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Author's Review

The 2H-Benzimidazoles (Isobenzimidazoles) as Synthons in Heterocyclic Chemistry

Hans Suschitsky

Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT, U. K.

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This article reviews for the first time the chemistry of isobenzimidazoles (2H-benzimidazoles) with special emphasis on their synthetic application in organic chemistry. Some ideas for future work in this area are outlined.

CONTENTS

I. Introduction

The present article seeks to review for the first time the chemistry of the comparatively novel 2H-benzimidazoles (isobenzimidazoles) with special emphasis on their synthetic utility. Isobenzimidazole (*I*) can be regarded as a derivative of the highly unstable *o*-benzoquinone-di-imine (*II*; R = H) which, in spite of efforts at its preparation going back to Willstätter's[1] attempts, has still not been obtained in a pure form. Stabilization of the di-imine (*II*) is usually observed when the nitrogen is associated with substituents containing hetero-atoms[2,3] (*II*; R = OH, PhCO. $PhSO_2$ *etc.*). It was, therefore, surprising that isobenzimidazole is rendered stable by the presence of an sp^3-hybridised carbon bridge, especially if it is part of a cyclohexyl ring (*I*; R — R =—$[CH_2]_5$—).

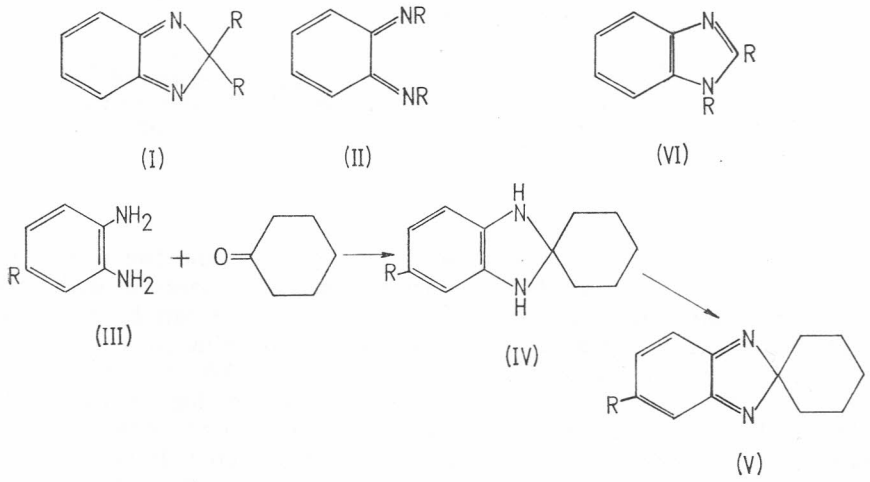
The isobenzimidazole (V_i R = H) which can be regarded as a protected *o*-phenylenediamine (*III*) reacts readily with various nucleophiles (R_2'NH, R'SH, R'OH) to give mono- (V_i R = R_2'N, R'S, R'O) or disubstituted products. Reductive ring-opening yields nucleophilically substituted *o*-phenylene diamines which are not easily accessible by conventional routes. Their utilization for further synthesis represents a convenient method of preparing a range of heterocycles with unusual substituents.

II. Synthesis of 2H-Benzimidazoles

The most convenient preparation of 2H-benzimidazole-2-spirocyclo-hexane is carried out by a two-step reaction[4] (*cf.* Scheme 1): To a hot, aqueous solution of *o*-phenylenediamine, cyclohexanone is added with shaking or stirring causing the separation of the 2,3-dihydrobenzimidazole-2-spirocyclo-hexane (*IV*; 90%). Oxidation of crude (*IV*) occurs in benzene (or methylene chloride) with activated manganese dioxide by vigorous stirring at room temperature within 1 h. The use of other solvents (*e. g.* benzene[5]) to bring about the condensation to give the dihydrobenzimidazole-2-spirocyclohexane

(*IV*) proved less effective. If the *o*-phenylenediamine lacks water-solubility the reaction proceeds well in excess of cyclohexanone. A less efficient oxidation occurs with commerical MnO_2 (pyrolusite) sodium hypochlorite or by treatment of a dichloromethane solution of the dihydro-compound with an aqueous solution of potassium permanganate in presence of a catalytic amount of tetrabutylammonium bromide. Efficient oxidation was also observed when a benzene solution of the dihydro-compound was stirred for 5 h with suspended Al_2O_3 (type H).

Various 5-substituted isobenzimidazoles have been made by the above described condensation followed by oxidation (Scheme 1; R = Cl, Me, OMe, NO_2, CO_2Et; Table I).



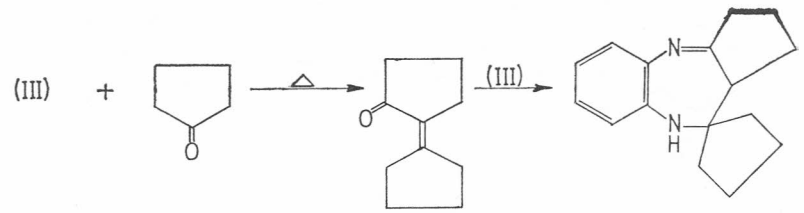
Scheme 1

TABLE I

Isobenzimidazole-2-spirocyclohexanes

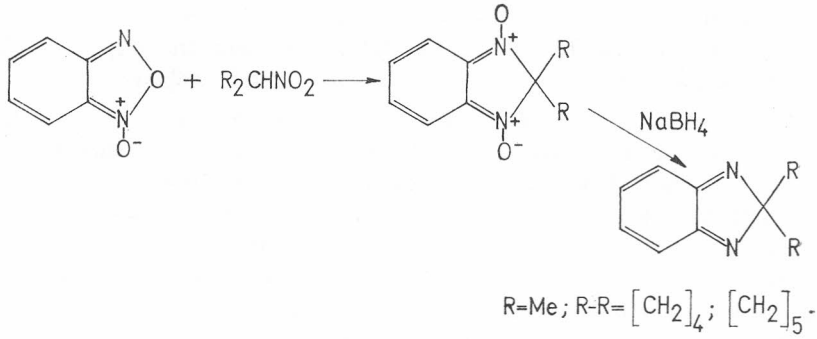
(*V*)	*M. p.*	*Yield*
R	(°C)	(%)
H	65	95
Me	70	65
OMe	112	60
Cl	58	90
NO_2	100	85
CO_2Et	66	90

Unexpectedly, when *o*-phenylenediamine was condensed with larger or smaller ring ketones or acyclic ketones, diazepines were formed.[6] For instance, 2,3-dihydro-1H-1,5-benzodiazepines resulted from the condensation of *o*-phenylenediamine with cyclopentanone (Scheme 2), as was also confirmed



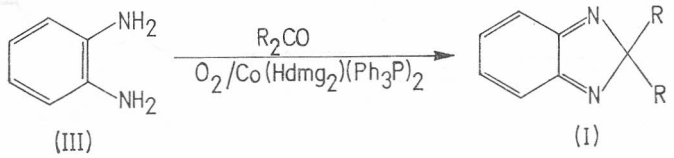
Scheme 2

recently,[6b] probably via the intermediacy of 2-cyclopentylidenecyclopentanone. Addition of BF_3—Et_2O to the reaction mixture represents in fact a high-yield method for preparing these diazepines. We ascribe the inability of other cyclic ketones to form dihydrobenzimidazoles by direct condensation to the intervention of I-strain.[7] Conversion of cyclohexanone to the spirocompound (*V*) involves change of the C=O from sp^2 to sp^3 leading to a stable chair conformation, while hybridisation for sp^2 to sp^3 of the carbonyl carbon in cyclopentanone for instance increases I-strain by bond opposition and thus militates against formation of a spirocompound. It is, however, possible to produce other 2-spiro-compounds or 2,2-dialkyl-substituted isobenzimidazoles by treating benzofuroxanes with secondary nitroalkanes.[8] The intermediate red 1,3-dioxides can be smoothly reduced to the corresponding isobenzimidazoles with sodium borohydride (Scheme 3). However, only the cyclohexane derivatives (*V*) proved stable to air and temperature.



