THE SYNTHESIS OF IMIDAZOLES

VIA TETRAZOLES

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For my parents Ōg and Eleanor

with love and gratitude.

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Michael Casey

ABSTRACT

The preparation and properties of 4*H*-imidazoles are reviewed.

Eighteen 1-(alk-1-enyl)tetrazoles, bearing a hydrogen methyl or phenyl group at C-5, and bearing alkyl or aryl or alkoxycarbonyl groups on the alkene were prepared using three methods. (i) Alkylation of 2-(tri-*n*-butylstannyl)tetrazoles with epoxides and cleavage of the resulting stannyl ethers with acids gave 1-(2-hydroxyalkyl)tetrazoles regioselectively. The alcohols were dehydrated by treatment with methyltriphenoxyphosphonium iodide in HMPA or DMF followed by aqueous sodium hydroxide. This method is a considerable improvement on earlier procedures. (ii) Amides were condensed with carbonyl compounds to give enamides and these were converted to the alkenyltetrazoles *via* the enimidoyl chlorides in the case of benzamides and acetamides, and the alkenylisonitrile in the case of a formamide. (iii) Conjugate addition of 2-(tri-*n*-butylstannyl)tetrazoles to methyl propiolate and DMAD afforded tetrazolylacrylates.

Photolysis of the 1-alkenyltetrazoles gave 1*H*-imidazoles. The yields varied greatly with solvent, 60-80° petroleum ether, ethanol, and water giving the best results. In the 5-phenyltetrazole series photocyclisation to give fused tetrazoles was a competing reaction. When the alkene was 2,2-disubstituted, 4*H*-imidazoles were formed. These reactive compounds were isolated only in the 2-phenyl and 2-methyl series. 4,4-Dimethyl-4*H*-imidazole was generated in solution but attempts to isolate it failed.

The 4*H*-imidazoles were found to be very susceptible to attack at C-5 by nucleophiles such as methanol and organometallics. On thermolysis they underwent [1,5] methyl migrations to give 1*H*-imidazoles.

6-Acetoxy—2,4,6-trimethylcyclohexadienone reacted with N-phenyl-triazoldione to give the expected cycloadduct. However, attempts to fuse a 4*H*-imidazole ring onto this bicyclic compound and hence use it to prepare 3a*H*-benzimidazoles were unsuccessful. The acetoxyketone and the corresponding hydroxy ketone did not condense with amidines and attempted Ritter reactions on the α-hydroxyketones gave only hydroxyoxazolines.

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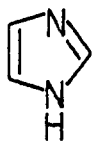
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1. REVIEW

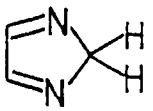
THE CHEMISTRY OF 4*H*-IMIDAZOLES

1.1. INTRODUCTION

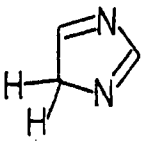
Imidazoles may exist in three tautomeric forms (1), (2), (3) of which the aromatic 1*H*-form is by far the most stable. Because of the



(1) 1*H*-



(2) 2*H*-



(3) 4*H*-

driving force of aromatisation the non-aromatic isomers (2) and (3) are isolable only when the tetrahedral carbon bears two " blocking" groups which do not undergo migration to nitrogen.

In contrast to the extensive studies on the biologically and pharmacologically important 1*H*-imidazoles,[1] very little attention has been paid to the 4*H*-tautomers. However, these are of interest because of their unusual structures and because they afford an opportunity to study the isomerisation processes which give rise to their aromatic isomers. While few attempts have been made to study 4*H*-imidazole chemistry systematically some of the more readily accessible examples have been studied in detail and this has resulted in a rather fragmented development of this area.

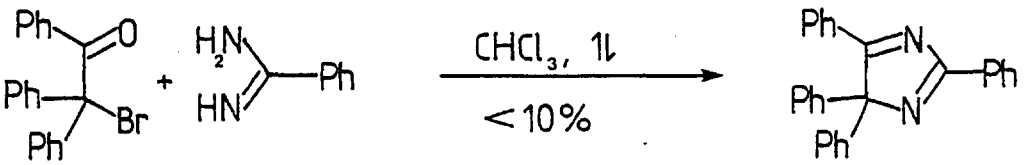
This review will attempt both to describe and to correlate the methods of preparation and the physical and chemical properties of 4*H*-imidazoles. 4*H*-Imidazol-4-ones will not be included, and 4-diazo and 4-alkylidene derivatives will only be mentioned briefly.

1.2. SYNTHESIS

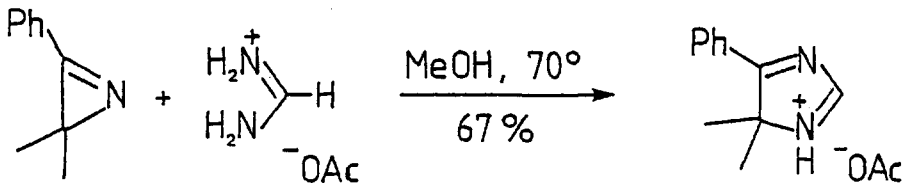
Most of the routes used to prepare 4*H*-imidazoles are adaptations of those used for 1*H*-imidazoles.[1] However, the necessity to incorporate blocking groups means that the intermediates are often more difficult to obtain, and less reactive, than the less highly substituted analogues used to give the 1*H*-isomers. As for 1*H*-imidazoles most methods of preparation are based on α-amino carbonyl compounds and these will be described first, followed by sections on oxidation and cycloaddition methods.

1.2.1. From Acyclic α-Substituted Ketone Derivatives.

There is only one report of the formation of a 4*H*-imidazole by condensation of an amidine with an α-bromo ketone.[2] Although this is

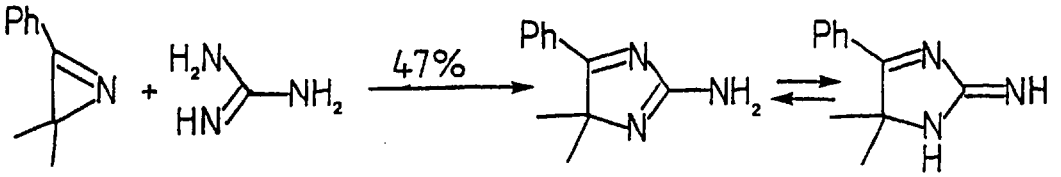


a powerful method for the preparation of 1*H*-imidazoles it is likely that the reduced reactivity of tertiary halides will greatly restrict its application to 4*H*-imidazoles. Curiously an attempt to prepare the tetra-4-chlorophenyl derivative in the same way gave only the intermediate α-amidino ketone.[3] Reaction of formamidinium acetate with an azirine (4), which is the synthetic equivalent of an α-amino ketone, gave a



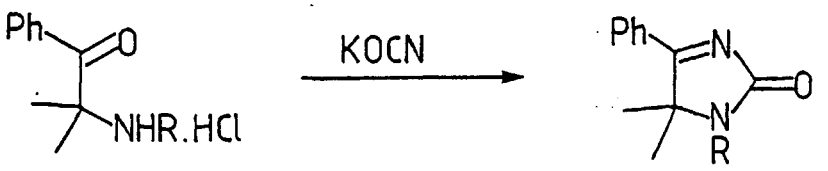
(4) (5)

4*H*-imidazolium acetate (5).[4] No attempt was made to prepare the free imidazole. Similarly the azirine (4) reacted with guanidine to give



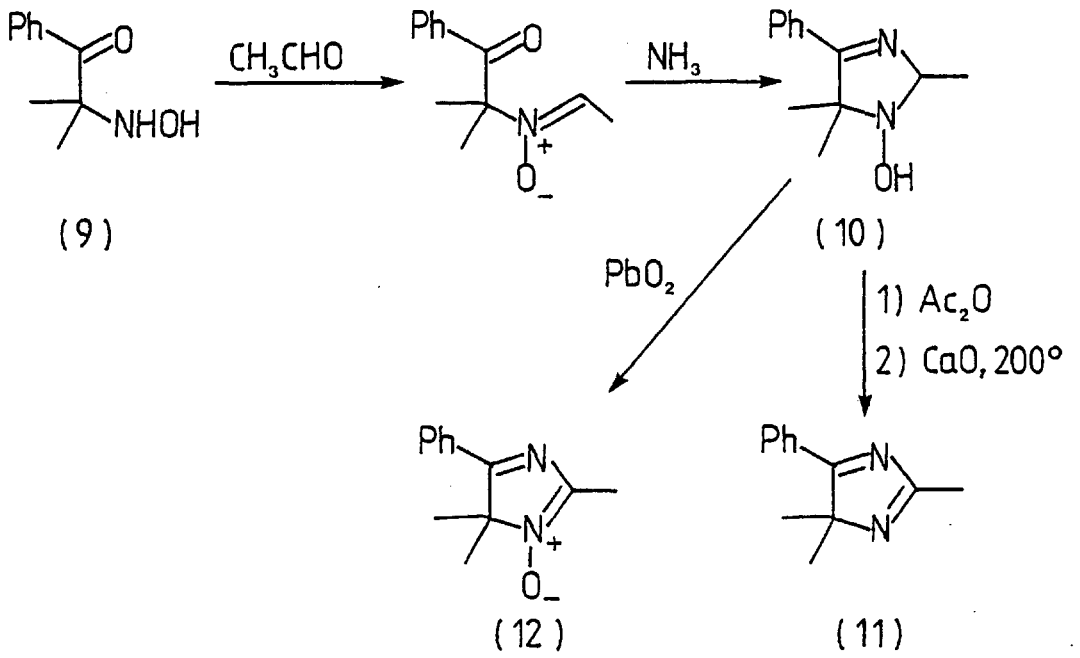
(4) (6) (7)

a 2-amino imidazole (6).[4] The position of the equilibrium between the amino (6) and imino (7) tautomers was not established. It has been shown that the Marckwald synthesis is successful for blocked imidazol-2-ones (8) and in principle this route could be adapted to produce 2-alkoxy-4*H*-imidazoles.[5] α-Hydroxylamino-isobutyrophenone (9) has been



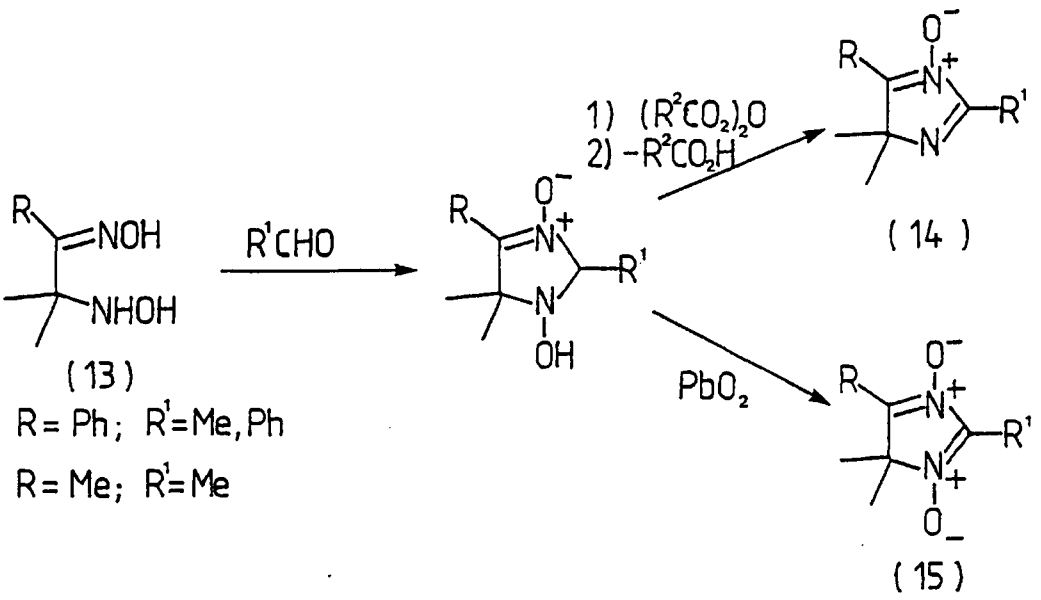
(8)

used to prepare an *N*-hydroxyimidazoline (10) which was dehydrated to



(9) (10) (12) (11)

give a 4*H*-imidazole (11) and gave the corresponding 3-oxide (12) on oxidation.[6] In a similar way, α-hydroxylamino oximes (13) gave the 1-oxides (14) and 1,3-dioxides (15) of 4*H*-imidazoles.[6,7] An *N*-oxide

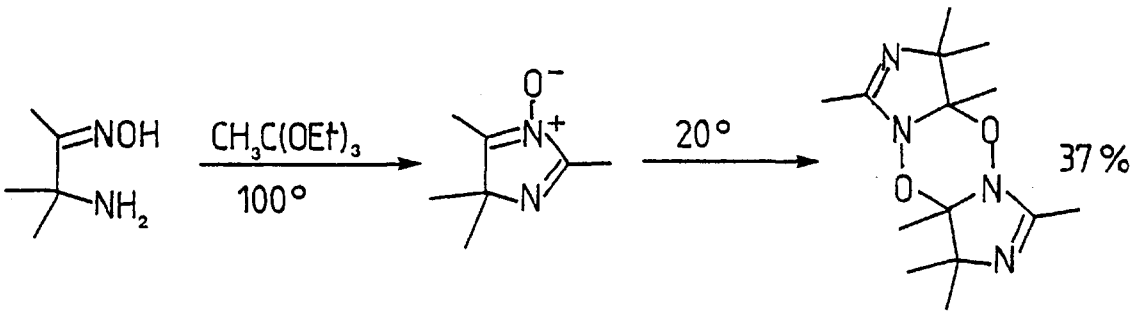


(13)
R = Ph; R' = Me, Ph
R = Me; R' = Me

(14)

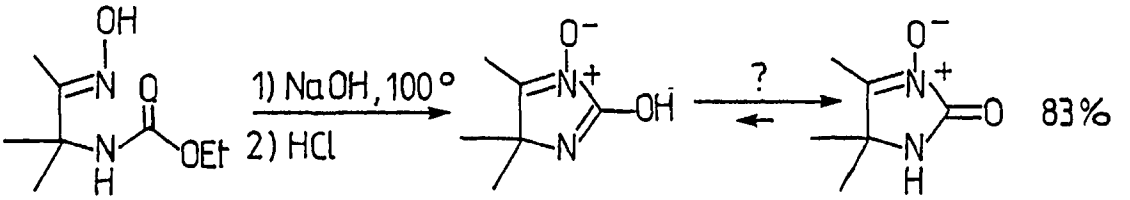
(15)

(17) has been prepared in one step by reaction of an α-amino oxime (16) with triethyl orthoacetate.[8] This oxide was found to form a dimer (18) on standing and this may explain the discrepancies in spectral data quoted by different workers.[7,8] A similar reaction was claimed to



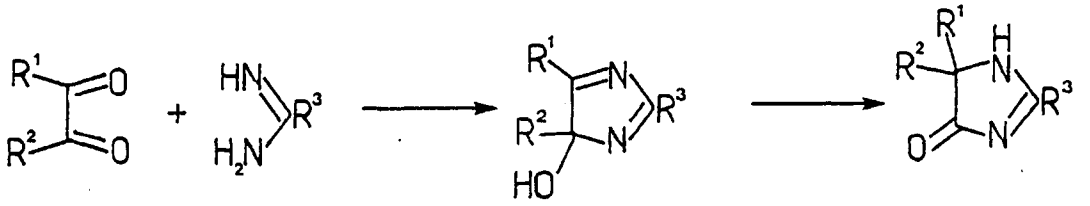
(16) (17) (18)

yield a 2-hydroxy-4*H*-imidazole (19) but in the absence of spectroscopic data in support of this structure it seems likely that the product exists as the imidazolone (20).[9]

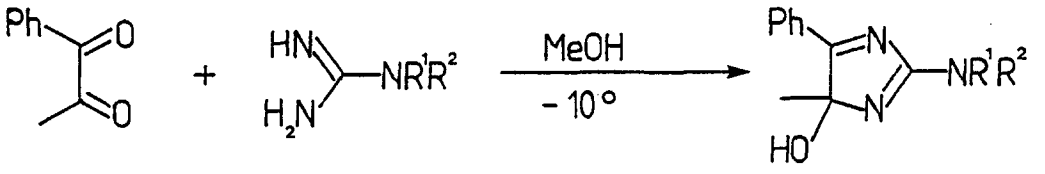


(19) (20)

The reactions of amidines with α-diketones generally gives imidazolones (Section 1.2.3.) *via* benzilic acid type rearrangement of the intermediate 4-hydroxy-4*H*-imidazoles, and early reports claiming isolation of these intermediates are almost certainly in error.[10,11,12]



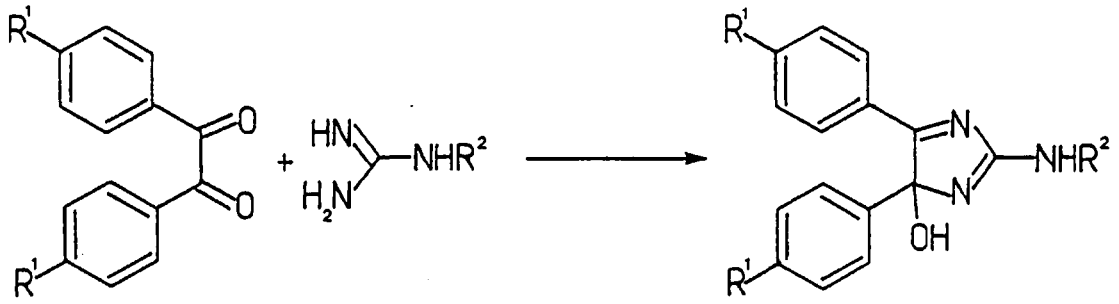
However, when guanidines were used the hydroxyimidazoles (21) were



(21)

isolated,[13] and another series (22), prepared from benzils in the same way, exhibits antiviral activity.[14]

Clearly only a small number of the possible routes based on α-substituted ketones have been exploited. The chief problem in routes of this kind seems to be the inaccessibility of the " blocked" precursors but with the addition of more recent methods, *e.g.*, the Neber reaction[15]



R^1 = H; R^2 = Me, Et, Pr^i, $PhCH_2$

R^2 = Me; R^1 = Me, Cℓ, MeO, Bu^t

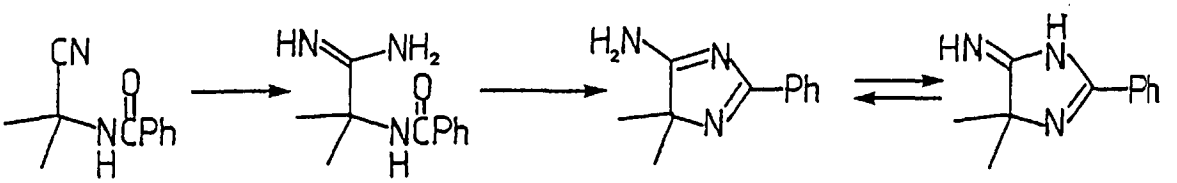
(22)

and ferricyanide amination,[16] for the preparation of such compounds to the classical routes based on α-halogenation, α-nitrosation *etc.*, their synthesis does not present insuperable difficulties. It is likely that a much wider range of α-substituted ketones could be used and many variations on the schemes described above would be successful.

