest sensitivity.[43] In order to improve the fluorescence detection of primary amines after the HPLC, a study was made of the factors influencing the stability of the isoindoles **41**.[41,48–50] It was established that their stability increases both when 3-mercapto-1-propanol **40d** is used instead of mercaptoethanol **40c** [41] and following the replacement of R = H in the structure of compound **41** by R = Me.[41,48] It was found that the stability of the isoindoles **41** is also influenced by the structure of the amino-component. It was shown[51] that amino-compounds with a sterically shielded amino-group (L-tryptophan, L-DOPA, etc.) have an appreciable stabilising effect on the fluorescence parameters of the isoindole derivative. This is why it has been suggested that L-tryptophan be used as a standard in the fluorimetric determination of various thiols.[51] Experiments have shown that an excess of OPD in the reaction mixture catalyses the decomposition of the isoindole,[41,48] while an excess of ethanethiol has a stabilising effect.[48] According to Stobaugh et al.,[48] ethanethiol forms more stable isoindole derivatives under these conditions than β-mercaptoethanol: the stability, estimated in terms of the time taken for a 10% decrease in the fluorescence level, improves by a factor of at least 5. Jacobs et al.[49] believe that, among all the destabilising factors (the structure of the thiol, the nature of the solvent, the influence of the pH, etc.), the presence of an excess of OPD in the reaction mixture is the most dangerous. They have shown that, in the absence of an excess of OPD, type **41** isoindoles are entirely stable, while the results presented by Mading and Jacobs[50] clearly confirm that the destabilisation of the isoindoles **41** and the associated decrease in the fluorescence level are a direct consequence of the electrophilic attack by the excess OPD on the free C(3) position in the isoindole **41** system. Furthermore, in a number of instances the products in the interaction of isoindoles **41** with OPD have been isolated and identified.[50] A special study had been made[52] of the factors inducing the quenching of the fluorescence of type **41** isoindoles obtained from biogenic amines.



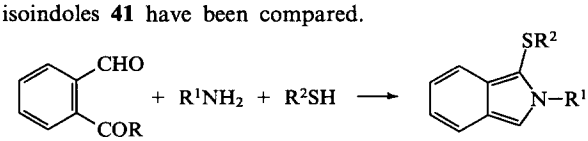
39 **41a–d**

R = H, Me

40a: R^2 = Et
40b: R^2 = Bu^t
40c: R^2 = $(CH_2)_2OH$
40d: R^2 = $(CH_2)_3OH$

41a: R^1 = R^2 = Et
41b: R^1 = Et, R^2 = Bu^t
41c: R^1 = Et, R^2 = $(CH_2)_2OH$
41d: R^1 = $(CH_2)_2COOH$, R^2 = Et

The individual disadvantages of the fluorescence analytical method examined above stimulated the search for new reagents among derivatives of *o*-acylbenzaldehydes.[44] The ketones **42a, b** have been examined and the stability and properties of the isoindoles **43** obtained from them and the corresponding isoindoles **41** have been compared.

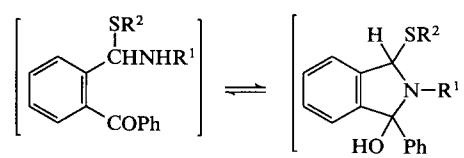


42a, b **43a–d**

42a: R = Me
42b: R = Ph

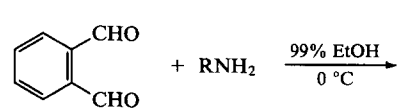
43a: R = Ph, R^1 = CH_2Ph, R^2 = Et
43b: R = Me, R^1 = Pr^i, R^2 = Bu^t
43c: R = Ph, R^1 = $(CH_2)_3COOH$, R^2 = Et
43d: R = Me, R^1 = $(CH_2)_3COOH$, R^2 = Et

Under similar conditions of the synthesis, the yield of the isoindole **43a** (42%) is higher than that of the isoindole **43b** (32%). Under identical experimental conditions (pseudo-first order kinetics), it was found that the rate of formation of compound **43c** is significantly lower than the rates of formation of compounds **41d** and **43d**. The authors explained this finding by the steric hindrance generated by the phenyl group in the intermediate **A** when the carbonyl group is attacked intramolecularly by the nitrogen atom, on the one hand, and by the resonance stabilisation of the reactant **42b**, on the other.[44]

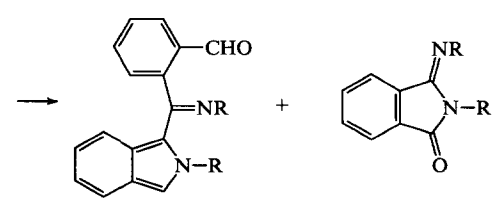


A

Having disproved the previous claim[1] that isoindoles are not formed from OPD and ammonia (or primary amines), Japanese workers[53] found the conditions for their isolation. They suggested that 99% alcohol be used as the solvent for the reaction and that the process itself should be carried out at 0 °C. The isoindoles **44** are isolated together with the imines **45** by column chromatography. It has been noted that, in the presence of tertiary butyl alcohol, the yield of the isoindoles **44** is somewhat better. *tert*-Butylamines does not react with OPD, which the authors explain by its being sterically hindered due to the presence of bulky *tert*-butyl groups. The use of aniline affords mainly 1-phenylimino-2-phenylisoindoline (79%) and only 2% of the corresponding imine **45** (R = Ph).[53]



39 R = Pr^n, Pr^i, C_6H_{11}

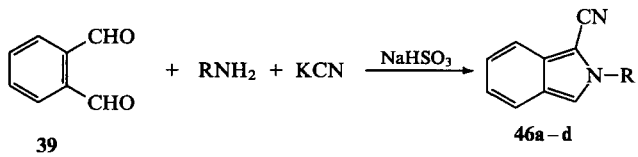


44a–c **45a–c**

44a: R = Pr^n (35%)
44b: R = Pr^i (20%)
44c: R = C_6H_{11} (34%)

45a: R = Pr^n (10%)
45b: R = Pr^i (22%)
45c: R = C_6H_{11} (11%)

The chemists of the Monsanto Company discovered a convenient and effective method of synthesis of 1-cyano-2-methyl-2*H*-isoindole (the yield of compound **46a** was 92%), involving the interaction of OPD with methylamine hydrochloride and cyanide in methanol. The molar reactant ratios were OPD : ($MeNH_2$ + HCl) : KCN = 1 : 2.2 : 2.[54]



39 **46a–d**

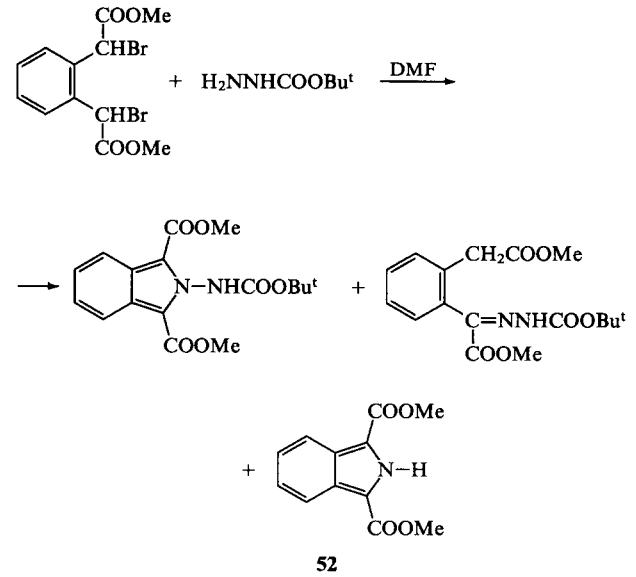
R = Me (**a**), Alk (**b**), 4-MeOPh (**c**), 3-HOOCPh (**d**)

It has been shown that, under the conditions of the Strecker reaction, OPD reacts with primary amines in the presence of sodium bisulfite to form 1-cyano-2-R-isoindoles **46** in very satisfactory yields in the case of alkylamines (59% to 86% for compound **46b**) and in poor yields of *p*-anisidine (33% for compound **46c**). The molar reactant ratios were OPD : RNH_2 : KCN : $NaHSO_3$ = 1 : 1.3 : 2.2 : 2.1.[55] *m*-(1-Cyano-2-indolyl)benzoic acid **46d** was obtained from *m*-aminobenzoic acid, OPD, and potassium cyanide in one stage.[56]

Japanese workers have been investigating the reactions of *o*-acylbenzophenone **47a** with ammonia derivatives for more than 25 years. The structures of the blue pigment **48**, formed from the diketone **47a** and phenylhydrazine in the presence of hydrochloric acid,[57] of the red pigments **49**, formed from compound **47a** and β-aminoethanol or its methyl ether in acetic acid,[58] and of the dark-blue pigments **50**, obtained from the same substances but in the presence of hydrochloric acid,[58] have been established during the last 10–15 years. It has been shown[57,59] that the diketones **47a,b** react with primary amines in the absence of acids to form 1,2-diaryl-3-(aryliminomethyl)isoindoles **51** (Scheme 2).

6. The synthesis of isoindoles from *ortho*-disubstituted benzenes

The interaction of dimethyl α,α′-dibromo-*o*-phenylenediacetate with *tert*-butyl carbazate has been investigated[21] and it has been shown that a mixture consisting of three compounds, including the known dimethyl 2*H*-isoindole-1,3-dicarboxylate **52**, is formed in DMF. The yield of the isoindole **52** is only 7% when the racemic dibromo-derivative is used and is lower still (5%) when it is obtained from the *meso*-form.[21]

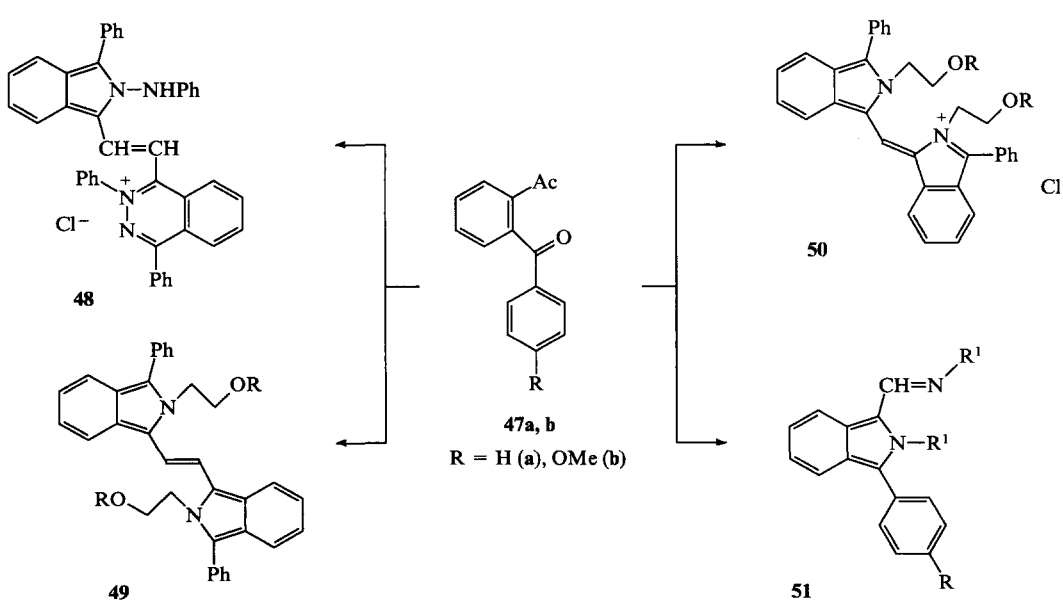


52

The interaction of *o*-chloro(bromo)methylbenzonitrile **53** with primary amines on heating in alcohol leads to 3-amino-2-R-1*H*-isoindolium salts **56** in one stage and in a high yield.[60,61] Derivatives of hydrazine, namely carboxylic acid hydrazides (R = $NHCOR^1$),[62,63] α-benzoyl-α-methylhydrazine [R = N(Me)COPh],[64] and *tert*-butyl carbazate [R = NHCOO.Bu^t],[65] also enter into this reaction on heating in DMF, forming the corresponding salts **56.**