Scheme 3

Some interesting one-step syntheses of the 2,2-dimtehyl (*I*; *R* = Me) and other isobenzimidazoles have been reported: It was found[9a] that certain cobaloxime (*II*) derivatives catalyse the aerial oxidation of *o*-phenylenediamine in the presence of various ketones to give the corresponding 2,2-disubstituted--2H-benzimidazoles (Scheme 4). Also, bis(*o*-phenylenediamine)copper(II) perchlorate yields (2,2dimethyl-2H-benzimidazole)copper(I) perchlorate when made to ract with acetone.[9b]



(III) (I)

Hdmg = dimethylglyoxime

Scheme 4

III. Structure and Physical Properties of 2H-Benzimidazole

Benzimidazole-2(3H)-spirocyclohexane (*IV*; R = H) shows bands in the infrared spectrum (nujol) at 3340 (sharp) and at 3247 cm^{-1}, typical for N—H vibration, while the grating spectrum in chloroform shows only one band at 3384 cm^{-1}. Its ultraviolet spectrum measured in ethanol absorbs at 214 (ε 29100), 258 (3720), 309 (4220) nm. The peaks shift hypsochromically in 0.1 M hydrochloric acid: 229 (ε 6350), 283 (1485) nm. The ^1H NMR spectrum (60 MHz, $CDCl_3$) displays resonances at δ 6.33 (4H aromatic), 5.56 (2 NH, exchangeable in D_2O), and at 1.55 (10 H, methylenes).

The isobenzimidazole (*V*; R = H) naturally shows a different electronic spectrum[2] with maxima at 240.5 (9680) and 343 nm (4690) and a typical band at 1530 cm^{-1} (C=N) in the infrared spectrum. Resonances in the ^1H NMR ($CDCl_3$) appear at 6.40 to 7.14 δ as an AA'BB' system for the vinylic protons (4H) and at 1.72 and 1.88 (10H) for the aliphatic protons.

Substituted dihydro- and iso-benzimidazoles (*IV* and *V*) show similar spectroscopic properties. In the proton NMR one sees the expected changes in the vinylic pattern of mono- and poly-substituted isobenzimidazoles.[4]

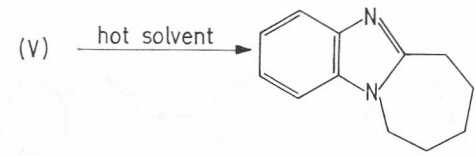
Owing to the presence of an sp^3 carbon atom the isobenzimidazoles are, unlike the isomeric benzimidazoles (*VI*), non-aromatic. Their chemical reactivity derives largely from the homodiene system of the 6-membered ring being co-conjugated to the heterodiene structure of the 5-membered ring. The reactivitiy of this frozen quinonedi-imine (*V*) coupled with its facile conversion into an aromatic system either by rearrangement or by reductive opening of the heterocyclic ring provides the basis for its synthetic utility. This will be illustrated in the following section.

IV. Reactions of 2H-Benzimidazoles

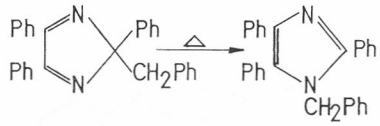
A. Thermal rearrangements

On heating the isobenzimidazole (*V*; R = H) at 180 °C dry or in a solvent (*e. g.* dichlorobenzene) the ring expanded 1,2-pentamethylenebenzimidazole (*VII*) is obtained in good yield (*ca* 50%). This thermally allowed 1,5-sigmatropic rearrangement is analogous to a benzyl shift described[10] for certain 2H-imidazoles (*e. g. VIII* → *IX*). Similarly the xanthines (*X*) can be made

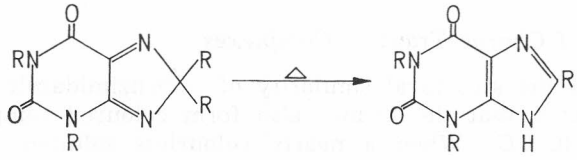
to rearrange sigmatropically[11] to give 7,8-disubstituted xanthines (*XI*) and the 2,2-diphenylisobenzimidazole (*I*; R = Ph) yielding the 1,2-diphenylbenzazadamantanebenzimidazole (*VIII*). Unsymetrically placed substituents on the cyclohexane ring give as expected a mixture of isomers which are often difficult to separate[13] (*cf.* *XIV* → *XV*; R^1 = Me or R^{1*} = Me R^2 = H) but the spiro-compound (*XIV*, R^1 = H, R^2 = Me) yielded only one product (*XV*; $R^{1 \text{ and } 1*}$ = H, R^2 = Me). Also 5-substituted isobenzimidazole[13] gave the expected mixture (*e. g.* XVI; R = NO_2 → *XVII*; R^1 = NO^2, R^2 = H and R^1 = H, R^2 = NO_2). However, the bisisobenzimidazole (*XVIII*) gave only one isomer in small yield (15%) to which the unsymmetrical diazocine structure (*XIX*) was assigned. The alternative cisoid structure (*XX*) possesses a plane of symmetry and position of the substituent on the isomer ratio has so far not be studied. and position o fthe substituent on the isomer ratio has so far not been studied. imidazole[12] (*VI*; R = Ph). Of synthetic interest is the quantitative thermal conversion of the isobenzimidazole-2-spiroadamantane (*XII*) into the homo-



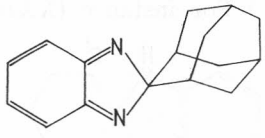
(VII)



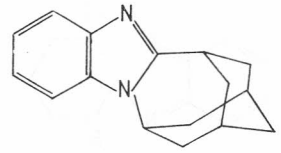
(VIII) (IX)



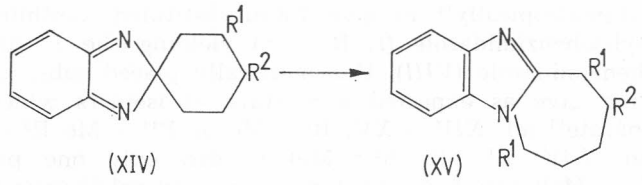
(X) (XI)