1.2.2. From Acyclic α-Substituted Acid Derivatives.

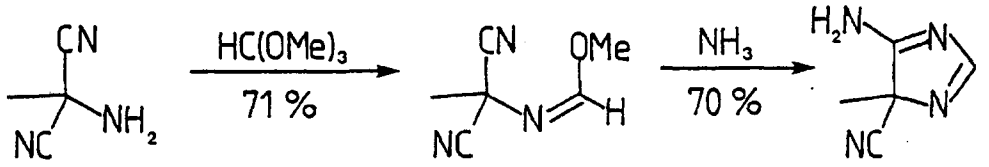
In general α,α-disubstituted α-amino acid derivatives are more easily obtained than the corresponding ketones. Most of the preparations based on them involve alkylation of the exocyclic heteroatoms of imidazolones, imidazoldiones and their thio- and imino derivatives, and since this forms a distinct class of reactions, routes involving cyclic precursors will be discussed separately in following sections.

An α-amido nitrile (23), prepared by the Strecker synthesis (Section 1.2.3), was converted into the α-amido amidine (24) in the standard way and on cyclisation in base yielded a 5-amino-4*H*-imidazole (25).[17] The product was formulated as the imino tautomer (26) on the basis of the



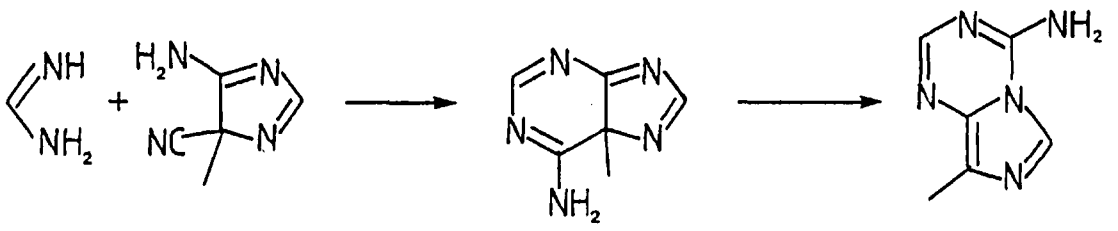
(23) (24) (25) (26)

i.r. spectrum but the position of the equilibrium is open to question. It appears from the small number of examples available that infrared spectroscopy can be used to distinguish between endocyclic imino groups (1590 to 1630 cm^{-1}) and exocyclic ones (1650 to 1700 cm^{-1}). Evidence such as this indicates that imidazoles bearing one or two potential hydroxy or mercapto groups, or two potential amino groups, generally exist only in the keto forms.[18,19] This problem recurs in the case of the 5-amino-4-cyano-4-methylimidazole (29) below.[20] Prepared from an α-amino malononitrile (27), *via* the imidate (28) and presumably the amidine, it is drawn as the amino isomer. However, the i.r. absorbances



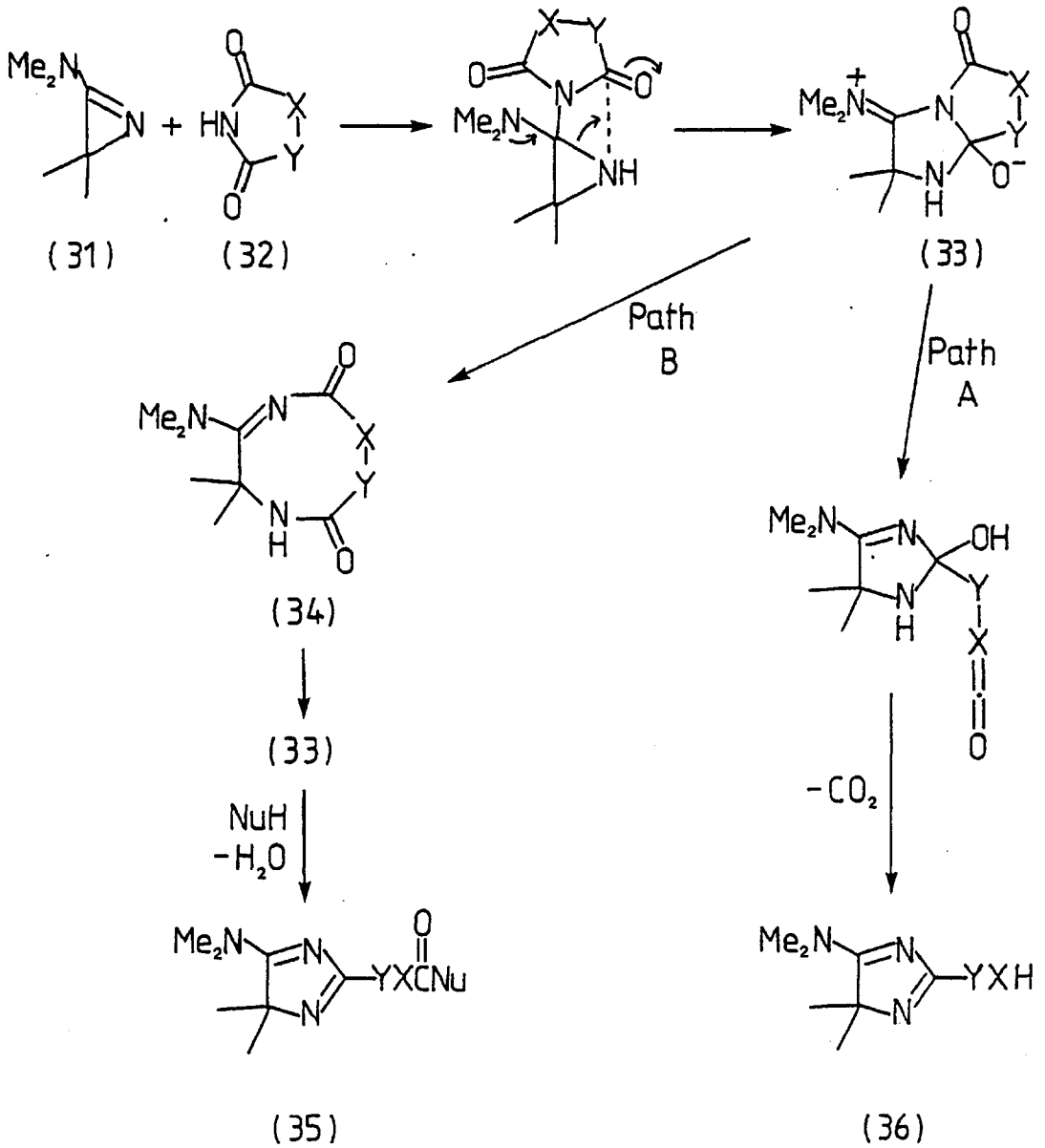
(27) (28) (29)

in the C=N region are not quoted, and although the ^{13}C n.m.r. spectrum is very similar to those of some 5-dimethylamino compounds (*v.i.*) this evidence is not conclusive in the absence of spectra of suitable model imino compounds. The aminocyano compound (29) was used in an attempt to prepare 5-methyladenine (30) but although this was probably formed it was not isolated because of rapid rearrangement. MINDO/3 Calculations indicated that the blocked intermediate (30) was very unstable (ΔH_f° = 94.5 kcal mol^{-1}) because the sp^3 carbon was almost tetrahedral forcing the molecule into a buckled conformation and diminishing the conjugation.



(29) (30)

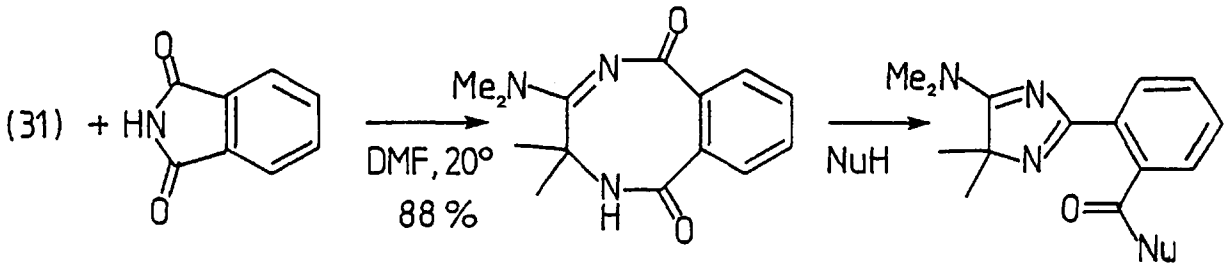
A large number of 5-dimethylamino-4,4-dimethyl-4*H*-imidazoles have been prepared by a Swiss group studying the reaction of 3-dimethylamino-2,2-dimethylazirine (31) with cyclic imides (32) (Scheme 1.1). When X



(31) (32) (33) (34) (33) (35) (36)

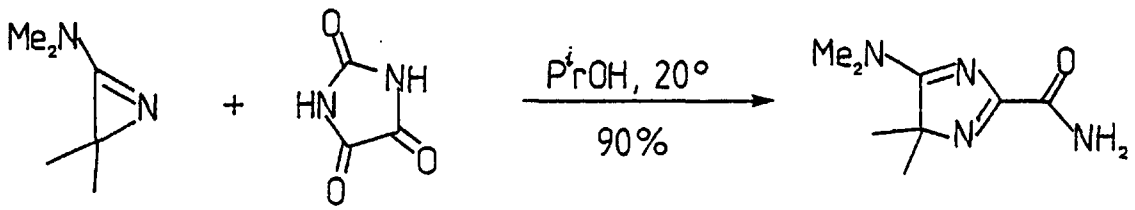
SCHEME 1.1

is an NH group, 4*H*-imidazoles (36) are obtained directly (Path A) and an outline of a probable mechanism is shown.[21] Otherwise (Path B), medium ring intermediates (34) are isolated and these give 4*H*-imidazoles (35) on reaction with nucleophiles.[22,23] Thus, phthalimide (37) gave



(37) (38)

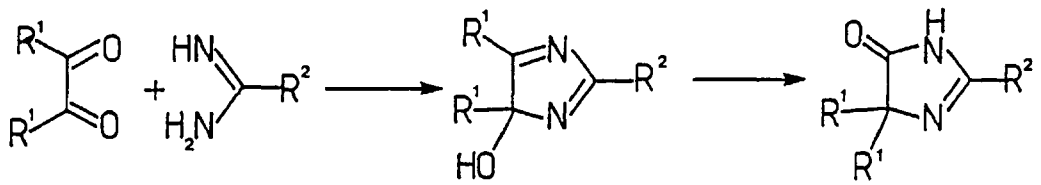
2-arylimidazoles (38) and parabanic acid (39) gave an imidazolecarboxamide (40).



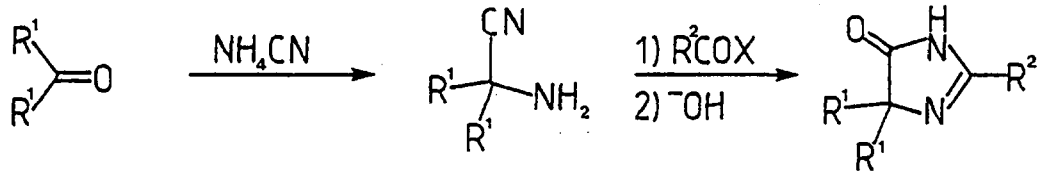
(31) (39) (40)

1.2.3. From Imidazolones.

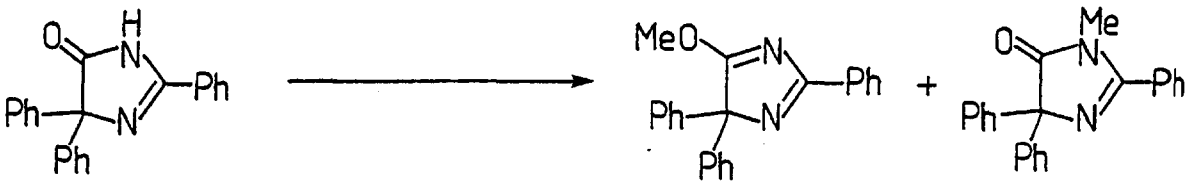
The preparation of imidazolones has been reviewed and only an outline of the methods used in 4*H*-imidazole syntheses will be given here.[24,25] Reaction of amidines with α-diketones gives imidazolones via benzilic acid type rearrangement of intermediate 4-hydroxy-4*H*-imidazoles. Reaction of ammonium cyanide with ketones provides a general synthesis of α-amino nitriles and these can be converted into



imidazolones by acylation and treatment with base. Thio and imino compounds are available using appropriate variations in these methods and by thiolating the oxo derivatives.



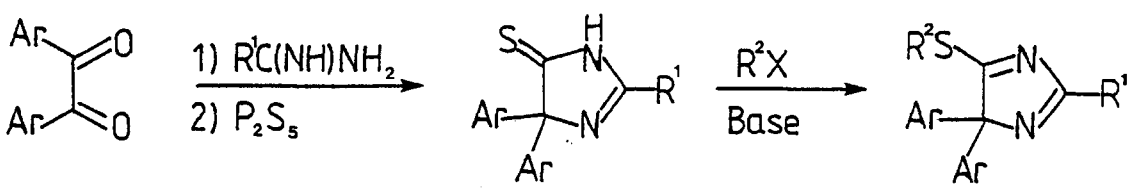
Alkylation of an imidazol-4-one (41) with methyl iodide and sodium ethoxide gave the *N*-methylated product (43) exclusively but some *O*-methylated imidazole (42) was obtained using diazomethane.[26]



(41)

	(42)	(43)
MeI, NaOEt	0%	78%
CH_2N_2	28%	26%

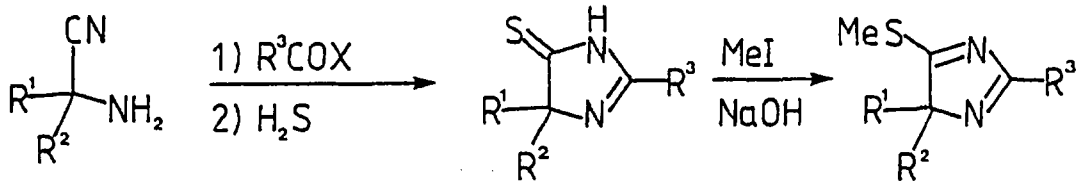
As expected however, the corresponding thiones (44) alkylated exclusively on sulphur.[26,27] A series of 5,5-dialkylimidazolthiones



(44) 37-97%

Ar = Ph, 4-CℓC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$

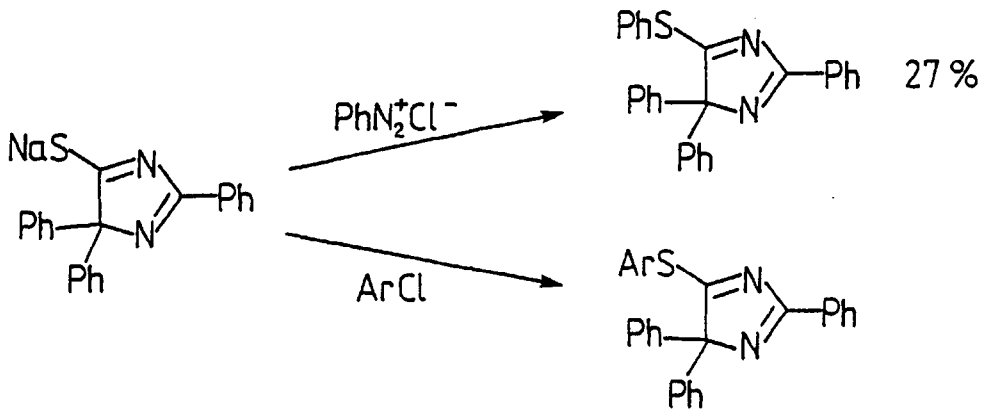
R^1 = Me, Ph; R^{2}X = MeI, PhCH$_2$Cℓ, Ar$'_2$CHCℓ



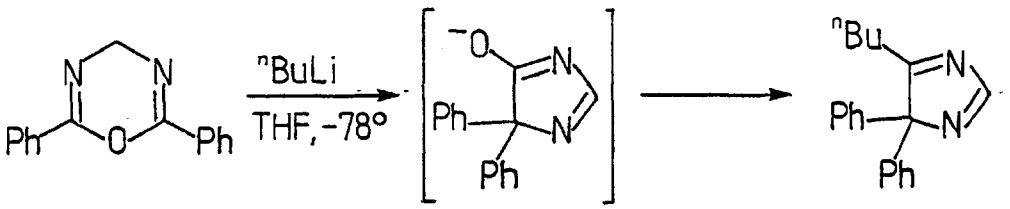
R^1, R^2 = Me,Me; Et, Et; $-(CH_2)_5$; Me, Et; Me, $PhCH_2$

R^3 = Me, Et, $PhCH_2$, Ph

was alkylated similarly.[28] Imidazol-4-thiones have been arylated on sulphur using phenyldiazonium chloride and activated aryl halides.[27]



Finally the formation of a 4*H*-imidazole (47) in the reaction of *n*-butyl lithium with an oxadiazine (45) is believed to involve addition of the

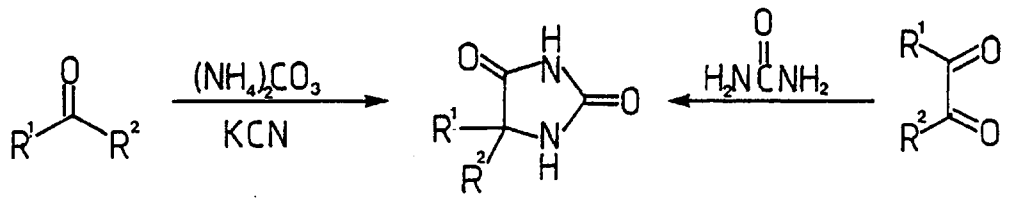


(45) (46) (47)

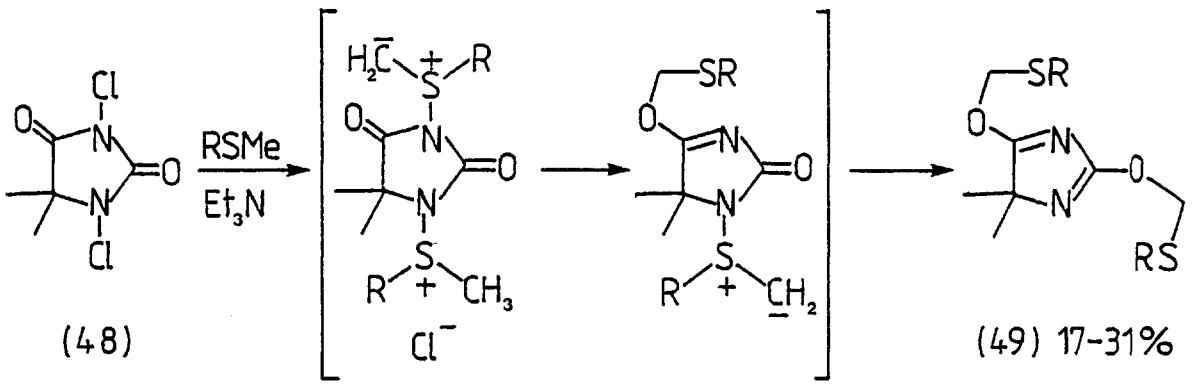
organometallic to an intermediate imidazolone (46).[29] Although the mechanism has not been confirmed this is an interesting and potentially very useful route to 4*H*-imidazoles.