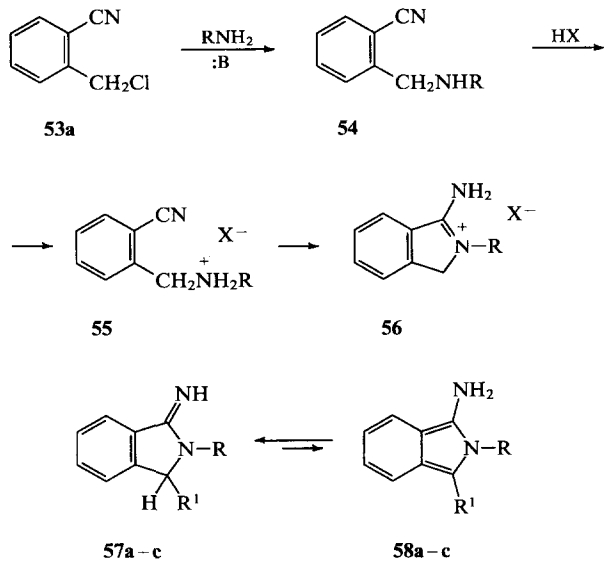
If the interaction of compound **53a** with amines is carried out in the presence of bases, it is possible to isolate benzylamines **54**, which are entirely stable during storage and show no tendency to cyclise. On the other hand, the corresponding simple salts **55**, which are obtained on treatment with inorganic acids in the cold,

Scheme 2



48 **49** **47a, b** R = H (**a**), OMe (**b**) **50** **51**

readily cyclise to aminoisoindolium salts **56** both in solution and in the solid phase. The study of the heterocyclisation of compound **55** to aminoisoindolium salts **56** by the ^{1}H NMR method in solution in DMSO-d_6 showed that this is a second-order reaction.[66] The salts **56** are deprotonated when they are treated with alkali or triethylamine and this leads to 1-imino-2-R-isoindolines **57a** and not be aminoisoindoles **58a** whatever the substituents.[67]

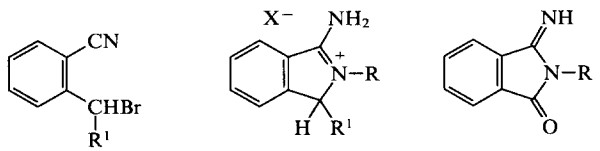


53a **54** **55** **56** **57a–c** **58a–c**

R^1 = H (**a**), Ph (**b**), CN (**c**)

α-Bromo-*o*-benzylbenzonitrile **59a** and α-bromo-*o*-cyanomethylbenzonitrile **59b** react with primary amines like the chloro-derivative **53a**.[60,68]

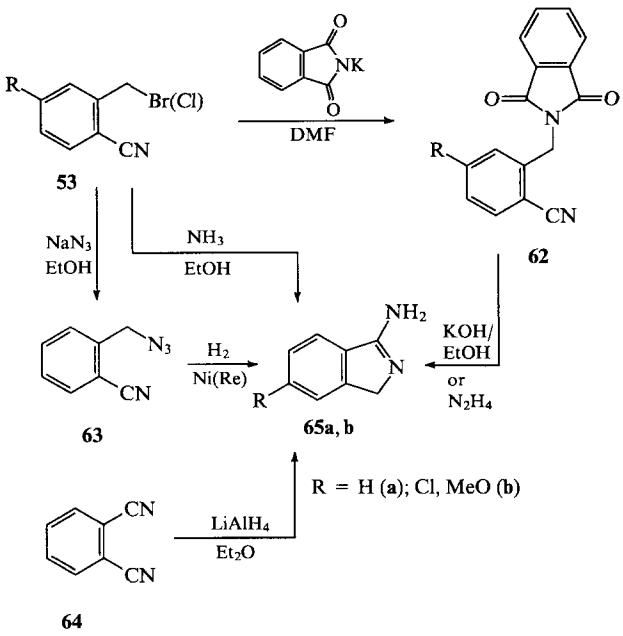
The salts **60a, b** are obtained in one stage and in a high yield and yet they are deprotonated in different ways. Whereas the salt **60a** gives rise to the corresponding stable imine of type **57b**,[67] the salts **60b** give rise to 1-amino-2-R-3-cyano-2*H*-isoindoles **58c**,[68] which are unstable in air, are readily oxidised, lose HCN, and are converted into the corresponding iminophthalimides **61**.



59a, b **60a, b** **61**

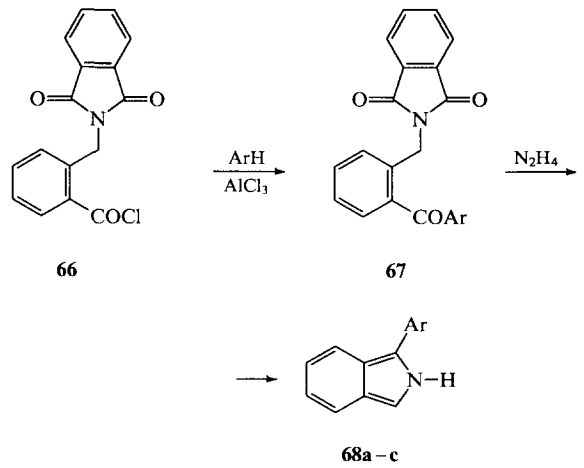
R^1 = Ph (**a**), CN (**b**) R^1 = Ph (**a**), CN (**b**)

o-Chloromethylbenzonitrile and its derivatives **53** can be transformed via different routes 3-amino-1*H*-isoindoles **65a, b**. The methods of synthesis of the latter compounds have been surveyed.[69] The reduction of the dinitrile **64** with lithium tetrahydroaluminate did not prove to be the best method of synthesis of compound **65a** and the authors, using the corresponding phthalimidomethyl derivatives **62**, obtained the aminoisoindoles **65a, b** in 38% and 51% yields respectively. The aminoisoindole **65a** has been synthesised in 23% yield by reducing *o*-azidomethylbenzonitrile **63**. The most convenient method of synthesis of the compound involves the direct amination of the nitrile **53** with an alcoholic solution of ammonia.[70]



53 **62** **63** **65a, b** **64**

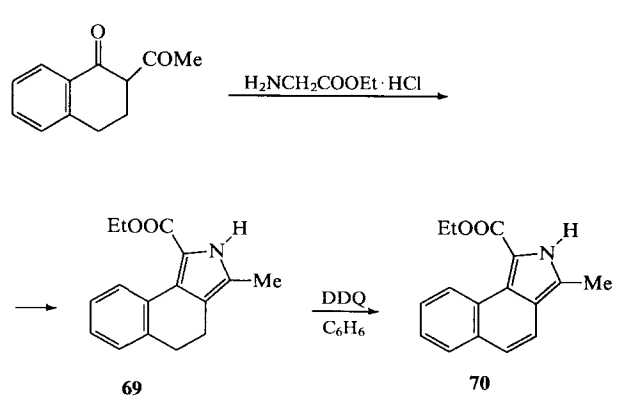
The earlier method of Weber and L'vovska has been used to obtain three 1-aryl-2*H*-isoindoles **68a–c**.[71] Their yields are not quoted, although it has been shown that the acylation of toluene and *p*-xylene by the acid chloride **66** proceeds with low yields (31% and 33% respectively).



66 **67** **68a–c**

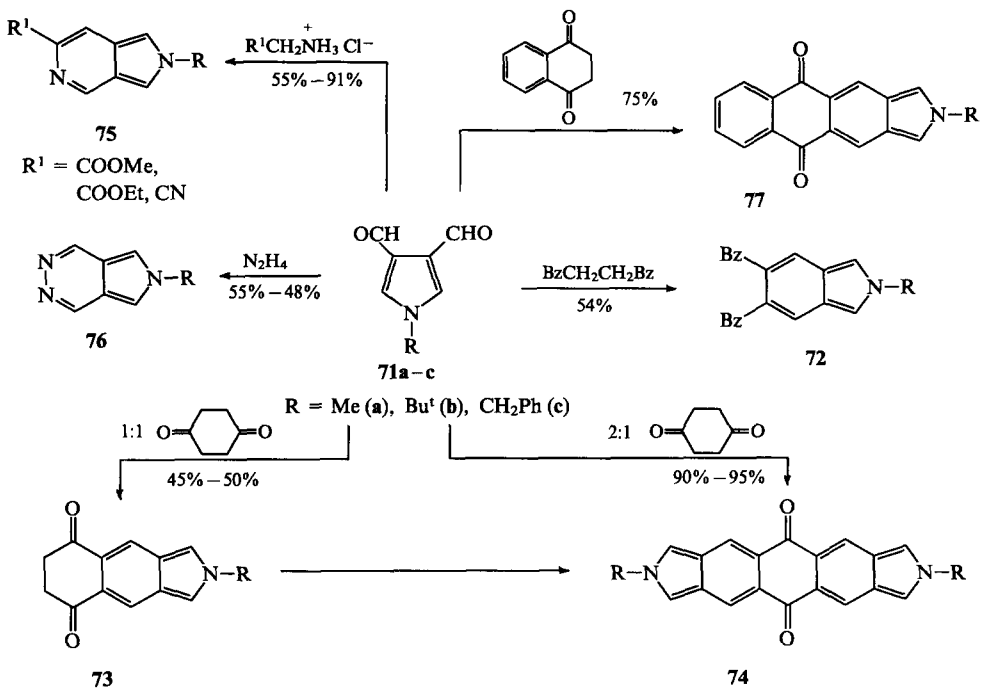
Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 2,5-$Me_2C_6H_3$ (**c**)

2-Acetyl-1-tetralinone interacts in boiling DMF with ethyl glycinate hydrochloride to form the dihydrobenzo[*e*]isoindole derivative **69** (43%), which may be dehydrogenated with DDQ over a period of 2 h to benzo[*e*]isoindole **70** in a low yield (12%).[72]



69 **70**

Scheme 3

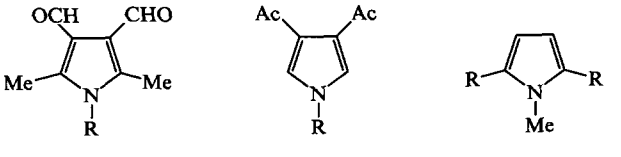


7. The synthesis of isoindoles from pyrroles

The conversion of 2,5-dimethylpyrroles into 1,3,4,7-tetramethylisoindoles has long been known,[1] but the fact that the latter can be formed in an aqueous medium at a high temperature has been demonstrated recently.[73] The studies on the reactions of 3,4-diformylpyrroles **71** initiated not so long ago have been continued and have yielded interesting results for the chemistry of isoindole (Scheme 3, see above).

Thus the condensation of compound **71** with γ-dicarbonyl compounds leads to high yields of 2*H*-isoindoles **72**–**74** and **77**,[74,75] whereas similar condensations with anhydrous hydrazine or glycine derivatives afford 5,6-diaza-2*H*-isoindoles **76** or 5-aza-2*H*-isoindoles **75**.[76]

It has been shown [76,77] that 3,4-diformyl-2,5-dimethylpyrroles **78a, b** as well as the 3,4-diacetyl derivatives **79a, b** enter successfully into similar reactions.

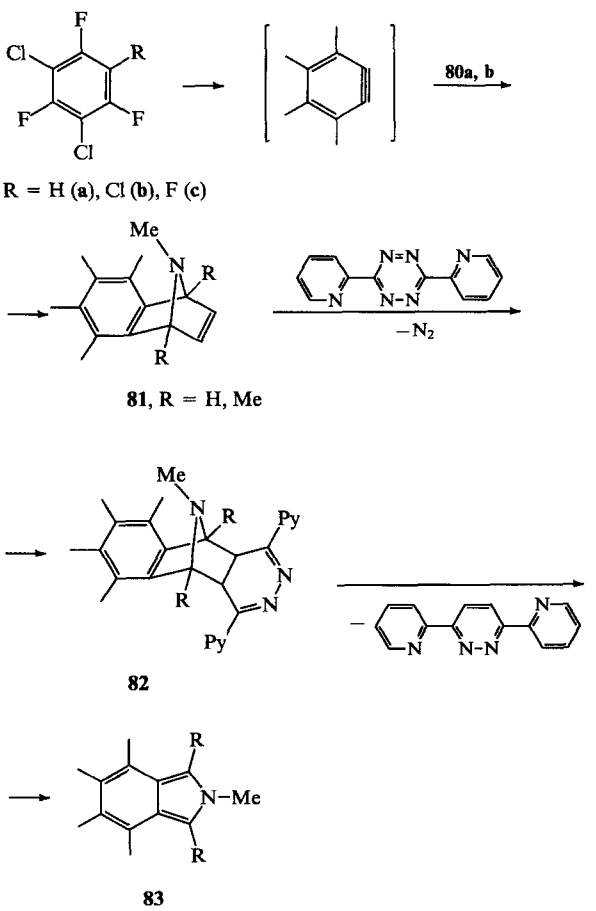


78a, b R = H (**a**), Me (**b**)

79a, b R = H (**a**), Me (**b**)

80a, b R = H (**a**), Me (**b**)

Pyrroles can be converted into the isoindole system also with the aid of the Diels–Alder retro-reaction.[78] The substituted dehydrobenzenes interact with the pyrroles **80a, b** and give rise to derivatives of 7-methyl- and 1,4,7-trimethyl-7-azabenzonorbornadienes **81**. As dienophiles, the latter undergo the [2 + 4]-addition reaction with 3,6-di-α-pyridyltetrazine, which leads to the dihydropyridazines **82** after the evolution of nitrogen and condensation with 7-azabenzonorbornane at the C(5)–C(6) bond. These complex polycyclic compounds readily decompose to 3,6-dipyridylpyridazine and 2-methyl- or 1,2,3-trimethyl-2*H*-isoindoles **83**, which contain in the benzene part of the molecule the substituents present in the initial dehydrobenzenes (yields 75%–89%). This process is used in the synthesis of various heterocycles and is called the Carboni–Lindsey reaction.