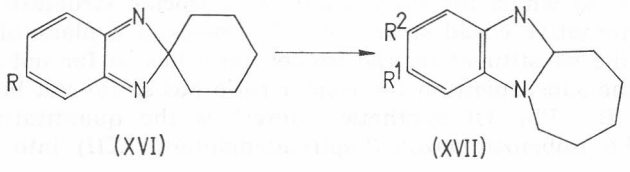
(XII)



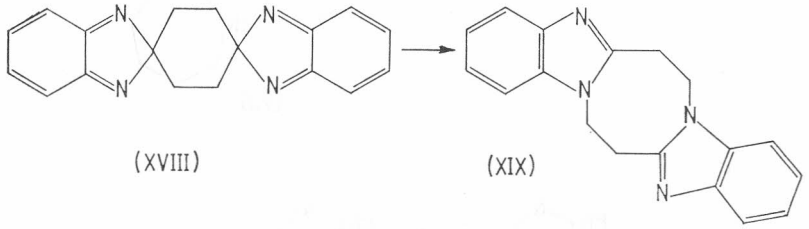
(XIII)



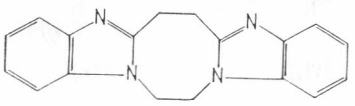
(XIV) (XV)



(XVI) (XVII)



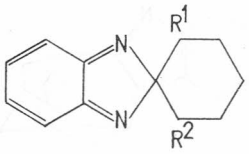
(XVIII) (XIX)



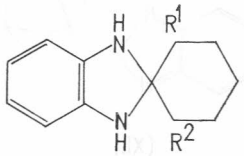
(XX)

B. Formation of Charge Transfer Complexes

In view of the structural similarity of isobenzimidazole and quinones it is not unexpected that the former also form coloured complexes of charge transfer type (C.T.C). When a nearly colourless solution of an equimolar mixture of the dihydrobenzimidazole and its corresponding isobenzimidazole (*e. g. IV* + *V*) was taken to dryness a dark-purple, crystalline solid remained. These complexes can be produced from a variety of partners constituting in essence a novel oxidation-reduction system.[14] For instance (*XXI*) and (*XXII;*



(XXI)



(XXII)

$R^1 = R^2 = H$; $R^1 = Me$, $R^2 = H$; $R^1 = R^2 = Me$) as well as the adamantyl- (*XII*) and its dihydrocompound gave rise to such complexes. The electron--asseptor bonds of the complex are obviusly weak, since it only exists as a solid, readily dissociating into its partners in solution. The PMR spectrum of the dissolved complex is an exact composite spectrum of the two constituent benzimidazoles. However, the ultraviolet spectrum (*e. g. XXI* and *XXII*; $R^1 = Me$, $R^2 = H$) showed an absorption at λ_{max} 564 nm not present in either compound, which is ascribed to an electron transfer band. The crystal and molecular structure of the (1 : 1) complex formed from the dihydrobenzimidazole (*IV*; R = H) and 5,6-(*N,N'*-dipiperidino)isobenzimidazole (*XXVI*; $Nu^1 = Nu^2 = C_5H_{10}N$) were studied[15] in some detail. The crystals are monoclinic and on X-ray investigation the dihydrobenzimidazole molecules are found to be arranged as a chain by hydrogen bonding. The isobenzimidazole components are bonded to this chain at right angles by H-bonds preventing electronic interaction of the π-systems of the two constituents (*cf.* Figures 1 and 2). These complexes are analogues to the well-known quinhydrones or

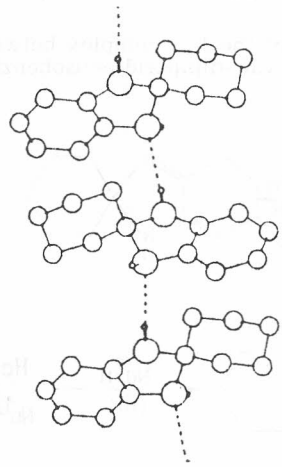


Figure 1. Hydrogen bonding in 2,3-dihydrobenzimidazole-2-spirocyclohexane

to the heterocyclic complexes formed between phenazine and 9,10-dihydrophenazine.[16] They constitute to our knowledge the first examples of 5-membered heterocycles forming such molecular compounds.

C. Reaction with Nucleophiles

Various nucleophiles react readily by a 1,4-addition[4] across the conjugated system C=C—C=N of isobenzimidazole.

1) Nitrogen Nucleophiles: For instance a secondary amine will give a red, crystalline 5-aminoisobenzimidazole (*XXV*; $Nu^1 = R_2N$) in ethanol at room temperature after a few hours and a yellow 5,6-diaminoderivative (*XXVI*; $Nu^1 = Nu^2 = R_2N$) if a three-fold excess of the amine is used.[4,17] The reaction proceeds according to Scheme 5. In warm DMSO (dimethylsulphoxide) the reaction can be accelerated and the addition of an oxidising agent (preferably activated MnO_2) will increase the yield of the monosubstituted derivative

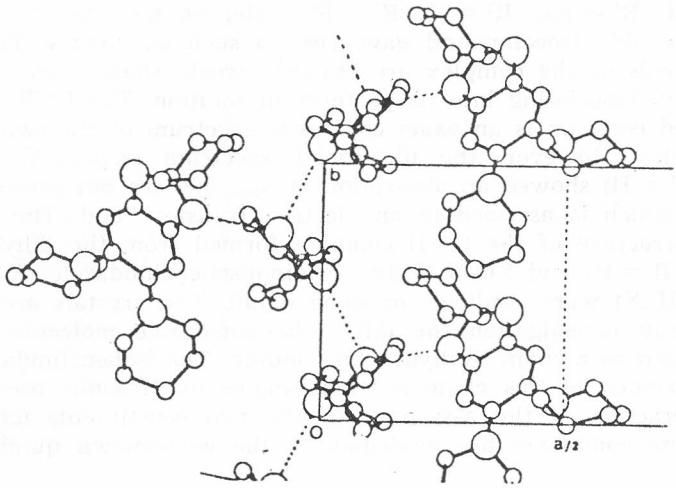
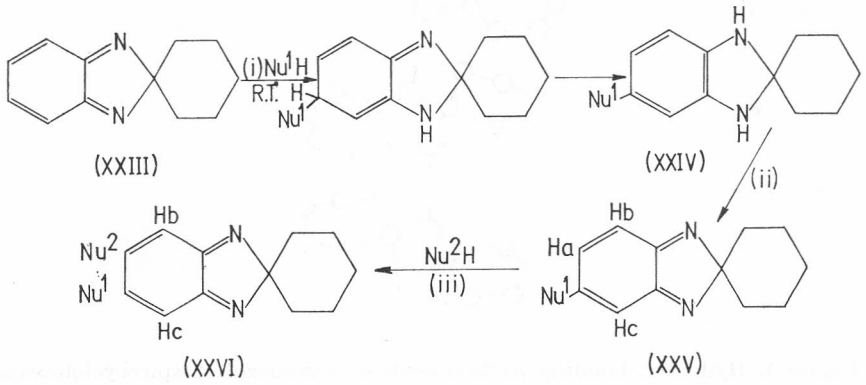


