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Advances in the Chemistry of Isoindole

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Data on the synthesis and physical and chemical properties of isoindoles published in 1968-1978 are examined and problems of the aromaticity of *o*-quinonoid heterocycles (isobenzofuran, isothionaphthene, and isoindole) are discussed. The bibliography includes 214 references.

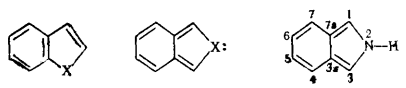
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I. INTRODUCTION

The annelation of benzene and aromatic five-membered heterocycles containing one heteroatom (pyrrole, furan, and thiophen) leads to two classes of bicyclic compounds isoelectronic with naphthalene. If the annelation takes place along the *b* side, the products are the so-called normal isomers or, according to recent chemical usage, type (I) Kekulé isomers: indole (X = NH), benzofuran (X = O), and thionaphthene (X = S). Annelation along side *c* of the five-membered ring leads to isomeric *o*-quinonoid heterocycles of type (II): isoindole (III), isobenzofuran (X = O), and isothionaphthene (X = S). These two classes of heterocycles exhibit fundamental differences of their electronic structure and properties.

Heterocycles of type (I) have been known for more than 100 years and comprise thoroughly investigated stable compounds. Their type (II) isomers have been obtained only comparatively recently after numerous unsuccessful attempts; they proved to be extremely reactive. Among these compounds, isoindole is particularly interesting.



(I) (II) (III)

Since the publication of the first review[1] on the isoindole chemistry, more than 10 years have elapsed. During this period, the parent compound (III) has been synthesised, new methods have been developed for the synthesis of isoindoles, their chemical properties have been investigated in detail, and practical applications have been found for isoindole derivatives. Certain new data on individual aspects of the isoindole chemistry have been described in reviews[2,3], but the information concerning isoindoles in monographs on the chemistry of benzopyrroles[4-7] does not go beyond the information contained in the review of White and Mann[1].

This survey includes all studies on the chemistry of isoindole mentioned in Chemical Abstracts during the last 10 years. It does not deal with condensed isoindoles, tetrahydroisoindoles, isoindolines, and also compounds of type (IV) (X = RC); Svirevski's review is devoted to compounds of the last type[8].

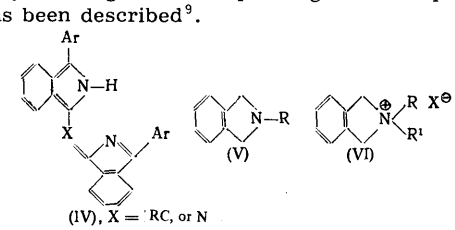
II. METHODS OF SYNTHESIS OF ISOINDOLES

1. Synthesis of Isoindoles from Isoindolines

Two ways of converting isoindolines (V) into isoindoles are possible: (a) the elimination method and (b) the oxidation method. In view of the lack of thoroughly developed methods for the single-stage mild oxidation of compounds (V), the elimination method is preferable.

(a) The Elimination Method

The Wittig method, which consists in treating quaternary ammonium salts (VI) (R = R^1 = alkyl) with strong bases, is not nowadays widely used. Only the synthesis of 2-methylisoindole by treating the corresponding salt with phenyllithium has been described[9].



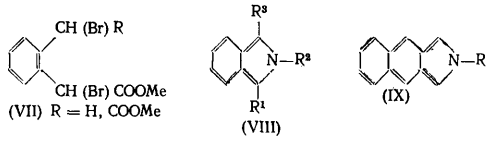
(IV), X = RC, or N (V) (VI)

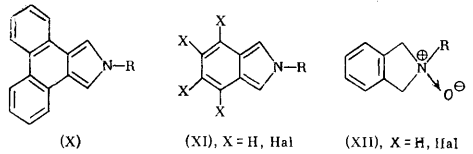
A method has been proposed recently[10] for the synthesis of 2-substituted isoindoles from hydrazinium salts (VI, R^1 = NHR^2) by treatment with an excess of alkali or a base; compound (V, R = $BuOOCNCH_2CH{=}CH_2$) and not 2-allylisoindole is formed from the salt (VI, R = $CH_2CH = CH_2$, R^1 = NHCOOBu) under these conditions. The initial salts (VI, R^1 = NHR^2) need not necessarily be isolated in a pure state from the reaction mixture in their synthesis from 1,2-bis(bromomethyl)benzenes and hydrazines[10]. Large series of 1,2,3-trialkylisoindoles have been synthesised by this method[14].

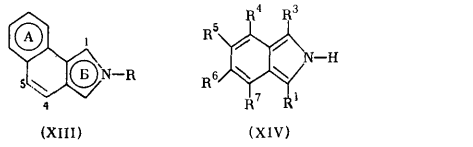
It has been shown that isoindoles are formed in a single stage from the esters (VII) with R = H[12,13] and R = COOMe[11,12] and the corresponding hydrazines with subsequent elimination of ammonia from the intermediate salt of type (VI). It was impossible to make hydrazine hydrate react with the dibromo-derivatives (VII) and obtain isoindoles (VIII, R^2 = H). The interaction of compound (VII) with phenylhydrazine is more complex, but in this case too it is possible to isolate the isoindoles (VIII, R^2 = Ph).[13] Isoindoles (IX) and (X)

with R = Me have been synthesised by the same method from 2,3-bis(bromomethyl)naphthalene and 9,10-bis(bromomethyl)-phenanthrene[15].

Isoindoles (XI, R = alkyl, X = Br) have been obtained in high yields by the acetolysis of the amine oxides (XII) on treatment with a mixture of acetic anhydride and triethylamine[16]. A somewhat different method has been used[17] to synthesise isoindoles (XI, X = H). For the mechanism of the acetolysis of amine oxides, see von Volz and Ruchti[18]. Pyrolysis of amine oxides (XII) is also used to obtain isoindoles[19,20].







Benzoisoindoles (X, R = H)[22] and (XIII, R = H)[23] have been obtained by treating substituted 2-tosylisoindolines with strong bases. It has been shown[24-26,177] that isoindoles (XIV) can be synthesised successfully from 2-methanesulphonyliso-indolines, which are treated with an excess of potassium t-butoxide in DMSO[21-25,28] or of sodionaphthalene[22] in dimethoxyethane (XXII).

The parent isoindole (III) was first obtained by Bonnett et al.[20,27] in 1972 by the pyrolysis of isoindoline (V, R = OCOOMe). Thermal decomposition of the same isoindoline in a solvent also gives rise to isoindole, which has been demonstrated by the formation of an adduct with *N*-phenylmaleimide[20]. The formation of isoindole from 2-hydroxyisoindoline when the latter is treated with acetic anhydride is indicated by the isolation of the same adduct[20].

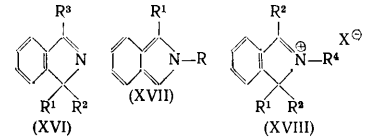
(b) The Oxidation Method

The method involving the direct single-stage oxidation of *N*-substituted isoindolines (V) for the synthesis of the corresponding isoindoles began to develop only recently. It has been shown[17] that the self-oxidation of 2-butylisoindoline depends on the nature of the solvent and is a free-radical process. 1,3-Dimethoxycarbonylisoindole and *N*-alkyl derivatives have been obtained by oxidising the corresponding isoindolines at room temperature with atmospheric oxygen. 1,3-Disubstituted isoindolines having the *cis*-configuration are oxidised to isoindoles much more readily than their *trans*-isomers[21].

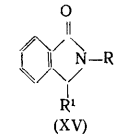
2-Arylisoindolines are entirely stable in air at the usual and elevated temperatures and other oxidants must be used to obtain isoindoles from them[21]. Thus the oxidation of compounds (V, R = Ar) to the corresponding isoindoles can be achieved with the aid of chloranil in high-boiling solvents. A heterolytic reaction mechanism, initiated by hydride transfer, is then postulated[29]. The aromatisation of isoindolines using chloranil has been used to synthesise a number of isoindoles (VIII) and gave various yields (23–80%)[13]. The use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and the synthesis of 4- and 5-azaisoindoles from the corresponding azaisoindolines have been described[30].

2. Syntheses of Isoindoles via Phthalimidines

Phthalimidines (XV) are structurally similar to isoindoles. Judging from ^{1}H NMR spectra[21], they do not show a tendency towards formation of one of the possible tautomeric lactim forms (XVI, R^3 = OH) or (XVII, R^1 = OH), but Wittig showed[1] that they can be successfully converted into isoindoles either by treatment with organolithium compounds or by reduction. Isoindoles (VIII) are formed in high yields when phthalimidines are treated with a solution of methyllithium[14,32]. 2-, 3-, and 6-Substituted phthalimidines have been used as starting materials in the reaction with methyllithium.



Together with methyl-lithium, ethyl-, butyl-, or vinyl-lithium can be employed in this reaction[14].



Previously Wittig obtained 2-methyl- and 2-phenyl-isoindoles by treating the corresponding phthalimidines with $LiAlH_4$ in ether and subsequent pyrolysis of the intermediate lithium alkoxide. In the case of 2-benzylphthalimidine the corresponding isoindole could not be obtained. The replacement of $LiAlH_4$ by sodium bis(2-methoxyethoxy)aluminium hydride (SBMAH)[33] gives a 60% yield of 2-benzylisoindole. In addition it has been found that the same isoindole can be obtained from *N*-benzylphthalimidine when the latter is treated with SBMAH, while the use of $LiAlH_4$ gives rise solely to the isoindoline (V, R = CH_2Ph).[33]

A new method of synthesising isoindole derivatives involving the use of the Vilsmeier reagent has been developed recently[34,35]. When phthalimidines (XV, R^1 = H) are treated with twice the amount of dimethylformamide (DMF) and $POCl_3$, the salt (XVIII, $R^1 + R^2 = CHNMe_2$, R^3 = Cl) is formed and on heating with alkali is converted into the isoindole (VIII, R^1 = Cl, R^3 = CHO). Treatment of the salts (XVIII, $R^1 + R^2 = CHNMe_2$, R^3 = Cl or Br, R^4 = H) with bases gives rise to the isoindolenine (XVI, $R^1 + R^2 = CHNMe_2$, R^3 = Cl or Br), which can also be converted in its turn into an isoindole of type (XIV)[34]. If the substrate : reactant ratio is altered to equivalent proportions, the reaction product is tris(1-oxoisoindolino)methane. The use of Vilsmeier reagents for the synthesis of azaisoindoles has also been described[36,171].

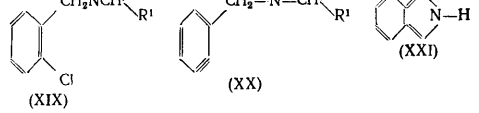
When phthalimidines (XV, R = H) were treated with cyclic immonium salts (formed on mixing pyridine, quinoline, or isoquinoline with benzoyl chloride), isoindoles (VIII) containing the residues of these heterocycles in the 1- and 3-positions were obtained[37]. Phthalimidines (XV), where $R^1 = CH_2Ar$ and R = H, can be aromatised in a similar manner. The reaction of cyclic immonium salts with phthalimidines is one of the examples of the heterylation reaction, the mechanism of which has been described[38].