1.2.4. From Hydantoin Derivatives.

Hydantoins are readily available, the principal methods of synthesis being the reaction of ammonium carbonate and potassium cyanide with ketones, and the condensation of urea derivatives with α-diketones.[24,25]

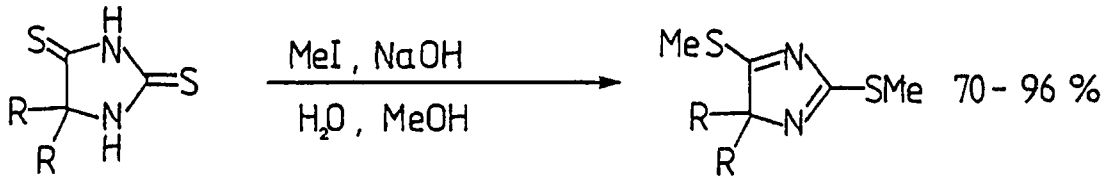


Alkyl halides, dimethyl sulphate and diazomethane do not give *O*-alkylation but " harder" reagents such as methyl fluorosulphonate have not been tried. The only example of *O*,*O*-dialkylation involved a Stevens rearrangement using 1,3-dichloro-5,5-dimethylhydantoin (48).[30] All other possible isomers were formed by sequences of [1,2] and [2,3]

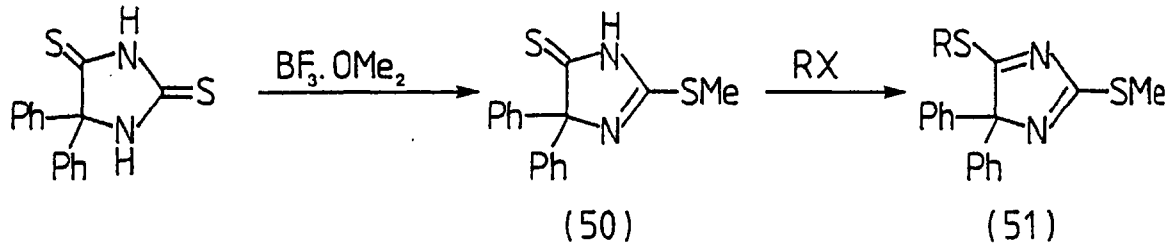


sigmatropic shifts but the 4*H*-imidazoles (49) were the major products. 2-Thiohydantoins and 4-thiohydantoins were alkylated on sulphur and nitrogen by methyl iodide and diazomethane but *O*-alkylation was not

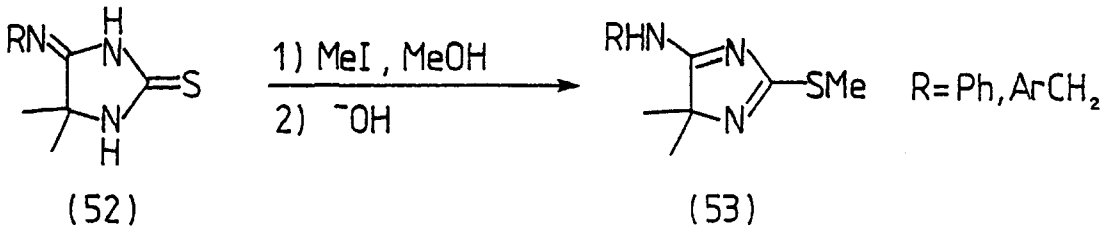
observed.[31] Dithiohydantoins, however, underwent smooth dialkylation on sulphur using excess methyl iodide and base.[31,32,33] Dimethyl sulphate and diazomethane were inferior because they gave partial



nitrogen alkylation.[31] Curiously boron trifluoride dimethyl ether complex gave 2-thiomethyl derivatives (50) selectively.[34] Further



alkylation using alkyl halides then gives mixed dithioalkyl-4*H*-imidazoles (51).[35] These may also be obtained by partial alkylation of dithiohydantoins, separation of the monoalkylated isomers, and further alkylation, but this procedure is tedious and inefficient.[35,36] Alkylation of 4-imino-2-thioimidazoles (52) with methyl iodide gave thiomethyl

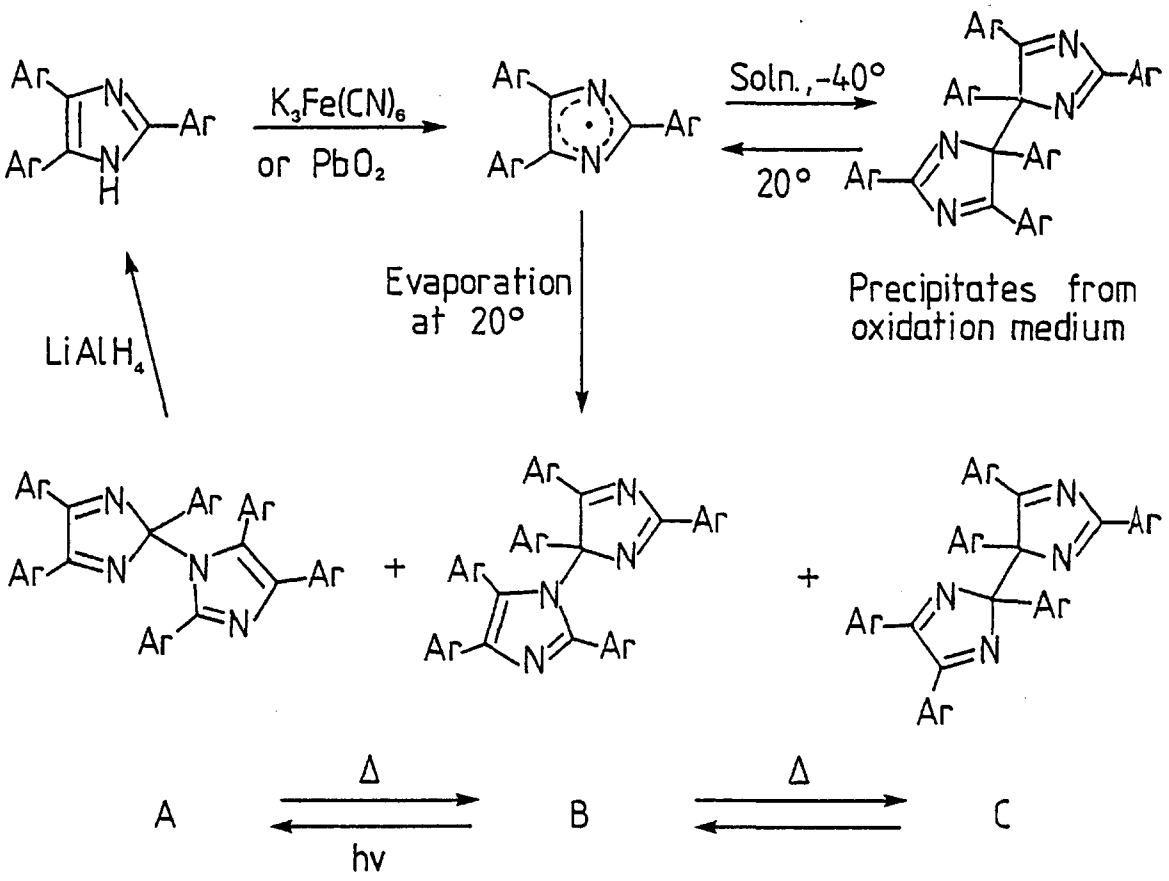


derivatives whose i.r. spectra indicated that they existed in the amino-4*H*-imidazole from (53).[37] Desulphurisation of alkylthio derivatives is a possible route to simple 4*H*-imidazoles but it has not been reported.

1.2.5. By Oxidation of 1*H*-Imidazoles: One Electron Oxidation.

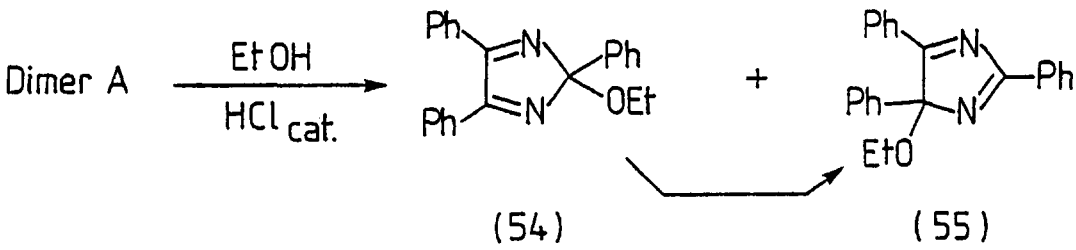
Diaryl and triarylimidazoles are very susceptible to oxidation and reaction with one electron oxidants such as potassium ferricyanide gives radicals which form a range of dimers, some containing the 4*H*-imidazole nucleus. The structure and chemistry of these radicals and their dimers have been studied in detail and since the area has been reviewed,[38] only an outline of the features particularly relevant to 4*H*-imidazole chemistry will be given here.

After much confusion in the early literature the structures of the triarylimidazole dimers were elucidated by spectroscopic methods, particularly i.r. and n.m.r.[39,40,41] The dimers (commonly identified by letters, as shown) and their interconversions are shown in Scheme 1.2,

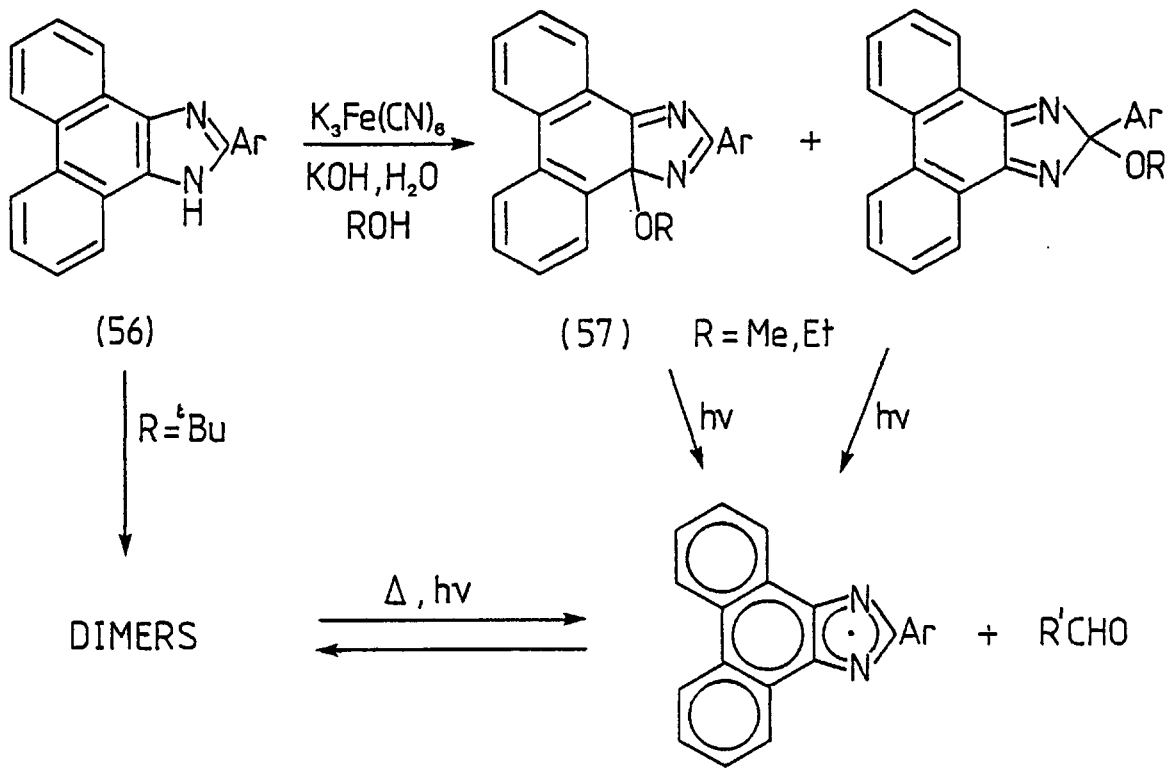


SCHEME 1.2

but there is still some doubt about the structural assignments.[3] Similar results were obtained by electrochemical oxidation,[42,43] and by oxidation of triarylimidazolyl anions with bromine.[44] Other dimers were obtained by irradiation at -85°C,[45] and by pyrolysis of dimer A at 200°.[3] Dimer A reacted with ethanol containing a catalytic quantity of hydrochloric acid to give a mixture of 2-ethoxy- (54) and 4-ethoxy-imidazoles (55) and the 2*H*-isomer was converted into the 4*H*- on standing.[40]

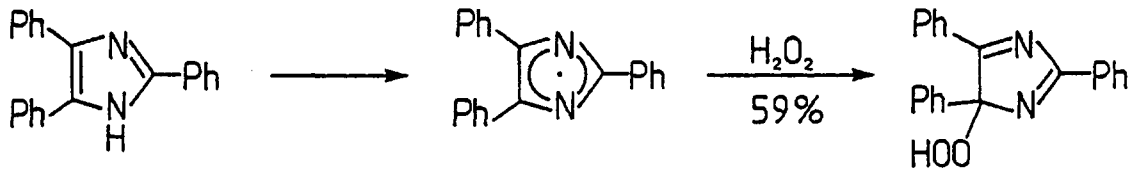


In the oxidation of a tetracyclic system (56) the radicals were trapped by the solvent presumably because dimerisation was slow for steric reasons.[46]



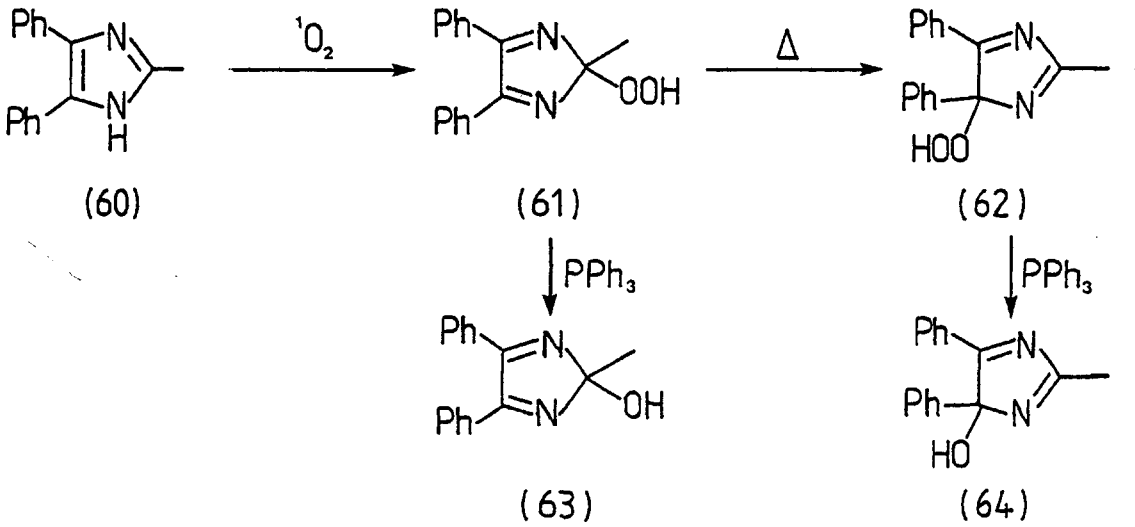
The behaviour of a 1,4-bis(diphenylimidazol-2-yl)benzene was intermediate between that of the triarylimidazoles and the tetracyclic system (56).[47] The 4*H*-imidazole (57) is the only known example of a stable 3a*H*-benzimidazole.

Photolysis of lophine (58) in the presence of singlet oxygen and reaction of the lophyl radical with hydrogen peroxide gave a 4-hydroperoxy-4*H*-imidazole (59).[48] Other hydroperoxides gave corresponding



(58) (59)

products. 4,5-Diphenyl-2-methylimidazole (60) gave the 2-hydroperoxy derivative (61) on reaction with singlet oxygen at -15°C and this isomerised to the 4*H*-isomer (62) on standing at room temperature.[49]



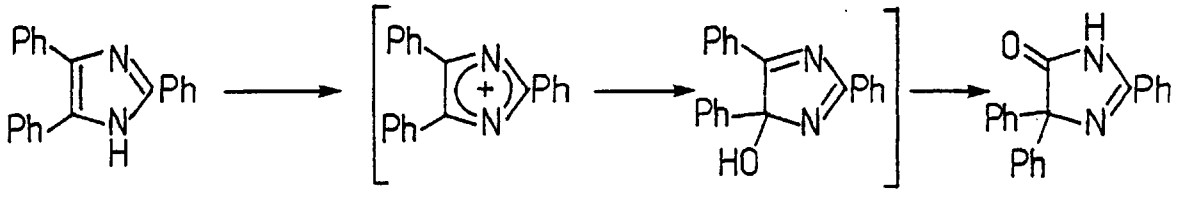
(60) (61) (62) (63) (64)

Reduction of the hydroperoxides with triphenylphosphine afforded the hydroxy derivatives (63) and (64).