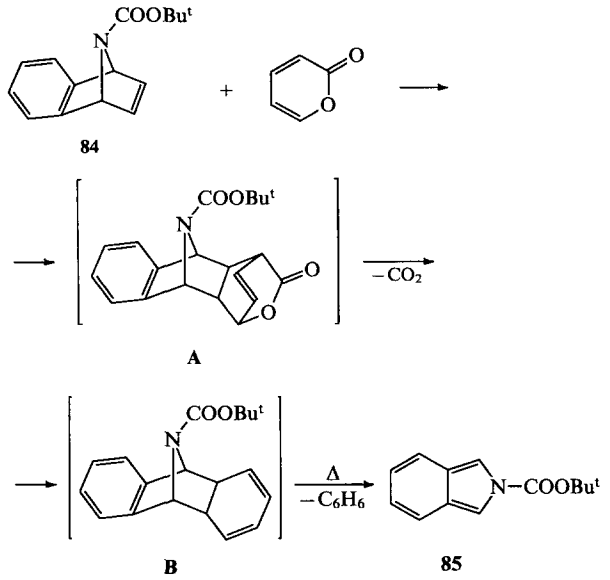
81, R = H, Me

82

83

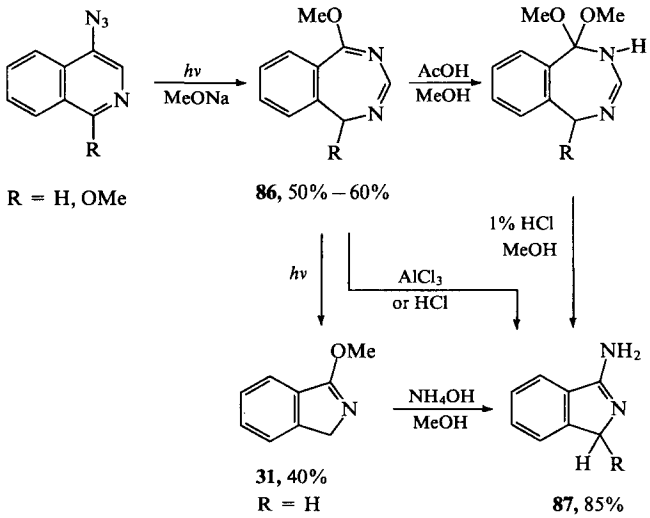
An improved procedure for the synthesis of isoindoles by refluxing a mixture of dipyridyltetrazine with derivatives of 7-azabenzonorbornadiene **81** in chloroform has also been described.[78] The end of the reaction is detected from the cessation of nitrogen evolution, which takes from 3–4 h (for R = H) to 24 h (for R = Me).

The 7-azabenzonorbornadiene **84**, obtained from the corresponding pyrrole and dehydrobenzene, gives rise to the adduct **A** on interaction with 2-pyrone. On heating, the adduct loses a carbon dioxide molecule and is converted into compound **B**. The isoindole **85** is formed subsequently as a result of the Diels – Alder retro-reaction with elimination of benzene.[79]

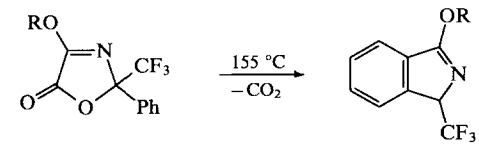


8. Other methods

The rearrangement of 2,4-benzodiazepines of type **86**, obtained by the photoisomerisation of 4-azidoisoquinolines, to isoindoles has been used to synthesise 3-amino-1-R-isoindoles **87** and 3-methoxy-1*H*-isoindole **31** (R = H).[80] Treatment of 1-R-5,5-dimethoxy-1*H*,4*H*-benzodiazepines with 1% hydrochloric acid solution in methanol leads to 3-R-1-aminoisoindolenines **87** in 85% yield. Irradiation for 6 h of a solution of 1-methoxy-5*H*-[2,4]-benzodiazepine **86** in methylene chloride affords 1-methoxyisoindolenine **31** (R = H), whilst treatment with HCl or $AlCl_3$ leads to the amino-derivative **87**.[80] Subsequently the authors extended the range of 4-azidoisoquinolines investigated and studied similar reactions for the benzodiazepines **86** with R = Me, Ph, or Cl.[81]

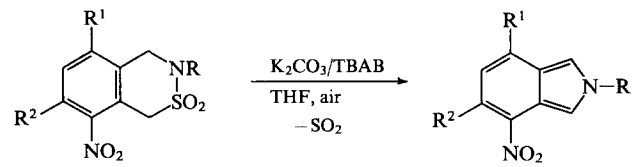


Racemic 1-ethoxy-3-(trifluoromethyl)-1*H*-isoindoles **89a, b** have been obtained by the thermal decarboxylation of oxazol-[2*H*]-one **88**.[82] It is emphasised that the reaction is possible only in the absence of dipolarophiles (for example, trifluoroacetophenone). Otherwise the latter (1,2-dipole) undergoes dipolar cycloaddition to the intermediate alkoxynitrile ylides (1,3-dipole) formed as a result of decarboxylation, which leads to dihydrooxazoles.[82]



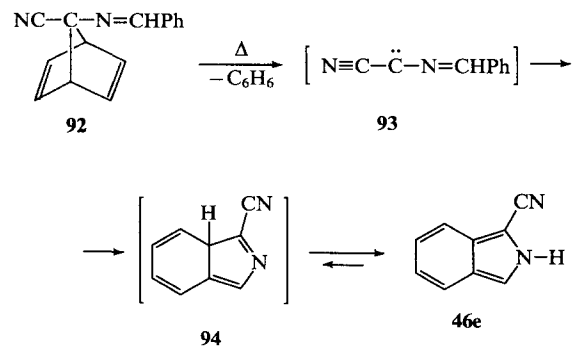
R = Et (**a**), Pr^i (**b**)

The oxidation of nitrobenzothiadiazine dioxides **90** with air in the presence of potassium carbonate and a phase-transfer catalyst (TBAB) leads to the corresponding isoindoles **91** after the elimination of sulfur dioxide. In the case of alkyl substituents at the nitrogen atom, the yields of compounds **91** are 53% – 74%, the yields falling sharply (39%) only for the *N*-phenyl derivative. If $R^1 = R^2 = H$ and R = Me, then 3-hydroxy-2,3-dimethyl-4-nitroisoindol-1-one is formed under the reaction conditions.[83]

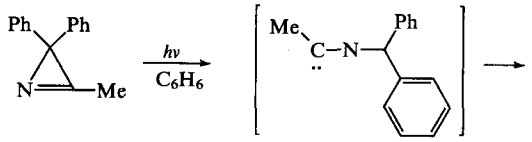


R = Me, Ph, $PhCH_2$
R^1 = H, F
R^2 = H, Cl

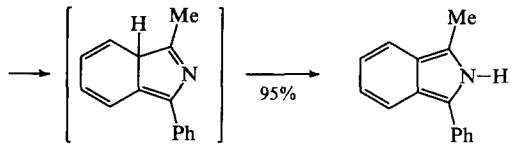
A novel approach to the synthesis of 1-cyano-2*H*-isoindole **46e** is based on the use of the norbornadiene **92** as the initial compound.[84] On heating in vacuo, the latter generates the carbene **93**, which undergoes intramolecular 1,5-electrocyclisation, forming the intermediate **94**. The subsequent 1,3-sigmatropic shift of the hydrogen atom from the carbon atom to the nitrogen atom in the intermediate **94** leads to the isoindole **46e**. The isoindole **46e** is isolated from the reaction mixture in 41% yield with the aid of preparative thin-layer chromatography and subsequent vacuum sublimation.[84]



The intramolecular heterocyclisation process, which is in many respects similar to that considered in the previous study, has been observed in the formation of the 2*H*-isoindole **98** from the azirine **95**. It has been reported[85] that the photochemical rearrangement of 3-methyl-2,2-diphenylazirine **95** to the nitrile ylide **96** and the cyclisation of the latter lead to the corresponding isoindole **98**. This reaction has been classified by the authors as a 1,5-electrocyclic process accompanied by the subsequent 1,3-sigmatropic shift of the proton in the intermediate **97**.

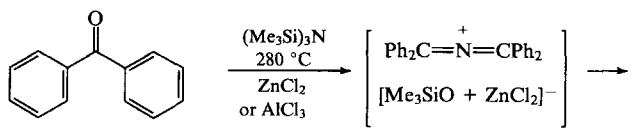


95 96

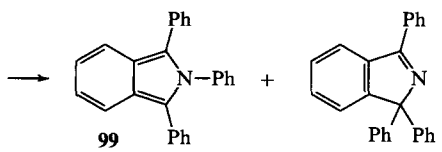


97 98

It has been shown that the cyclocondensation of benzophenone with tris(trimethylsilyl)amine at 280 °C in the presence of $ZnCl_2$ and $AlCl_3$ leads to a mixture of the isoindole **99** and 1,1,3-triphenyl-1*H*-isoindole. The yields of the isoindole **99** are 11% and 15% when zinc chloride and aluminium chloride are used respectively. The authors suggest that the intermediate in the formation of the above mixture of isoindoles is the azaallenium ion **100**.[86]

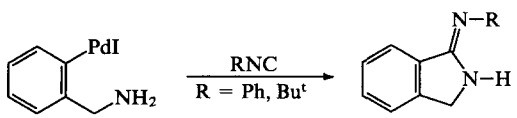


100



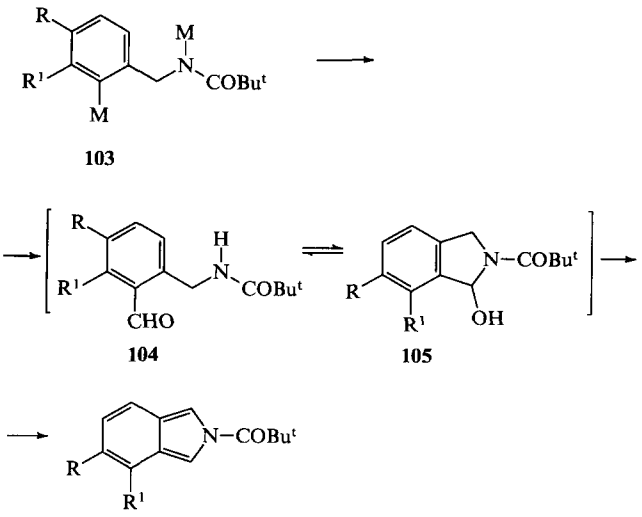
99

A method of synthesis of isoindoline imines **102** based on the insertion of isocyanides in a metal–carbon bond in the divalent palladium complex **101** has been described. The complex **101** is treated with the isocyanide in methylene chloride, after which the solvent is replaced by toluene and the reaction mixture is refluxed for 3 h. The imines **102** are isolated after making the mixture alkaline.[87]



101 102

Metallation of the amides **103** followed by treatment with DMF leads to the aldehydes **104**, which can be regarded as the open-chain form of the cyclic compound **105**. The existence of this kind of ring–chain tautomerism has been demonstrated by the NMR method. The conversion of the isoindolines **105** into the isoindoles **106** on refluxing in xylene has been described by isolating the adduct of the latter with *N*-phenylmaleimide.[88]

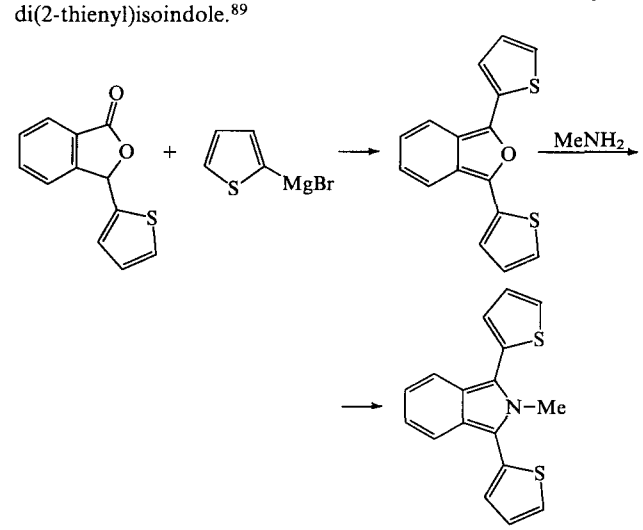


103 104 105

106

R, R^1 = H, Cl, OMe, $-OCH_2O-$
M = H, Li

1,3-Di(2-thienyl)isobenzofuran can be obtained by the reaction of 3-(2-thienyl)phthalide with 2-thienylmagnesium bromide. After oxidative opening of the furan ring and treatment with methylamine, the isobenzofuran is transformed into 2-methyl-1,3-di(2-thienyl)isoindole.[89]



III. Theoretical and physical aspects

1. Theoretical aspects

The phenomenon of isoindole has been discussed in a review[1] and in a monograph:[3] its aromaticity and high reactivity. Ideas concerning its electronic structure, with the aid of which attempts have been made to account for the above two properties which sometimes exclude one another, have been considered. In theoretical studies published recently, both semiempirical calculations (in terms of the Hückel,[90,91] PPP,[90,92] and CNDO[93], approximations) and nonempirical calculations[94] (the method of canonical molecular orbitals) have been employed; the resonance energies[90,92,95,96] various aromaticity indices,[92,95,97,98] enthalpies of formation,[91] and molecular geometry have been determined by the INDO[99] and MNDO[94] methods.