The lactim forms (XVI, $R^3 = OH$) and (XVII, $R^1 = OH$) can be stabilised by their *O*-alkylation. This reaction has been known for a long time, but interest in 1-alkoxyisoindolenines has increased recently in connection with their use in the synthesis of various nitrogen-containing isoindole derivatives[39-42]. The *O*-alkylation of phthalimidines takes place at room temperature on mixing solutions of phthalimidine and trialkyloxonium fluoroborates in inert solvents. The resulting salts (XVIII, $R^3 = OR$) are converted into 1-alkoxyisoindoles on treatment with strong bases[39-42]. The reaction of Meerwein reagents with 2-methyl- and 2-ethyl-phthalimidines also takes place smoothly, but with formation of salts giving rise to isoindoles (XVII, $R^1 = OAlk$) on treatment with bases[43].

The formation of aza-derivatives of isoindole (XVII, $R^1 = OAlk$) has been described[171].

3. Syntheses of Isoindoles via *o*-Disubstituted Benzenes

Heterocyclisation processes involving dehydrobenzene are known[44], but, when molecules with a potential aryne functional group (for example, a chlorine atom in an aromatic ring) have a side chain exhibiting nucleophilic properties [as in *o*-chlorobenzylamines (XIX)], then intramolecular cyclisation is possible at an intermediate stage in the generation of the aryne (XX). An example of such heterocyclisation is provided by the elegant synthesis of 2-methylisoindole from the amine (XIX, R = H, $R^1 = CN$) and potassium amide in liquid ammonia (89%)[44,45]. Isoindoles (XVII, R = Me, $R^1 = COOR^2$, $CONH_2$, or COPh) have also been obtained by this procedure in very low yields. The mechanism of the reaction (XIX) → (XVII) is still not altogether clear[46].

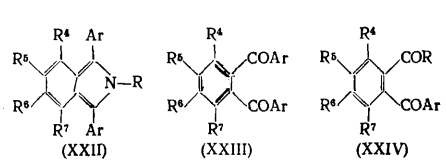


A very simple method of synthesising aminoisoindole (XXI, $R = NH_2$) from the dinitrile of phthalic acid by reduction with $LiAlH_4$ has been proposed[47,48]. The same isoindole can be obtained by the catalytic hydrogenation of *o*-azidomethylbenzonitrile[56].

Babichev and Tyltin[49,55] found that the reaction of *o*-chloromethylbenzonitrile on heating with amines produces in a single stage derivatives of aminoisoindole (XVII, $R^1 = NH_2$) and not benzylamine derivatives, as claimed previously[50], and not 2-substituted phthalimidines, as described in patents[51,183]. A series of similar compounds have also been obtained in other studies[52-54,57] as a result of the interaction of *o*-chloro(bromo)methylbenzonitriles with various primary amines. The corresponding bis-compounds have been obtained from *m*- and *p*-phenylenediamines[55].

Phthalonitrile and its substituted derivatives react with organomagnesium compounds to form red-violet compounds with structure (XIV, X = N); the isoindoles (XVI, $R^1 + R^2 = NH$) are intermediates in this reaction[58].

1,3-Diphenylisoindoles (XXII) can be obtained by condensing *o*-diacylbenzenes (XXIII) with primary amines or ammonium acetate[59,60].



This method[1], devised by Emmet, was developed further in other investigations[61-66]. The process can be regarded as a modified Leuckart reaction; when applied to compounds (XXIV), it leads to low yields of isoindoles[1,67]. In order to increase the yield, it has been suggested[63] that an alcoholic solution of methylamine be used and that sodium tetrahydroborate be added to the reaction mixture. A number of biologically active isoindoles have been obtained from the benzophenones (XXIV, R = COOEt or $CONR_2^1$)[65,66] on treatment with diethylaminoethylammonium formate.

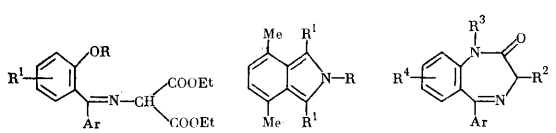
Maekawa and coworkers investigated the reaction of *o*-acylbenzophenones with ammonia[61,62] and primary amines[64,117]. Whereas the interaction of compound (XXIV, R = Ar) with ammonium formate leads to isoindoles, as shown above, the reaction of compound (XXIV, R = Me or Et) under these conditions results in the formation of low yields of isoindole self-condensation products—stable dark-blue pigments (IV, X = RC). Depending on the conditions, three types of compounds can be obtained in the reaction of compound (XXIV, R = Me) with primary alkylamines[64,117].

It follows from the study of Do Minh et al.[68] that none of the products of the interaction of *o*-phthalic aldehyde with ammonia and amines is an isoindole. On the other hand, a mixture of *o*-phthalic aldehyde and β-mercaptoethanol is a familiar and widely used biochemical reagent for the spectofluorimetric determination of aminoacids and proteins[69]. Simons and Johnson[70] suggested that the fluorescent products of the reaction of the above reagent with the *N*-terminal groups of aminoacids and proteins are isoindoles (XVII, $R^1 = SAlk$). To test this hypothesis, *o*-phthalic aldehyde was condensed with n-propylamine in the presence of ethanethiol, β-mercaptoethanol[70], t-butanethiol[71], thiophenol[72], and other thiols. Isoindoles have been isolated in the pure form only in the case of t-butanethiol and ethanedithiol. The formation of isoindoles (XVII, $R^1 = SAlk$) in alcoholic solutions has been investigated[72] by ultraviolet spectroscopy and NMR. The condensation products exhibit a strong fluorescence, which in general confirms the above hypothesis.

It has been shown[73] that, when *o*-acetylphenylacetic acid is condensed with hydroxylamine, the isoindole (XIV, $R^1 = Me$, $R^3 = COOH$) is formed in a high yield. A novel method of synthesising isoindoles has been described in a patent[74]. On heating with a large excess of imidazole (or alkylimidazoles), compounds (XXV) give rise to isoindoles (XIV, $R^1 = Ar$, $R^3 = COOEt$) in 16–60% yields; in the absence of imidazoles, the reaction does not take place.

On condensation with 1,2-dicyano- or 1,2-dibenzoylethanes, 3,4-diformyl-1,2,5-trimethylpyrrole gives rise to 5,6-dicyano(dibenzoyl)-1,2,3-trimethylisoindoles[75]. Derivatives of 5-aza- and 5,6-diaza-isoindoles have also been obtained from this pyrrole[75].

4. Condensation of 1,4-Diketones with Amines or Pyrroles

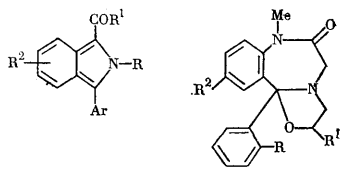


If both α-positions of the pyrrole ring are occupied, as, for example, in 2,5-dimethylpyrrole, then condensation with 1,4-diketones results in the formation of isoindole derivatives (XXVI)[1]. When a mixture of 1-R-2,5-diphenylpyrrole[19] or 1-R-2,5-dimethylpyrrole[19,28,76] and hexane-2,5-dione is refluxed in acetic acid, the corresponding isoindoles (XXVI)

are formed. The isoindole (XXVI, R = Me) was obtained in a single stage from methylamine and hexane-2,5-dione[19,76]. It was shown[28] that refluxing of a solution of 2,5-dimethylpyrrole in aqueous acetic acid results in the formation of the isoindole (XXVI, R = H) in 82% yield as a result of self condensation. This finding is of interest, because it had been observed earlier[1] under similar conditions that 2,5-dimethylpyrrole undergoes reductive self condensation with formation of a mixture of *cis*- and *trans*-1,3,4,7-tetramethylisoindolines.

5. Isoindoles as Products of the Isomerisation of 1,4-Benzodiazepinones

The rearrangement of 1,4-benzodiazepinones to isoindoles, noted by White and Mann[1], has been used to obtain several series of biologically active isoindoles[65,66,77]. Thus 1,4-benzodiazepinones (XXVII) give rise to a high yield of the amides (XVIIIa, R = H) on treatment with NaH in DMF[65,66,77]. A rearrangement of the above type also takes place with thioanalogues of compounds (XXVII), which gives rise to high yields of thioamides[77].



(XXVIII) (XXIX)

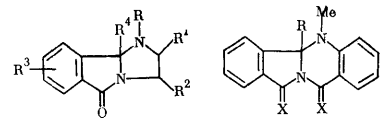
(a) R^1 = NHMe; (b) R^1 = OR^3

It has been shown[65,66] that, if the isomerisation is carried out in the presence of carbonic acid esters, then, instead of amides, the products are the esters (XXVIIb). A method of carrying out the single-stage transformation (XXVII) → (XXVIIIb, $R^3 = CH_2CH_2NEt_2$) has been described in a patent[65].

Like 1,4-benzodiazepin-2-ones, the esters (XXVII, R^2 = COOR) can be converted into isoindoles; the products are the isoindoles (XXVIIIb, R = H). An interesting difference in the behaviour of condensed benzodiazepinones (XXIX) under the conditions of isomerisation to isoindoles has been discovered[78]. It was found that compound (XXIX, R = Cl) isomerises to the corresponding isoindole, while compound (XXIX, R = H) gives rise to other products.

6. Reduction of Condensed Isoindoles with $LiAlH_4$

According to Sulkowski et al.,[80] treatment of imidazoisoindoles (XXX) with $LiAlH_4$ in diethyl ether yields 2,5-benzodiazocines. However, it has been shown[81-85,178] that, in the presence of an excess of $LiAlH_4$ and after prolonged refluxing of the reaction mixture, 2-(*N*-alkylaminoethyl)isoindoles are formed together with the corresponding diazocines. Under identical conditions, pyrimidoisoindoles are reduced by $LiAlH_4$ to 2-(aminopropyl)isoindoles[81,83,84] with high yields, while 1-methyl-1,3,4,10*b*-tetrahydro-2*H*-pyrimido[2,1-*a*]isoindol-6-one is reduced to the isoindole [XVII, $R = (CH_2)_3NHMe$].[86] The reduction of the benzo-analogue (XXX, $R = R^3 = H$) with an excess of $LiAlH_4$, followed by treatment with alcohol, gives rise to the isoindole (XVII, $R = 2'\text{-}C_6H_4NH_2$).[83]



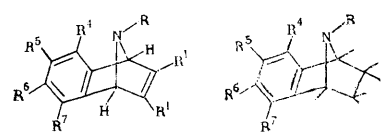
(XXX) (XXXI)

A pattern, which is similar in broad outline, is observed in the reduction of compounds of type (XXXI, X = O) with $LiAlH_4$. The reduction product is compound (XXXI, $X = H_2$) which isomerises during chromatography to the isoindole (XVII, $R = 2'\text{-}CH_2C_6H_4NHMe$).[83,87]

7. Synthesis of Isoindoles by the Diels–Alder Retro-Reaction

The study of the Diels–Alder retro-reactions, taking into account their similarity with mass-spectrometric, thermal, and photochemical processes, contributed much new information to the chemistry of simple isoindoles and isobenzofurans and yielded extremely useful results[88]. The first data on the thermal decomposition of derivatives of 7-azabenzonorbornadiene (XXXII) were obtained as early as 1963 by Wittig[89], who isolated α-naphthylamine in the thermolysis of the hydrobromide of compound (XXXII, $R = R^{4-7} = H$). In 1966 Carpino and Barr[90] obtained similar results.