1.2.6. By Oxidation of 1*H*-Imidazoles: Two Electron Oxidation.

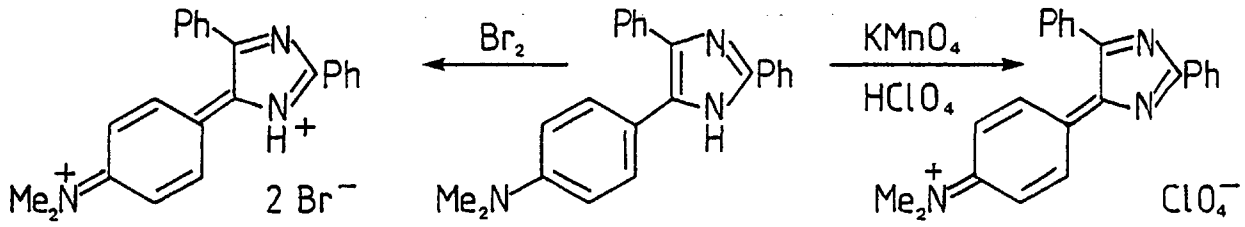
Although the cations formed by two electron oxidation of imidazoles are formally antiaromatic species they can be prepared quite readily when electron donating groups are present, and they are attacked by nucleophiles to give 2*H*- or 4*H*-imidazoles. Only reactions which involve cationic intermediates will be described in this Section, those in which a formal two electron oxidation occurs, *e.g.*, chlorinations, will be discussed later.

In the electrochemical oxidation of lophine (58) it was found that in the presence of aqueous base an imidazolone (41) was formed in good yield.[43] It was suggested that this reaction involved oxidation of the lophyl radical and/or a dimer to the cation (65), followed by trapping with water to give a 4*H*-imidazole (66) and base catalysed rearrangement



(58) (65) (66) (41)

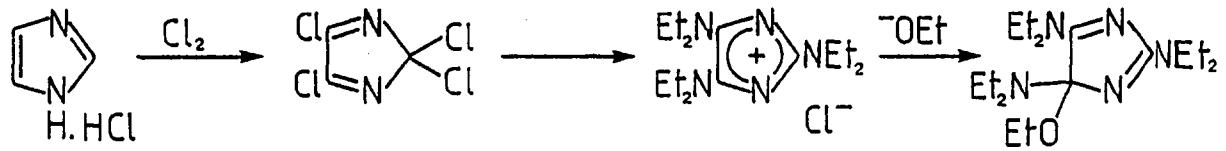
(Section 1.2.3.). Oxidation of a 4-(dimethylaminophenyl)imidazole (67) with potassium permanganate in aqueous perchloric acid gave an imidazolium perchlorate (68) which may be regarded as a 4*H*-imidazole.[50] Oxidation



(69) (67) (68)

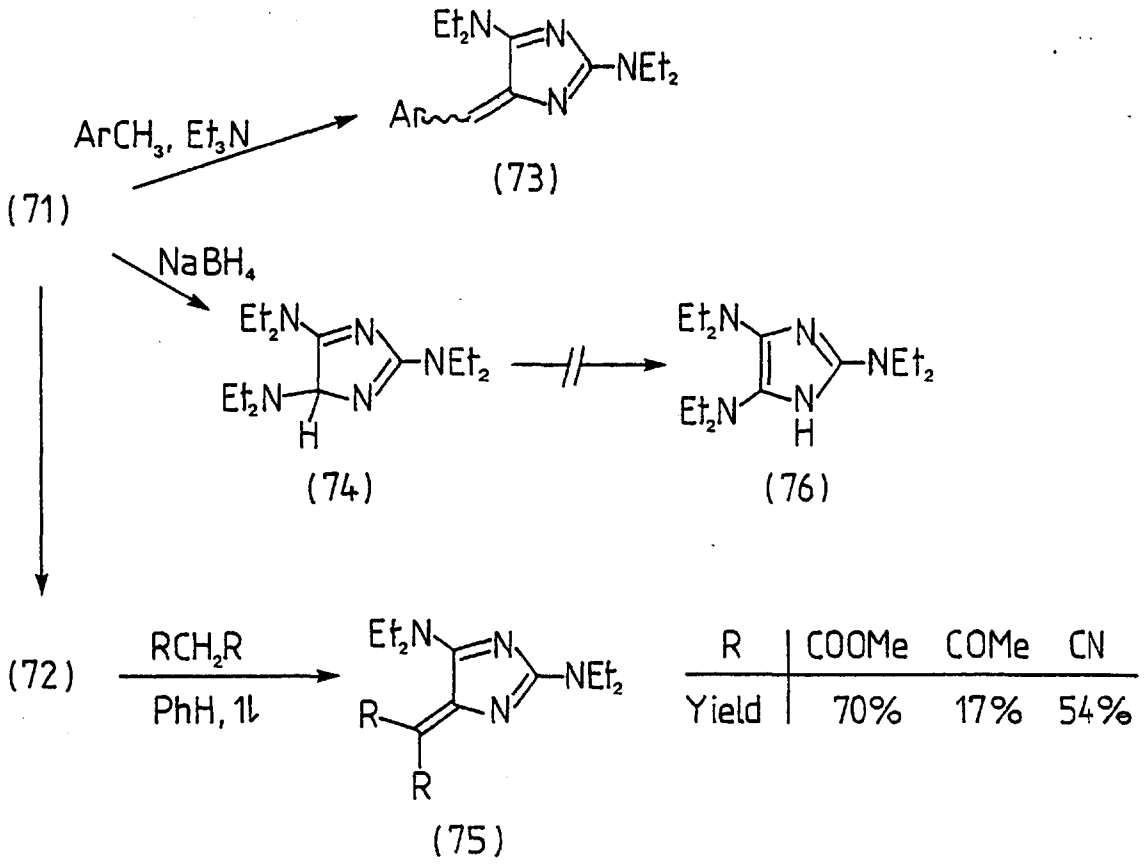
with bromine gave a corresponding dication (69) indicating that the monocation (68) is quite basic because the charge is largely localised on the dimethylamino group.

Chlorination of imidazole hydrochloride gave 2,2,4,5-tetrachloro-2*H*-imidazole (70) which reacted with trimethylsilyl diethylamide to give 2,4,5-tris(diethylamino)-imidazolium chloride (71).[51,52] Replacement of chloride with the more nucleophilic ethoxide gave a 4-ethoxy-4*H*-



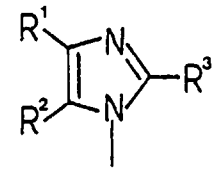
(70) (71) (72)

imidazole (72).[53] Both the salt (71) and the ethoxy derivative (72)

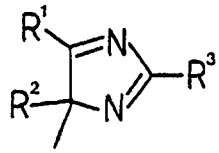


R	COOMe	COMe	CN
Yield	70%	17%	54%

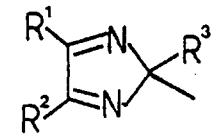
reacted with nucleophiles to give a variety of 4-alkylidene-4*H*-imidazoles, *e.g.*, (73) and (75).[52,53] Surprisingly, reduction of the salt (71) with sodium borohydride gave a 4*H*-imidazole (74) bearing a hydrogen at the tetrahedral carbon and attempts to isomerise this to the 1*H*-isomer (76) were unsuccessful.[54] The unexpected stability of this isomer was supported by MNDO calculations which indicated that the 4*H*-form is more stable than the 1*H* in diamino and triamino compounds.[54] Presumably this inversion is due to the amidine type stabilisation in the 4*H*-isomers.



1H-



4H-



2H-

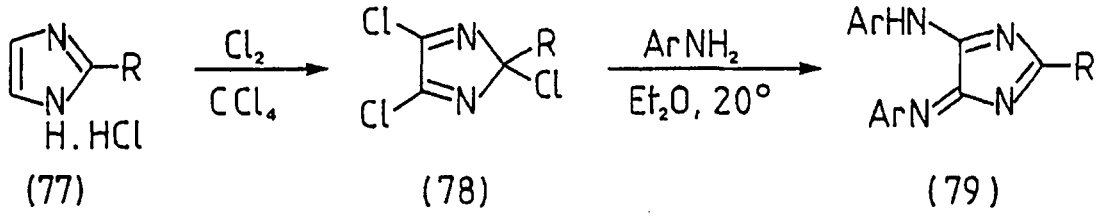
Table 1.1. Heats of formation of imidazole isomers.

R^1	R^2	R^3	1*H*-	4*H*-	2*H*-
H	H	H	33	42	44
NH_2	H	H	37	39	43
NH_2	H	NH_2	40	36	50
NH_2	NH_2	NH_2	52	47	51

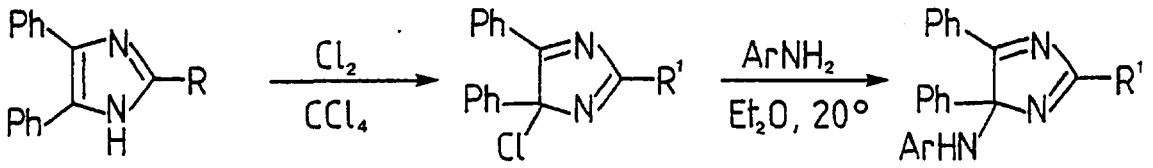
The accompanying table of calculated heats of formation (in kcal mol^{-1}) illustrates this effect.

1.2.7. By Electrophilic Substitution of 1*H*-Imidazoles.

Chlorination of the hydrochlorides of 2-substituted imidazoles (77) gave trichloro-2*H*-derivatives (78) which reacted with anilines to give

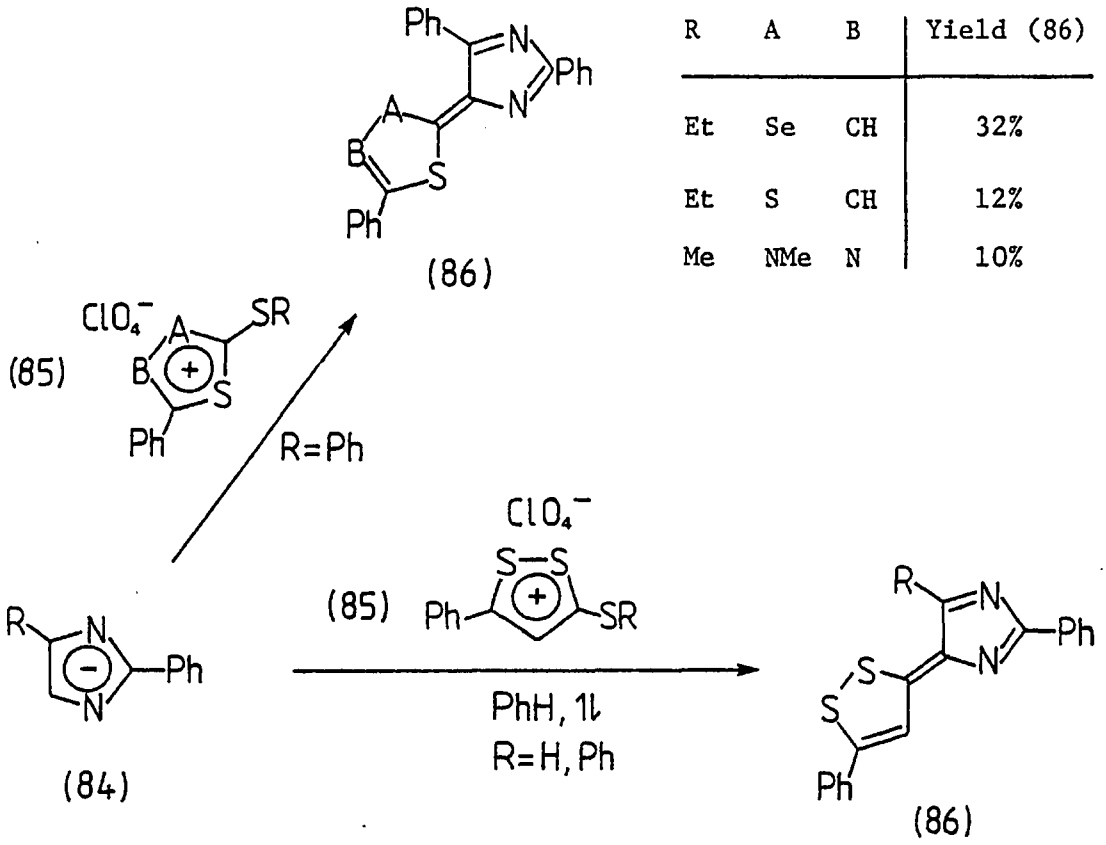


4*H*-imidazoles (79).[55] The formation of the 2*H* derivatives in these cases runs counter to the general tendency of imidazoles to undergo electrophilic attack at the 5-position. However, chlorination of 4,5-disubstituted imidazoles (80) gave the 4-chloro-4*H*-imidazoles (81).[55] Again, the chloride in the 4-position was easily displaced to give amino (82) and ethoxy (83) 4*H*-imidazoles.



R	R^1	Yield (81)
H	Cℓ	65%
Me	$CCℓ_3$	63%
Ph	Ph	88%

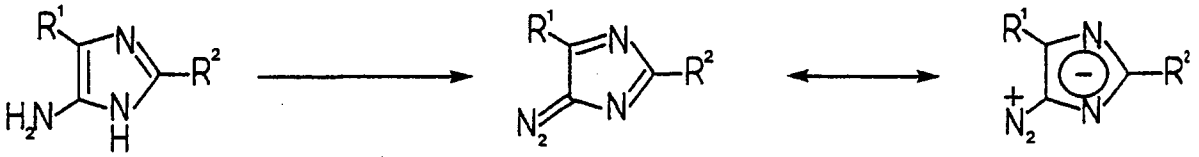
Reaction of imidazolyl anions (84) with several heteroaromatic cations (85) gave heterofulvalenes (86) by electrophilic substitution followed by elimination of a thiol.[56] Anomalous 2-substitution was found in the case of 4-phenylimidazole, and imidazole itself was inert to all conditions tried.



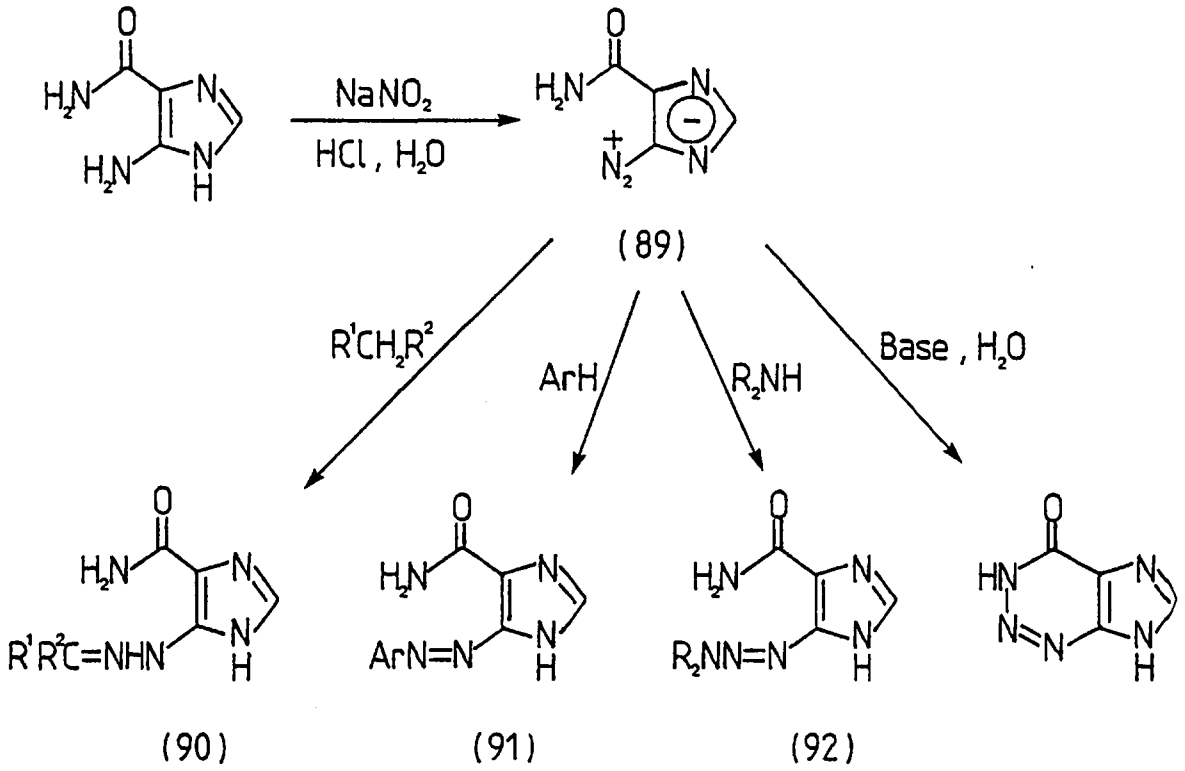
R	A	B	Yield (86)
Et	Se	CH	32%
Et	S	CH	12%
Me	NMe	N	10%