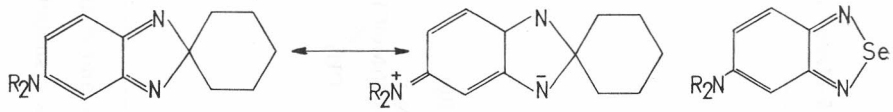
Figure 2. Molecular structure of the 1 : 1 complex between 2,3-dihydrobenzimidazole--2-spirocyclohexane and 5,6-(*N*,*N*'-dipiperidino)isobenzimidazole-2-spirocyclohexane



Scheme 5

(*XXV*) to *ca* 65% and that of the di-substituted compound (*XXVI*) to about 40%. Without the presence of an oxidising agent part of the starting material will be used up for the oxidation of (*XXIV* → *XXV*) and thereby be converted into dihydrobenzimidazole. The disubstitution can be carried out stepwise, which enables introduction of two different substituents. The colour of the aminoderivatives is very characteristic and often allows visual recognition of a mono- or disubstituted derivative, which is helpful in chromatography. The 5-monoaminoderivatives are red or deep orange, due to participation of the *p*-quinonoid structure (*XXVII* → *XXVIII*) while the diaminoderivatives are yellow. Regardless of the nature of the amino-substitutent the UV

spectrum shows three bands, the long wavelength band being at 430—470 nm. Similar spectral features were observed for 5-amino-2,1,3-benzoselenodiazoles[18] (*XXIX*) and a *p*-quinonoid structure was suggested as a contributor.[19] The yellow 5,6-diaminoisobenzimidazoles (*XXVI*; Nu^1, $Nu^2 = R_2N$) showed only two absorption bands in the UV (*ca.* 225 and 360 nm). Steric congestion will prevent either amino-group from becoming coplanar with isobenzimidazole ring, as is borne out by molecular models. Hence the contribution of the *p*-quinonoid form will be much decreased. A recent X-ray study[15] of the dipiperidino-derivative (*XXVI*; $Nu^1 = Nu^2 = C_5H_{10}N$—) confirms that the piperidine groups lie above and below the plane of the benzimidazole ring connected to it equatorially. It was expected that the steric hindrance in the 5,6-diamino-compound (*XXVI*; $Nu^1 — Nu^2 = MeN — [CH_2]_n — NMe$, n = 2 or 3) prepared from the corresponding diamine would be sufficiently reduced to allow coplanarity with the isobenzimidazole ring. However, the compounds were yellow, *i. e.* lacking *p*-quinonoid structure and their UV-spectra were similar to other 5,6-diamines. The $—[CH_2]_2—$ or $—[CH_2]_3—$ chain appears to assume the preferred staggered rather than the eclipsed conformation which tends to hold the nitrogens out of the plane of the isobenzimidazole ring. It would be of interest to prepare an 8-membered fused ring (*XXVI*; $Nu^1 — Nu^2 = MeN — [CH_2]_4 — NMe$) which according to a model is large enough to allow coplanarity of one of the nitrogens with the ring and thus induce a red colour. By contrast the 5,6-(*N*,*N*^{1}-dianilino)-isobenzimidazole (*XXVI*; $Nu^1 = Nu^2 =$PhNH) is deep-red with a band at 460 nm. The steric congestion is relieved in this case by a twist orientation which is keeping the phenyl rings apart. The tautomeric form (*XXX*) assumes the *p*-quinonoid structure. Although 5-chloro-6-(*N*-piperidino)-isobenzimidazole (*XXVI*, $Nu^1 = C_5H_{10}N$—, Nu^2 = Cl) is yellow it has an absorption band at 416 nm. This signifies a higher conjugation of the piperidine with the isobenzimidazole ring than in the case of diamines (*XXVI*; $Nu^1 = Nu^2 = R_2N$; *ca* 360 nm).



(XXVII) (XXVIII) (XXIX)

(XXX) (XXXI)

A few examples of 5-mono- and 5,6-diaminosubstituted izobenzimidazoles are given in Table II.

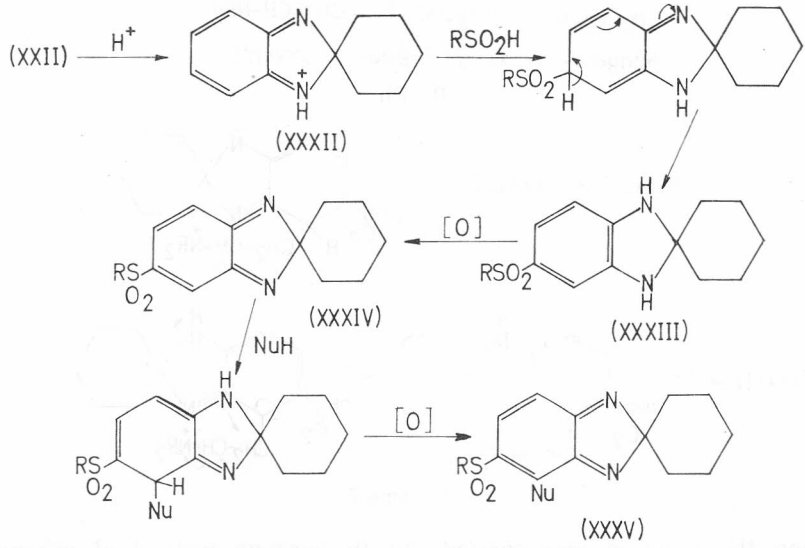
TABLE II

5-Mono- and 5,6-Diamino-Substituted Isobenzimidazoles

Compound (*XXXV*) Nu[1]	*Yield** %	*M. p.* °C	δ ($CDCl_3$; p.p.m./60 MHz)*** $H_a + H_b$	H_c	Aliphatics
Morpholino	65	103	7.2(br)	6.3(br) 6.25(br)	3.9(4Hm) 3.3(4Hm) 1.8(10H)
$C_5H_{10}N$	68	99	7.1(br)	5.8(br)	3.3(4Hm) 1.6—1.8(16Hm)
C_4H_8N	65	178	7.3(br)	5.9(br)	3.4(4Hm) 2.2—2.5(14Hm)
$C_6H_{12}N$	38	109	7.1(br)	5.8(br)	3.4(4Hm) 1.6(18Hm)
MeNH	30	219	7.2(br)	6.4(s)	3.1(3Hd) 1.8(10Hm)
PhNH	35	77	6.6—7.4(7Hm)		5.2(1HbrNH) 1.5—2.0(10Hm)
Compound (*XXVI*) Nu[1]	Nu[2]				
Morpholino	Morpholino	40	222	6.6(s)	3.9(8Hm) 3.3(8Hm) 1.8(10Hm)
$C_5H_{10}N$	$C_5H_{10}N$	40	174	6.5(s)	
$C_5H_{10}N$	$CH_2 \cdot CH_2N(Me)CH_2$ | ———N · CH_2	41	181	6.5(s)	3.1(8Hm) 1.7(22Hm) 3.2(8Hm) 2.7(4Hm) 2.4(3Hs) 1.7(16H)
PhNH	PhNH	36	218		7.5(12Hm) 6.33(1Hs) 1.9(10Hm)**
MeN—$[CH_2]_2$—	NMe	28	192	5.9(s)	3.4(4Hs) 3.0(6Hs) 1.8(10Hm)
MeN—$[CH_2]_3$—	NMe	21	140	6.1(s)	3.4(4Ht) 3.0(6Hs) 1.8(12Hm)