The first evidence for the possibility of obtaining isoindoles from compounds (XXXII) was obtained by Coe and Uff[91]. Subsequently it was found that the loss of ethylene in the mass-spectra of 7-azanorbornenes (XXXIII) constitutes the principal type of fragmentation of the molecular ion (XXXIII, R = Me, R^{4-7} = F), and the isoindole (XI, R = Me, X = F) was isolated quantitatively in the thermolysis of the above compound at a temperature as low as 120 °C.[88] The essential feature of the Diels–Alder reaction consists in the thermolysis of the products (XXXII) and (XXXIII) obtained initially by the Diels–Alder reaction. An example of the direct conversion of compound (XXXII, $R = R^{4-7} = H$) into isoindole with elimination of acetylene has been described[92,187].



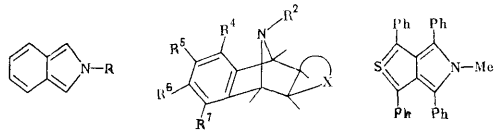
(XXXII) (XXXIII)

Thermolysis of derivatives of compound (XXXIII) leads to the loss of an ethylene molecule and the formation of the corresponding isoindole. The isoindoles obtained by the Diels–Alder retro-reaction are very pure. The isoindoles (XXIV)[93], (XI, R = H, Me, or CH_2Ph, X = F),[94,95] and benzo[*f*]isoindole[95,176] have been obtained by this method.

An interesting version of the Diels–Alder retro-reaction has been proposed in a study[96] where it was shown that the derivatives (XXXII) readily undergo the [2 + 4] cycloaddition reaction with 3,6-dipyridyl-*sym*-tetrazine to form the 1,1-adducts [XXXV, X = C(α–Py) = N–N = C(α–Py)], whose thermolysis gives rise to a mixture of isoindole and 3,6-di-α-pyridylpyridazine. This procedure was used by Anderson[97] to obtain isoindoles, but the adduct [XXXV, X = –NPh–N= C(Ph)–] then undergoes pyrolysis.

The synthesis of the isoindole (III) by the high-vacuum pyrolysis of compound (XXXIII, R = COOBu) has been described[98]. 1-Methyl- and 1,3-dimethyl-isoindoles have

been obtained by this method from the corresponding derivatives (XXXIII). It has been established in relation to the Diels–Alder retro-reaction for 7-azabenzonorbornene (XXXIII) and 7-azanaphtho[2,3]norbornene that the pyrolysis of both compounds at 125 °C leads exclusively to deamination (i.e. results in the formation of naphthalene and anthracene respectively); the relative yield of isoindole increases with increase of the pyrolysis temperature and reaches a maximum at 700–800 °C.[99]

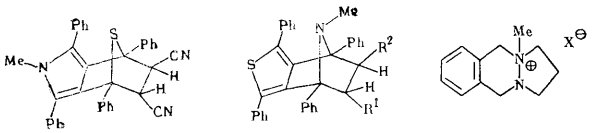


(XXXIV) (XXXV) (XXXVI)

The 1:1 adducts of the Diels–Alder reactions with condensed thiophens (XXXVI) are capable of giving rise to isoindoles under the conditions of the Diels–Alder retro-reaction[100,101]. Thus, when a mixture of equimolar amounts of compound (XXXVI) and fumaronitrile is refluxed in xylene for 12 h, the isoindole (XXII, $R^{4,7}$ = Ph, R = Me, $R^{5,6}$ = CN) is formed in 53% yield. On being refluxed in toluene for 12 h, fumaronitrile and compound (XXXVI) form compound (XXXVII) in 67% yield, while refluxing in benzene for 1 h gives a 63% yield of compound (XXXVIII). Both compound (XXXVII) and compound (XXXVIII) are capable of being converted into the above isoindole in a high yield on being refluxed in xylene. The adduct (XXXVII) can be converted into isoindole also on mixing its solution in methanol with sodium methoxide. The thienopyrrole (XXXVI) undergoes similar reactions with acrylonitrile and ethyl acrylate[100,101].

8. Synthesis of Isoindoles by the High-Vacuum Pyrolysis of Heterocyclic Compounds

High-vacuum pyrolysis—one of the modern methods of synthesising new heterocyclic systems[102]—has also been used to obtain isoindoles. Thus it has been shown[103] that isoindole derivatives can be obtained by the vacuum flash pyrolysis of phenyl-1,2,4-triazoles. The possible mechanism of the formation of isoindole in the thermolysis of triazoles includes the 1,5-sigmatropic shift of the *N*-phenyl group and the formation of a non-aromatic intermediate, the elimination of molecular nitrogen, and the cyclisation of the iminocarbene (or the 1,3-biradical) to 1,3-diphenylisoindole[103].



(XXXVII) (XXXVIII) (XXXIX)

The vacuum pyrolysis of *N*-(2-hydroxy-3-isoquinolinyl)-urethane at 600 °C affords 1-cyanoisoindole in quantitative yield[104,105,179]. It has been mentioned in patents[105,179] that this method can be used to synthesise also 1-cyanoisoindoles substituted in the benzene ring. The necessary condition is then the stability of the substituent on pyrolysis; the most suitable substituents proved to be the fluorine and chlorine atoms and the Me and CN groups[179].

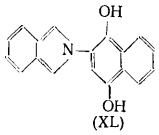
9. The Formation of Isoindoles in the Isomerisation of Heterocyclic Compounds

The rearrangement of 1-(4′-chlorophenyl)-2,5-benzodiazocine to derivatives of 2-aminoethylisoindole under the influence of strong bases is a familiar example[82,85]. The isomerisation is accompanied by the dehydrochlorination of the initial compound and, if there is no chlorine atom in the *p*-position in the benzene ring, which corresponds to the 1-position in benzodiazocine, then the product is 2-(β-aminoethyl)-1-phenylisoindoline[82].

A study of the reactions of isoquinoline derivatives with nucleophiles yielded interesting results for the chemistry of isoindole[106,107]. Thus it has been found that the amination of 3-amino-4-bromoisoquinoline with potassium amide in liquid ammonia gives rise to a mixture of 1-cyanoisoindole and 3-aminoisoquinoline[106]. The condensed hydrazinium salt (XXXIX) gives rise to 2-(3-methylaminopropyl)isoindole on treatment with potassium t-butoxide[86].

10. Other Methods of Synthesis of Isoindoles

When a benzene solution of *N*-(2-naphthoquinonyl)isoindoline is irradiated with light from a mercury lamp, an intramolecular oxidation–reduction reaction takes place with formation of the isoindole (XL).[108]



(XL)

Together with other products, the addition of di-t-butylthioketen to benzophenone methylimine results in the formation also of the isoindole (XVII, R = $CHPh_2$, R^1 = Ph).[109]

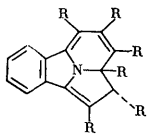
The oxidation of *N*-aminophthalimide produces phthalimidonitrene, while the reaction of the latter with isobenzofuran derivatives has been shown[110] to constitute a pathway leading to a high yield of 2-phthalimidoisoindole.

The two-electron polarographic reduction of 1,2-dihydrophthalazines in an acid medium initially produces isoindole and then isoindoline[111].

III. PHYSICAL PROPERTIES

1. Bond Orders and Lengths

There are no literature data on the X-ray diffraction analysis of isoindole derivatives. The geometrical parameters of compound (XLI), whose structural element is an isoindoline fragment, are known[112].



(XLI)

The bond orders and lengths in isoindole, 1-phenylisoindole[114], 2-phenylisoindole, 1,3-diphenylisoindole[114], benzo[*f*]isoindole[15,114], benzo[*e*]isoindole[114,115], and dibenzo[*e*,*g*]-isoindole[14,114] have been calculated by the SCF MO[15,113–115] and *ab initio*[116] methods. It has been noted[115] that the calculated bond lengths in benzo[*e*]isoindole (XIII, R = H) indicate an appreciable localisation of the bonds between the (A) and (B) ring systems (see Section II, 1a).

2. Distribution of π-Electron Density and Dipole Moments

The results of the calculations of the distribution of π-electron density in the isoindole molecule and the calculated dipole moments have been published (Table 1)[15,115,116,118–120]. Analysis of these data indicates unambiguously the order in the variation of the π-electron density in isoindole (III): $q_1^\pi > q_{3a}^\pi > q_5^\pi > q_4^\pi$. According to the above sequence in the variation of the π-electron density, assignments were made to the corresponding protons in the ^{1}H NMR spectrum of 2*H*-isoindole[27]. The calculations showed that the effective π-electronic charges on the carbon atoms of the pyrrole ring in 1-phenylisoindole are greater, as in benzo[*e*]isoindole (XIII, R = H), than on the remaining carbon atoms[114]. The following sequence in the distribution of π-electron density holds for compound (XIII): $q_3^\pi > q_1^\pi \gg q_5^\pi$.

Table 1. The distribution of electron density in isoindole (III).

q_1^π	q_2^π	q_{3a}^π	q_4^π	q_5^π	μ, D	Computational methods	Refs.
1.14	1.59	1.05	1.00	1.02	2.66	SCF CI P—P—P	[118]
1.1553	1.5380	1.0468	1.0107	1.0182	—	SCF P—P	[115]
1.108	1.626	1.049	1.010	1.020	—	SCF P—P—P	[15]
1.0909*	1.6615	1.0424	1.0069	1.0136	2.29	SCF P—P—P	*
1.1275			1.0115	1.0251		SCF P—P—P	[119]
1.0589	1.8066	1.0308	0.9983	1.0087	—	SCF Pople	[114]
1.1261	1.5525	1.0725	1.0017	1.0236	2.94	*ab initio* (GTO)	[116]
1.1336**	1.5243	1.0729	1.0027	1.0258	3.43	*ab initio* (GTO)	[116]
1.1043	1.6305	1.0586	1.0040	1.0177	2.20	*ab initio* (STO–3G)	[120]

* 2-Phenylisoindole. Calculation carried out by V.I.Minkin.
** 2-Methylisoindole.