1.2.8. By Diazotisation of Aminoimidazoles.

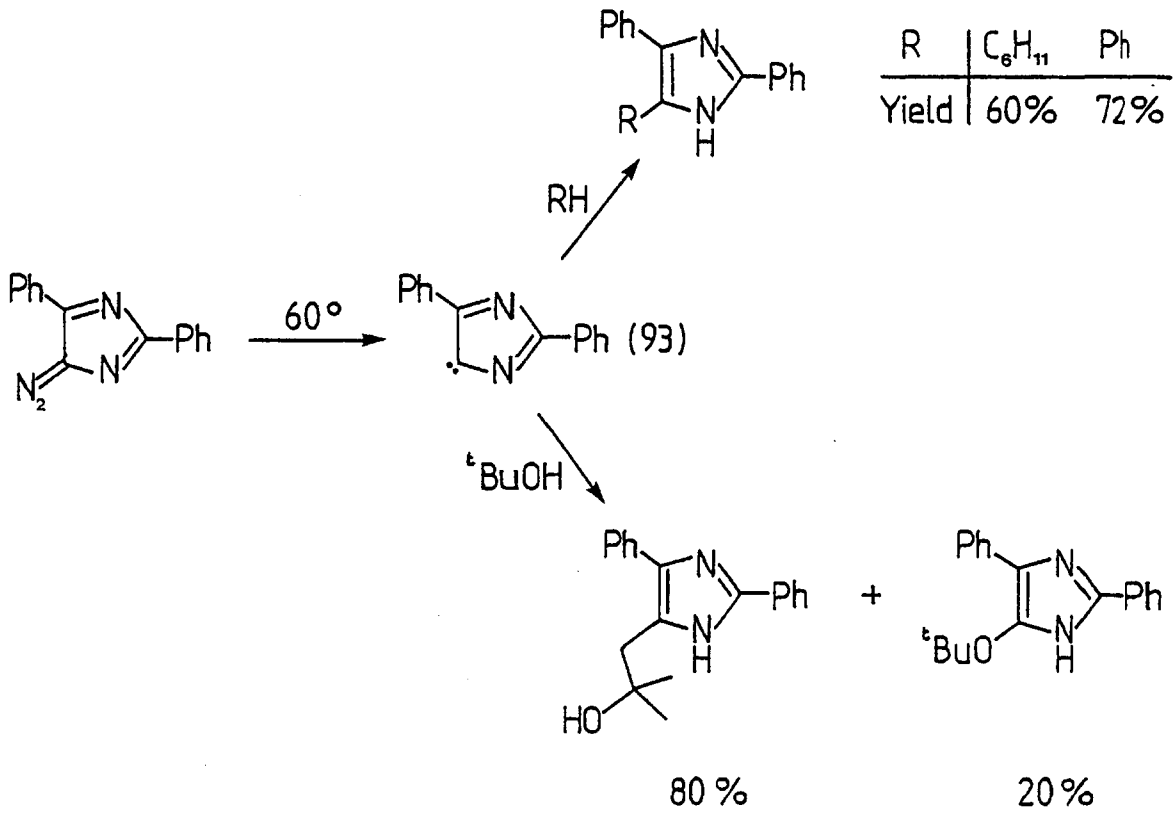
Diazotisation of 5-aminoimidazoles gives diazo compounds which may be represented as 4*H*-imidazoles (87) but are probably better regarded as heteraryl diazonium compounds (88).[57,58,59]



The series in which the 4-substituent is an amide has been studied in considerable detail because some of these compounds (89) and their azo derivatives (90-92) are potent anti-cancer agents.[58,60,61] 4*H*-Imidazolyl



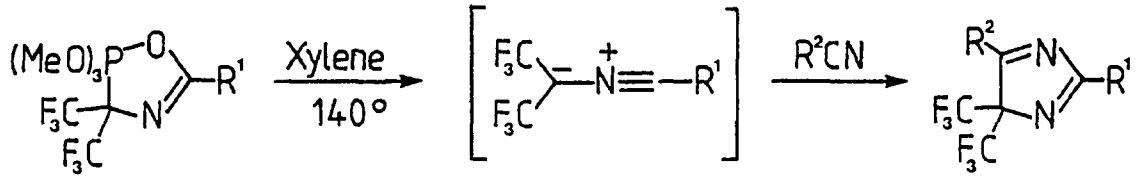
carbenes, *e.g.*, (93) are probably intermediates in the photolysis and thermolysis of some diazo compounds.[61,62] These carbenes inserted into carbon hydrogen bonds with unusually high efficiency.



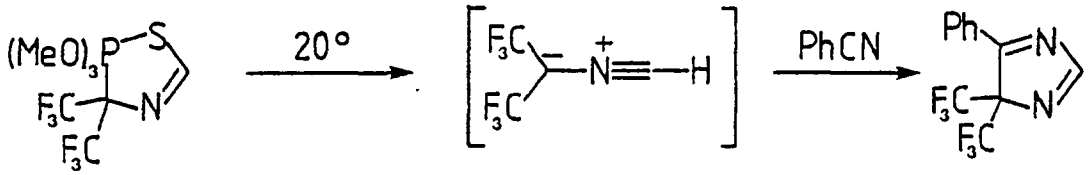
R	C_6H_{11}	Ph
Yield	60%	72%

1.2.9. By Cycloadditions.

Nitrile ylids can react with nitriles to give either 2*H*- or 4*H*-imidazoles and both regiochemistries have been observed. The relatively stable bis(trifluoromethyl) ylids (95) and (98), formed by fragmentation of oxaphosphazoles (94) and thiaphosphazoles (97), reacted with nitriles

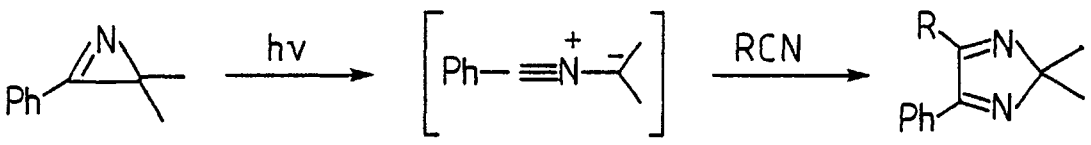


(94) (95) (96)



(97) (98) (99)

to give 4*H*-imidazoles (96) and (99).[63,64] However, the nitrile ylid (100) formed by photolysis of 3,3-dimethyl-2-phenylazirine gave 2*H*-imidazoles (101) exclusively.[65] Other nitrile ylids were found to react only with electron deficient nitriles and to give the same regiochemistry as the azirine derived ylid (100).[66,69] Indeed, the regio-

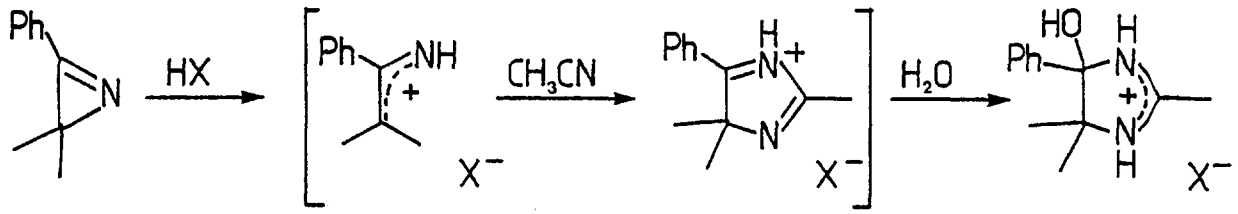


(100) (101)

selectivity shown by the trifluoromethyl compounds is the reverse of that shown in the great majority of nitrile ylid cycloadditions,[68] so it may

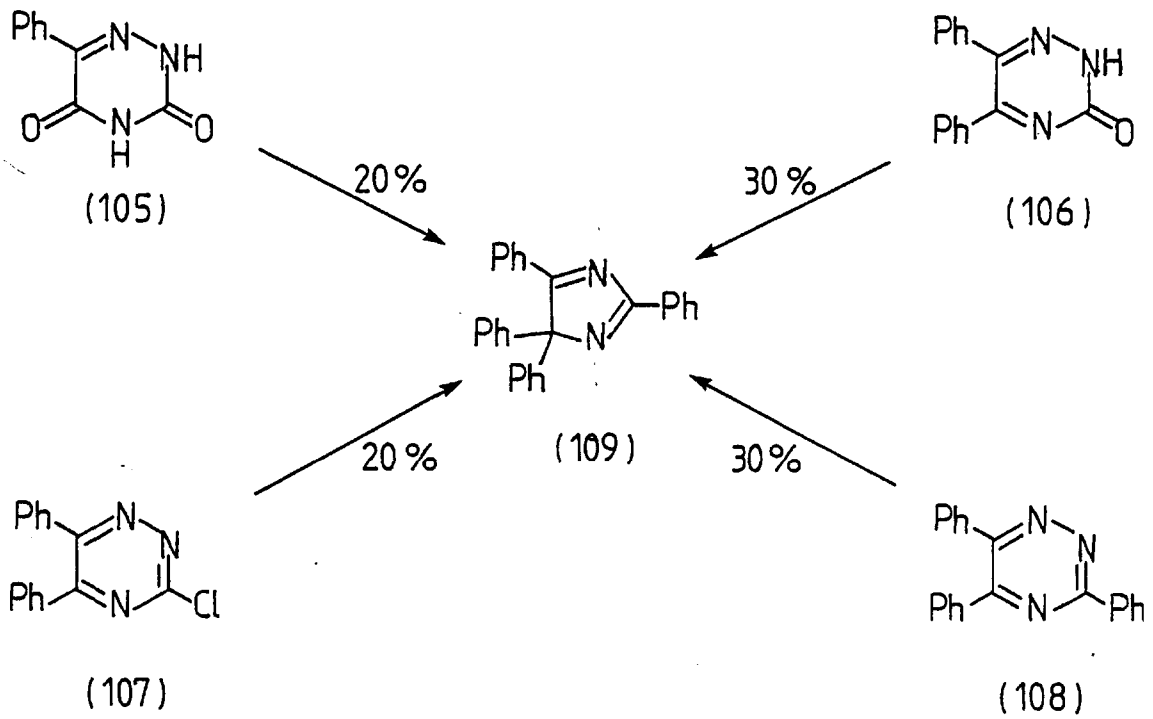
be anticipated that only ylids bearing two electron withdrawing substituents on the disubstituted carbon will give 4*H*-imidazoles.

Reaction of 2,3-dimethyl-2-phenylazirine with acetonitrile in the presence of acids probably involved cycloaddition of an azallyl cation (102) with the nitrile to give a protonated 4*H*-imidazole (103).[69] However, this intermediate was extremely susceptible to hydration and it proved impossible to isolate the imidazole, a protonated hydrate (104) being the only product. The corresponding reaction of 2-monosubstituted azirines gave 1*H*-imidazoles.[70]

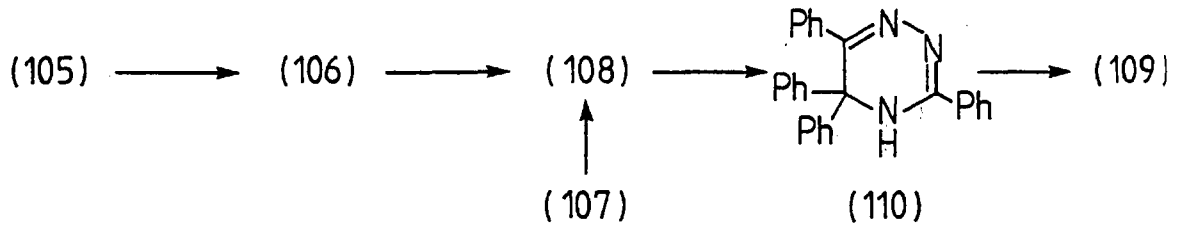


(102) (103) (104)

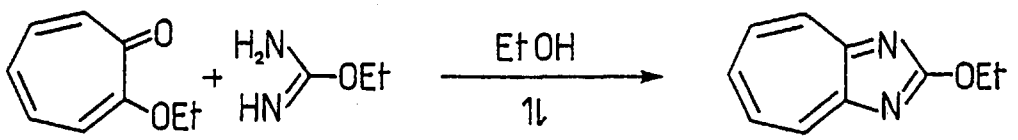
1.2.10. Miscellaneous Methods.



The reaction of phenylmagnesium bromide with several triazine derivatives (105-8) gave mixtures of products including low yields of 2,4,4,5-tetraphenyl-4*H*-imidazole.[71,72] This is not a general reaction and on the basis of the product mixtures it probably proceeds *via* (110).

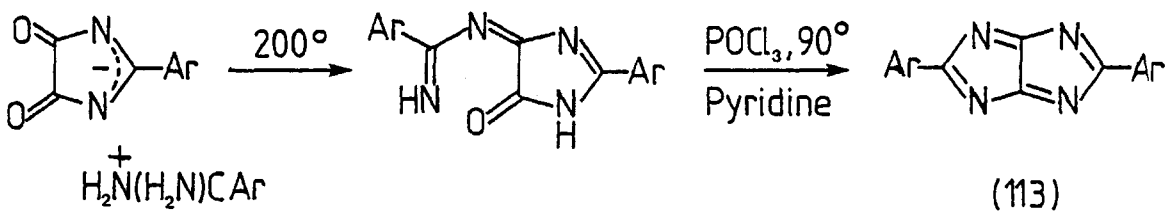


A diaza-azulene (112) has been prepared by condensation of an isourea with a tropolone (111)[73] but this cannot be regarded as a true



(111) (112)

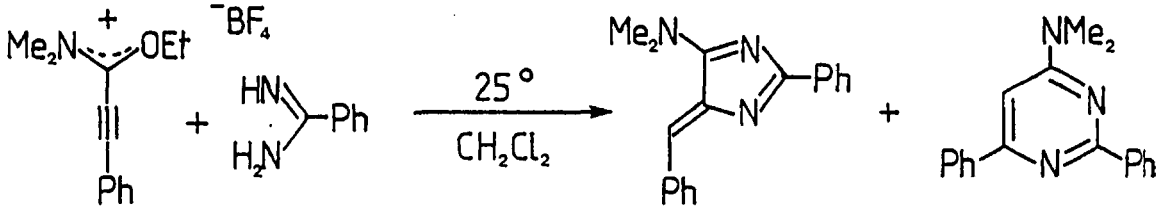
4*H*-imidazole. Interestingly, a series of tetra-azapentalenes (113) has also been reported but in view of the instability of the parent system



(113)

and the failure of these workers to reduce (113) to imidazoimidazoles, this claim was investigated and shown to be incorrect.[74]

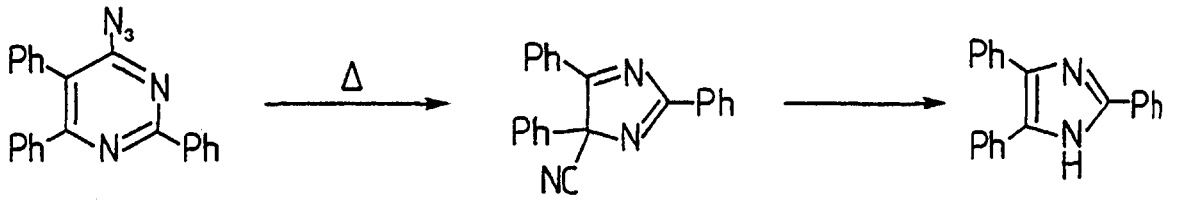
Reaction of benzamidine with an acetylenic salt (114) gave a 4*H*-imidazole (115) in addition to the expected pyrimidine (116).[75]



(114) (115) (116)

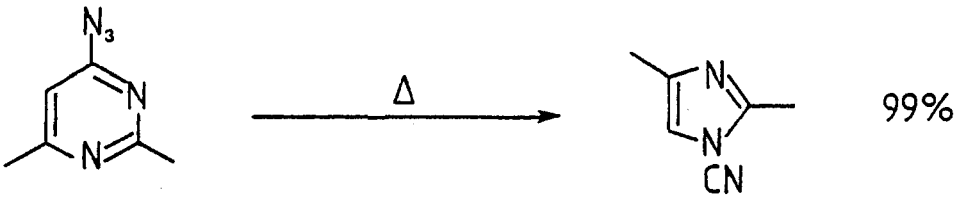
The formation of the five-membered ring is ascribed to the stereoelectronic constraints governing ring closure reactions.

Thermolysis of an azidopyrimidine (117) was reported to give a 4-cyano-4*H*-imidazole (118) which was hydrolysed and decarboxylated to give a 1*H*-imidazole (119).[76] However, it is very unlikely that the



(117) (118) (119)

4*H*-imidazole ring would survive the hydrolysis and the ring contraction of other pyrimidyl nitrenes was shown to give 1-cyanoimidazoles[77] so



the assignment of structure (118) may be in error.

1.3. SPECTROSCOPIC PROPERTIES.

Since relatively few 4*H*-imidazoles have been prepared, most of those are heavily substituted, and spectral data are often omitted, it is difficult to deduce firm generalisations about their spectroscopic properties. However, valuable information can be obtained from their spectra, and in the following sections some guidelines on their interpretation are presented, together with representative examples.

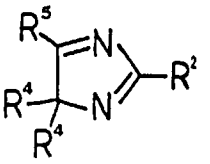
1.3.1. Infrared.

The most characteristic feature is a strong band due to C=N stretching at 1600-35 cm^{-1} and this is frequently accompanied by a medium to strong absorbtion at 1560-90 cm^{-1}. The positions of these bands seem relatively insensitive to the substituents. I.r. has been very useful in determining the structures of triarylimidazole dimers[39,40] and the spectra of some 5-methylthio derivatives have been studied in detail.[78,79] Table 1.2 lists i.r. and u.v. data for some representative examples.

1.3.2. Ultraviolet.

The simplest reported derivative, 5-butyl-4,4-diphenyl-4*H*-imidazole (49), absorbs at 251 nm so the basic absorbtion of the ring system is probably in this region. Conjugating substituents such as aryl and amino groups at C-2 and C-5 appear to raise the position of the maximum by 10-30 nm but a fuller analysis must await further data. See Table 1.2 for some examples.

Table 1.2. I.r., and U.v. absorbtions of 4*H*-imidazoles:

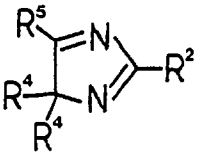


R^4, R^4	R^2	R^5	ν/cm^{-1} [Phase]	λ/nm [Solvent]	Ref.
Ph,Ph	H	Bu^n	1604(s),1588(m) [KBr]	291,251 [EtOH]	80
Me,Me	Me	Ph	1635 [$CC\ell_4$]	282 [EtOH]	6
Ph,Ph	Ph	Ph	1602,1594,1563 [KBr]	269,257 [EtOH]	2,39
Me,Me	CR_3	NMe_2	1605,1578 [$CC\ell_4$]	275.5 [EtOH]	23
Me,OH	NMe_2	Ph	1635(s),1567(m) [KBr]	273 [MeOH]	12
Me,Me	Me	SMe	1613,1511 [KBr]		78
$PhCH_2$,$PhCH_2$	SMe	SMe		290,261 [EtOH]	32
Ph,Ph	Ph	OMe	1610,1580		26

1.3.3. Proton Magnetic Resonance.

Again the shortage of data hinders interpretation but some features can be discerned (Table 1.3) (i) C-4 Methyl protons generally resonate at δ1.4-1.6.(ii) C-2 Methyl protons occur at δ2.15-2.5. (iii) Methylene

Table 1.3. Proton n.m.r. spectra of 4*H*-imidazoles:



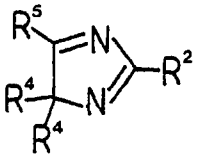
R^4, δ(H)	R^2, δ(H)	R^5, δ(H)	Solvent	Ref.
C_6H_5, 7.25-7.52	H, *ca.* 7.3	Pr^nCH_2, 2.73	$CDC\ell_3$	80
CH_3, 1.58; CN	H, 7.6	NH_2, 8.45	$(CD_3)_2SO$	20
CH_3, 1.44	CH_3, 2.33	C_6H_5, 7.88-8.14	CD_3OD	6
CH_3, 1.48	CH_3, 2.16	$N(CH_3)_2$, 3.19	$CDC\ell_3$	21
CH_3,1.46; OH,5.43	$N(CH_3)_2$, 3.15	C_6H_5,7.3-7.63, 8.16-8.46	$CDC\ell_3$	12

groups in compounds in which C-4 is chiral generally occur as complex multiplets. (iv) The *ortho* protons or aryl groups on C-2, and sometimes C-5, are shifted to low field, typically, δ8.1-8.5.