* Some yields are recent work and differ from ref. 4
** in CF_3CO_2H
*** d = doublet, m = multiplet, s = singlet, t = triplet

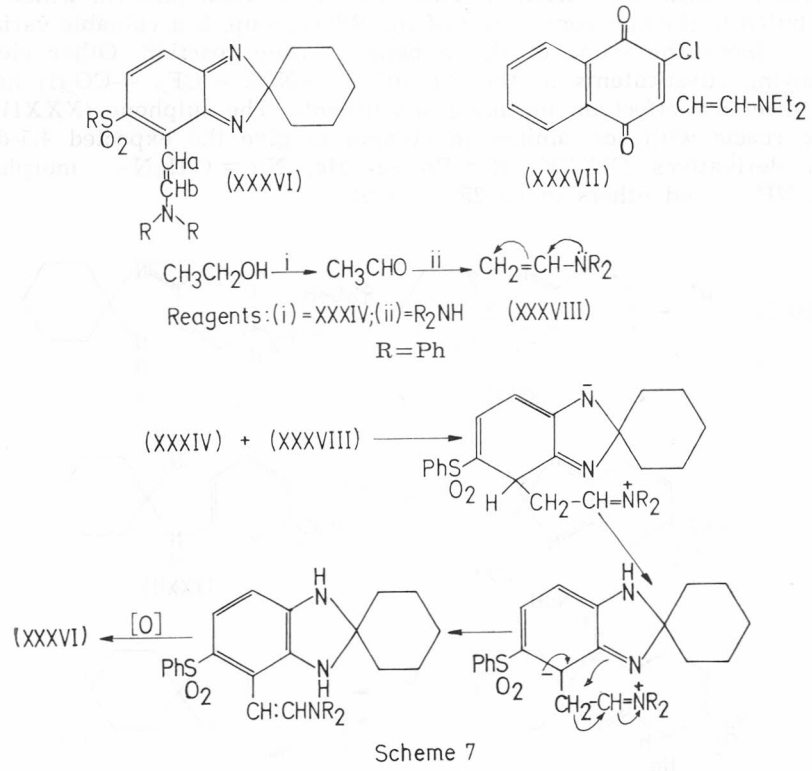
2) Sulphur Nucleophiles: Thiols, owing to their greater nucleophilic character, react vigorously with isobenzimidazole to give usually 5,6-disubstituted products (*XXVI*; $Nu^1 = Nu^2 = RS$). Howeved, 5-substituted isobenzimidazoles will only be substituted by one thiol group (*e. g. XXV*; $Nu^1 = C_5H_{10}N \rightarrow XXVI$; $Nu^1 = C_5H_{10}N—$; $Nu^2 = RS—$). The interesting deep-red thiazines (*XXXI*; without ring A, and *XXXI*; with ring A) were obtained with 2-aminoethanethiol and 2-aminobenzenethiol, albeit in low yields (6% and 34% respectively) which could undoubtedly be improved by dilution techniques. Sodium benzenesulphinate ($PhSO_2Na$) in presence of acetic acid behaves as an S-nucleophile and yields the stable benzimidazolyl phenylsulphone (*XXXIII;* 93%) which is readily oxidised (MnO_2) to isobenzimidazole[4,20] (*XXXIV*). The reaction is of course analogous to the addition of sulphinic acids to *p*-[21a] or *o*-benzoquinones[21b] yielding sulphones and proceeds presumably via the immonium ion (*XXXII*). Further substitution of the sulphone occurs in the 4-position, *i. e.* by a 1 : 6 — addition leading to a 4,5-disubstituted derivative (*cf.* Scheme 6, *XXXV*). This new substitution pattern, which must be attributed to the electronic effect of the RSO_2-group, is a valuable variation, since it widens the scope of the isobenzimidazole reaction. Other electron withdrawing substitutents in the 5-position (—NO_2, —CF_3, —CO_2H) have a similar directing effect on incoming substituents. The sulphone (*XXXIV*) for instance reacts with *sec.* amines in ethanol to give the expected 4,5-disubstituted derivatives (*XXXV*; R = Ph or Me, Nu = $C_5H_{10}N$—, morpholino, Et_2N—, NH_2— and others in ca 25% yield).



Scheme 6

However, a second, dark-blue product (16—30%) was invariably isolated. On the basis of elemental analysis and spectral data it was recognised to be the correspoding dialkylaminovinylisobenzimidazole (*XXXVI*). For instance in the case of piperidine the mixture consisted of (*XXXV*; R=Ph, Nu=NC_5H_{10}

23%, and *XXXVI*; R = Ph R—R' = —$[CH_2]_5$—, 16%). These enamines shown characteristic doublets (J = 16.6 Hz) at ca. 8.9 and 6.4 for H_a and H_b respectively, owing to a shielding and deshielding effect on these two protons as a result of the contributing structure $>N^+ = CH_b - CH_a$—. The analogous blue dialkylaminovinylquinone[22] (*XXXVII*) shows a similar pattern for the enaminic protons.[4] The vinyl moiety (—CH = CH—) is obviously derived from ethanol as in its absence (*e. g.* in benzene) no enamine is formed. Also the reaction occurs only in light. A plausible mechanism involves the following steps (Sheme 7); A photo-redox reaction between ethanol and the sulphone leads to acetaldehyde by dehydrogenation; interaction with a *sec.* amine produces the dialkylvinylamine (*XXXVIII*) known to be unstable;[23] its addition to the starting sulphone leads to the enamine (*XXXVI*). Some supporting evidence for this scheme was adduced by replacing ethanol by acetaldehyde in the reaction which yielded the corresponding blue enamine (*XXXVI*) in high yield.



Scheme 7

When the reaction was carried out in benzene instead of ethanol the only product in excellent yield was the expected 4-amino-compound (*XXXV*, Nu = R_2'N). Examples of these reactions are to be found in Table III. Primary amines also reacted readily with the sulphone (*XXXV*; R = Ph), but gave lower yields than secondary amines (*e. g.* *XXXV*; Nu = NH_2, 55%; Me_2CHNH, 41%). Primary α,ω-diamines reacted in any solvent to give the expected bis-diamines (*e. g.* *XXXIX*; n = 2, 4 or 6).