The data on the distribution of π-electron density make it possible to attempt an approach to its quantitative estimation in the series of *o*-quinonoid heterocycles (II) and their isomers (I) on the basis of the concept of the excess π-electron density in heterocycles. According to Pozharskii[121], the average negative charge per carbon atom of the heterocyclic system can serve as a measure of the excess π-electron density. Thus, according to the results of calculations[114], the average effective π-electronic charges on all the carbon atoms of pyrrole, isoindole, indole, and carbazole are respectively −0.040, and −0.024, −0.015, and −0.008, while on the carbon atoms of the pyrrole ring in the above compounds they are −0.040, −0.044, −0.024, and −0.013 respectively. The above results indicate a higher excess π-electron density in isoindole compared with indole.

The same conclusion can be arrived at by comparing the distribution of π-electron densities in the above compounds, obtained from SCF MO[115,118] and *ab initio*[120] calculations. Comparison of the effective π-electronic charges on the carbon atoms of the pyrrole ring in the above benzopyrroles and the parent compound indicate a higher excess of π-electron density in isoindoles (III) even by a comparison with pyrrole. Similarly the results of calculation[114] permit the conclusion that the excess π-electron density in isobenzofuran (II, X = O) is greater than in benzofuran (I, X = O); the results of calculations of the distribution of π-electron density in compounds (II, X = NH, S, or O)[116] when the latter are examined from the standpoint of effective π-electronic charges of the carbon atoms indicate a comparatively greater excess of π-electron density in isoindoles (III) compared with the remaining *o*-quinonoid heterocycles.

3. The Reactivity Indices of Isoindoles

Qualitative conclusions concerning the direction of electrophilic and nucleophilic attack as well as addition reactions have been reached on the basis of the calculated charge densities within the framework of the isolated molecule approximation[115]. The 1(3)-position in *o*-quinonoid heterocycles (II) is most likely to undergo electrophilic attack, while the 4(7)-position is most favourable for nucleophilic attack. Analysis of the bond orders of *o*-quinonoid heterocycles (II) led to the conclusion that the $C_{(4)}$–$C_{(5)}$ (or $C_{(6)}$–$C_{(7)}$) bond should be most reactive in addition reactions[115]. The calculated free valence indices of the above compounds made it possible to determine the preferential direction of attack in free-radical reactions; for all the *o*-quinonoid heterocycles, these are the $C_{(1)}$–$C_{(3)}$ atoms. According to Klasinc et al.,[115] in benzo[*e*]isoindole the $C_{(4)}$ atom is subjected to electrophilic attack, while nucleophilic and radical attack is directed to the $C_{(3)}$ atom. It is noteworthy that these conclusions[115] are inconsistent with the results of the determinations and calculations of the electron density in the molecule of compound (XIII).[114]

4. The NMR Spectra of Isoindoles

The first calculation of the chemical shifts of isoindoles (III) was carried out by Black et al.[122] With the aid of a modified VESCF method, the authors calculated the delocalised contribution (the contribution of ring currents) to the diamagnetic anisotropy Δχ of heteroaromatic molecules.

Heterocycle	$-10^6\,\Delta\chi$
Indolisine	39.39 — 39.58
Isoindole	43.76 — 44.94
Indole	45.12 — 45.83
Isobenzofuran	40.68 — 41.78

Calculation of the chemical shifts of the isoindole protons[122] led to the following sequence: $\delta_{4,7\text{-H}} > \delta_{1,3\text{-H}} > \delta_{5,6\text{-H}}$. Later the same sequence was established experimentally.[20,27,93] Recently attempts have been made to relate the ring current data to the degree of aromaticity of the entire molecule itself. Corradi et al.[119] calculated the contributions of the ring currents to the shielding constants. The results of the calculations support the idea of a limited degree of aromaticity of the above compounds. The conversion of the five-membered heterocycles into their benzo-derivatives results in an increase of the ring current effects relative to the sum of the currents of the individual constituent rings. The annelation of the benzene ring to the *b* side of the five-membered heterocycle [the Kekulé structure (I)] has been shown by calculation[119] to entail a greater delocalisation of electrons than the annelation to the *c* side [the *o*-quinonoid heterocycle (II)].[119]

Analysis of the ^{1}H NMR spectra of substituted isoindoles showed that, following the absorption of resonance energy by the protons, the following sequence obtains: $\delta_{4,7\text{-H}} > \delta_{1,3\text{-H}} > \delta_{5,6\text{-H}}$, although it can break down in certain cases for $\delta_{1,3\text{-H}}$, depending on the nature of the substitution in the system. For the chemical shifts of the protons of the methyl groups in 2*H*-isoindole derivatives, it is more difficult to observe a similar rule; however, the relation $\delta_{1,3\text{-Me}} > \delta_{4,7\text{-Me}}$ holds at least in many instances.

The ^{1}H NMR spectrum of the parent isoindole (III) has been obtained quite recently[20,27,93]. The four-spin system of the AA'BB' spectrum, corresponding to the spin–spin interaction of the protons in isoindole, has been analysed[15,116,123,125] with the aid of the LAOCN3[123–125], LAOCOONII[15],

LAMS[116], and NMRIT[125] programmes. In the first stage of the computations based on the LAMS programme calculations were made for the four-spin system AA'BB' (protons in the 4-, 5-, 6-, and 7-positions) and then for the six-spin system of the AA'BB'XX' spectrum (i.e. for additional H in the 1- and 3-positions). In order to determine the accurate spin–spin interaction constants (SSIC) of isoindoles, the results of the calculation were compared with experiment. The SSIC of isoindoles are compiled in Table 2. The ^{19}F NMR spectrum of 4,5,6,7-tetrafluoroisoindole has been recorded[97].

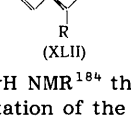
Table 2. The spin–spin interaction constants (SSIC) (J_{H-H}, Hz) of isoindoles.

Isoindole	$J_{4,5}=J_{6-7}$	J_{5-6}	$J_{4-6}=J_{5-7}$	J_{4-7}	Refs.
(III)	8.49	6.29	0.89	0.98	[123, 124]
(XXXIV) (R=Me)	8.60	6.28	0.86	0.98	[15]
ditto	8.690	6.456	0.899	0.790*	[116]
(VIII) (R^1=R^3=Ph, R^2=Me)	8.63	6.35	0.98	1.02	[15, 125]

* In addition, the transannular constants $J_{1-4} = 0.457$, $J_{1-6} = -0.070$, $J_{1-7} = -0.081$, and $J_{1-5} = 0.070$ are presented.

Data have been published[116,188] on the ^{13}C NMR spectrum of 2-methylisoindole. The similarity of the resonance absorption of energy by different carbon atoms is striking. The most characteristic feature of the 2-methylisoindole spectrum is the overall upfield shift of the absorption due to the carbocyclic ring carbon atoms (by ~ 6 p.p.m.); an even greater shift is observed for the $C_{(1)}$, $C_{(3)}$ atoms of isoindole, particularly in relation to the corresponding $C_{(2)}$ atoms of pyrrole or indole.

The ^{1}H NMR method combined with the shift reagent method [Eu(DPM)$_3$][126] made it possible to determine the structure of the preferred conformer of acyl derivatives of the isoindole (XLII, R = COR^1, R^1 = H or Me). In both cases the phenyl substituent in the 2-position is displaced from the ring of the bicyclic system, while the carbonyl group is located in space in such a way that it influences the resonance absorption of the $H_{(4)}$ proton due to a non-bonding interaction. The signal of the $H_{(4)}$ proton is displaced downfield, the strongest signal (~ 1 p.p.m.) being observed for the formyl derivative[126].



(XLII)

It has been shown by ^{1}H NMR[184] that even at very low temperatures the free rotation of the dimethylamino-group of the isoindole (XLII, R = H) is unhindered.

5. Photoelectron Spectra

A correct method for estimating the energy of the highest occupied molecular orbital (HOMO) may be based on the first ionisation potential (IP) of the molecule. Information about the ionisation potential can be obtained from photo-electron spectra. The photoelectron spectra of isoindole and other *o*-quinonoid heterocycles were determined in 1976 by three groups of investigators[15,116,127]. In all cases a helium lamp served as the source of radiation. Inspection of the experimental and calculated Franck–Condon (vertical) values of IP[114,124] shows that not all methods of calculation yield satisfactory results.

The method of structural representations for the theoretical description of electronic spectra, the foundations of which were laid by Simpson[130], has been used successfully to predict the IP in studies by Koenig and coworkers[127,131,185]. The method has been used[127] to calculate the IP of 2-methylisoindole.

Inspection of the data in Table 3 permits the following conclusions.

(1) the IP diminishes successively in the series pyrrole–indole–isoindole, i.e. an increase in the size of the aromatic system entails an increase of the HOMO energy.

(2) The nitrogen-containing heterocycles (I), (II), and (LVII) have more marked π-donor properties than their oxygen and sulphur analogues.

(3) the benzo[*c*]-derivatives of the monocyclic compounds (LVII) have lower IP (higher HOMO) than the benzo[*b*]-derivatives, i.e. the heterocycles with the *o*-quinonoid structure have a more pronounced π-donor capacity than their positional isomers.

Table 3. The first ionisation potentials (IP, eV) of *o*-quinonoid heterocycles, their positional isomers, and the monocyclic compounds.

X			
>N—CH$_3$	7.95 [127]	7.87 [127]	7.2 [116]
—S—	8.86 [129]	8.17 [121]	7.7 [116]
—O—	8.89 [129]	8.29 [121]	8.0 [116]

Note. The numbers in square brackets denote references (Ed. of Translation).

The capacity of isoindoles for the formation of charge-transfer complexes (CTC) on interaction with electron acceptors may be regarded as confirmation of the existence of the π-donor capacity. A stable complex of 2-methylisoindole with trinitrobenzene has been described[14]. Similar complexes had been obtained earlier for pyrrole, indole, and other heteroaromatic compounds.

6. Electronic Spectra

The above photoelectron spectroscopic data show that the *o*-quinonoid heterocycles require less excitation energy than their structural isomers. This conclusion is also confirmed by a comparison of the electronic spectra of indoles and isoindoles. Whereas the long-wavelength absorption maximum in the spectra of indoles is displaced towards shorter wavelengths compared with that in the naphthalene spectrum, in the spectra of isoindoles it is actually at longer wavelengths. Analysis of the ultraviolet spectra of isoindoles permits certain generalisations. Three regions of absorption in the ultraviolet are characteristic of 2*H*- and 2-alkyl-isoindoles:

(a) Band *A* (230 ± 5 nm) with an intensity lg ε = 4.2–4.5 (one maximum);

(2) band *B* (260–290 nm) with an intensity lg ε = 3.1–3.3 (from one to three maxima);

(3) band *C* (320–350 nm) with an intensity lg ε = 3.6–3.7; solutions of isoindoles in n-hexane absorb in region *C* in the form of several closely spaced maxima, which is associated with the vibronic interactions.