It is essential to note that a trend has arisen during the past period towards the introduction of new aromaticity indices and the derivation of correlations between the new and already existing indices. Fabian[90] proposed that the aromaticity of heterocycles, and especially isoindole, be estimated from the difference between the π-electronic energies of the heterocycle and the

corresponding iso-π-electron [9]annulenium ion. A new version of the iterative procedure of the Hückel molecular orbital method (the so-called χ-technique) has been used to calculate the HOMO energies and the enthalpies of formation of a series of heterocycles. According to this approach, the HOMO energies are 7.26 eV for isoindole, 7.71 eV for indole, and 8.08 eV for pyrrole. The result demonstrated a satisfactory agreement with the earlier calculations by Dewar and experimental data.[91] Kruszewski[92] formulated a rule on the basis of calculations for a large number of monocyclic and polycyclic heterocycles, including benzopyrroles (indole and isoindole) by the PPP method in terms of the variable β approximation. According to this rule, the condensation of an additional aromatic ring with the heterocycle gives rise to a more stable compound the greater the π-electron index of the bond involved in the process. One of the examples confirming this rule is the familiar difference between the properties of indole and isoindole. Analysis of the energy gaps by the HOMO–LUMO method for a large number of cyclic conjugated molecules (including benzopyrroles) suggested to the authors[98] the introduction of the concept of the absolute and relative 'hardness', which in their view reflects most effectively all three aspects of aromaticity: high stability, low reactivity, and the existence of ring currents. Although the 'hardness' of isoindole (0.482β) is significantly lower than that of indole (0.716β), it is nevertheless sufficient to conclude that isoindole is aromatic. Calculation of the topological resonance energies for benzopyrroles and their comparison with the analogous energy for benzene enabled the authors[95] to determine the degree of their aromaticity. It was found that the aromaticities, expressed as a percentage of that of benzene, are 83% for indole, 71% for isoindole, and only 63% for 2*H*-benzo[*f*]isoindole. Bird[97] introduced his aromaticity index from calculations based on experimental geometries of heterocyclic systems. According to this index, the aromaticity of, for example, 2-benzylisoindole **72** is slightly higher than that of benzimidazole **71** and indole **70**. New calculations of the Bird, Jalg,[100] and Pozharskii[100] structural aromaticity indices for isoindole have been published.[101] They were performed on the basis of the geometry obtained in accordance with the AM1 program; the following series of indices were obtained: 66.5 (Bird), 1.311 (Jalg), and 0.23 (Pozharskii) for indole and 68.9, 1.378, and 0.22 respectively for isoindole. It is important to note that the results of previous calculations, based on the analysis of canonical molecular orbitals, and the conclusions concerning the aromaticity of isoindoles have never been questioned, not even in recent years. However, the symmetry properties of the canonical molecular orbitals are known a priori to give rise to a significant delocalisation, which in fact hinders the comparison of the characteristics of individual chemical bonds and the structural fragments of different molecules (including isomers in terms of the position of the heteroatom of the indole–isoindole type), giving rise to various structural representations in order to reflect the specificity of their properties.[3] The above disadvantages are eliminated to an appreciable extent when localised molecular orbitals are considered. They make it possible to estimate a measure of the interaction of identical fragments with the rest of the complex molecule and hence serve as a test of the classical structural representation. This approach has in fact been applied to the indole–isoindole pair of isomers[93] and was then extended to the benzofuran–isobenzofuran and thionaphthene–benzo[*c*]thiophene.[102] Whilst confirming the conclusions concerning the aromaticity of isoindole, the authors believe that the π-electron system of isoindole is more integrated than that of indole. For the latter, they suggest that the electron system consisting of three fairly localised π-subsystems be considered: benzene rings, the C(2)–C(3) double bond, and the nitrogen atom with its electron pair.[93] Katritzky and coworkers[101] compiled and correlated the aromaticity characteristics based on geometrical, energy, and magnetic data for a series of benzo-condensed five-membered heterocycles, including condensed pyrroles.

For the vast majority of structures investigated,[103–106] there is a satisfactory correlation between different characteristics used to estimate the aromaticity but here too the uniqueness of isoindole has been manifested [the data of Terent'ev et al.[107] (10 characteristics) virtually deviate from these correlations]. In a comparative quantum-chemical study of the polarisabilities (α) and hyperpolarisabilities (β) of a series of 'positional' isomers (including indolizine, indole, and isoindole), the authors[103] noted that the structural differences have a significantly smaller effect on α (109, 107, 109 a.u. respectively) than on β (2.93, −2.89, and −5.93 a.u. respectively). A theoretical study has been made[99] by the INDO method (with complete optimisation of the geometry) of the populations of the conformations of the still unknown 2-amino-2*H*-isoindole and it has been shown that the disposition of the free electron pair of the nitrogen atom of the amino-group at right angles to the plane of the bicyclic molecule is most favourable. In the course of the development of quantitative approaches to the resonance theory, Pipeng and Wengui[96] calculated the resonance energies of the various tautomeric forms in order to predict the preferred tautomer and the tendency towards a shift of the tautomeric equilibrium in a series of related structures. 1-Amino-2*H*-isoindole was included within the range of their interests. It exists in the form of the 3-amino-1*H*-tautomer,[1] which was confirmed on the basis of theoretical conclusions.

2. Spectroscopic data

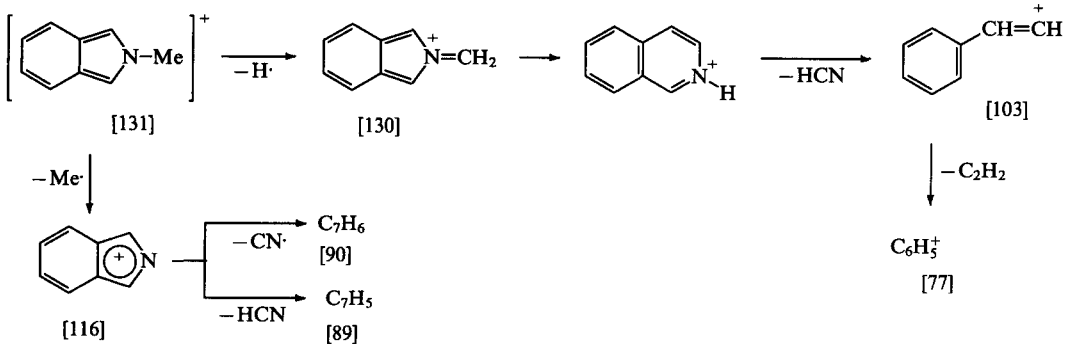
Spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, and UV) for various isoindoles have been described in detail in reviews[1,2] and in monographs.[3] The period which has elapsed has been characterised by the accumulation of quantitative information about the spectra of isoindoles. We therefore quote here only references to publications containing fairly extensive data on the spectroscopic characteristics of new isoindoles: ^{1}H NMR,[5,35,36,39,61,72,84,85] ^{15}N NMR,[99,104] ^{13}C NMR,[4,5] IR,[5,35,36,39,61,69,85,105] and UV.[35,36,39,61,85]

As regards the interpretation of studies on electronic spectra, the latter were surveyed in previous reviews.[1,2] The electronic structure of phthalocyanines without a central metal atom has been investigated[94] by means of nonempirical and semiempirical methods. The study was combined with the analysis of the constituents of this system: benzene, pyrrole, and isoindole. The electronic spectra of dimethinecyanines and merocyanines based on 1-dimethylamino-2-phenylisoindole have been discussed.[106] It has been noted that positive solvato-chromism is characteristic of merocyanines.

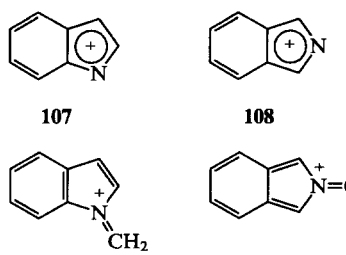
3. Mass-spectra of isoindoles

An attempt has been made in recent years to fill the gaps in the mass-spectrometric study of isoindoles. The decomposition of a series of isoindoles under electron impact, including those condensed along the *a* face, has been analysed.[107] It follows from these data that the molecular ion derived from 2-methylisoindole has the highest intensity in the spectrum and that the intensities of the peaks due to the other ions formed on fragmentation do not exceed 50% of that of M^+. The spectra have the usual overall form for aromatic compounds and confirm the electronic structure of isoindole put forward by Kovtunenko et al.[93] The appreciable π-bonding via the nitrogen atom in 2-methylisoindole has been demonstrated by the fact that the introduction of phenyl substituents in the 2-position (i.e. for 2-phenylisoindole) lowers the intensity of M^+ to 93% as a consequence of the competing conjugation of the free electron pair of the nitrogen atom with the benzene ring. In 2-(*p*-anisyl)isoindole, this type of competition has a smaller effect owing to the positive mesomeric effect of the methoxy-group. Comparison of the mass-spectrometric decomposition of 1-methylindole[107] with that of the isomeric 2-methylisoindole can also serve as confirmation of the postulated electronic structure of isoindole.[93] The stability of the ion **107** is lower than that of the ion **108**, which indicates a greater degree of

Scheme 4



inter-ring conjugation in the isoindole system — indicated by the values of $[M-CH_3]^+/M^+$. On the other hand, the intensity of the $[M-H]^+$ peak is much higher for *N*-methylindole than for *N*-methylisoindole, since here one is dealing with systems of a different kind: **109** and **110**, within the limits of which the π-bonding via the nitrogen atom is ruled out. In this case, the ion **110** loses the advantages of isoindole as an integrated 10π-electron system and is in fact an open-chain polyene, while the ion **109** remains aromatic in view of the aromaticity of the benzene ring, which to a large extent determines the stability of the indole system as a whole.[93] The routes leading to the fragmentation of different isoindoles have also been indicated,[107] for example, we have for *N*-methylisoindole.



107 **108**

109 **110**

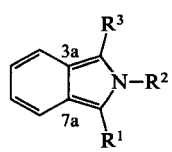
The mass spectra of new 2-R-isoindoles (R = Bu^t, Bu^{t}CH$_2$, PhCH$_2$, adamantyl) have also been used for the purpose of their identification (Scheme 4).[5]

4. X-Ray diffraction data

Fairly numerous studies on the X-ray diffraction of isoindoles, which permit objective inferences about their geometry, have been published.[39,54,93,105,108–110] These data are presented in Table 1 and they all confirm the conclusion that isoindole is aromatic as a 10π-electron system. The molecules are planar. For example, the deviation of the atoms in 2-methylisoindole from the mean square plane passing through the atoms of the bicyclic system do not exceed 0.015(4) Å.[108] The tabulated data demonstrate the similarity of the bond lengths in the benzene fragment of isoindole structures and in naphthalene [in the latter, the bond lengths are 1.410 Å for C(3a)–C(7a); 1.425 Å for C(3a)–C(4); 1.361 Å for C(4)–C(5); and 1.421 Å for C(5)–C(6)], which in an argument in support of the delocalisation of the electron density.[108,109] The C(3a)–C(4) and C(7)–C(7a) bond lengths are close to those in classical aromatic compounds and differ significantly from the values characteristic of a single bond. This means that the electronic structure of isoindole cannot be represented by two independent components (a combination of butadiene and pyrrole). These two components are conjugated. The C–N bond lengths in the pyrrole fragment of the first four structures (see Table 1) are somewhat smaller than in pyrrole itself (1.383 Å). On the other hand, the C(3)–C(3a) bond lengths in isoindoles are somewhat greater than in pyrrole (1.371 Å). This probably indicates a greater delocalisation of the π-electron density in the pyrrole component of the bicyclic system compared with the parent heterocycle.