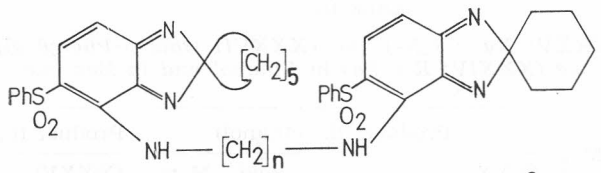
TABLE III

Yields of Products (XXXV; Nu = R_2N-) and (XXXVI) from 5-Phenylsulphonylisobenzimidazole (XXXIV; R = Ph) in Ethanol and in Benzene

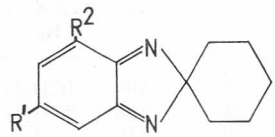
(XXXV) Nu	Yield (%)	M. p. (°C)	Products (in ethanol) (XXXVI) R_2	Yield (%)	M. p. (°C)	Product (in benzene) (XXXV) Nu	Yield (%)
$C_5H_{10}N$	23	100	—$[CH_2]_5$—	16	180	$C_5H_{10}N$	83
Morpholino	24	128	$[CH_2]_2$—O—$[CH_2]_2$	18	175	Morpholino	89
C_4H_8N	20	110	—$(CH_2)_4$—	16.5	183	C_4H_8N	87
Et_2N	18	96	Et_2	30	162	Et_2N	85

3) Oxygen Nucleophiles: The reaction of sodium alkoxides or aryloxides with isobenzimidazole (*V*; R = H), contrary to that with other nucleophiles, is impracticable because of its slowness. However, the readily available 5-chloroderivative (*V*; R = Cl) yields for instance the 5-methoxy-compound (*V*; R = OMe) when made to react with NaOMe in cold methanol, while on reflux the 4,6-dimethoxy-isobenzimidazole (*XL*; $R^1 = R^2$ = MeO) is produced which is an unexpected orientation. The alkoxyde substituent is replaceable by *N*-nucleophiles, which adds to the positional variety of the substitutions observed in isobenzimidazole. Thus heating the dimethoxy-compound in piperidine yields 4,6-dipiperidino (*XL*; $R^1 = R^2 = C_5H_{10}N$—) and 4-methoxy--6-piperidino-isobenzimidazole (*XL*; $R^1 = C_5H_{10}N$—, R^2 = OMe). It thus appears that the 6-methoxygroup is nucleophilically more labile than that in the 4-position. Sodium ethoxide gave simliar results (*XL*; $R^1 = R^2$ = OEt) while the reaction with aryloxides led only to monosubstitution (*e. g. V*; R = PhO). To account for the unforeseen substitution pattern observed with oxygen nucleophiles we advance the mechanism outlined in Scheme 8: The intermediacy of an oxonium structure is in our view responsible for directing the incoming group into the 4-position. The question may be asked why amino- or thio-substituents (*V; R* = >N— or —S—) do not at least in part engender a similar substitution pattern. The rason for this may lie in the fact that the corresponding 'onium structures make a smaller resonance contribution than the oxonium ion.

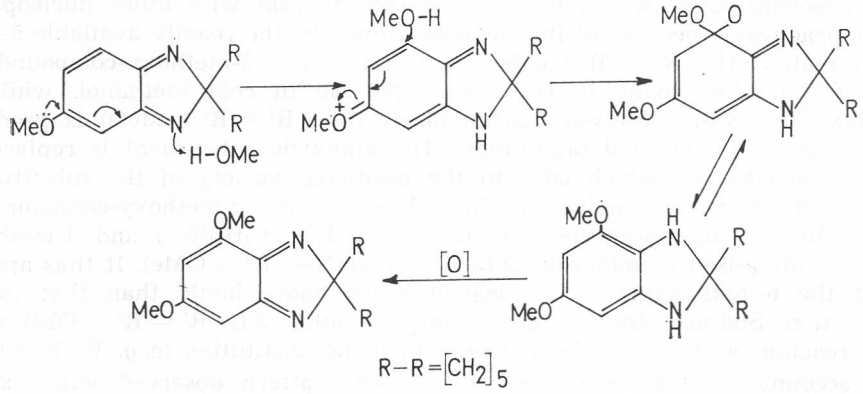
4) Carbon Nucleophiles: Malonitrile reacts with the isobenzimidazole (*I*; R = Me, or R—R = —$[CH_2]_5$ on standing in ethanol to give the 5-dicyanomethylene derivatives (*XLI*; $R^1 = R^2$ = CN; R^3 = Me or R^3—R^3 = —$[CH_2]_5$). Interaction of excess of malononitrile with the above dicyano-compound produces a green linear tricyclic or tetracyclic quinonoid heterocycle (*XLII*: R = Me or R—R = —$[CH_2]_5$— respectively.[24,25] With cyanoacetic ester an analogous result was recorded, but the product consisted at least in solution of the two stereoisomers (*XLI*; R^3—R^3 = $[CH_2]_5$—, R^1 = CN; $R^2 = CO_2Et$ or $R^1 = CO_2Et$; R^2 = CN). The structures (*XLI*) were readily interpreted by spectroscopic data (IR, PMR) and especially by the ^{13}C NMR spectrum which shows some high field peaks due to the enaminic effect. For example the C-7 and $C(CN)_2$ peaks (*cf. XLI*; $R^1 = R^2$ = CN) appear at 87.7 and 64.3 p. p. m.



(XXXIX)

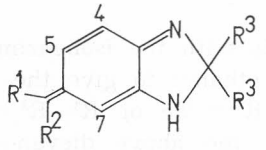


(XL)

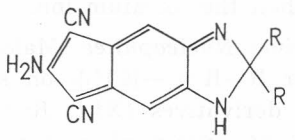


Scheme 8

i. e. in line generally reported for a cyanoenamine structure. The cyano--groups by contrast absorb at very low field (155.3 and 156.4 p. p. m.) as observed for a similar molecular environment.[26]



(XLI)

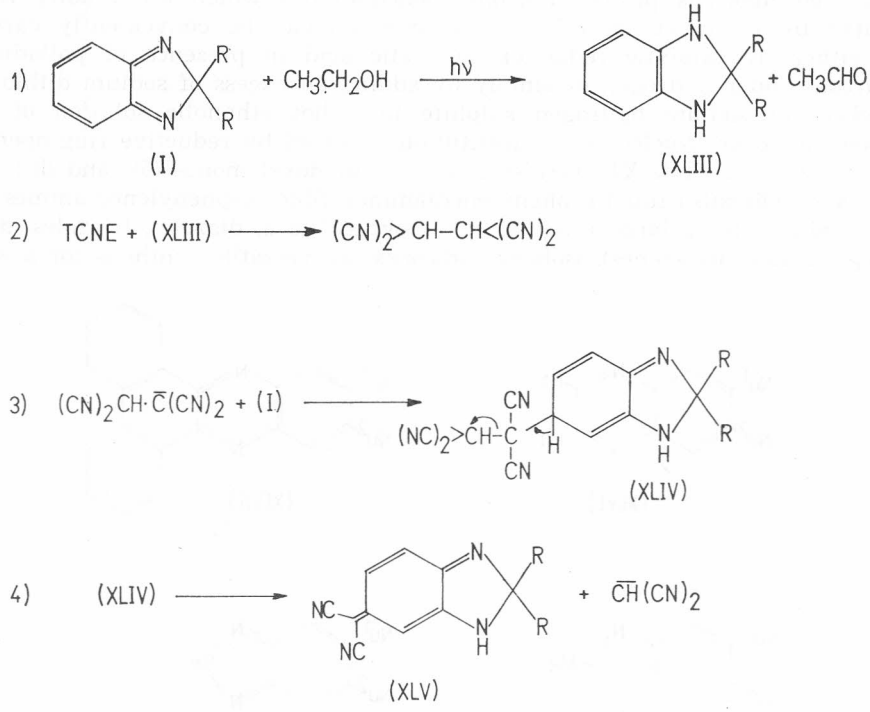


(XLII)