A bathochromic shift of bands *A*, *B*, and *C* has been observed for 2-arylisoindoles compared with 2-alkyl-substituted derivatives. The intensity of the bands in regions *A* and *C* does not then change, while the intensity of the *B* band increases somewhat. The introduction of phenyl substituents in the 1,3-positions of isoindole results in a bathochromic shift of the absorption in region *C* accompanied by a slight hyperchromic effect for bands *B* and *C* compared with the parent isoindole and 2-alkylisoindoles.

The absorption spectra of benzoisoindoles are determined by the type of annelation of the benzene ring. Thus benzo[*e*]- and dibenzo[*e*,*g*]-isoindoles[15] absorb in the same region of the ultraviolet spectrum as the parent isoindole, while the long-wavelength absorption maximum in the spectrum of benzo[*f*]isoindole is displaced to the visible region[15]. Furthermore, the intensity of the *B* band is much higher in the spectra of benzoisoindoles.

Calculations of the energies of the singlet–singlet transitions for isoindole and its benzo-derivatives have been made by semiempirical methods in the π-electron approximation[15, 113,115,118,134]. Calculated data closest to the experimental values have been obtained by Rettig and Wirz[15] and Klasinc et al.[115] The directions of polarisation of the absorbed light in the transitions to the S_1 and S_2 states of the isoindoles (XXXIV, R = Me) and (IX, R = Me) have been predicted on the basis of calculations[15] and then confirmed experimentally. Tests showed that the $S_0 \rightarrow S_2$ transitions in the above compounds are polarised along the major molecular axis, while the $S_0 \rightarrow S_1$ transition, which should have been polarised along the short molecular axis, in fact exhibits a mixed polarisation due to the excess vibrational energy, which the molecule receives on excitation[15].

A phenomenological approach to the analysis of the electronic spectra of isoindoles has been made[118] on the basis of the indene anion model as a general perturbed system. An intense fluorescence corresponds to the long-wavelength absorption band of isoindoles. It has been shown[15] that in 2-methylisoindole 8% of the excitation energy is emitted in the form of phosphorescence with a lifetime of 0.4 s, and that its first triplet level is lower relative to naphthalene, for which $E_T = 21266$ cm^{-1} according to Gordon and Ford[129].

The mechanism of the spectral chemiluminescence of two arylisoindoles has been investigated[135]. The authors concluded that a cooperative effect is responsible for the excitation of electrochemiluminescence.

7. Infrared Spectra of Isoindoles

No systematic studies have been made of the infrared spectra of derivatives of isoindoles in order to discover and assign their characteristic absorption bands. Within the framework of a study of the tautomerism and association of cyclic amidines, their infrared spectra, including those of 1-aminoisoindole, have been obtained[48]. Theoretically, three tautomeric structures are possible for 1-amino-isoindoles, but, according to the results of the study of its infrared spectra in the solid state and in solution, it exists mainly in the form (XVI, $R^1 = R^2 = H$, $R^3 = NH_2$).

8. Mass Spectra of Isoindoles

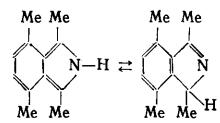
A general characteristic feature of all the known data for the mass-spectra of isoindoles may be noted, namely the fact that the most intense peak in the spectrum is that of the molecular ion M^+. In the majority of studies of isoindole the mass-spectrometric data are confined to those for M^+. The complete set of mass-spectrometric data is available for the following isoindoles: compound (III)[20,27], 2-methylisoindole[44], compound (IX)[15], compound (X)[15], 2-butylisoindole[20], and 2-ethyl-1,3,4,7-tetramethylisoindole[76]. The fragmentation of 1,3-diphenylisoindole and 1,3-diphenylisobenzofuran has been analysed in detail in only one study[136].

9. The Tautomerism of Isoindoles

One of the most characteristic features of isoindole (III) is its ability to undergo rapid tautomeric transformations into the corresponding 1*H*-isoindoles (isoindolenines) (IIIa). Since the *o*-quinonoid structure (III) and the isoindolenine structure (IIIa) differ insignificantly in their thermodynamic stabilities, which precludes the isolation of the tautomeric forms in a pure state, the equilibrium (III) ⇌ (IIIa) was investigated by ultraviolet and infrared spectroscopy and mainly by NMR.

The first studies[20,27,94] on the NMR spectra of isoindole (III) at low temperatures (−40 °C) showed that this compound is a mixture of tautomers (III) and (IIIa) with the *o*-quinonoid structure predominating in the equilibrium. However, it was found later[123] that, when a mixture of compounds (III) and (IIIa) is dissolved in solvents of different polarity, the content of compound (III) in solution increases with time, its accumulation obeying a kinetic first-order law ($T_{1/2}$ = 16 min). It has been established by ^{1}H NMR that the content of the *o*-quinonoid structure (III) increases at −40 °C in initial mixtures in solvents of different polarity. In all cases the NMR signals corresponding to the isoindolenine structure (IIIa) disappear altogether after a definite time interval, i.e., regardless of the polarity of the medium, the process stops only when the isoindolenine form (IIIa) is completely (or almost completely) converted into the thermodynamically more favourable *o*-quinonoid structure (III).

1-Methyl-, 1,3-dimethyl-, and 1,3,4,7-tetramethyl-isoindoles as well as the parent isoindole (III) exist in solution in equilibrium with their isoindolenine tautomers and the equilibrium position depends significantly on the nature of the solvent employed[98]. The study of deuterium exchange for 1-phenylisoindole confirmed unambiguously the earlier observation of equilibrium between isoindole and its isoindolenine tautomer[98,123]:



(XLIII) (XLIV)

It has been shown with the aid of infrared, ultraviolet, and ^{1}H NMR spectra that the isoindole (XLIII) exists in solution as well as in the solid state in a mixture with its tautomer (XLIV) with the latter predominating[28]. It has been found that the state of tautomeric equilibrium is greatly influenced by the ability of solvents to form intermolecular hydrogen bonds with compound (XLIII).

The position of the isoindole–isoindolenine equilibrium depends on two effects[137]—electronic and steric. Electron-donating groups in the 1- and 3-positions of the bicyclic system stabilise the isoindolenine tautomer. For example,

the amount of the isoindolenine tautomer in deuterochloroform is 9% for compound (XXI, R = Ph), 31% for (XXI, R = 4′MeOC$_6$H$_4$), and 100% for (XXI, R = OEt). On the other hand, electron-accepting groups increase the content of the *o*-quinonoid structure in the tautomeric mixture in deuterochloroform. 5-Methyl-1,3-diphenylisoindole[60], 1-cyanoisoindole[104], 1-methoxycarbonylisoindole[13], and 1,3-dimethoxycarbonylisoindole[11] have the 100% *o*-quinonoid structure. On the other hand, the steric effect is manifested in compounds (XLIII), where there are two peri-interactions involving the methyl groups in the 1,7- and 3,4-positions and exerting a destabilising influence. In the tautomeric form (XLIV) one of these interactions has been eliminated which is undoubtedly associated with a considerable energy gain[137].

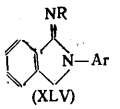
The type of annelation of benzene rings to the isoindole molecule influences significantly the position of the tautomeric equilibrium. In agreement with quantum-chemical calculations[1], the isoindoles (X, R = H)[22] and (XIII, R = H)[23] exist exclusively in the o-quinonoid form, while benzo[*f*]-isoindole (IX, R = H) exists preferentially in the corresponding tautomeric isoindolenine form (IXa), but the formation of an adduct with *N*-phenylmaleimide confirms the presence of a certain amount of the tautomer having the isoindole structure (IX)[176]. Halogen (fluorine[94,95,97], chlorine[25], and bromine[24]) atoms in the isoindole ring suppress the formation of the isoindolenine tautomer and stabilise the system as a whole compared with the parent compound. The presence of the isoindolenine tautomer has not been observed for any of the halogenoisoindoles. We mentioned above the unsuccessful attempt to isolate both tautomeric forms of isoindoles. However, in the case of compound (XXVI, R = H) each tautomeric form was obtained in a pure state. When a solution of the methylamide (XXVIII, R = H) in DMF is treated with sodium carbonate, the isoindolenine (XVI, R^1 = CONHMe, R^2 = H, R^3 = Ph) is formed. On treatment with acid, this compound is converted into the tautomer with the isoindole structure[77].

IV. CHEMICAL PROPERTIES

1. Alkylation of Isoindoles

The alkylation of isoindoles unsubstituted at the nitrogen atom can proceed in two ways: either at the N$_{(2)}$ atom with formation of 2-R-isoindoles or at the C$_{(7)}$ (or C$_{(3)}$) atom of the pyrrole component of the bicyclic system. Thus methylation of 1,3-dimethoxycarbonylisoindole with diazomethane in ether gives a high yield of the *N*-methyl derivative[21]. Alkylation of aminoisoindole with phenacyl bromide also involves the N$_{(2)}$ ring nitrogen atom with formation of the salt (XVIII, R^3 = NH$_2$, R^4 = CH$_2$COPh)[138].

Interesting results have been obtained[49,139] in the alkylation of cyclic amidines having the general formula (XLV, R = H) with dimethyl sulphate (DMS). The interaction of compound (XLV) with DMS gives rise to the corresponding *N*-methylisoindolenine methosulphates (XLV, R = Me). The bases (XLV, R = Me) react with DMS to form salts, which are converted into the isoindoles (XLII, R = H) on treatment with bases[139]. 1,3- and 1,4-Bis(1-dimethylamino-2-isoindolyl)benzenes have been obtained similarly from the corresponding cyclic amidines[55]



(XLV)

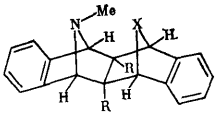
The alkylation of 1-alkoxyisoindolenines[43,56] with trialkyloxonium fluoroborates involves the nitrogen atom N$_{(2)}$ with formation of the salts (XVIII, R^3 = OAlk), from which the isoindoles (XVII, R^1 = OAlk) can be obtained by treatment with bases. The vast majority of instances of the alkylation of isoindoles unsubstituted at the N$_{(2)}$ atom involve the preliminary generation of isoindole anions with the aid of alkali metal hydrides[28,65,66,94,140,141], alkoxides[77,78], or hydroxides[58] in suitable solvents. Thus the alkylation of the esters (XXVIIIb, R = H) and the amides (XXVIIIa, R = H) at the ring nitrogen atom has been described in patents[65,66].

The alkylation of the 3-(4′-chlorophenyl)-1-ethoxyisoindole anion with alkyl halides[42,141] or bromoacetic esters[140, 180–182] involves the C$_{(3)}$ carbon atom with formation of racemic isoindolenines of the type (XVI, R^3 = OEt). On alkylation with benzyl bromide, the anion of the isoindole (XLIII) yields 1-benzyl-1,3,4,7-tetramethyl-1*H*-isoindolenine[28]. The anions of the methylamides (XXVIIIa, R = H) are alkylated with ethylene bromohydrin[78] and methyl iodide[77] at the N$_{(2)}$ ring nitrogen atom, but in the latter case the *C*-alkylation product is also isolated. More complex compounds containing the ring of the isoindole (IV) are alkylated by dialkyl sulphates at the N$_{(1)}$ atom in the presence of bases[58].