X-Ray diffraction of isoindole derivatives, including 2-methylisoindole, confirmed their electronic structure put forward on the basis of the analysis of localised molecular orbitals.[93]

Table 1. X-Ray diffraction data for isoindole derivatives.



2*H*-Isoindole			Bond length/Å										Ref.
R^1	R^2	R^3	1–2	2–3	1–7a	3–3a	3a–7a	7a–7	3a–4	6–7	4–5	6–5	
H	Me	H	1.362	1.360	1.380	1.382	1.429	1.420	1.432	1.347	1.357	1.416	93,108
CN	Me	H	1.374	1.348	1.407	1.395	1.426	1.412	1.405	1.355	1.369	1.422	54
H	PhCH$_2$	H	1.362	–	1.384	–	1.429	1.416	–	1.357	–	1.415	109
H	Bu^{t}CH$_2$	H	1.360	–		–	1.431	1.412	–	1.358	–	1.406	110
Et	Pr	MeOOCCH=C(COOMe)	1.381	–	1.394	–	1.431	1.417	–	1.359	–	1.426	39
CHO	H	Ph	1.376	1.348	1.412	1.428	1.420	1.414	1.414	1.365	1.367	1.409	105

Note. The bond lengths are 1.468[93,108] and 1.460[54] for N–Me, 1.405[54] for C–CN, and 1.458[110] for N–CH$_2$.

IV. Chemical properties

Isoindole and its derivatives are distinguished by a high reactivity. This is indicated by experimental data[111] on the rate constants for the acid-catalysed detritiation of a series of heterocycles (including *N*-methylisoindole). For example, in the indolizine (3-position), *N*-methylisoindole (1-position), and indole (3-position) series, the partial rate factors for the exchange reactions are in the proportions 1798.9 : 11 992.7 : 1. The authors calculated the values of σ^+ for the above heterocycles (−1.94, −2.04, and −1.57 respectively) and found that isoindole is one of the most reactive compounds among the known heterocyclic systems.[111] A mechanism has been proposed[112] for the tautomerism of 1,3,4,7-tetramethyl-2*H*-isoindole, taking into account the solvent effect on the basis of its spectrophotometric study.

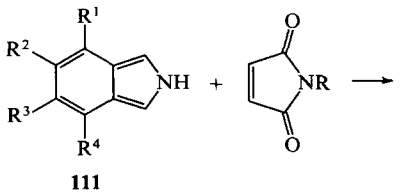
1. The Diels–Alder reaction

One of the most characteristic properties of isoindole and its derivatives is their ability to enter readily into the [2 + 4]-cycloaddition reaction. Furthermore, the usual method for the identification of unstable isoindoles involves their conversion into Diels–Alder adducts with maleimide derivatives.[1–3] We may mention in this connection a review[113] of the quantum-chemical methods used to predict the stereospecificity of the Diels–Alder reaction.

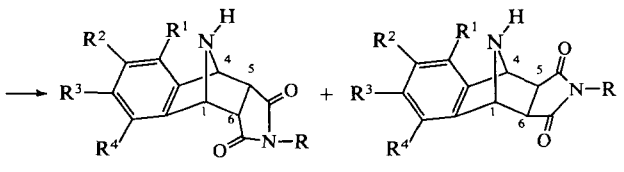
a. The interaction of isoindoles with maleimide derivatives

During the period considered, numerous communications were published in which mention is made of the adducts of isoindoles with maleimide derivatives. Certain generalisations facilitating the identification of the isomers formed are also known.[114,115]

NH-Isoindoles. The isoindoles **111** unsubstituted at the nitrogen atom give rise readily and in high yields (on average 80%) to a 1 : 1 mixture of the *endo*-adduct **112** and the *exo*-adduct **113** in which the endo-isomer predominates.[13,14,16,18] It is sometimes possible to separate these mixtures by chromatography,[16] but usually they are converted smoothly, after being kept for a short time in solvents (for example, in xylene), into the corresponding *exo*-isomers **113**.[14,16] The isomerisation **112** → **113** also occurs with participation of the solvent and under much milder conditions: at room temperature in DMSO over a period of 30 min (the ^{1}H NMR spectrum of the solution of the adduct **112** reveals its complete conversion into compound **113**).[16]

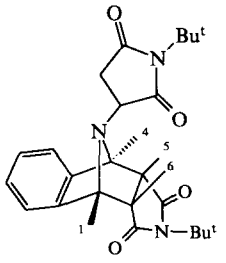


111



endo-**112** *exo*-**113**

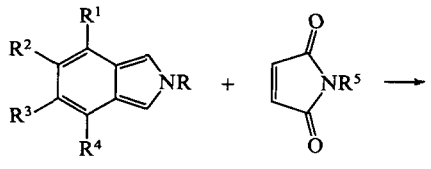
When the isoindole **14** is allowed to react with *N*-*tert*-butylmaleimide, the formation of a 1 : 2 adduct was observed. On the basis of spectroscopic characteristics, the structure **114** was attributed to it.[16]



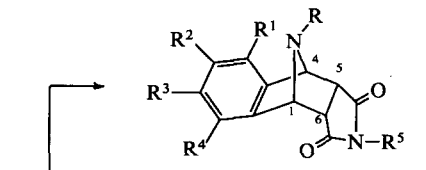
114

2-R-Isoindoles. The isoindoles **115** substituted at the nitrogen atom readily form 1 : 1 adducts.[6–8,19,20,79,116–118] Under kinetically controlled reaction conditions,[116] one then obtains exclusively the *endo*-isomers **116**,[7,8,19,79,88,116–118] while under thermodynamically controlled conditions the *exo*-isomers **117** are produced.[19,116–118] The diene reactivity of the isoindoles **115** is determined by the nature of the substituents in the benzene component of the bicyclic system; a decrease in the diene reactivity has been observed in 2-*tert*-butyl-5-nitroisoindole[7] and 2-R-4,5,6,7-tetrachloroisoindole,[118] while in 2-R-dibenzo[*e*,*g*]isoindole[6] it is not manifested at all on interaction with maleimide derivatives. It has been shown[118] that the Diels–Alder addition to 2-R-4,5,6,7-tetrachloroisoindole may be initiated by adding a catalyst—a Lewis acid ($AlCl_3$). The configurational stability of the *endo*-isomers depends to a large extent on the nature of the substituent at the nitrogen atom of the 7-azabenzonorbornene system **116**.

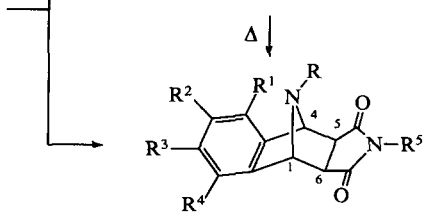
If this is an alkyl group, then the isomerisation **116** → **117** takes place relatively readily (for example, on refluxing in alcohol or xylene).[19,116–118] In the case of an aryl substituent, the attempts to isomerise the *endo*-isomer to the *exo*-isomer were unsuccessful.[119] The example of the *endo*-adduct of the isoindole **20b** is remarkable:[19] on refluxing in xylene or diglyme, isomerisation was not observed and only after heating for 19 h in Carbitol was it possible to achieve the isomerisation with 8% yield. The adducts **116** obtained from the isoindoles **106** cannot be isomerised to the corresponding *exo*-compound **117**. However, if the preliminary hydrolysis of the *N*-acyl group is carried out, then the isomerisation of the *exo*-adduct **113** proceeds extremely readily.[88] A series of unstable isoindoles **115** have been characterised in terms of the adduct **116**.[19,88,117] The unstable methyl ester of isoindole-2-acetic acid has been identified via the adduct with *N*-phenylmaleimide, to which the *exo*-structure was attributed without proof.[20] It has been shown[116] that the ^{1}H NMR spectra of the adducts **116** and **117** are more complex for R = Me than might have been foreseen: they demonstrate the occurrence of the *syn*- and *anti*-isomerism of the methyl group at N(7). The isomerism disappears when the lanthanide shift reagent Eu(fod)$_3$ is added to the test solution. Furthermore, the constant $J \approx 2$ Hz, for spin–spin coupling of the protons across four σ-bonds in the *W*-conformation, has been noted. All the features of the cycloaddition of maleimides to the isoindoles **115** are characteristic of their 5-aza-analogue 6-ethoxycarbonyl-2-methyl-2*H*-pyrrolo[3,4-*c*]pyridine[120] and of 2-methyl-6,7-diazabenzo[*f*]isoindole {7-methyl-1,4-diphenyl-7*H*-pyrrolo[3,4-*g*]-phthalazine}.[74]



115



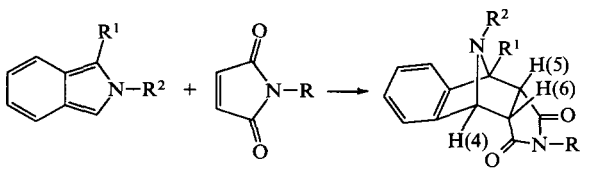
endo-116



exo-117

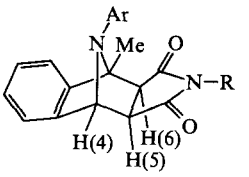
1,2-Di- and 1,2,3-tri-substituted isoindoles. The identification of the isomeric Diels–Alder *exo*- and *endo*-adducts comprising isoindoles **118** asymmetrically substituted in the pyrrole component in terms of the spin–spin coupling pattern of the H(4), H(5), and H(6) protons in the ^{1}H NMR spectra becomes more complicated, which leads to possibile erroneous assignment of the configurations of the isomers.[35, 114, 121]

As a rule the 1 : 1 adducts **119** with the *endo*-configuration are formed from the type **118** isoindoles on interaction with maleimides under the conditions of kinetic control.[31, 32, 35, 114, 122] The majority of the isoindoles **118** investigated do not withstand the conditions of thermodynamically controlled cyclo-addition. Only one instance of the formation of the *exo*-adduct from such isoindoles is known — a series of compounds of structure **120** have been obtained from 2-methyl-1-phenylisoindole.[122] The corresponding *endo*-adducts are configurationally stable and do not isomerise to the *exo*-isomers **120**. The isoindoles **118c** unexpectedly react with maleimides, forming the dihydronaphthalene derivatives **121** under mild conditions.[114, 123] The isoindoles **118a, b** react with maleimides, affording the 1 : 2 adducts **122**, the formation of which is interpreted [31, 32, 124] as the initial Michael addition of one maleimide molecule with subsequent addition, this time of the Diels–Alder type, of a second dienophile molecule to the 1,2,3-trisubstituted isoindole formed. The establishment of the *endo*-configuration of the type **122** adducts is fairly difficult and has been carried out usually with the aid of X-ray diffraction [32] or from indirect ^{1}H NMR spectroscopic data.[31, 32, 124]

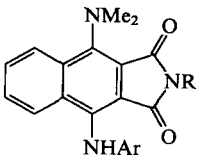


118a–c **119**

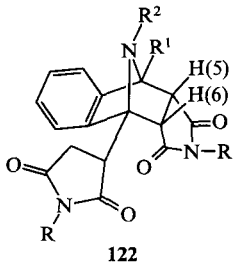
118a: R^1 = OMe, OEt
118b: R^1 = Ph
118c: R^1 = NMe_2



120

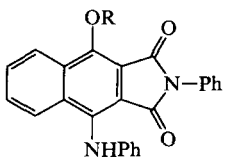


121

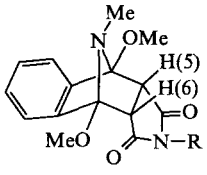


122

A similar problem was solved in the determination of the configuration of the adduct of the unstable 1,2,3-trisubstituted isoindoles **24** and **28** with maleimide. The interaction of a solution of compound **24b** with phenylmaleimide at room temperature afforded a mixture of two naphthalene derivatives: **123a** (10%) and **123b** (54%).[23] On the other hand, it has been shown [27] that type **28** isoindoles form with maleimides type **124** *endo*-adducts in a low yield (not more than 25%).