The product obtained from the interaction of tetracyanoethylene (TCNE) with the dimethyl or cyclohexyl isobenzimidazole (*I*; R = Me or R—R = = —$[CH_2]_5$—) in cold ethanol was completely unexpected since it was identical to that obtained with malononitrile (*XLI*; R^3 = Me or R^3—R^3 = —$[CH_2]_5$—; $R^1 = R^2$ = CN). The formtaion of this unforseseen product can be rationalized as shown in Scheme 9: In the first step (1) a redox reaction subject to light produces acetaldehyde and the dihydrocompound (*XLIII*). In propyl alcohol

acetone is formed, while in non-protic solvents or in the dark the reaction does not occur, which confirms the first reaction sequence. Moreover, the final product is obtained when the dihydro-compound (*XLIII*) is made to react with TCNE in any solvent. In the next step (2) TCNE is reduced by the dihydrobenzimidazole (*XLIII*) to give tetracyanoethane, a hydrogenation[27] typical of TCNE. Michael addition of the cyanoethane which is a strong acid (pK_a 3.6) in step (3) to the isobenzimidazole yields the non-isolable adduct (*XLIV*) from which by loss of malonitrile the purple dicyano-compound (*XLV*; R = Me or R—R = —$[CH_2]_5$—) is produced. We know only of one other case of an analogous fragmentation, namely that of TCNE reacting with indane-1,3-dione to form 2-(dicyanomethylene)indane-1,3-dione by loss of malonodinitrile.[28]

It is noteworthy that TCNE showed no tendency to react with the substrate (*I*) in a Diels-Alder fashion.



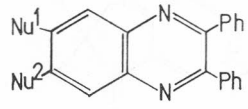
Scheme 9

5) Inorganic Anions: The parent isobenzimidazole (*V*; R = H) did not react with a range of inorganic anions (*e. g.* NO_2^-, HSO_3^-, SCN^-, CN^-) in various protic and dipolar aprotic solvents. However, the 5-chloro-derivative (*V*; R = Cl) reacted smoothly with NaN_3 and KCN especially in DMSO to give the corresponding derivatives (*V*; R = N_3 or —CN). Apart from this ipso-substitution a small amount (6—10%) of the vicinal product (*XXVI*: Nu^1 = Cl, Nu^2 = N_3 or CN) was also obtained. Organic *N*-nucleophiles (*e. g.* piperidine)

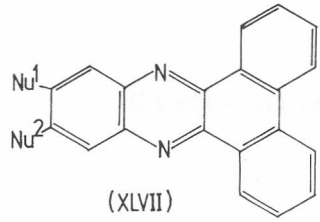
also gave predominantly ipso-substitution with the 5-chlorocompound (*V*; $R = Cl$) and only a small quantity of vicinal *i. e,* 5,6-disubstituted product (*XXVI*; $Nu^1 = Cl$, $Nu^2 = C_5H_{10}N$—) in contrast with oxygen nucleophiles (*cf.* above) which underwent exclusively ipso-substitution. This regiospecificity appears to be reserved for the hard nucleophiles, which has also been observed for nucleophilic substitutions in 2-chloro-*p*-napthoquinones.[29]

D. Conversion Into Other Heterocycles

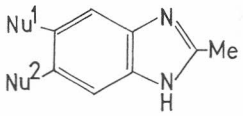
As has been discussed in some detail isobenzimidazole is prone to attack by nucleophiles. In contrast its precursor *o*-phenylenediamine is subject to electrophilic substitution (*e. g.* halogenation, nitration) either direct or after temporary conversion into a benzothia- or benzoselenadiazole.[30,31] The transformation into 2H-benzimidazole-2-spirocyclohexane can thus be regarded as an 'umpolung' of *o*-phenylenediamine. Alternatively isobenzimidazoles can be looked upon as protected *o*-phenylenediamines which are readily regenerated by reductive hydrolysis. The reaction can be conveniently carried out either by catalytic reduction in acetic acid in presence of palladium--charcoal under hydrogen or simply by adding an excess of sodium dithionite ($Na_2S_2O_4$) or sodium hydrogen sulphite to a hot ethanolic solution of the isobenzimidazole. Nucleophilic substitution followed by reductive ring-opening of (*V*; *XXVI, XXXV*; *XL*) furnishes a serial of novel mono- (5)- and di-(5,6)-, (4,5-, and (4,6)-substituted *o*-phenylenediamines. Since *o*-phenylenediamines are intermediates for a large range of heterocycles[32] (*e. g.* diazoles, triazoles, diazines, triazines, diazepines), isobenzimidazoles are versatile synthons for a wide



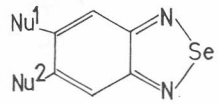
(XLVI)



(XLVII)

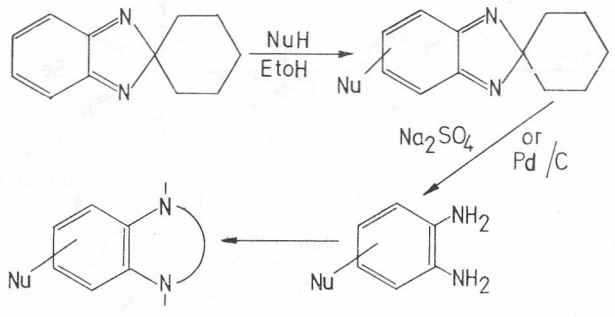


(XLVIII)



(IL)

spectrum of such compounds with nucleophilic groups. The dearth of literature in this field is a fair reflection of the multistep conventional and. therefore, cumbersome synthesis necessary to prepare heterocycles possessing such substituents (*e. g.* piperidinobenzimidazole[33]). A general sequence demonstrating the simple approach of using isobenzimidazole for preparing heterocycles with nucleophilic substituents is set out in Scheme 10. A few examples of mono and di-substituted heterocycles synthesised expediently by this method[4,17]



Scheme 10

are given in Table IV. Representatives of several other heterocyclic systems have similarly been prepared or are under active investigation.

TABLE IV

Heterocycles from Isobenzimidazoles (XXV) and XXVI)