2. The Diels–Alder Reactions

(a) The Addition of Dimethyl Acetylenedicarboxylate (DMAC)

Isoindoles combine extremely readily with DMAC to form products with different proportions of isoindole and DMAC[2]. Thus Wittig showed[1] that 2-methylisoindole forms a 2:1 adduct (XLVI) with DMAC. However, the majority of isoindoles give rise to 1:1 adducts (XXXII, R^1 = COOMe), i.e. substituted 7-azabenzonorbornadienes[92,187].



(XLVI)

The reactions of isoindoles with DMAC are exothermic. An increase of the temperature of the reaction mixture in the presence of an excess of DMAC can entail the deamination of 7-azabenzonorbornadiene and the formation of the corresponding naphthalene, which has been observed[108,142]. On reaction with DMAC, certain 2*H*-isoindoles form 1:2 adducts with the structure (XXXII, R = MeOOCC = CHCOOMe, R^1 = COOMe). This applies particularly to tetrachloro-(bromo)isoindoles. The isoindole (XLIII) reacts with DMAC at room temperature to form a 1:1 adduct of the type (XXXII), which rearranges to a 1:2 adduct of the type (XLVII) on refluxing with DMAC in benzene. *N*-Ethyl- and *N*-n-butylisoindoles react with DMAC at 0 °C to give the corresponding compounds (XLVII), the mechanism of the formation of which has been described[137]. Ethyl propiolate does not form adducts with isoindoles[19].

(b) The Addition of Dehydrobenzenes to Isoindoles

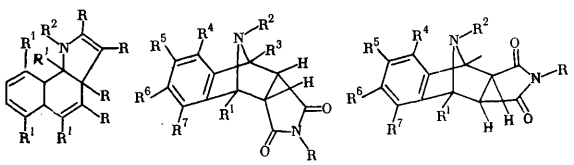
Isoindoles readily combine with dehydrobenzene to form derivatives of 7-azadibenzonorbornadienes. Wittig showed for the first time[1] that *N*-methyl- and *N*-phenyl-isoindoles react with dehydrobenzene to form the adducts [XXXII, R^1 + R^1 = (CH = CH)$_2$], which can react further with an

excess of dehydrobenzene to form anthracene derivatives[1]. Dehydrobenzene, generated in different ways, reacts with 2-methyl-1,3-diphenylisoindole to form adducts of the above type[143]. The reaction of 2,4,7-trimethyl-1,3-diphenylisoindole with dehydrobenzene gives rise to the corresponding derivatives of 7-azadibenzonorbornadiene[144].

A new method of generating dehydrobenzene from chlorobenzene and the lithio-derivatives of tetramethylpiperidine has been tested in relation to the synthesis of 7-methylazadibenzonorbornadiene from 2-methylisoindole[145]. A large group (more than 40 compounds) of substituted 7-azadibenzonorbornadienes have been obtained from substituted isoindoles and dehydrobenzenes (15 types), dehydronaphthalenes, and heteroarynes (8 types)[14]. A series of new adducts of isoindoles with dehydrobenzene and dehydronaphthalene have been used in the oxidative deamination reaction in order to obtain new derivatives of anthracene and benzanthracene which are otherwise difficult to synthesise[146]. Krick and Vernon[144] explained the extremely unusual result of the reaction of 2-benzyl-1,3,4,7-tetramethylisoindole with dehydrobenzene by the deamination of the 7-azadibenzonorbornadiene derivative, the formation of the corresponding anthracene, and the subsequent cycloaddition of dehydrobenzene in the 9,10-positions of the latter.

(c) The Addition of Maleic Acid Derivatives to Isoindoles

The formation of an adduct with *N*-phenylmaleimide is the usual method of identifying isoindole[93,103]. The addition of *N*-phenylmaleimide to isoindoles can theoretically lead to two products: the *endo*-product (XLVIII) and the *exo*-product (XLIX). One of the most correct methods of determining the configuration of the adducts is ^{1}H NMR, since the patterns of the signals due to the protons in the 1-, 4-, 5-, and 6-positions in these compounds are significantly different[20,96]. A mixture of compounds (XLVIII) and (XLIX), with the *exo*-adduct predominating, is obtained from isoindole and *N*-phenylmaleimide. If this mixture is heated in xylene, then the *endo*-adduct is transformed into the thermodynamically more stable *exo*-isomer[20,27].



(XLVII) (R=COOMe) (XLVIII) (XLIX)

Benzo[*e*]isoindole, benzo[*f*]isoindole, and dibenzo[*e*,*g*]isoindole also form an adduct with *N*-phenylmaleimide[22,23,96], although, according to spectroscopic data, benzo[*f*]isoindole has the isoindolenine structure[95]. The geometry of the adduct of isoindole (X, R = H) with *N*-phenylmaleimide precludes its assignment to a definite type, since it dissociates in concentrated solutions and the ^{1}H NMR spectrum reflects a mixture of the initial substances[22].

4,5,6,7-Tetrafluoro-[94] and 4,5,6,7-tetrachloro-isoindoles[25] react with *N*-phenylmaleimide to form the corresponding exo-adducts, while the π-electron system of tetrabromoisoindole is so deactivated that it does not form an adduct with maleic anhydride[24]. It has been shown[97] that treatment of tetrafluoroisoindole with *N*-phenylmaleimide gives rise to a mixture of the *exo*- and *endo*-adducts, which can be separated by column chromatography on silica gel. This is perhaps the only example where the *exo*- and *endo*-adducts were isolated in a pure state.

The isoindole (XLIII) and maleic anhydride form an adduct, which has the structure (XLVIII) or (XLIX) in the solid state; however, in solutions the adducts associate into the initial substances, which react anew but now with formation of adducts of the Michael type[137]. The cyclic 1:1 adduct of the isoindole (XI, X = Cl) with 4-phenyl-1,2,4-triazoline-3,5-dione has been described[25]. 2R-Isoindoles form adducts with dienophiles just as readily as the 2*H*-derivatives.

N-Methylmaleimide reacts with 2-ethoxycarbonylisoindole and 2-methyl-4,5,6,7-tetrafluoroisoindole to give a mixture of *exo*- and *endo*-adducts according to ^{1}H NMR data[96]. Mixtures of the same composition are also formed by the reaction of *N*-phenylmaleimide with the isoindole (XI, R = Me, X = F)[88]. Adducts of the isoindoles (XI, X = Br, R = Me) with *N*-phenylmaleimide could not be obtained[16]. 2-Acetylisoindole *in statu nascendi* reacts with *N*-phenylmaleimide to produce a low yield of the *exo*-adduct[20]. The isoindole (XI, X = F, R = CH_2Ph) reacts with *N*-phenylmaleimide at 0 °C to form the adduct (XLVIII). A series of endo-adducts have been obtained from the isoindole (XL) by the reaction with *N*-methyl- and *N*-phenyl-maleimides and also with 1,4-benzoquinone[108].

The isoindole (XLII) reacts readily with maleimide and *N*-phenylmaleimide to give high yields of adducts, which we assign to the *endo*-series on the basis of the ^{1}H NMR spectra quoted in the relevant communication[147]. 1-Alkoxy-2-methyl-isoindoles react with maleimide derivatives to form 1:2 *exo*-adducts; initially electrophilic addition probably takes place at the free $C_{(3)}$ position in the isoindole and then the usual addition at the $C_{(1)}$ and $C_{(3)}$ carbon atoms[43]. The addition of 1,4-epoxy-1,4-dihydronaphthalene to 2-methylisoindole gives rise to the isomeric *exo-exo*-adduct (XLVI, X = O) and *exo-endo*-adduct, which were separated chromatographically[9].

3. Isoindoles under the Conditions of Attack by an Electrophile

(a) Electrophilic Addition Involving Isoindoles

The protonation of isoindoles—the simplest example of the electrophilic addition reaction—takes place at the $C_{(1)}$ or $C_{(3)}$ carbon atom in view of their symmetrical structure. The ionisation constants of the two isoindoles (XXII, R = R^5 = Me) and (XXII, R = Ph, R^4 = Me) have been determined spectrophotometrically[148]. The greater basicity of isoindole derivatives compared with that of the corresponding *N*-methyl- and *N*-phenyl-indoles can be accounted for by the greater resonance stabilisation of the latter. There are virtually no data on the protonation of the asymmetrically substituted isoindole (VIII). On protonation, the isoindoles (XLII, R = H)[139] and (XVII, R^1 = OAlk) form cations with the structures (XVIII, R^3 = NMe_2 or OAlk) respectively. This has been confirmed by ^{1}H NMR.

Comparison of the ultraviolet spectroscopic data for tetra- and penta-substituted isoindoles (XXII) in neutral and acid media revealed interesting features[60]. It was found that the methyl group in the 4-position in isoindole promotes the formation of the cation. The transition of the $C_{(1)}$ or $C_{(3)}$ atom from trigonal to tetrahedral hybridisation enables one of the phenyl substituents to deviate from the plane in which the methyl group at the $C_{(4)}$ or $C_{(7)}$ atom is located, which entails a decrease of steric strain, favouring an increase of the fraction of the isoindolenine form of the cation[60].

Examples of reactions involving electrophilic addition to isoindoles have been published[25,55,70,77,139]. It was found that, as a result of electrophilic addition, the reaction of

DMAC with isoindoles of the type (XVII, R^1 = SAlk) gives rise to the product (VIII, R^1 = SAlk, R^3 = MeOOCC = CHCOOMe)[70]. An analogous type of addition has been observed[25] in the reaction of azodicarboxylate esters with tetrachloroisoindole. The isoindoles (XLII, R = H) readily add to phenyl isocyanates and isothiocyanates, giving rise to high yields of the corresponding 3-substituted derivatives[55,139]. The reaction of 2-methyl-1-phenylisoindoles with methyl isocyanate leads to the methylamide of 2-methyl-3-phenylisoindole-1-carboxylic acid[77].

(b) Electrophilic Substitution Reactions of Isoindoles

The rates of the simplest electrophilic substitution reaction (deuterium exchange) in the series of bicyclic 10-π-electron compounds have been determined[149] and it was found that 2-methylisoindole is more reactive by four orders of magnitude than 1-methylindole.

The available information about the electrophilic substitution reactions of isoindoles is scanty. Thus the treatment of the isoindoles (XLII) with acetic anhydride or benzoyl chloride leads to acyl derivatives as a result of the electrophilic substitution reaction[139]. Interesting compounds have been obtained via the electrophilic substitution mechanism from 1,2-disubstituted isoindoles and the trimethylsilyl ester of 6-isocyanatopenicillanic acid[150]. 2-Benzyl-1-methoxycarbonylisoindole does not undergo the electrophilic substitution reactions (the Mannich reaction and acetylation)[13].