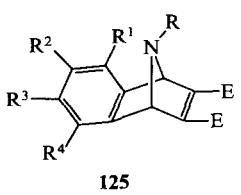
123a–b
R = H (**a**), $SiMe_3$ (**b**)



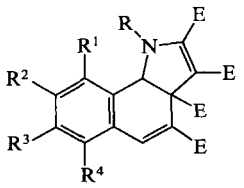
124

b. The interaction of isoindoles with ethynedicarboxylic acid esters

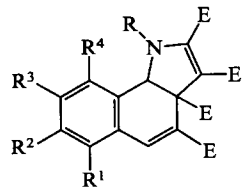
When the dimethyl ester of ethynedicarboxylic acid [acetylenedicarboxylic acid] (DMAC) is added to type **115** isoindoles, the latter give rise readily and in high yields to the 1 : 1 adducts **125** in the first stage. These can then be converted (in the presence of an excess of DMAC) into the 1 : 2 adducts **126** (**127**). The tendency to form compounds **127** is apparently determined by the bulk of the substituent R. For example, 2-*tert*-butyldibenzo-[*e*, *g*]isoindole **6a** does not form a type **126** adduct at all, whereas for its benzyl analogue **6b** under similar conditions the reaction path giving rise to such an adduct is the main one (the yield of compound **126** is 68%), the 7-azabenzonorbornadiene derivative **125** being formed only as a side product (yield 23%).[6]



125

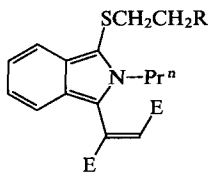


126



127 E = COOMe

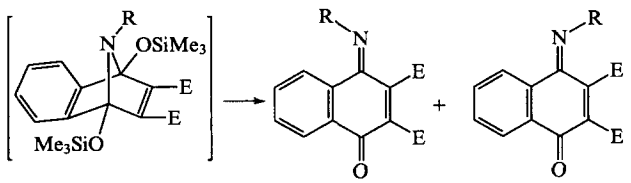
2-*tert*-Butyl-5-nitroisoindole,[7] 2-*tert*-butylbenzo[*f*]isoindole,[8] and the isoindoles **74**, **75**,[120] and **77**[35] afford type **125** products. A separable mixture of complex three-dimensional molecules with the *syn*- and *anti*-configurations is formed from the terminal pyrrole rings of the isoindole **74** when the latter reacts with DMAC.[35] The isomeric compounds **126** and **127** were isolated on treating with an excess of DMAC the corresponding type **125** adduct obtained from 2-methyl-5-azaisoindole.[120]



128a, b

128a: R = H, 51%

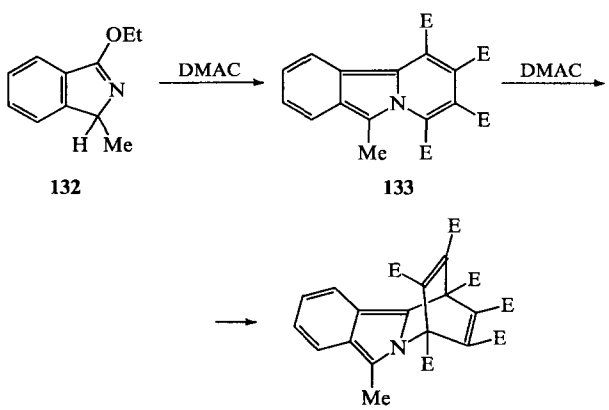
128b: R = OH, 33%



129 **130** **131**

E = COOMe

7-Methyl-1,4-diphenyl-7*H*-pyrrolo[3,4-*g*]phthalazine, a derivative of 2*H*-6,7-diazabenzo[*f*]isoindole, reacts similarly, forming initially a type **125** adduct and then a type **126** adduct.[74] Interaction of the isoindoles **40a, b** with DMAC is interesting. They give rise to the adducts **128a, b** with retention of the 10π-electron system.[39] On interaction with DMAC, the isoindoles **24b, c** afford the isomeric *syn*- and *anti*-imines **130** and **131** via intermediate type **129** adducts.[25,26] The isoindole **132** reacts with DMAC to form initially the 1:2 adduct **133**, while in the presence of an excess of DMAC the product is the 1:3 adduct **134**.[29] In contrast to compounds **24b, c**, the isoindole **24a** reacts with DMAC to form the dimethyl ester of (2-methyl-1-oxo-3-trimethylsiloxy-1,3-dihydroisoindol-3-yl) fumaric acid in 53% yield.[26]

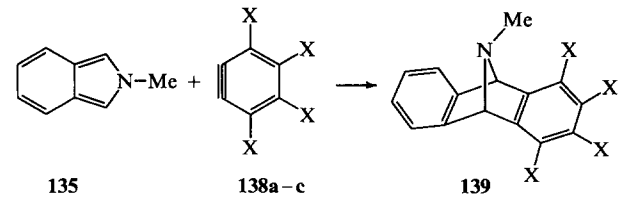


132 **133** **134**

E = COOMe

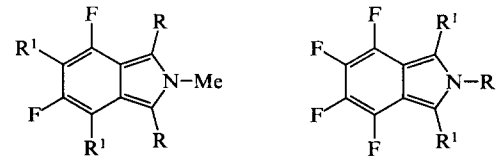
c. The addition of dehydrobenzenes

The study of the addition of dehydrobenzenes and dehydronaphthalenes to isoindoles has recently acquired special significance in view of the discovery of effective reagents for the deamination of 7-azabenzonorbornadiene derivatives formed as a result of this reaction.[125] Such deamination constitutes a convenient method of synthesis of angularly and linearly condensed polycyclic hydrocarbons containing various substituents, which are difficult to obtain.[78,126-128] The isoindoles **6a, b** and **135** react readily with the arynes **138b, c** respectively, affording high yields of 1:1 adducts.[6,125-128] The isoindoles **7** and **8** likewise give rise to similar adducts but this time with the 1:2 composition, the imine bridges in these structures assuming the *anti*-configuration relative to one another.[10] The interaction of the isoindoles **137a, b** with the arynes **138** produces 1:1 adducts, but in all cases the 7-methyl-7-azadibenzonorbornadienes are obtained in significantly lower yields than the *N*-benzyl derivatives.[129] Complex polycyclic systems are formed on interaction with the naphthynes **140** and **141** and the 1,5- and 2,6-naphthadiynes **142** with the isoindoles **135**, **136a-c**, and **137a, b**. The last two naphthadiynes react with the isoindoles **135** and **137a** affording moderate yields of the 2:1 adducts **143a, b** and **144** with the *anti*-configuration of the imine bridges.[127,128]



135 **138a-c** **139**

X = H (a), Me (b), Cl (c)

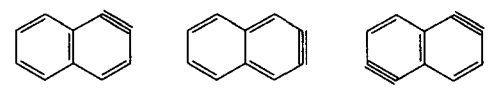


136a-c

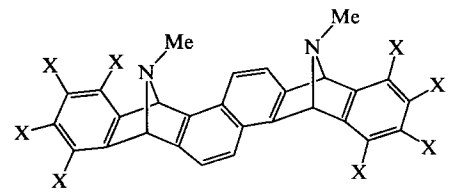
136a: R = H, R^1 = Cl
136b: R = Me, R^1 = Cl
136c: R = H, R^1 = H

137a-c

137a: R = Me, R^1 = H
137b: R = Bn, R^1 = H
137c: R = Me, R^1 = Me

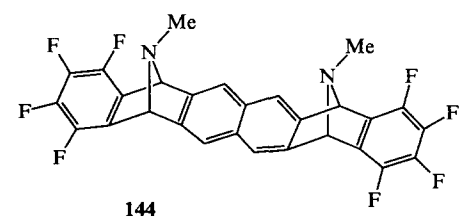


140 **141** **142**



143a, b

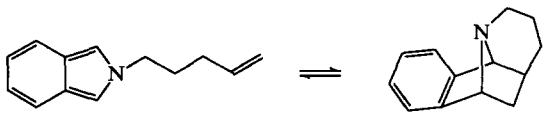
X = H (a), F (b)



144

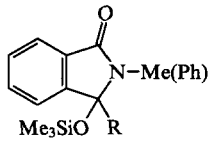
d. The addition of other unsaturated compounds

The intramolecular addition of a double bond to a diene isoindole system has been described:[28] on heating for 8 h (at 150 °C), *N*-(4-pentenyl)isoindole **29** partially forms the adduct **145**. Judging from ^{1}H NMR spectroscopic data, the ratio of the open-chain and cyclic forms which can be obtained at this temperature is 1 : 1, whereas after heating to 200 °C the equilibrium shifts towards the open-chain form **29**. On slow fractionation of the unpurified isoindole **29** at a reduced pressure, it is possible to obtain the pure adduct **145** in 80% yield.



29 **145**

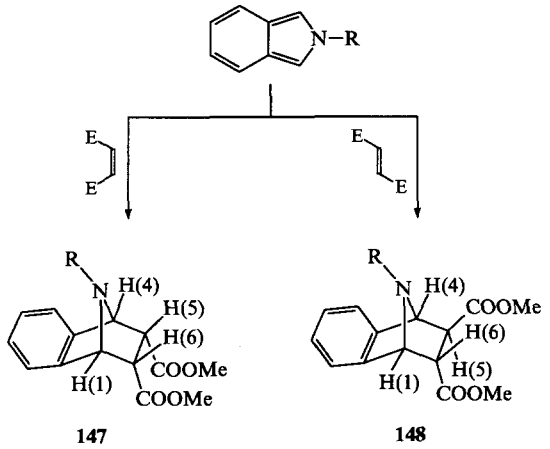
It is of interest that a similar cyclisation is not observed for *N*-(5-hexenyl)isoindole.[28] The 1,3-di(trimethylsiloxy)isoindoles **24a, b** interact with methyl acrylate,[26] methyl vinyl ketone,[26] 1,2-dibenzoylethene,[23] and dimethyl maleate[26] to form exclu-sively the lactams **146a–e**. When dibenzoylethene is used, the isoindole **24a** affords a 27% yield of compound **146b** and traces of compound **146a**, while the isoindole **24b** shows the opposite behaviour, affording 51% of compound **146a** and traces of compound **146b**.[23]



146a–e

146a: R = C(Bz)CH=C(Ph)OSiMe$_3$
146b: R = CH(Bz)CH$_2$Bz
146c: R = CH$_2$CH$_2$COOMe
146d: R = CH(COOMe)CH$_2$COOMe
146e: R = CH$_2$CH$_2$Ac

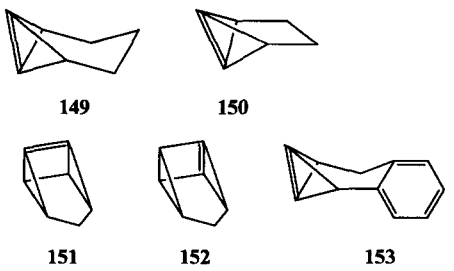
N-Methyl- and *N*-aryl-isoindoles readily combine with dimethyl esters of maleic and fumaric acids, affording the diastereoisomeric Diels–Alder adducts **147** and **148**. The high configurational stability of the *endo*-adduct **147** has been noted.[130]



147 **148**

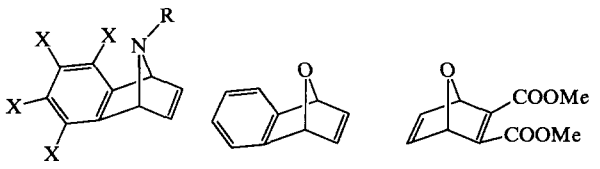
E = COOMe

The synthesis of the structures obtained from 2-methyl-,[132] 1,2-dimethyl-,[131,132] and 1,2,3-trimethyl-2*H*-isoindoles[131–135] and the alkenes **149–153** has been described in a series of communications by German workers.[131–135] In the case of the alkenes **151–153**, one may expect theoretically the appearance of stereoisomers, although they have been actually identified only in the case of the adducts derived from compounds **151**[135] and **153**.[131,134]



149 **150** **151** **152** **153**

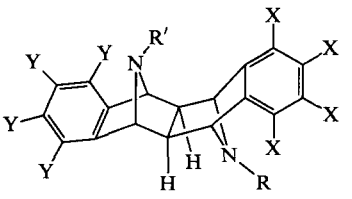
Prolonged refluxing of *N*-benzyl-4,5,6,7-tetrafluoroisoindole and the isoindoles **135** and **137a** with 7-R-7-azabenzonorbornadienes **154a–d** under a nitrogen atmosphere gives rise to between 6% and 61% yields of the 1 : 1 adducts **157** with the *exo, endo*-junction between the cyclic systems.[134] Equally elegant structures have been synthesised[79] by means of cycloaddition to the isoindole **85.**



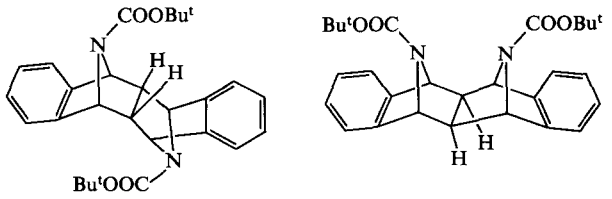
154a–d **155** **156**

154a: X = F, R = Me
154b: X = F, R = Bn
154c: X = Cl, R = Me
154d: X = H, R = COOMe