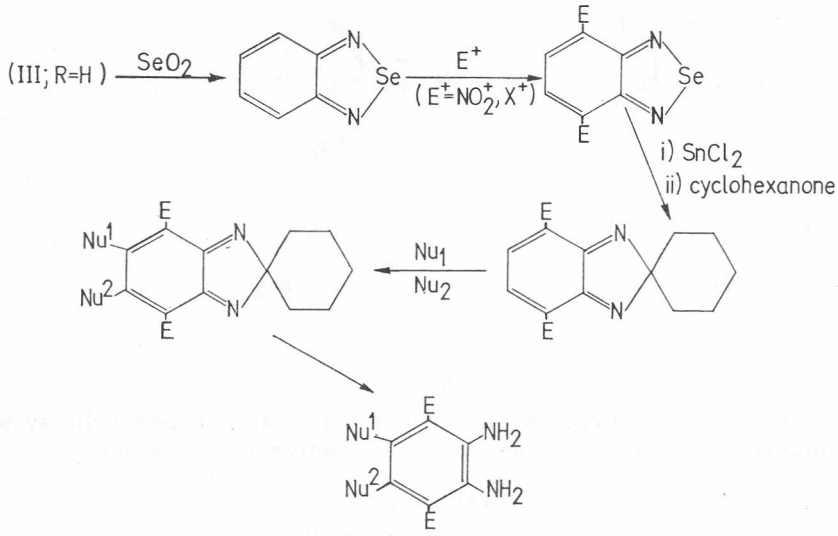
Heterocycle	Nu^1	Nu^2	*Yield**	*M. p.*
(XLVI)	$C_5H_{10}N$	H	76	171
(XLVII)	Morpholino	H	60	228
(XLVII)	$C_5H_{10}N$	$C_5H_{10}N$	63	245
(XLVII)	PhS	PhS	81	288
(XLVIII)	$C_5H_{10}N$	H	63	172
(XLVIII)	$C_5H_{10}N$	$C_5H_{10}N$	83	281
(IL)	$C_5H_{10}N$	H	55	105
(IL)	$C_5H_{10}N$	$C_5H_{10}N$	76	171

* Calculated on substituted isobenzimidazole

E. Synthetic Prospects of Isobenzimidazoles

Future research will no doubt widen the scope of isobenzimidazole as a heterocycle in organic synthesis. Some obvious areas for further investigation, some of which are currently being undertaken, are outlined below.

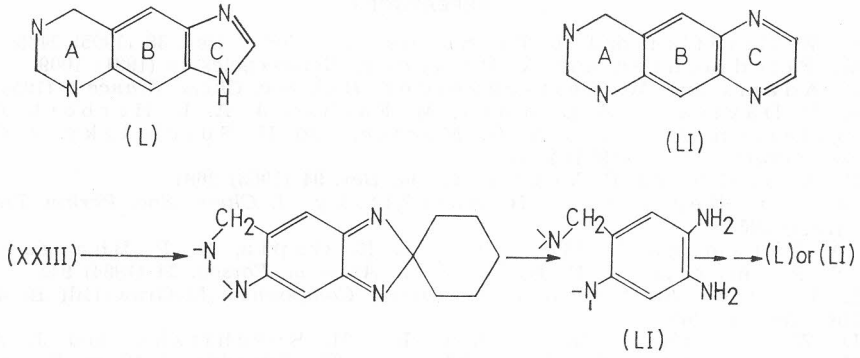
1) Preparation of hexasubstituted benzenes: By a succession of electrophilic and nucleophilic substitution of o-phenylenediamine certain hexa-substituted benzenes should become more easily available than by conventional synthesis. Scheme 11 outlines this new approach: The o-phenylenediamine undergoes nitration (or halogenation) readily in the 3- and 6-position when protected as selenadiazole.[31] Ring-opening ($SnCl_2$), conversion into the corresponding isobenzimidazole, nucleophilic substitution and regeneration of the diamine will furnish a hexa-substituted benzene of known orientation. The scheme clearly demonstrates the complementary relationship of benzoselenadiazole and 2H-benzimidazole, *i. e.* for electrophilic and nucleophilic substitution respectively.



Scheme 11

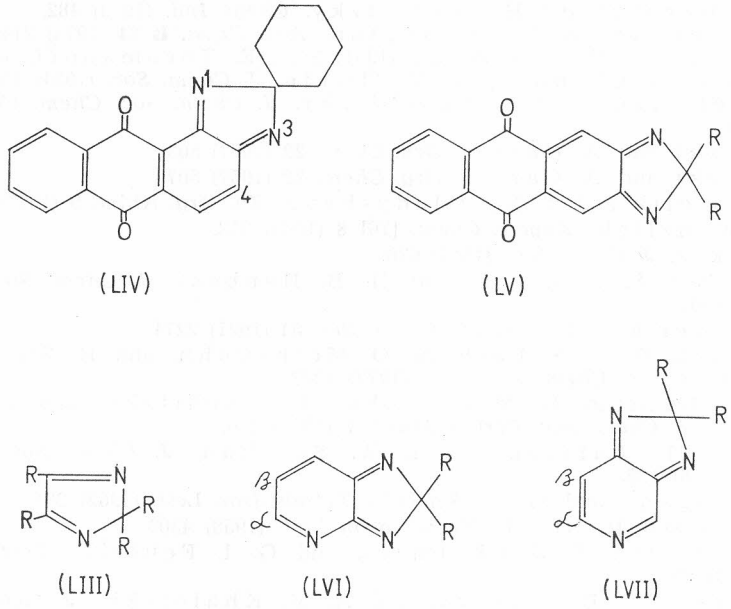
2) The synthesis of 'extended' purine and pteridine systems: An important approach to analysing enzyme-coenzyme binding sites in naturally occurring purines[34] and pteridines[35] is of current interest. For this purpose so-called 'stretched out' linear and angular purines and pteridine analogues, *i. e.* with an intercalated benzene ring (*L* and *LI*) are required. The reported preparations[34,35] are cumbersome involving multistep, conventional syntheses. A rational and tempting alternative to the problem lies in utilising the synthetic potential of isobenzimidazoles in which rings B and C in (*L*) and (*LI*) are potentially preformed. By introducing two ortho-substituents (*cf.* Scheme 5) suitable for annelating a pyrimidine ring on to the existing system for which methods have been recently reviewed[36] the synthesis of (*L*) and its derivatives should be considerably simplified. The required precursor would formally correspond to contour (*LII*) which is prepared from (*XXIII*) as indicated in Scheme 12. The synthesis of (*LI*) could be developed analogously. The method has already proved successful for preparing other linear or angular tricyclic or tetracyclic structures.[37]

3) Study of isobenzimidazole analogues: Very few examples of other fused 2H-imidazoles have so far been reported, but of related interest is a recent comprehensive review of the parent 2H-imidazole[38] (*LIII*). Some work on the spectral and chemical properties of 2*H*-anthraquinonoimidazoles (*LIV* and *LV*) has, however, appeared[39] which shows that the former (*LIV*) not unexpectedly adds various nucleophiles (HX, RSO_2H, RSh, NO_2^-) to give 4-substituted imidazolines (*cf. LIV*). It would be of considerable interest and chemically challenging to widen the study of 2*H*-benzimidazole by preparing common heterocyclic analogues derived from pyridine (*LVI, LVII*), quinoline, quinoxaline *etc.* The change in the induced electronic propensity of these systems towards substitution would no doubt lead to novel and synthetically



Scheme 12

valuable derivatives. For instance direct nucleophilic addition in the α and more importantly in the β-position of the pyridine (*LVI* and *LVII*) can be predicted with confidence.



The author hopes that this brief survey of using a novel and readily available heterocycle in organic synthesis will stimulate some readers to apply this method to their own problems.

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POVZETEK

2H-Benzimidazoli (Izobenzimidazoli) kot sintoni v heterociklični kemiji

H. Suschitzky

To je prvi pregledni članek, ki obravnava kemijo 2H-benzimidazolov (izobenzimidazolov) s posebnim povdarkom na sintetsko uporabnost v organski kemiji. Predstavljene so tudi nekatere ideje za bodoče delo na tem področju.