4. Isoindoles under the Conditions of Attack by a Nucleophile

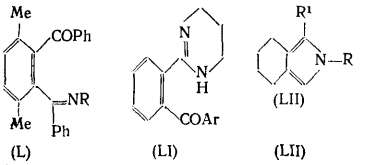
Nucleophilic substitution of isoindoles has been mainly studied for 1-alkoxyisoindoles having the structure of isoindolenines and structurally similar to the iminoesters of carboxylic acids. All the reactions described below can be readily understood and accounted for from this point of view. Thus the reaction of 1-ethoxyisoindole with primary aromatic and heterocyclic amines involves the substitution of the ethoxy-group by an arylamino-group[151]. More than 40 compounds have been obtained in this way. Benzylamine[152] and its substituted derivatives[151-152] as well as 2-(β-dialkylamino)-ethylamine[152] react with salts of 1-ethoxyisoindole to form the same products as in the reactions with the bases, but the yields are higher[56]. The reaction of 1-ethoxyisoindole with hydrazine produces 1-hydrazinoisoindole[56,152], while 3-aryl-1-ethoxyisoindole gives a high yield of aminophthalazines[42]. Phenylhydrazine and hydroxylamine are also capable of substituting an alkoxy-group in the 1,3-positions of the bicyclic system[56]. On being refluxed with aziridinium tetrafluoroborate in toluene, 1-ethoxyisoindoles give rise to the derivatives of imidazo[2,1-*a*]isoindole as a result of the nucleophilic substitution of the ethoxy-group and simultaneous cyclisation[40,41].

5. Heterocyclisation Based on Isoindole Derivatives

1-Amino-2-phenylisoindole and its hydrobromide are converted into 2-phenyl-5*H*-imidazo[2,1-*a*]isoindole on heating[138]. On heating in acetone, 2-aminoethylisoindoles cyclise to pyrazinoisoindoles[82,85]. On condensation with α-acetyl-γ-butyrolactone in acid, 1-aminoisoindole gives rise to a mixture of isomeric condensed pyrimidoisoindoles[153]. When a solution of 3-phenylisoindole-1-carboxamide in acetic anhydride was stirred with boron trifluoride etherate, an orange product, consisting of a derivative of imidazo[5,1-*a*]isoindole was isolated[77]. On prolonged refluxing with orthoesters in isopropyl alcohol, 1-hydrazinoisoindole forms triazoloisoindoles in moderate yields[154]. Tetrazoloisoindole is formed from 1-hydrazinoisoindole and nitrous acid in a high yield at a low temperature[155].

6. Oxidation of Isoindoles

Isoindoles are extremely sensitive to the action of atmospheric oxygen. Isoindoles unsubstituted at the $N_{(2)}$ atom can give rise to two types of products on mild oxidation: compounds containing two residues of the corresponding phthalimidine, which is observed in the oxidation of 1-methoxycarbonylisoindole[13], and tertiary alcohols of the type (XVI, R^1 = OH), with formation of a hydroperoxide of the type (XVI, R^1 = OOH) as an intermediate in the latter case[156]. The oxidation of isoindoles gives rise to a wide variety of products whose structure depends on the reagents employed and the reaction conditions. The reactions of permanganate in an alkaline medium with 1-cyanoisoindole[105] and 1,3,4,7-tetramethylisoindole[28] or of hydrogen peroxide in acetic acid[157] (or in alcohol[77]) with the isoindoles (IV, X = HC) and (XXVI, R = H) give rise to phthalic acid derivatives. Treatment of the isoindole (IV, X = HC) with chromium trioxide in an acid medium leads to *o*-benzoylbenzoic acid[157], while nitrous acid converts compound (XXII, R^4 = R^7 = Me) into 1,2-dibenzoyl-3,6-dimethylbenzene[156].



(L) (LI) (LII)

The self-oxidation of 1,2,3,4,7-pentamethylisoindole produces the corresponding phthalimide[76]. Benzophenones (L) are obtained by the self-oxidation of the isoindoles (XXII, R^4 = R^7 = Me, R^5 = R^6 = H). On the other hand, in the case of the isoindole (XXII, R = Ph) self-oxidation is achieved following additional irradiation with ultraviolet light and the imine (L) formed initially is converted subsequently under the experimental conditions into a phenanthridine derivative[156]. In the absence of oxygen the above isoindoles are entirely stable on both heating and irradiation. Oxidation of the isoindoles (XVII, R^1 = COOMe) with oxygen gives rise to the corresponding phthalimidines (XV)[13]. Irradiation of a solution of isoindole (XXVIIIa, R = Me) with access of air leads to a mixture consisting of the phthalimidine (XV, R^1 = Ph) and its 3-hydroxy-derivative[77]. Prolonged oxidation of solutions of 2-(γ-aminopropyl)isoindoles with oxygen and sometimes with $K_2Cr_2O_7$, $KClO_3$, and H_2O_2 leads to pyrimidoisoindoles and not to benzophenones (LI), as believed previously[166]. More than 40 compounds of this series have been described in a number of patents[158,165].

7. Reduction of Isoindoles

The catalytic hydrogenation of isoindoles in the presence of 10% Pd/C in ethanol[13] or in acetic acid[84] at a pressure of 3–5 atm gives rise to products of the addition of hydrogen to the pyrrole component of the molecule. Thus 1-methoxycarbonyl-2-phenylisoindole[13] and 2-γ-aminopropyl-1-arylisoindoles[84] form racemic mixtures of isoindolines under these conditions. Under the same conditions, the isoindole (VIII,

$R^1 = R^3 = COOMe$, $R^2 = Ph$) forms three products: the *meso*- and *d,l*-forms of the corresponding isoindolines[13]. The catalytic hydrogenation of the isoindoles (XXVIII, R^2 = 5-H or 5-Cl) in the presence of palladium chloride produces the same isoindoline[77]. Hydrogen adds readily only to the double bond of 2-vinylisoindoles on catalytic hydrogenation[79]. The use of Raney nickel as the catalyst of the hydrogenation of 2-(γ-methylaminopropyl)isoindole yields results similar to those of the catalytic hydrogenation on Pd/C, i.e. hydrogen adds to the pyrrole component of the molecule[86].

The final result of the hydrogenation reaction probably depends to a large extent on the nature of the substituents in the pyrrole component of the bicyclic system. Thus the hydrogenation of the isoindoles (XVII, $R^1 = COOMe$) yields products of the addition to the carbocyclic moiety with formation of compounds (LII), in contrast to 1-methoxycarbonyl-2-phenylisoindole mentioned above. A similar result has been obtained[167] in the hydrogenation (in the presence of the $Pd/BaSO_4$ catalyst) of the isoindole (VIII, $R^1 = CHO$, $R^2 = CH_2CH_2Ph$, $R^3 = Cl$)—the pyrrole (LII, $R^1 = CH_2OH$, $R = CH_2CH_2Ph$) was isolated as the hydrogenation product.

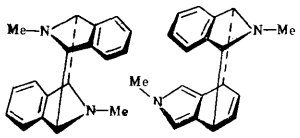
In all the known instances of the reduction of isoindoles with zinc dust in acetic acid, the corresponding isoindolines were obtained. This reduction method has been used for 4,5,6,7-tetrafluoroisoindole[94,95], benzo[*e*]isoindole[23], dibenzo-[*e,g*]isoindole[22], and 1,2-dimethyl-3-phenylisoindole[32]. It is of interest to note that in the latter case the mixture of diastereoisomers formed as a result of the reaction was resolved. Similarly the reduction of the isoindole (XLIII) with zinc dust in acetic acid yielded the isomeric *trans*- and *cis*-iso-indolines, which were separated. The catalytic hydrogenation of compound (XLIII) in the presence of PtO_2 in alcohol gives rise to mixtures of isoindolines with similar compositions[28].

8. Other Reactions of Isoindoles

Isoindoles are known to undergo reactions involving a functional group but not the ring. Thus the nitrile of isoindole-1-carboxylic acid is smoothly converted into the amide on treatment with 10% alkali[104]. The phthalyl protecting group is removed almost quantitatively from the isoindole (VIII, $R^1 = R^3 = Ph$, $R^2 = NCOC_6H_4CO$) on treatment with hydrazine[110]. The isoindole (XXVI, $R = CH_2CH_2OH$) is acetylated under different conditions, with the preferential formation of diacetyl derivatives—the products of the reaction involving the oxygen atom of the alcoholic group and the nitrogen atom of the *N*-methylcarbamoyl group[78,79]. On hydrogenation in methanol with added sodium methoxide and in the presence of the $Pd/BaSO_4$ catalyst, the isoindoles (VIII, $R^1 = CHO$, $R^3 = Cl$) retain the isoindole structure but lose chlorine atoms, forming 1-formyl-2R-isoindoles in 80% yield[167]. The isoindole (XXVIIIa, $R^2 = Cl$) is dehydrochlorinated similarly[77]. On being refluxed with an excess of hydrazine in ethanol for 2 h, the 5,6-dibenzoyl-1,2,3-trimethylisoindole gives rise to derivatives of 6,7-diazabenzo-[*f*]isoindole[75].

A number of coloured products (IV, X = RC) are formed on condensation of 1-phenylisoindole with aldehydes in pyridine with very low yields[62,169]. When the isoindole (XLIII) is heated with metal (copper, nickel, manganese, etc.) acetates, the corresponding coloured octamethyltetrabenzoporphyrins are formed. Similar molybdenum and cobalt compounds have been isolated in the form of complexes in which the central metal atom coordinates additionally other ligands (for example, pyridine, etc.)[137,169].

Under the conditions of the Vilsmeier reaction, the isoindole (XXVIIIa) forms 5-chloro-1-dimethylaminomethylene-3-phenyl-1*H*-isoindole, i.e. the carbamoyl group is eliminated and the $C_{(1)}$ atom is formylated[77].



(LIII) (LIV) (LV)

The photolysis of a solution of the isoindole (XXXIV, R = Me) leads to a 60% yield of the $[{}_{\pi}4_S + {}_{\pi}4_S]$ photodimer (LIII). Together with compound (LIII), the isomeric dimer (LIV) was isolated in 7% yield. When both dimers are irradiated with ultraviolet light at 254 nm, they dissociate and the initial isoindole is formed. Pyrolysis converts the isoindole (XXXIV, R = Me) into a condensed isoquinoline (LV)[170].

9. Practically Useful Properties of Isoindoles

In patents there are indications of the possibility of practical applications of isoindole derivatives, particularly in medicine. Thus antihypertonic[152], anti-inflammatory[152], contraceptive[138], and anorectic[65,66] effects and the sedative[87] and stimulating[81,84] influences on the central nervous system by various isoindole derivatives have been reported.

A series of preparations have been tested in electroluminescent systems[67] and as agricultural fungicides[85].

V. AROMATICITY OF *o*-QUINONOID HETEROCYCLES

The data on the physical and chemical properties of isoindole discussed above indicate a number of characteristic features of this system and other *o*-quinonoid heterocycles of type (II). In the discussion of the differences between the properties of indole and isoindole, attention must be concentrated on the differences between the degrees of their aromaticity.