For example, it has been shown that the addition of the substituted 7-azabenzonorbornadiene affords a mixture of the diastereoisomeric adducts **158** and **159** in proportions of 2.3 : 1.[79] On the other hand, the addition of the alkene **155** takes place with the preferential formation of the *exo, exo*-adduct **160**. The *exo, exo*-diastereoisomer is also formed exclusively in 74% yield on interaction with the alkenes **156.**

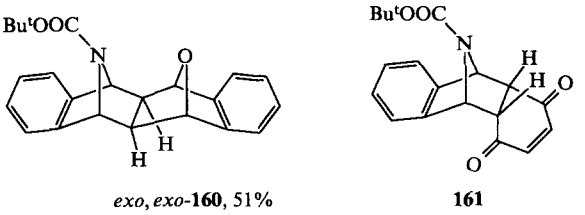


exo, endo-**157**



endo, exo-**158** *exo, exo*-**159**

The interaction of 1,4-benzoquinone with the isoindole **85**, gives rise to 1 : 1 *endo*-adduct **161** in 62% yield.[79]



exo, exo-**160**, 51% **161**

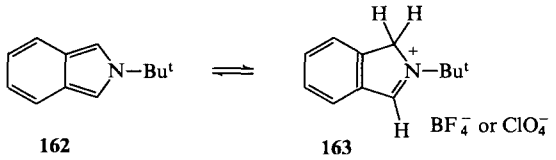
2. Electrophilic attack on isoindoles

a. Protonation

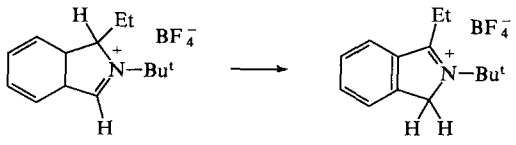
The available information about the basicity of isoindoles is extremely limited. The study of the basicity[36] of 2-R-isoindoles **4** by potentiometric titration in nitromethane showed the *N*-aryl-isoindoles are weaker bases by 5–6 orders of magnitude than *N*-methylisoindole (ΔpK_a† of the latter is 1.2). For comparison, we may note that in nitromethane ΔpK_a is +5.69 for pyridine and −0.6 for piperidine. For a series of *N*-(4-R-phenyl)isoindoles (R = H, Me, OMe, Br), the ΔpK_a depend linearly on the Hammett constant σ_p.[136] The loss of a proton by the isoindolium salts **33**, **36**, **56**, and **163** and its addition to isoindoles are reversible processes which can be readily detected from UV and ^{1}H NMR spectra. Thus the protonation of isoindoles entails the loss of the long-wavelength absorption [band C (Ref. 1)] in the electronic spectrum and an increase in the intensity of band B. In a number of instances, it is possible to obtain a high yield of isoindolium salts in a crystalline state from isoindoles: for example, from the isoindoles **5**[8] and **162**[11,137] 2-*tert*-butyl-5-nitroisoindole,[7] and 1-alkylthio-2-aryl-3-trifluoroacetylisoindole.[138]

b. Alkylation

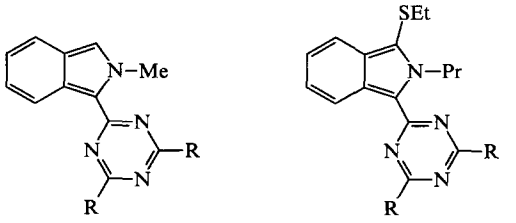
The alkylation of 2-R-isoindoles, which are incapable of tautomeric transformations, takes place at the C(1) carbon atom with formation of type **166–168** indoles via compounds **163–165**. Thus treatment of 2-methylisoindole **135** with 2-chloro-4,6-difluoro-[139] or 2,4,6-trichloro-1,3,5-triazine[140] affords moderate yields of C(1)-alkylated isoindoles **166a, b**. The same compounds react with the isoindole **40a** to form the trisubstituted isoindoles **167**.[141]



162 **163**

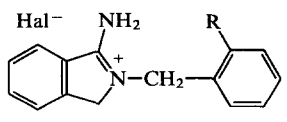


164 **165**



166a, b
R = F (**a**), Cl (**b**)

167

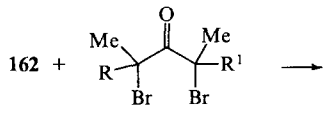


168a, b
R = H (**a**), CN (**b**)

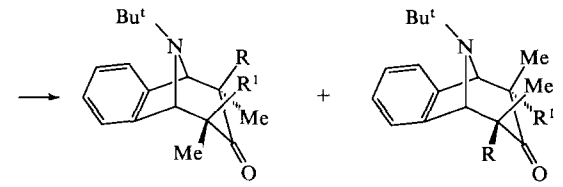
† ΔpK_a is the difference between the pK_a for a standard (diphenylguanidine) and the given substance.

The alkylation of the isoindole **162** with the Meerwein reagent leads initially to a high yield of the salt **164**, which isomerises to the more stable cation **165**.[11,137] It has been shown that alkylation of compound **162** with the aid of methyl iodide in methylene chloride gives rise to type **165** salts in 19% yield.[11]

The interaction of the isoindole **162** with 2,4-dibromo-3-pentanones **169a–c** in the MeCN–Cu–NaI system (method A) or the dioxane–Zn–CuCl–ultrasound system (method B) can probably be regarded as reductive alkylation.[142] The diastereoisomeric structures **170** and **171**, resembling tropanone, are then formed in 50%–60% yields (**170a** : **171a** = 2.4 : 1; **170b** : **171b** = 2.2 : 1). The use of the ketones **169a, b** entails the application of method A, while the use of compound **169c** entails the application of method B.[142] It has been shown[143,144] that the alkylation of the aminoisoindole **65a** by benzyl chlorides involves exclusively the endocyclic nitrogen atom with formation of aminoisoindolium salts of type **158a, b**. The alkylation of compound **65a** by α-haloketones proceeds similarly.[143]



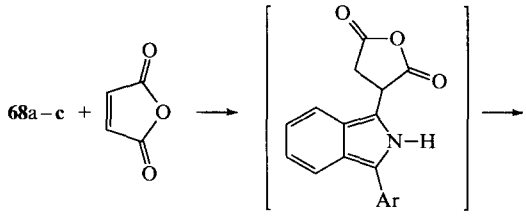
169a–c
169a: R = H, R^1 H
169b: R = Me, R^1 = H
169c: R = Me, R^1 Me



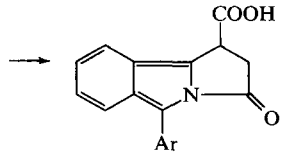
170a–c **171a–c**

c. Other electrophilic addition reactions

Maleic anhydride reacts in ether with the isoindoles **68a–c** unsubstituted at the nitrogen atom. The intermediate **172** formed initially via a Michael reaction recyclises with formation of derivatives of the pyrrolo[2,1-*a*]isoindoles **173**.[71] A process similar to that described above takes place in the interaction of the isoindoles **4** (R = Et), **5**, and **162** with azodicarboxylic acid esters.[7,8,145] The Diels–Alder reaction has not been observed in this instance, the Michael addition occurring with retention of the isoindole structure.

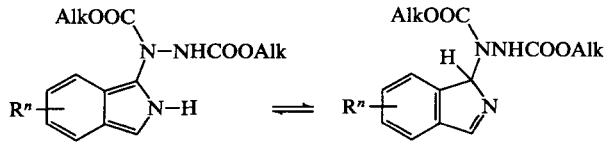


172

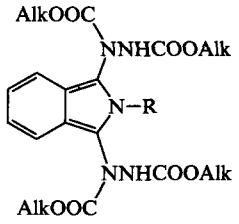


173

The added hydrazine-1,2-dicarboxylate diester residue activates the isoindole structure **174**. As a rule, the reaction proceeds further, which leads exclusively to the 2:1 adduct **176**. The 1:1 adducts have been isolated only for 2-*tert*-butyl-5-nitroisoindole, the electronic system of which is somewhat deactivated by the presence of the nitro-group.[7] On the other hand, in the case of the isoindoles **4** (R = Et, Bu^t) and **5**, compounds of type **176** are formed exclusively.[8,145] Interesting results have been obtained in a study of the interaction of azodicarboxylic acid esters with NH-isoindoles **13** ($R^1 = R^3 = Me$, $R^2 = R^4 = H$, and $R^1 = R^2 = R^3 = R^4 = Me$),[145] **15** and **16**.[13] In the first three cases, the corresponding 1:1 adducts **174** are formed exclusively in 70%, 59%, and 45% yields, demonstrating the occurrence of prototropism (for example, in solvents of different polarity different contents of the isoindole structure **174** and the isoindolenine structure **175** are observed). On the other hand, the isoindole **16** affords under these conditions a 38% yield of the 2:1 adduct, which exists predominantly in the isoindolenine form.[13] The appearance of the isoindolenine tautomer has been explained by the formation of an intramolecular hydrogen bond between the ring nitrogen atom and the NH group of the hydrazine side group.

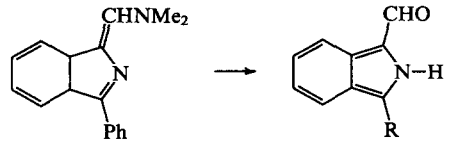


174 **175**

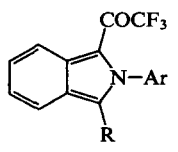


176

Electrophilic substitution in the isoindole series has been investigated in formylation[105] and trifluoroacetylation reactions.[138] The attempts to introduce the isoindole **68a** into Mannich, nitrosation, and nitration reactions were unsuccessful.[19] 1-Phenylisoindole **68a** reacts with the Vilsmeier reagent and gives rise to a 68% yield of 1-(*N*,*N*-dimethylaminomethylidene)-3-phenylisoindolenine **177**, which gives the 1-formyl-3-phenylisoindole **178** in 48% yield on alkaline hydrolysis.[105] *N*-Tolylisoindoles and 1-alkylthio-2-arylisoindoles **37** interact in pyridine with trifluoroacetic anhydride, forming the trifluoroacyl derivatives **179a, b**.[138]



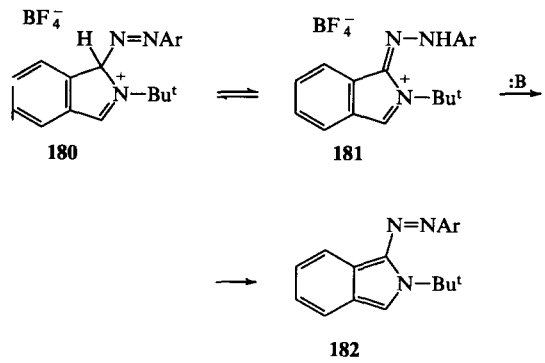
177 **178**



179a, b

R = H (a), SAlk (b)

Isoindoles readily enter into the azo-coupling reaction in aqueous alcohol[19] or acetone[6,9,10,137] solutions exclusively via the pyrrole component of the bicyclic system. In the latter case, it is possible to observe the formation of the salt-like intermediate adducts of types **180** and **181**, which are converted into type **182** azo-dyes after treatment with bases.

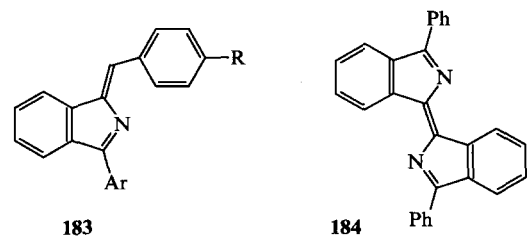


180 **181** **182**

This reaction has been investigated particularly widely in relation to the isoindole **162** with which six arenediazonium salts have been coupled.[11,137] Only *p*-nitrobenzenediazonium tetrafluoroborate has been coupled with the isoindoles **6a, b**,[6] **8**,[10] **9**, and **10**[9] and both type **182** azo-dyes and intermediate salts have been obtained. In the absence of steric hindrance in the initial isoindoles, the yields of the azo-dyes are as a rule nearly quantitative. An interesting reaction has been observed with the isoindole **182** (Ar = 4-ClC_6H_4) on treatment with *p*-nitrobenzenediazonium tetrafluoroborate: the salt **180** (Ar = 4-$O_2NC_6H_4$) was obtained in 39% yield, i.e. the phenylazo-group containing a chlorine atom was displaced and was replaced by the *p*-nitrophenylazo-group.[11] The coupling by the classical method of the isoindole **68a** unsubstituted at the nitrogen atom with toluene-*p*-diazonium chloride has been described:[19] the corresponding azo-dye was isolated in 63% yield and has λ_{max} = 467 nm.