1.3.4. Carbon-13 Magnetic Resonance.

^{13}C n.m.r. has proved very useful in identifying the 4*H*-imidazole nucleus because it gives a distinctive pattern of one high field carbon (C-4) and two low field signals (C-2 and C-5).[3] Recently coupling experiments have shown that the lowest field resonance is due to C-5, and not to C-2 as assumed in much of the earlier literature.[20,21] The position of the C-4 peak is strongly dependent on the substituents it bears, but C-2 (δ165-75) and C-5 (δ180-210) resonate within relatively narrow ranges. The methyl carbons of 4,4-dimethyl compounds give signals at δ19-23. Table 1.4 lists some illustrative examples.

Table 1.4. ^{13}C n.m.r. of 4*H*-imidazoles:



R^4, R^4	δ(C-4)	R^2	δ(C-2)	R^5	δ(C-5)	Solvent	Ref.
Me, CN	66.4	H	170.1	NH_2	184.0	$(CD_3)_2SO$	20
Me, Me	73.2	CEt_2CO_2Et	174.0	$N(CH_3)_2$	188.2	$CDC\ell_3$	23
Ph, Ph	84	Ph	172	Ph	195	$CDC\ell_3$	3
4-$C\ell C_6H_4$, 4-$C\ell C_6H_4$	94.2	4-$C\ell C_6H_4$	170.0	CH_3S	201.9	$CDC\ell_3$	3
Et_2N, EtO	115.9	Et_2N	168.3	Et_2N	179.6	C_6D_6	53

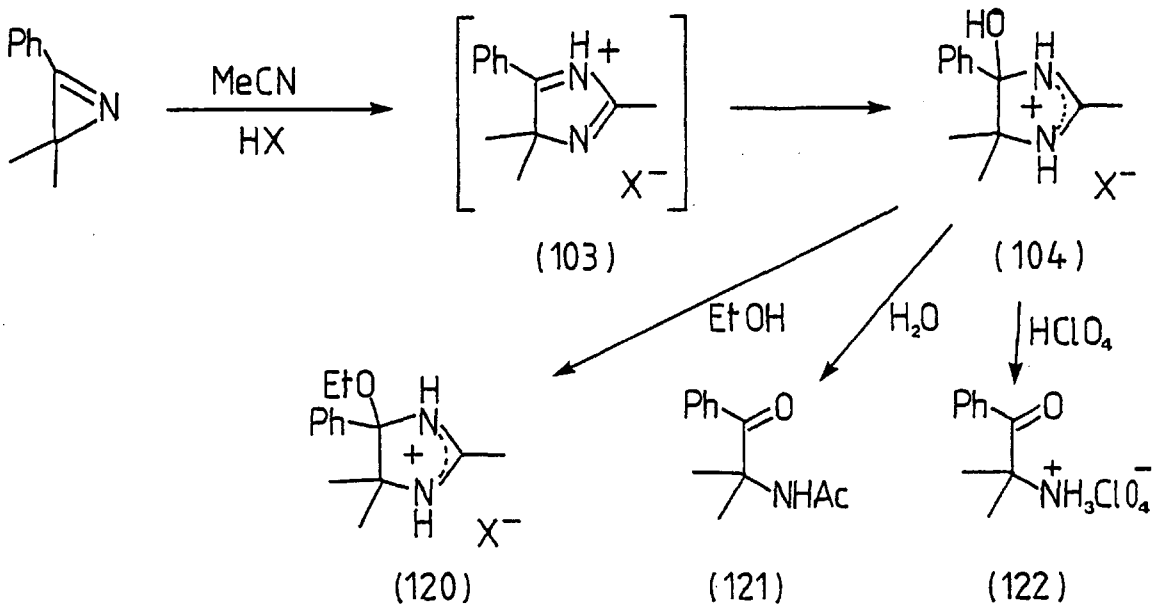
1.3.5. Mass Spectra.

There has not been any detailed study of the mass spectral fragmentation of 4*H*-imidazoles but a few trends can be observed. (i) Loss of R^5-C≡N is often a major pathway. (ii) Loss of R^2-C≡N is less common but is sometimes observed. (iii) Loss of a substituent from C-4 is common especially if a stabilised cation can be formed.

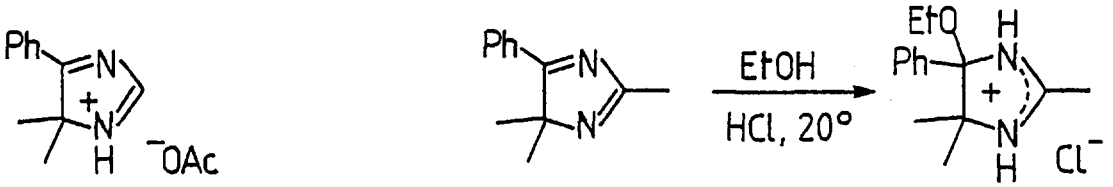
1.4. CHEMICAL PROPERTIES

1.4.1. Hydrolysis.

The hydrolysis of a variety of 4*H*-imidazoles has been studied and a fairly consistent pattern has emerged. Compounds which do not have a heteroatom substituent at C-2 or C-5 are very susceptible to covalent hydration in acidic conditions. Indeed hydration in acid was so rapid that it proved impossible to isolate a 4*H*-imidazole (103) from acidic reaction mixtures no matter how carefully water was excluded.[69] The

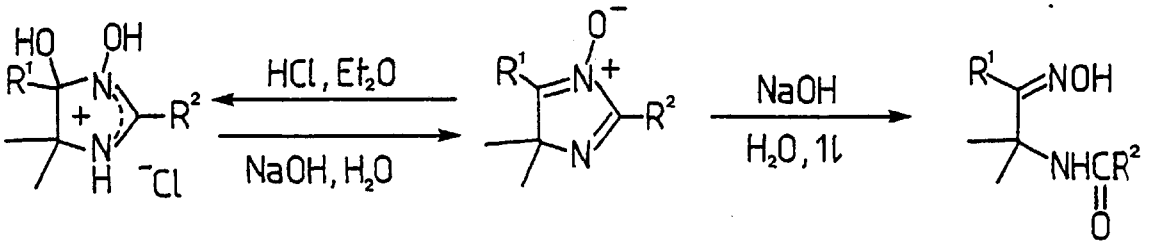


hydrate (104), formed by attack of water at C-5, gave the corresponding ethoxy derivative (120) on refluxing in ethanol, and was hydrolysed further to the α-amido ketone (121) and the α-amino ketone (122), on refluxing in water and aqueous perchloric acid respectively. However, a very closely related cation (5) was isolated from a reaction carried out in methanol and apparently was not attacked by the solvent.[6] Further



(5) (11) (123)

doubt is cast on this report by independent confirmation that the phenyltrimethylimidazole (11) is very susceptible to hydration.[6] The *N*-oxides in this series (14) were also extremely prone to acid hydrolysis.[6] They

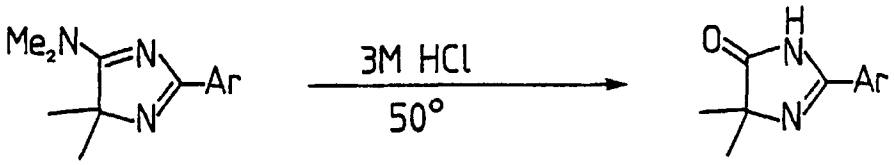


(124) (14)

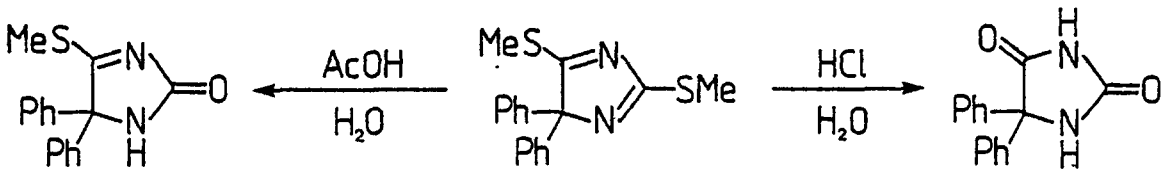
were stable to water, and in aqueous hydroxide the *N*-oxides were reformed from the hydrates (124). However, other authors claim that one of these *N*-oxides (17) formed a stable hydrochloride on treatment with hydrogen chloride in dry ether but the confusion in this case may be due to the problem of dimerisation which was referred to previously (1.2.1).[8] This susceptibility to covalent hydration in acidic media imposes a general limitation on the conditions which may be used to make and purify simple

4*H*-imidazoles, and it is anticipated that the problems will be more acute in handling derivatives which do not have a substituent at C-5. Much less is known about hydrolysis in basic conditions but it seems from the study of the *N*-oxides (14) that more vigorous conditions are required and attack occurs at C-2 rather than C-5.[7,8]

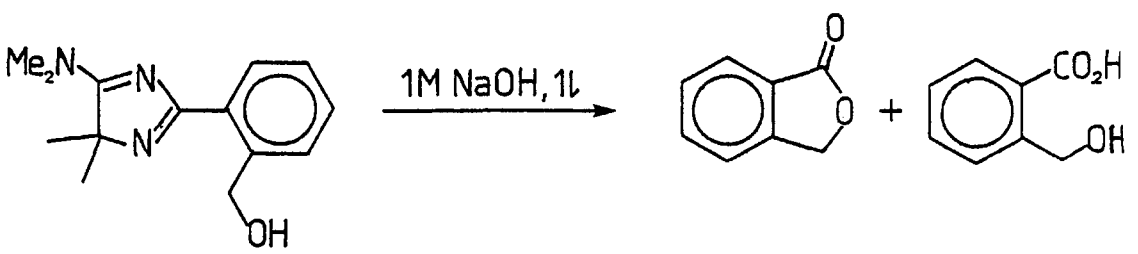
Compounds bearing heteroatoms at C-2 or C-5 are much more resistant to hydrolysis. However, in acid the reaction followed a similar course and attack by water at C-5 gave imidazolones.[21,22] Alkoxy[30] and methyl-



thio derivatives behaved similarly but selective attack at C-2 was observed in one system.[31] In the case of a 5-dimethylamino derivative

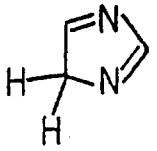


basic hydrolysis was found to cause complete destruction of the imidazole ring.[22]



1.4.2. Reactions with Nucleophiles.

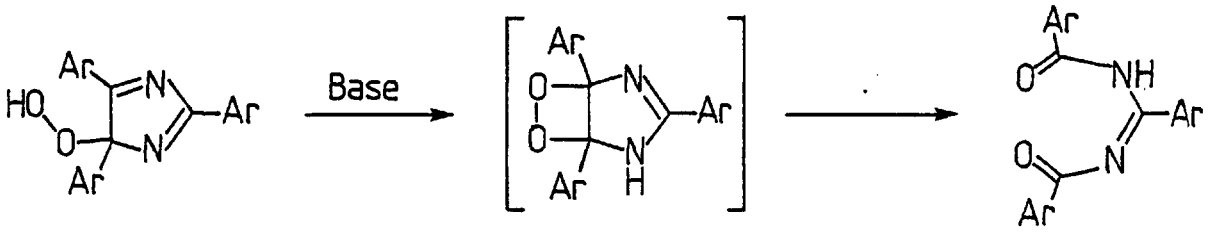
The 4*H*-imidazole nucleus might be expected to undergo nucleophilic attack at C-2, C-4 or C-5, depending on the substituents. MNDO calculations of the orbital coefficients of the LUMO in a model system (125) suggested that C-5 would be more susceptible to attack than C-4.[81] Although no study of nucleophilic attack on simple derivatives has been reported the results of the hydride reductions (1.4.4.) and the hydrolyses (1.4.1.) suggest that this is correct. Attack at C-5 by an intramolecular



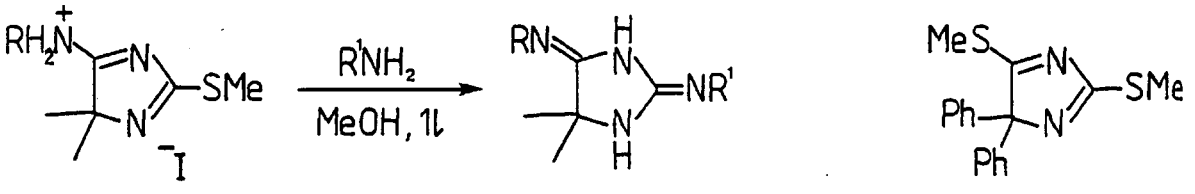
(125)

LUMO Coefficients		Atomic Charges	
C-2	C-5	C-2	C-5
0.42	0.62	0.0879	0.0162

nucleophile is probably the first step in the base catalysed chemiluminescence of 4-hydroperoxy derivatives.[48,82] A 5-amino-2-methylthio

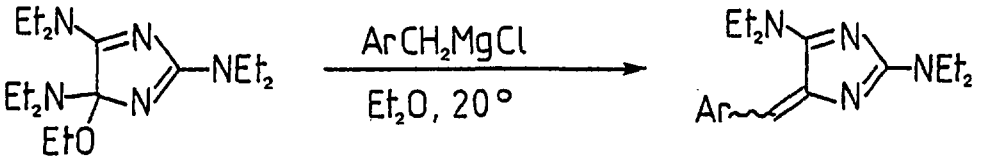


derivative (53) was attacked at C-2 by amines and the products (126) existed as the 2,4-diimino tautomers.[37] The regiochemistry of attack



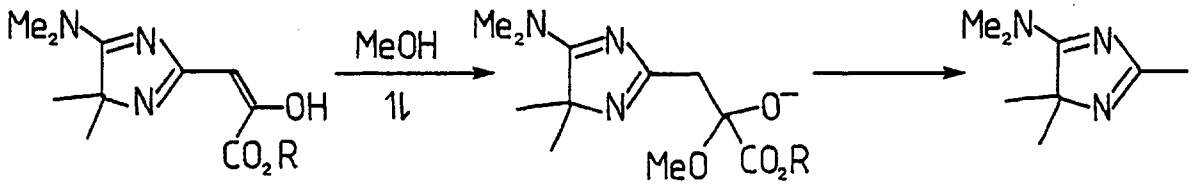
(53) (126) (127)

in this case may be determined by the substituent effects. 2,5-bis-(Methylthio)-4,4-diphenyl-4*H*-imidazole (127) was resistant to attack by amines.[31] Tetraphenyl-4*H*-imidazole (109) can be isolated from reactions involving phenyl Grignard reagents indicating that it is not very reactive toward nucleophiles. In systems of this kind bearing conjugating or electron donating substituents at C-2 and C-5 substitution is frequently observed at C-4 if a leaving group is present. Examples of this are the reaction of triarylimidazole dimer A with ethanol (1.2.5.)[40] and the nucleophilic displacement of ethoxide in tris(diethylamino) compounds (72) (1.2.6.).[54] Nucleophilic attack by methanol on



(72) (128)

the side chain of an imidazolylpyruvate (129) caused a retro-Claisen type fragmentation confirming that the intermediate anion is stabilised.[21]

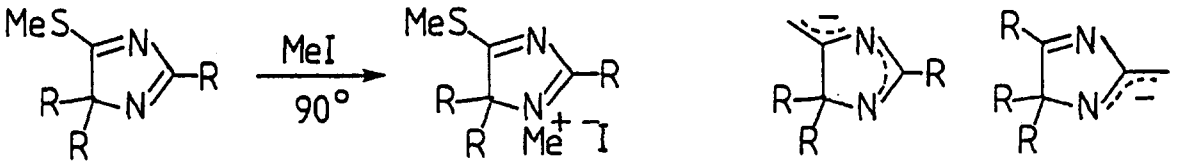


(129) 70%

1.4.3. Reactions with Electrophiles.

Apart from protonation, the methylation of some 5-methylthio derivatives (130) appears to be the only reported reaction of 4*H*-imidazoles with

electrophiles.[28] The products were formulated as the 3-methyl derivatives (131) but no evidence for this assignment was presented and the relative nucleophilicities of N-1 and N-3 remain unknown. It is likely that in addition to the nitrogens, methyl groups at C-2 and C-5 would be nucleophilic especially in basic conditions in which delocalised anions (132) and (133) would be formed.