A common characteristic of indole and isoindole is the presence of the 10-π-electron cloud and the identity of the electronic configurations of the atoms. The only difference, which determines the entire set of the physicochemical properties of systems (I) and (II), is that between the positions of the heteroatom in the 10-π-electron cloud and the consequent difference between the perturbations in the two cases.

Isoindole derivatives are more reactive than the corresponding indoles; isoindole itself is an extremely unstable readily polymerisable compound, i.e. its chemical behaviour does not indicate its aromaticity. Nevertheless, according to data obtained by various quantum-chemical computational methods[114,132,133,172,173], isoindole possesses a significant resonance energy, although it is smaller than that of indole (Table 4).

The resonance stabilisation of isoindole is indirectly confirmed by the spontaneous and irreversible transformation of the isoindolenine form into the isoindole form[123].

Consequently it is necessary to explain two mutually exclusive facts, namely why is isoindole so reactive if it is at the same time aromatic in the usual sense of the term.

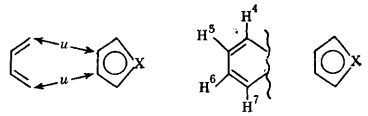
We may point to several studies[15,116,123,124,175] whose authors noted the above contradiction and attempted to resolve it. Apparently the best founded hypothesis,

capable of reconciling the high reactivity of *o*-quinonoid heterocycles with their aromaticity, is that put forward by Bornstein and coworkers[124], according to which the *o*-quinonoid heterocycles (II) consist of adjacent but in essence non-interacting π-electron systems and therefore possess a wide region of aromaticity due to the presence of the five-membered heterocyclic rings together with the reactivity imparted to the bicyclic system (II) by the adjacent butadiene component.

Table 4. The resonance energies of indole (I, X = NH) and *o*-quinonoid heterocycles (II).

Heterocycle	In units of β (Ref.172)	In units of β (Ref.173)	in kcal mol^{-1} (Ref.114)
(II) (X = NH)	0.29	0.32	11.6
(II) (X = S)	0.25	0.29	9.3
(II) (X = O)	0.02	0.11	2.4
(I) (X = NH)	0.47	0.38	23.8
(XLIV) (X=NH)	—	—	8.4

As a structural equivalent of the above hypothesis, it has been suggested[124] that *o*-quinonoid heterocycles be represented with the aid of formulae of type (LVI). The above structural ideas were first used[127] to calculate the ionisation potential of 2-methylisoindole. They have been confirmed primarily by the spin–spin interaction constants for isoindole and other *o*-quinonoid heterocycles[15,115,123–125]. According to Crews et al.,[125] the spin–spin interaction constants of the $H_{(4)}$–$H_{(7)}$ vinyl protons, obtained for various *o*-quinonoid systems (LVII), or more precisely the ratio $J_{rel} = J_{H_{(5)}-H_{(6)}}/J_{H_{(4)}-H_{(5)}}$, can serve as a characteristic of the degree of delocalisation of electrons in the butadiene fragments indicated.



(LVI) (LVII) (LVII)

Analysis of the data in Table 5 shows that, if the degree of delocalisation of electrons can indeed be estimated with the aid of J_{rel}, the implication is that the electron distribution in the carbocyclic component of *o*-quinonoid heterocycles is insensitive to perturbations in the five-membered rings. Consequently the constancy of J_{rel} for systems with such a widely variable stability (from the extremely unstable isobenzofuran to the comparatively stable isothionaphthene) can be understood only on the basis of the structural representations (LVI).

The subsequent discussion will be based on the resonance energies of structures (I), (II), and (LVII) calculated by Dewar. According to Dewar[128], the resonance energy of butadiene is zero. Consequently the difference between the calculated Dewar resonance energies of isoindole and pyrrole makes it possible to estimate the degree of stabilisation (annelation energy) as a result of the interaction in compound (LVII) between the butadiene and the five-membered heterocycle along side *c*. The annelation energy of butadiene and the five-membered heterocycle corresponding to the interaction along side *b* can be determined similarly.

Analysis of experimental data shows that, in contrast to heterocycles with the Kekulé structure, in which the annelation energy is ~15.4–18.8 kcal mol^{-1} (*o*-quinonoid heterocycles have an extremely insignificant annelation energy of 0.8–3 kcal mol^{-1}), annelation along side c of the second ring in compound (LVII) leads to only a very slight stabilisation of the system as a whole.

The structural representations (LVI) can be confirmed by comparing the bond orders of indole and isoindole. In the carbocyclic part of isoindole they are in essence the same as in acyclic polyenes, whereas the bond orders in the five-membered ring are close to those found for the monocyclic compounds (LVII).

Table 5. The spin–spin interaction constants (SSIC) for a series of derivatives of *o*-quinonoid heterocycles.

SSIC, Hz	(II) (X = NH) [123–124]	(XXXIV) (R = Me) [15]	(VIII) (R^1=R^2=Ph, R^3 = Me) [125]	(II) (X = O) [116]	(II) (X = S) [116]	(II) (X = Se) [124]
$J_{H(5)-H(6)}$	6.29	6.28	6.39	6.22	6.35	6.79
$J_{H(4)-H(5)}$	8.49	8.60	8.63	8.52	8.64	9.16
J_{rel}	0.74	0.73	0.74	0.70	0.72	0.74

Note. The numbers in square brackets denote references (Ed. of Translation).

If the above considerations are valid, then one must explain from the above standpoints the entire set of properties of *o*-quinonoid heterocycles, particularly isoindole. This can be done within the framework of the method of perturbed molecular orbitals (the PMO method)[128], in which *o*-quinonoid heterocycles are treated as combined residues of butadiene and the monocyclic π-system along side *c* in (LVI).

The diagram for the interaction of the molecular orbitals of butadiene and pyrrole, leading to the formation of the π-electron system of isoindole, obtained as a result of such treatment, is illustrated in the Figure taking into account the first- and second-order perturbations.

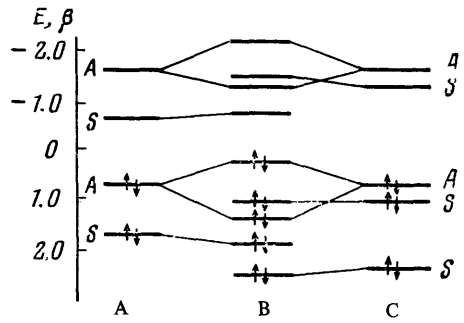


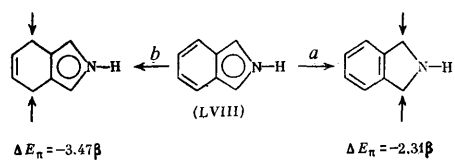
Diagram illustrating the interaction of the orbitals in the formation of the π-electron system of isoindole (B) by combining butadiene (A) and pyrrole (C).

When the residues of butadiene and of the monocyclic π-electron system of pyrrole are combined, two types of interaction are observed.

(1) Interaction between the highest occupied molecular orbitals (HOMO) of butadiene and pyrrole with the same energies, which leads to a decrease of the difference between the energies of the HOMO and the lowest unoccupied molecular orbitals (LUMO), i.e. is responsible for the low value of the first-ionisation potential and the long-wavelength absorption maximum; this type of interaction does not entail an energy gain (i.e. the stabilisation of the compound). Since the HOMO is antisymmetric in the symmetry plane $\sigma_v(y)$ and the energy of the interaction under consideration is independent of the nature of the heteroatom, all the *o*-quinonoid heterocycles exhibit a similar reactivity.

(2) Interaction with unfilled molecular orbitals, which leads to a slight decrease of the lowest occupied (symmetrical) molecular orbital of both butadiene and the monocyclic compound; this interaction depends on the nature of the heteroatom and is responsible for the annelation energy. In other words, the nature of the "aromaticity" of *o*-quinonoid heterocycles (II, X = NH, O, or S) is the same as that of the corresponding monocyclic compounds.

The structural ideas examined above should also account for the exclusively high reactivity of the *o*-quinonoid heterocycles (II) and in the first place for their tendency to enter into the Diels–Alder reaction. According to the structural representation (LVIII), there is a possibility of two types of cycloaddition reactions: to the pyrrole ring and to the carbocyclic part of the molecule. The energy of activation of π electrons (ΔE_π) in the molecule or, in other words, the reactivity of the molecule is determined mainly by the difference between the energy of the π electrons in the transition state and the energy of the π electrons of the reactants[128]. The formation of transition states in the above instances is illustrated graphically below (the arrows indicate the direction of cycloaddition) together with the calculated energies of activation of π electrons; the complete absence of interaction between the butadiene and pyrrole π-systems is postulated:



(LVIII)

$\Delta E_\pi = -3.47\beta$ $\Delta E_\pi = -2.31\beta$

Both values of ΔE_π presented are significantly smaller than for pyrrole itself and indicate an appreciable increase of the reactivity of isoindole.

Special mention should be made of the fact that the calculated activation energy for pathway *a* is smaller than that necessary for attack on the isolated butadiene fragment (pathway *b*). The activation energy in Diels–Alder reactions in relation to *o*-quinonoid heterocycles can be regarded as comprising two contributions: (1) the endothermic contribution due to the decomposition of the π-electron system of the five-membered ring and (2) the exothermic contribution due to the formation of the benzene ring on cycloaddition. The ratio of these two contributions is determined by the height of the activation barrier and, when account is taken of the considerations adduced above, it is clear that the higher resonance stabilisation of the "parent" five-membered heterocycle entails a corresponding decrease of the reactivity of the *o*-quinonoid heterocycle. Thus isobenzofuran, derived from the "weakly aromatic" furan, is much more reactive than isothionaphthene or isoindole, which are derived from more aromatic monocyclic compounds.

During the preparation of the manuscript for printing, a number of studies on the chemistry of isoindole were published. Thus-2-t-butylisoindole[208,213], 2-methylbenzo[*f*]isoindole[192,195], 4,7- and 5,6-dimethylisoindoles, 4,5,6,7-tetramethylisoindole[202], as well as substituted 2-methylisoindole[201], 1-methylisoindole[209], 1-azidoisoindole[203], 2-methyl-5-azaisoindole[210], 2-arylisoindole[211], and 2-(4′-pentenyl)isoindole[212] were obtained. The relevant calculations were made[190,193,200] and the ^{14}N NMR spectrum of 2-methylisoindole was measured[189,196]. The radical-cation derived from 1,3,4,7-tetramethyl-2-(4″-tolyl)isoindole was detected in the EPR spectrum[194]. Diels–Alder adducts involving isoindole derivatives[192,195,201,202,209,212,214], electrophilic reactions[213], and alkylation[197,204,207] have been studied for the isoindole series. The condensation of 1-aminoisoindole with β-diketones has been investigated[206]. The anorectic effect of substituted indoles has been observed[197,204,207]. Spectrofluorimetric methods for the determination of the lowest concentrations of aminoacids and proteins, by converting them into 1-thioisoindole derivatives, have been proposed[191,198,199,205].

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