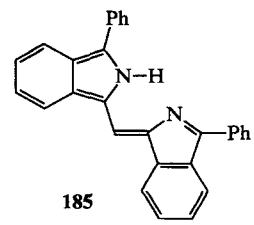
3. Condensation with aldehydes and their derivatives

In the interaction of the isoindoles **68b, c** with benzaldehyde and anisaldehyde in the presence of akali, type **183** isoindolenines were obtained in 13%–30% yields.[71] Under these conditions, the isoindole **68a** gives only small amounts of the yellow dimer **184**,[66] which can also be obtained in 53% yield by treating the isoindole **68a** with nitrous acid[19] or simply by refluxing in benzene.[71] The application of the latter operation to the isoindole **68b, c** makes it possible to isolate the corresponding dimers in yields not exceeding 15%. In the Mannich reaction with the isoindole **68a**, the dimer **184** is formed in 25% yield together with the blue pigment **185** (20%).[19]



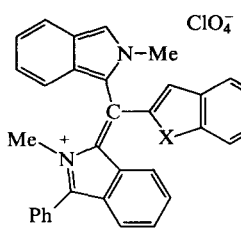
183 **184**

The same blue pigment has been isolated as a result of the condensation of compound **68a** with paraformaldehyde in an alkaline medium (yield 15%) or in 63% and 44% yields on condensation of compound **68a** in an acid medium with the isoindole **178** or the isoindolenine **177** respectively.[19]



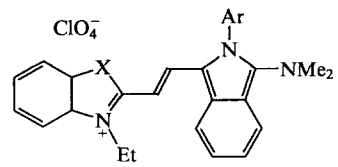
185

The condensation of benzaldehyde and a series of heterocyclic aldehydes with 2-methyl-1-phenylisoindole led to a series of coloured bis(2-methyl-1-phenylisoindol-3-yl)aryl(heteroaryl)-methanes **186**, which have been studied in detail both theoretically and spectroscopically.[146] The methods of synthesis of the dimethinecyanine and merocyanine dyes **187**, obtained from 2-aryl-1-dimethylaminoisoindoles, have been described.[106] Positive solvatochromism is characteristic of merocyanines of this type. The parent isoindole **14** and its 4,5,6,7-tetrafluoro-analogue condense with formaldehyde and benzaldehyde to form the tetrabenzoporphyrins **188**.[147] It was found that the most important factor governing the formation of such systems is the involvement of a metal ion, since in the absence of the latter the yields of compound **188** are significantly lower. The type of the complex-forming reagent also influences the yield considerably: the zinc ion is best. The replacement of the latter by nickel or copper ions gives rise to only traces of the corresponding porphyrin derivative. The attempts to introduce the sterically hindered 2,4,6-trimethylbenzaldehyde into this reaction have been described.[148] A later investigation[149] threw doubts on the purity of the zinc complex of *meso*-tetraphenyltetrabenzoporphyrin **188** isolated.



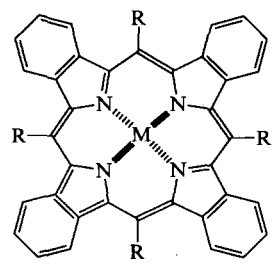
186a–c

X = S (a), NMe (b)
CH=CH (c)



187a–d

187a: X = CH=CH, 610 nm
187b: X = S, 589 nm
187c: X = O, 542 nm
187d: X = CMe_2, 534 nm

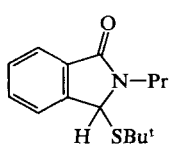


188

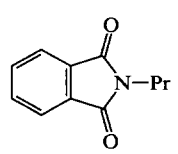
4. Other reactions of isoindoles

a. Oxidation

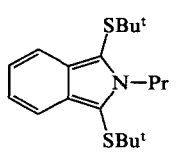
The autoxidation of the isoindole **40c** as a model compound for a whole series of fluorescent isoindoles has been investigated.[42] It was established that, when a solution of compound **40c** in aqueous acetonitrile is kept in air for 24 h, a mixture of four compounds **189–192** is produced.



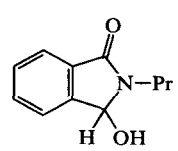
189, 35%



190, 16%

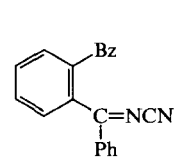


191, 12%

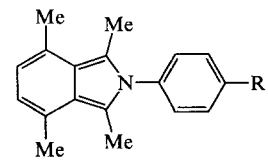


192, 4%

The pure nitrosyl cyanide, generated from its adduct with anthracene, reacts with 1,3-dienes to form new cyclic adducts. However, the interaction with 2-methyl-1,3-diphenylisoindole entails the dissociation of the C–N bond in the latter and the formation of the imine **193** in 66% yield.[150] In order to investigate the possibility of the formation of isoindole radicals, a study has been made[151] of the electrochemical oxidation of the isoindoles **194a, b** in anhydrous acetonitrile. It was shown that the nature of the substituent at the N(2) nitrogen atom hardly affects the oxidation potential. The oxidation takes place in two stages, the first involving the formation of relatively stable radical-cations. In order to investigate the chemiluminescence reactions with fluorescent organic compounds, the isoindole **195** was oxidised by 4,5-dichlorophthaloyl peroxide in dimethyl phthalate.[152]

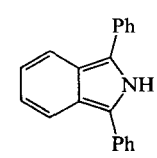


193



194a, b

R = H (a), Me (b)

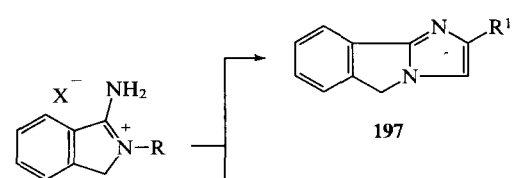


195

b. Heterocyclisation

Refluxing of the quaternary salt **196b** in aqueous solution of hydrobromic acid leads to a high yield of derivatives of 5*H*-imidazo[2,1-*a*]isoindole **197**.[153,154]

Even higher yields of compound **197** have been noted on refluxing aqueous solutions of type **196b** salts.[155] On the other hand, prolonged refluxing of the quaternary salt **196a** in the presence of sodium ethoxide leads to the condensation of the diazepine residue with the isoindole fragment and the formation of a 5-imino-5,13-dihydro-11*H*-isoindole[2,1-*a*][2,4]benzodiazepine **198** derivative.[144]



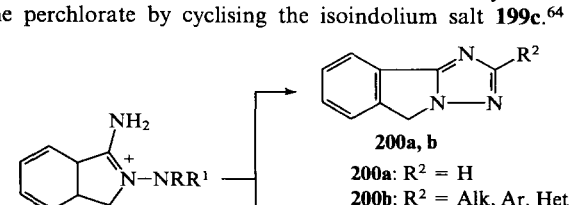
196a, b

196a: R = $CH_2C_6H_4CN$-*o*
196b: R = CH_2COR^1

197

198

Derivatives of 5*H*-1,2,4-triazolo[5,1-*a*]isoindole **200a** are formed in 32% yield on refluxing the salt **199a** with an excess of orthoformic ester.[65] Refluxing of the salts **199b** with phosphoryl chloride makes it possible to obtain the triazoloisoindoles **200b** [R = C_5H_{11} (17%) and R = Ph (97%)].[57,58,156] 3-Methyl-2-phenyl-3*H*-1,2,4-triazoloisoindole **201** has been synthesised as the perchlorate by cyclising the isoindolium salt **199c**.[64]

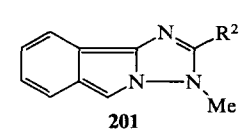


199a–c

199a: R = R^1 = H
199b: R = H, R^1 = COR^2
199c: R = Me, R^1 = COR^2

200a, b

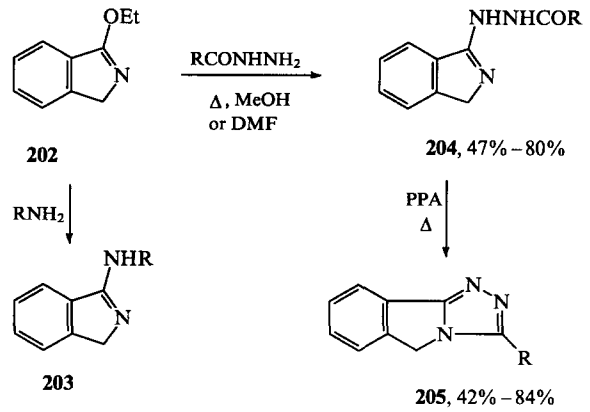
200a: R^2 = H
200b: R^2 = Alk, Ar, Het



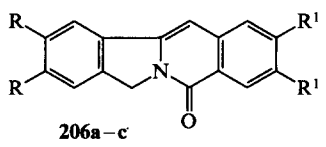
201

R^2 = Ph

During the nucleophilic substitution of the ethoxy-group, 1-ethoxyisoindole **202** reacts relatively readily with primary amines to form derivatives of the aminoisoindole **203**,[69] while the reaction with carboxylic acid hydrazides affords compounds of type **204**.[156] The latter cyclise in polyphosphoric acid (PPC) to derivatives of 5*H*-1,2,4-triazolo[3,4-*a*]isoindole **205** in satisfactory yields.[156]



Homophthalic anhydrides give rise to isoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones **206a–c** in satisfactory yields (75%) on heating with ethoxyisoindole **202** and its 5,6-dimethoxy-derivative in chlorobenzene.[34]

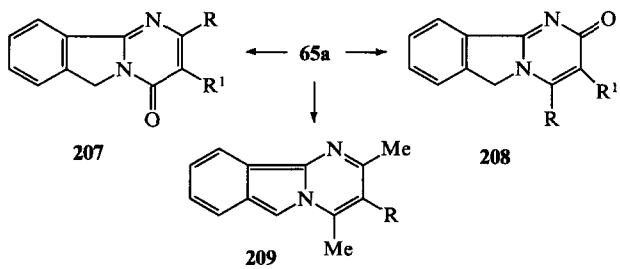


206a–c

206a: R = R¹ = H

206b: R = MeO, R¹ = H

206c: R = R¹ = MeO



It has been shown[157] that the condensation of the aminoisoindole **65a** with acetoacetic and benzoylacetic esters leads to derivatives of 6*H*-pyrimido[2,1-*a*]isoindol-4-one **207**. Further experiments also confirmed the possibility of the isolation from the reaction mixture of not only the 6*H*-pyrimido[2,1-*a*]isoindol-4-ones **207** but also their isomers **208**.[158,159] The criteria governing the differences between the isomeric systems **207** and **208** have been formulated and the conditions for the specific formation have been analysed in a number of investigations.[160–162] The condensation of the perchlorate **65a** with acetylacetone and methylacetylacetone, leading to a high yield of pyrimido[2,1-*a*]-isoindoles **209**, has also been described.[163]

V. Applications of isoindoles

One of the most important applications of isoindole derivatives involves their use as fluorescent labels. With the aid of isoindoles, it is possible to label the terminal amino-groups in various biological objects. The amino-groups are included in the 1-alkylthio-2*H*-isoindole system by treating them with *o*-phthalic dialdehyde and alkanethiols. An extensive literature, recently surveyed in a review,[45] has been devoted to this question. A comparatively new aspect of the employment of isoindole fluorescent labels is the detection with the aid of compounds such as **166** and **167** of the hydroxy-groups of steroids (17α- and 17β-estradiols, cortisone, estrone, etc.). The sensitivity of the method is of the order of 3 pmol in a 10 μl specimen.[139,140] It has been shown that the use of the isoindole **167** labels is an order of magnitude more effective than the use of compound **166** labels.[141] Other workers proposed the acyl azide obtained from the isoindole derivative **46d** for the detection of the same compounds.[56] Fluorescent isoindoles bound covalently to spectrin have been used to investigate the interaction of the latter with the phospholipids of pig erythrocytes.[164] 5-Fluoro-2-(1*H*-imidazol-2-yl)-2*H*-isoindole has been investigated together with other guanidine derivatives to achieve the treatment and prophylaxis of insulin-independent obesity.[165] Derivatives of compounds **200**[153,166] and **197**[154] exhibited a high contraceptive activity, while the preparation **203** with R = 3,4-$CH_2C_6H_3(OMe)_2$ exhibited the activity of a local anaesthetic which was twice as high as that of procaine.[69] It has been suggested that 1*H*-isoindoles be used as ligands in chromium pentacarbonyl complexes.[167] The electrical conductivities of polymer films obtained from isoindoles and their derivatives have been investigated.[168] Isoindoles have also been proposed as stabilisers and additives influencing the brightness of the electroplated tin layer on steel.[169]

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