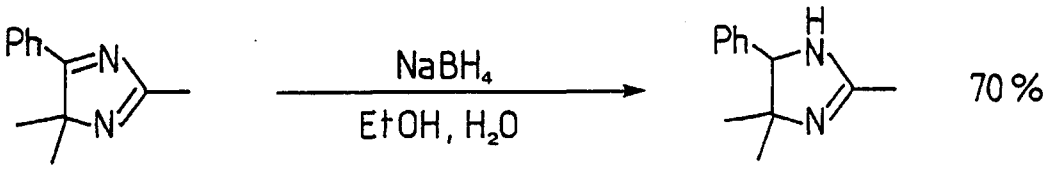


(130) (131) (132) (133)

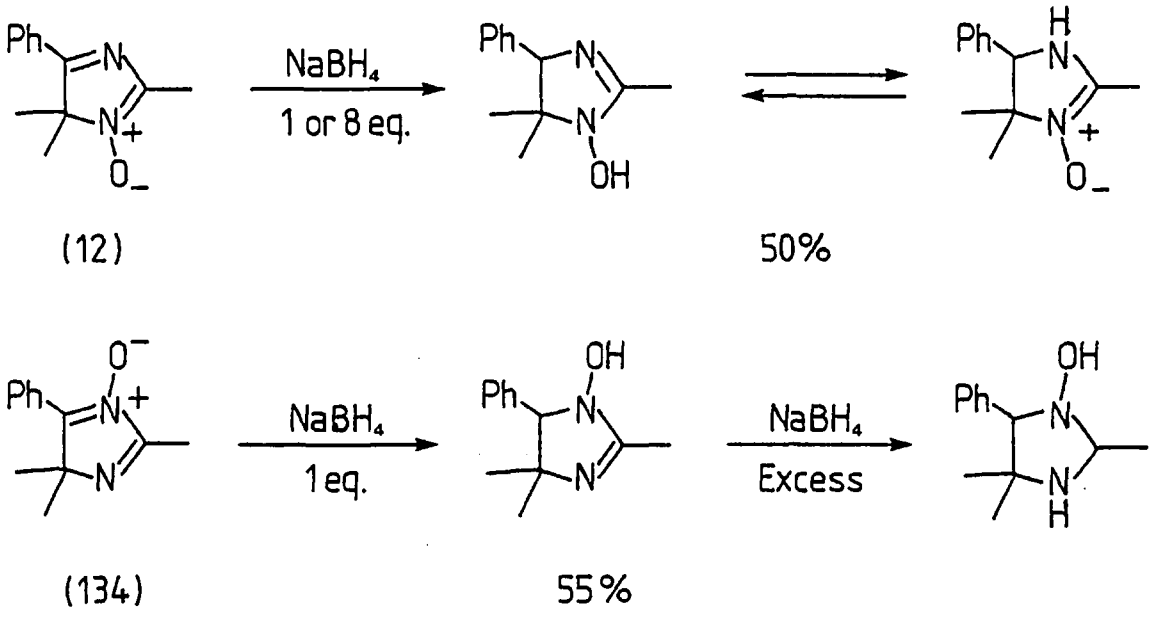
1.4.4. Oxidation and Reduction.

Nothing is known about the reaction of 4*H*-imidazoles with oxidising agents. In particular, there has been no report of *N*-oxidation.

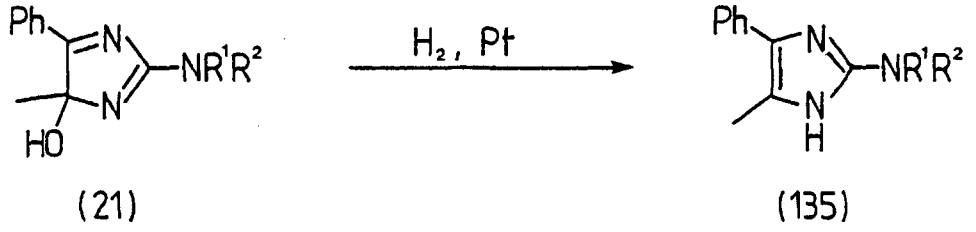
Hydride reductions of two series of simple imidazoles occurred by attack of hydride at C-5 to give amidines.[64,83] These results indicate



that C-5 is more electrophilic than C-2 (1.4.2.). A 3-oxide (12) behaved very similarly, but the 1-oxide (134) underwent further reduction.[83] The *N*-oxides have not been deoxygenated. Reduction of a tris(diethylamino)

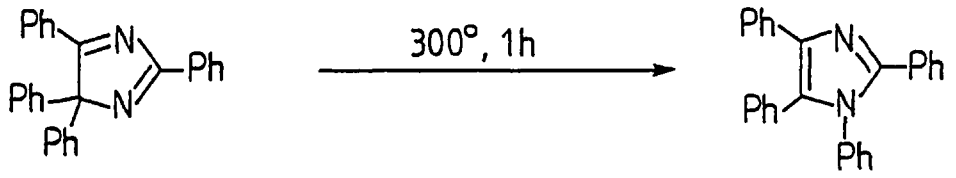


compound has already been described (1.2.6.),[54] as has the reduction of 4-hydroperoxy to 4-hydroxy derivatives using triphenyl phosphine. 4-Hydroxy-4*H*-imidazoles (21) were reduced to the 1*H*-imidazoles (135) on hydrogenolysis.[12]

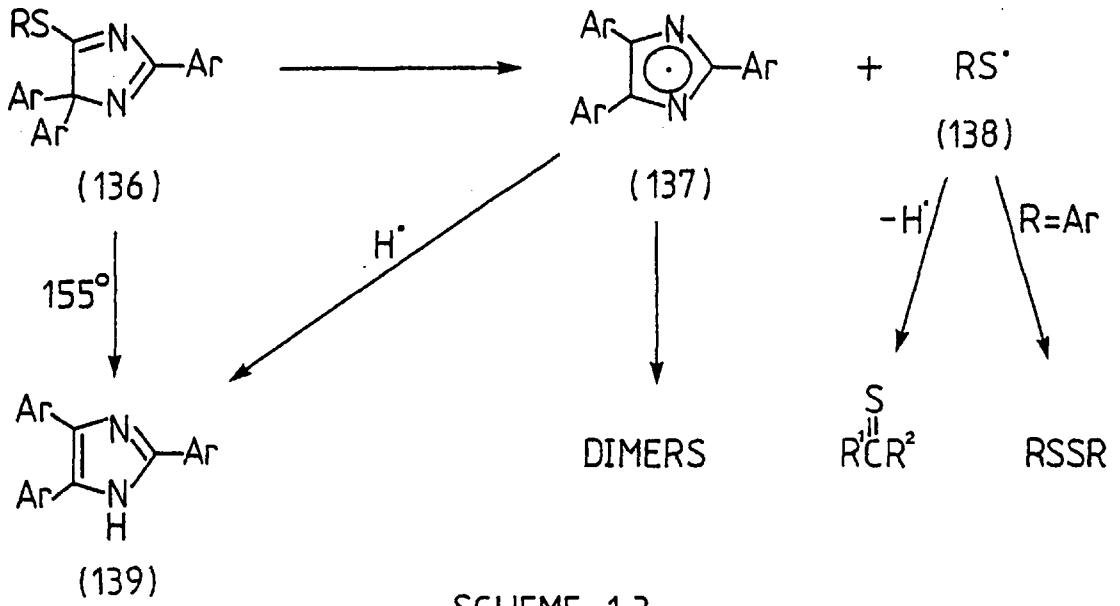


1.4.5. Rearrangements.

Rearrangement of a 4*H*-imidazole to a 1*H*-imidazole by migration of a blocking group has only been reported once.[84] The temperature required for the phenyl shift seems very high but this may be due to the fact that carbon to nitrogen migration is an unfavoured process, as found in related systems, *e.g.*, 2*H*-pyrazoles.[85]

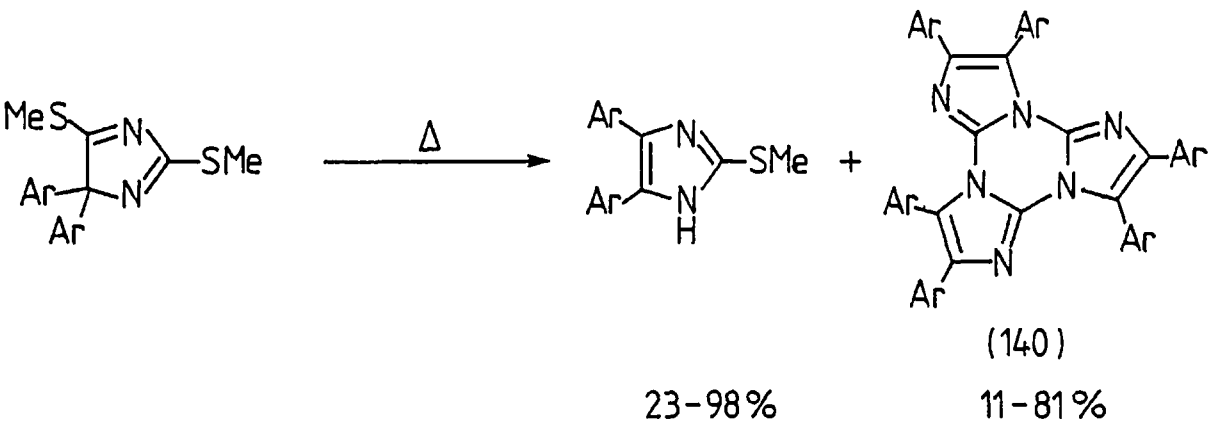


The reductive rearrangement of a series of 5-alkylthio and 5-arylthio-4,4-diaryl-4*H*-imidazoles (136) has been explored in detail and the mechanism has been worked out (Scheme 1.3).[27] Thermally, it proceeds by

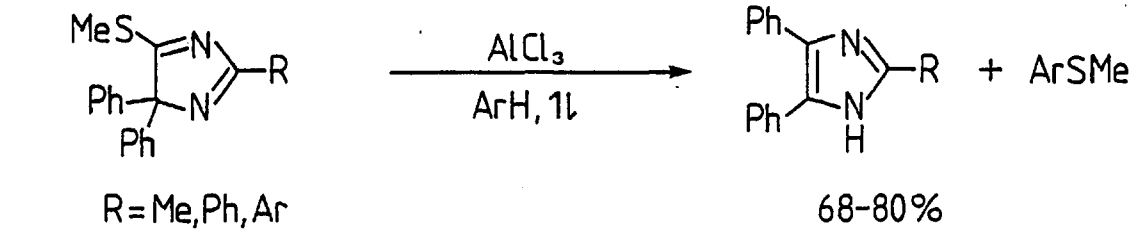


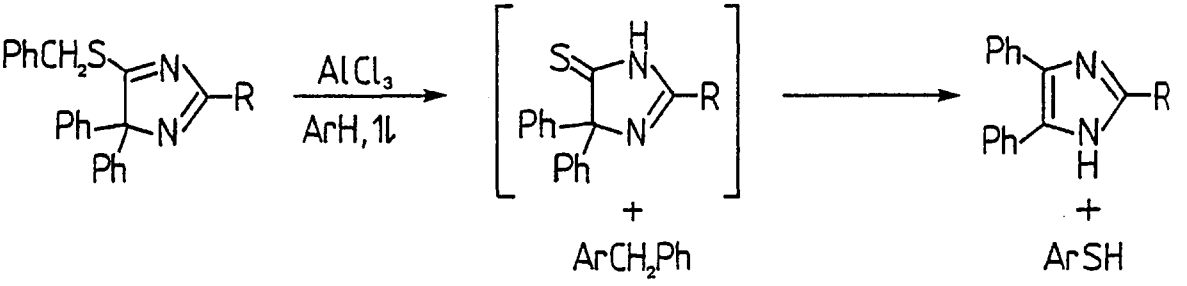
SCHEME 1.3

synchronous aryl migration and C-S bond cleavage to give triarylimidazolyl (137) and alkyl (or aryl) thio radicals (138) which lead to the products by standard radical reactions. The proposed mechanism is supported by e.s.r. detection of the triarylimidazolyl radicals (137) and by kinetic studies and crossover experiments.[86,87] Trimers (140) were obtained from thermolysis of 2,5-bis(alkylthio) derivatives.[83]

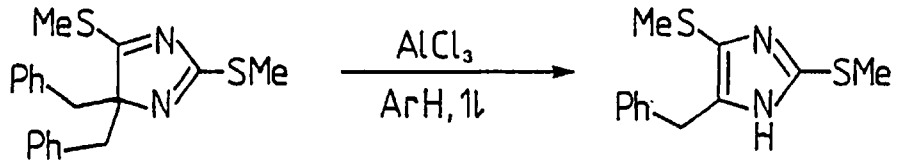


Similar reductive rearrangements are induced by heating with Lewis acids in aromatic hydrocarbons.[26,32,35,34] The details of the mechanism have not been determined but the alkylthio groups are incorporated into the solvent so cationic intermediates are probably involved. In the case



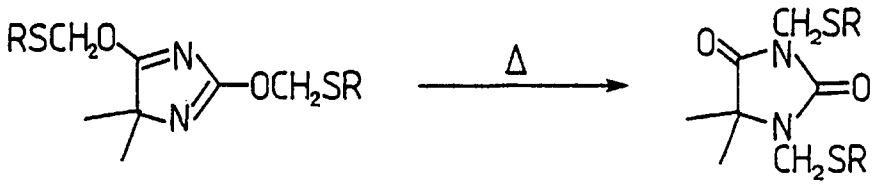


of a 4,4-dibenzyl derivative (141), cleavage of a benzyl group occurred in preference to that of the thiomethyl group presumably because of the stability of the benzyl cation.[32]



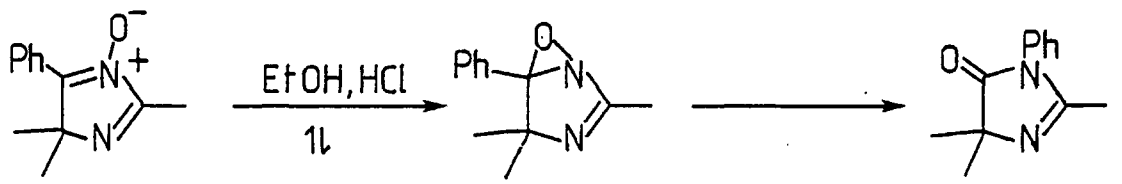
(141)

On attempted distillation, at an unspecified temperature, *O*,*O*-dialkylhydantoins (142) rearranged to the *N*,*N*-dialkyl isomers (143).[30]



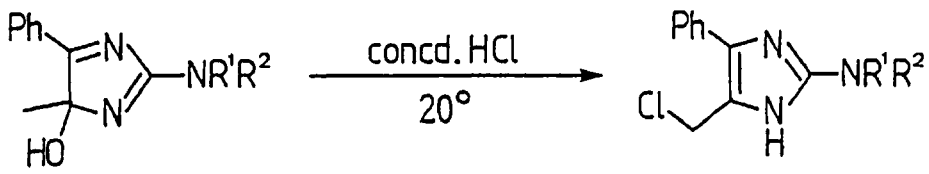
(142) (143)

An *N*-oxide (134) was found to rearrange to an imidazolone (145) on refluxing in ethanol containing hydrogen chloride.[88] An oxaziridine (144) intermediate was suggested but it seems likely that in the acidic conditions ethanol adducts are involved.



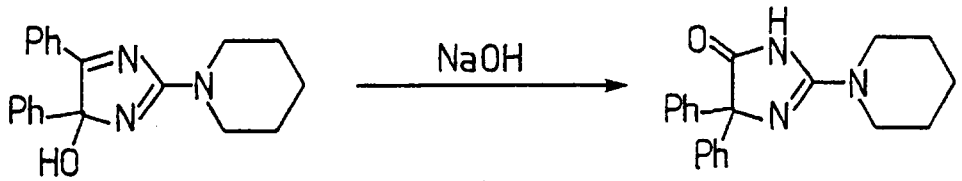
(134) (144) (145)

4-Hydroxy-4*H*-imidazoles (21) are very reactive and rearrange on treatment with acid or base.[12,89] The mechanism of the acid-promoted rearrangement is not known but probably involves imidazolium cations.



(21)

In basic conditions a semibenzilic acid type rearrangement occurs (1.2.3.).[89]



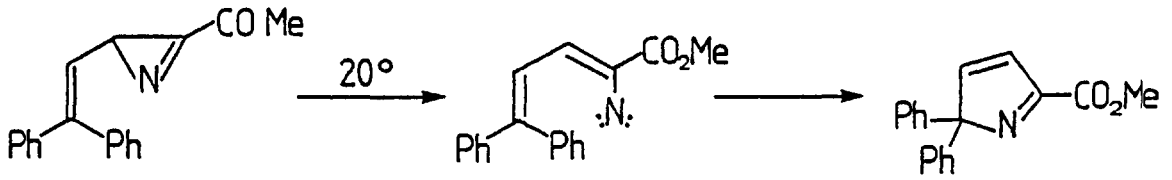
1.5. CONCLUSIONS

Hopefully the arrangement of the material in this review has emphasised the basic framework underlying the many different syntheses and reactions of 4*H*-imidazoles. However, it is also clear that large gaps in their chemistry remain. In particular there has been no systematic attempt to prepare and study lightly substituted examples and until this omission is rectified the chemistry of the more complex derivatives (forming the bulk of this review) cannot be properly interpreted. The results of some attempts to remedy this omission are presented in Part 2.

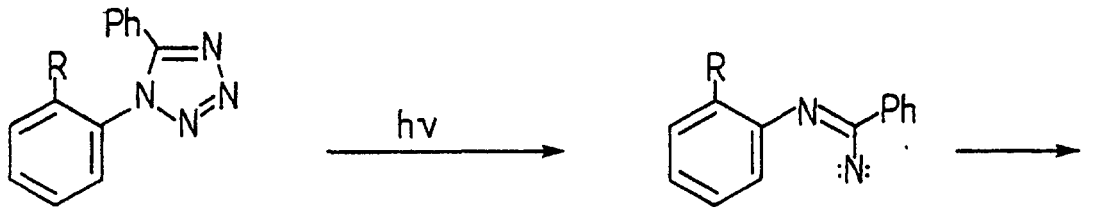
2. RESULTS AND DISCUSSION

2.1. INTRODUCTION

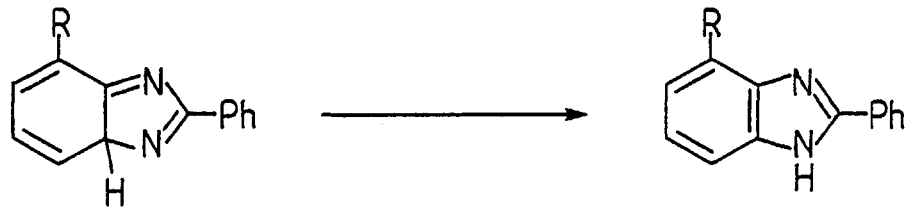
The formation of five membered ring heteroaromatic compounds by electrocyclic ring closure of dienyl- and heterodienylnitrenes is well known and has been reviewed.[90,91] Examples include the formation of 2*H*-pyrroles (3) by thermolysis of azirines (1)[92] and the preparation of benzimidazoles (7) by photolysis of 1,5-diaryltetrazoles (4).[93,94,95] The latter reaction proceeds *via* 3a*H*-benzimidazoles (6),[93,94] and



(1) (2) (3)



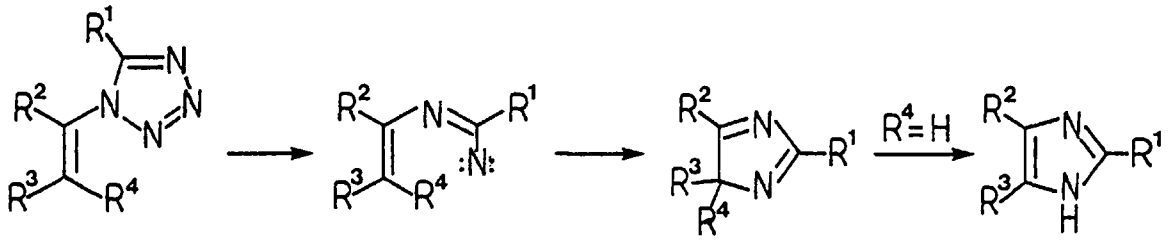
(4) (5)



(6) (7)

stimulated investigation of the properties of unstable non-aromatic fused systems of that type.[96,97,98] As a continuation of this work it was decided to attempt to extend the reaction to the preparation of imidazoles.

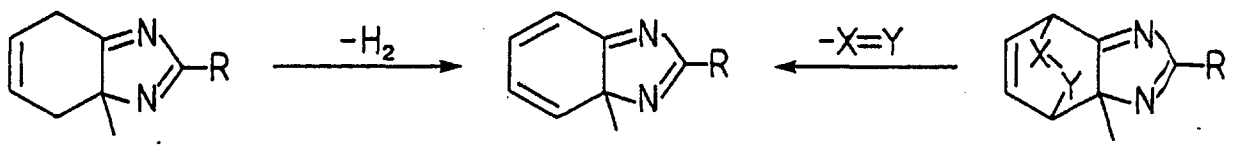
It was hoped to prepare 1-alk-1-enyltetrazoles (8) and to study their photolysis and thermolysis. If their decomposition paralleled that of the 1-aryltetrazoles (4), then 1*H*-imidazoles (11) would be formed *via* alkenylimidoylnitrenes (9) and 4*H*-imidazoles (10). It was anticipated



(8) (9) (10) (11)

that if R^3 and R^4 were suitable " blocking groups" the 4*H*-imidazoles (10) might be isolated and studied.

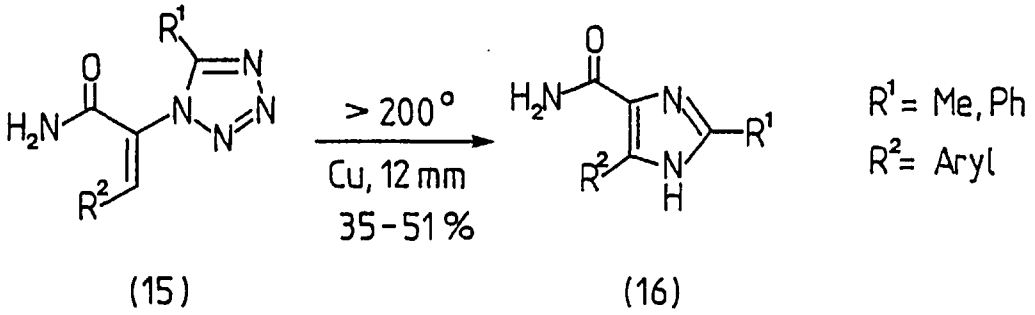
In order to confirm that 3a*H*-benzimidazoles were intermediates in the decomposition of 1,5-diaryltetrazoles it was decided to attempt to generate them by other means, *e.g.*, from precursors such as (12) and (14) in which



(12) (13) (14)

the 4*H*-imidazole ring could be formed by conventional means, or by the alkenyltetrazole method described above.

There is one previous report of the decomposition of 1-alkenyltetrazoles to give imidazoles.[99] A series of tetrazolylacrylamides (15) gave the corresponding imidazoles (16) on thermolysis at 200-230°C. This work was encouraging but the route used to prepare the alkenyltetrazoles (15) is very limited[100] and the pyrolysis involved harsh conditions.

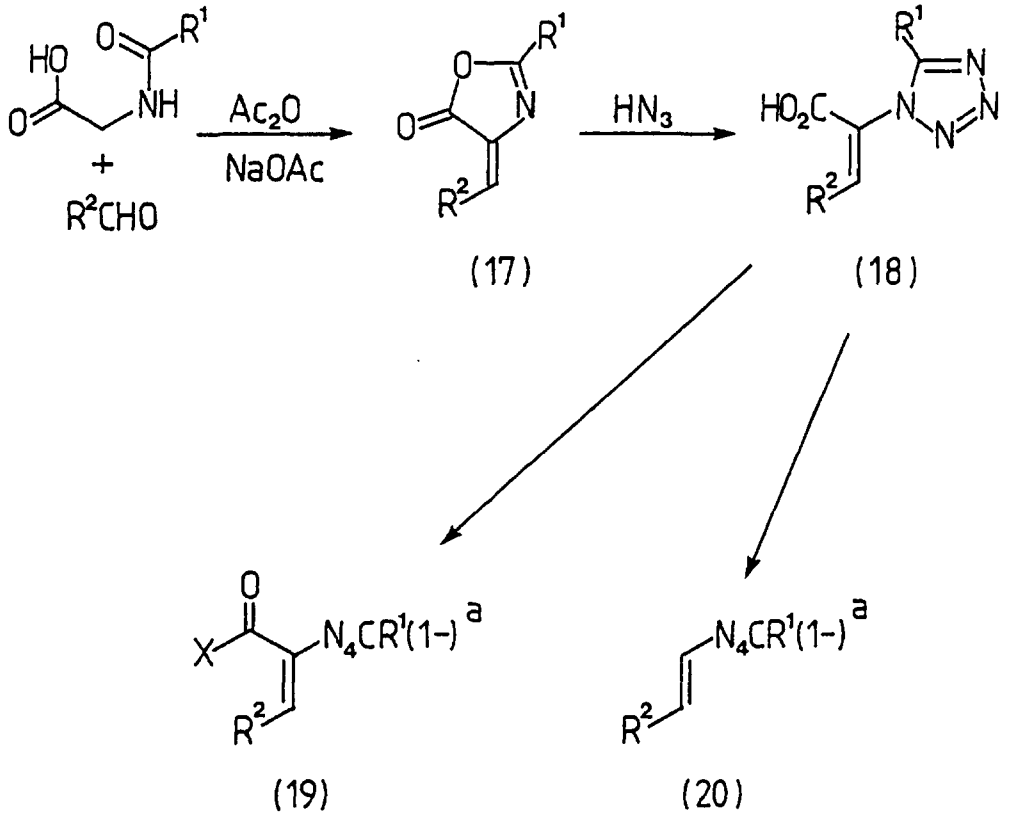


(15) (16)

The principal objectives of the work described here were to develop general routes to 1-alk-1-enyltetrazoles and to find mild conditions under which they could be converted into imidazoles.

2.2. PREPARATION OF 1-ALKENYL TETRAZOLES.

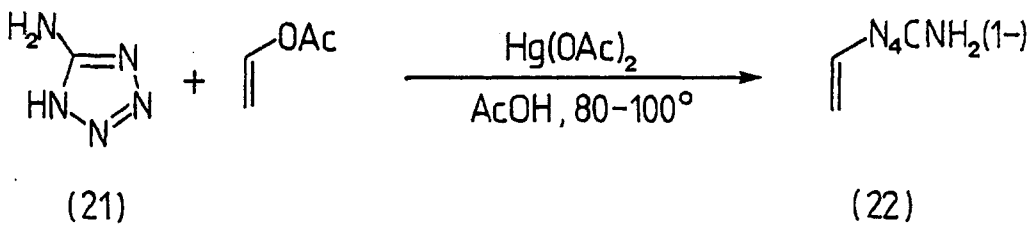
Four routes to 1-alkenyltetrazoles have been reported. The one most commonly used is based on the azidolysis of azlactones (17) to give tetrazol-1-ylacrylic acids (18) (Scheme 2.1).[100,101,102] Standard manipulation gave the corresponding acrylamides, *etc.* (19)[100] and copper catalysed decarboxylation gave 1-(2-arylalk-1-enyl)tetrazoles (20).[101] The limitations of this route are that the condensation of the azlactone with the aldehyde works well only for aromatic aldehydes and that the products necessarily bear a carboxylic acid group on the 1-position of the alkene.[101,102,103]



SCHEME 2.1

[a] For convenience 1,5-disubstituted tetrazoles will be represented as $R^2N_4CR^1(1-)$ and 2,5-disubstituted tetrazoles as $R^2N_4CR^1(2-)$.

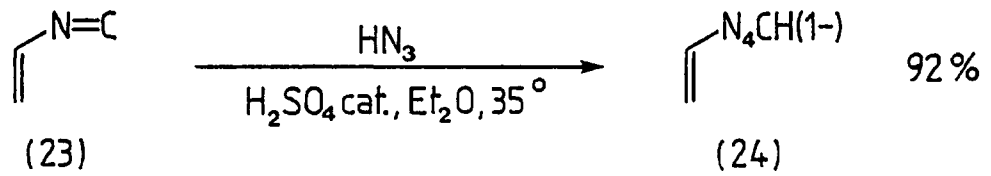
Direct vinylation, by treatment with vinyl acetate and mercuric acetate, was successful in the case of 5-aminotetrazole (21).[104] However,



(21) (22)

severe conditions were required and it is unlikely that selective 1-vinylation would occur for other 5-substituents since 5-aminotetrazole is known to show an exceptionally high preference for 1- rather than 2-alkylation.[95,105]

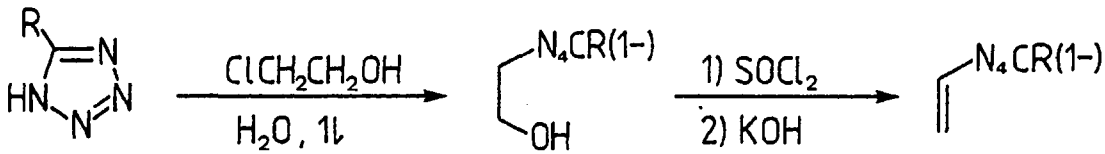
Reaction of vinylisonitrile (23) with ethereal hydrazoic acid gave 1-vinyltetrazole (24) in high yield.[106] This is a potentially attractive



(23) (24)

route to 5-unsubstituted 1-alkenyltetrazoles, but the preparation of vinylisonitrile is tedious.[107]

The most promising method involved alkylation of tetrazoles with 2-chloroethanol, followed by a two-step dehydration procedure.[108] This



may be a fairly general method but is limited by poor regioselectivity in the alkylation.

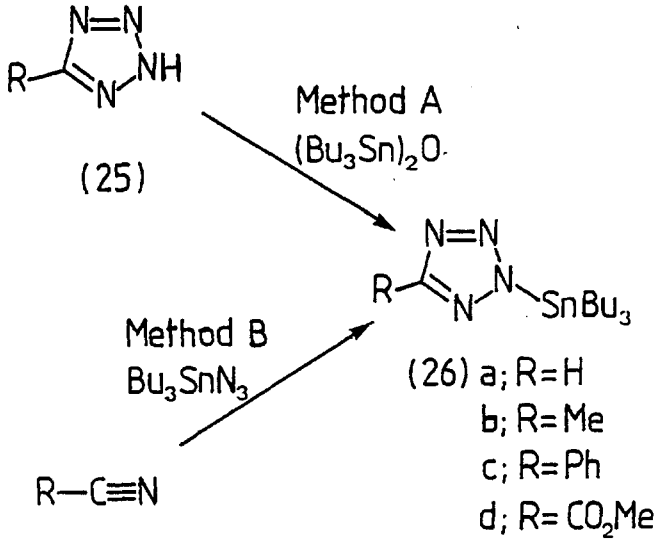
None of these routes is entirely satisfactory and in the present study some new methods have been developed.

2.2.1. Preparation of 1-Alkenyltetrazoles using Epoxides.

In principle 1-alkenyltetrazoles could be prepared by alkylation of tetrazoles with epoxides followed by dehydration of the resulting β-hydroxyalkyl derivatives. This strategy has been employed in the synthesis

of other *N*-alkenyl heterocycles, *e.g.*, pyrroles[109] and imidazoles[110] and has now been successfully applied to tetrazoles.

2.2.1.1. Alkylation. The alkylation of tetrazoles with epoxides presents two problems. (i) Tetrazole anions are poor nucleophiles and might not react with epoxides. (ii) Most tetrazoles alkylate preferentially on N-2 but 1-alkylation is required in this case.[95] Both of these difficulties were overcome by using 2-tributylstannyltetrazoles, rather than alkali metal salts. These are readily available and are reported to react with alkyl halides to give mostly 1-alkylation.[111] The 2-tributylstannyl derivatives of tetrazole, 5-methyltetrazole, methyl tetrazole-5-carboxylate, and 5-phenyltetrazole were prepared according to literature methods (Scheme 2.2).[112]



R	H	Me	Ph	CO_2Me
Method	A	B	A	B
Yield (26) (%)	100	83	98	90

SCHEME 2.2

The stannyltetrazoles (26a-c) reacted with epoxides under mild conditions and cleavage of the resulting stannyl ethers by addition of hydrogen chloride or acetic acid to the reaction mixtures gave 1-(2-hydroxyalkyl)tetrazoles (27) in moderate to good yields (Table 2.1,

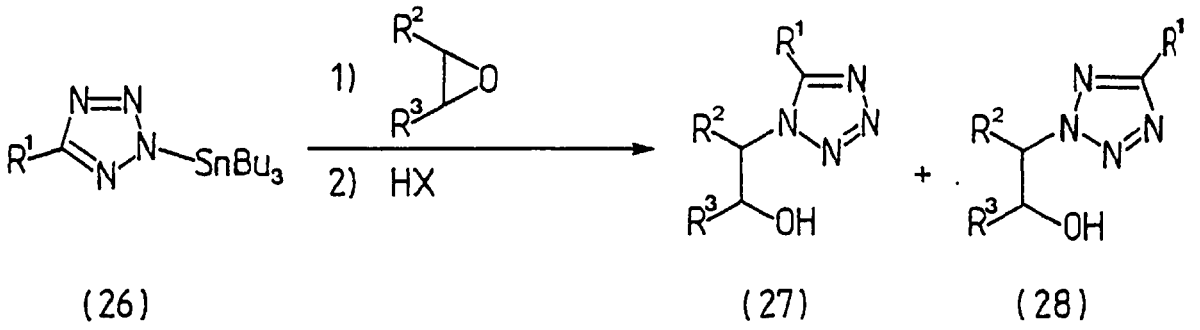


TABLE 2.1. Alkylation of 2-tributylstannyltetrazoles with epoxides.

(27),(28)	R^1	R^2	R^3	Procedure[a]	Conditions[b]	Yield (27) (%)	Yield (28) (%)
a	H	H	H	A	E, 43h	36	28
a	H	H	H	B	E, 25h	44	28
a	H	H	H	C	E, 25h	43	16[c]
b	H	H	Me	A	E, 36h	33	37
b	H	H	Me	B	E, 80h	48	44
c	Me	H	Me	C	E, 39h	70	20
d	Ph	H	H	A	E, 72h	80	8
e	Ph	H	Me	A	E, 90h	69	7
e	Ph	H	Me	B	E, 90h	78	18
f	Ph	$-(CH_2)_4-$		A	E, 140h	57	15
f	Ph	$-(CH_2)_4-$		A	Bz, 10h	51	36
g	Ph	H	Ph	A	Bz, 10h	45	6
h	Ph	Ph	H			34	7
i	Ph	Ph	CO_2Et	A	Bz, 22h	72	10

[a]Procedure A: 1) (26)+epoxide, 2) Excess HX. Procedure B: 1)(25)+epoxide+ 10 mol % (26), 2) 10 mol % HOAc. Procedure C: 1) (25)+epoxide+5mol% (Bu_3Sn_2O, 2) 10 mol% HOAc. 1.5 to 2.5 mol of epoxide was used.

[b]E: Ether at room temperature. Bz: Benzene at reflux.

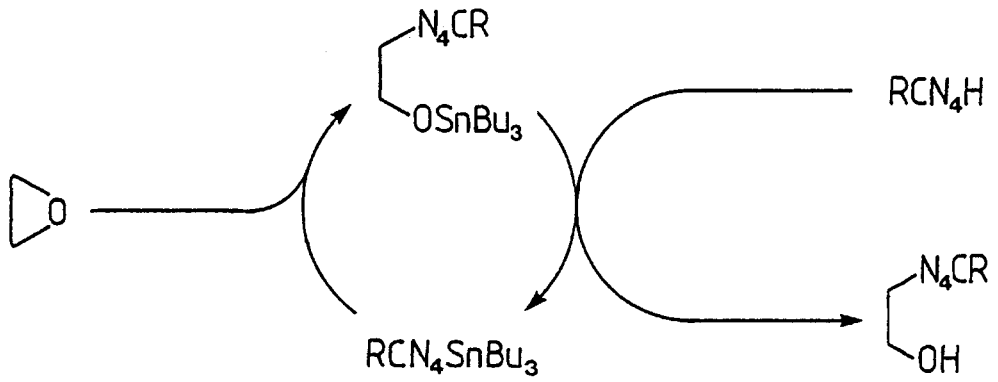
[c]This yield is almost certainly too low due to loss during isolation. N.m.r. of the crude in a smaller scale experiment showed a ratio of (27) to (28) of 62 to 38 so that a yield of 26% of (28a) was expected.

Procedure A). An exploratory alkylation of the ester (26d) with propylene oxide gave the decarboxylated tetrazole alcohol (27b) as the major product and no further experiments were carried out. For (26a-c) ether and benzene were found to be the best solvents, dichloromethane was slightly inferior, and ethanol and *N,N*-dimethylformamide (DMF) gave very poor results. The reaction was general for a range of unsubstituted, monosubstituted and 1,2-disubstituted epoxides. The facility of these reactions may be due, at least in part, to the development of a strong Sn-O bond in the transition state. The possibility of Lewis acid type behaviour by the tin is supported by the formation, from styrene oxide, of 41% of products resulting from attack at the substituted position, whereas exclusive attack at the unsubstituted carbon would be expected from a purely nucleophilic reaction. Likewise, ethyl phenylglycidate underwent attack exclusively at the carbon bearing the phenyl group. These results indicate that the regiochemistry of the epoxide ring opening is determined by a balance of steric factors and the ability of substituents to stabilise a partial positive charge on the ring carbons.

In all cases a mixture of 1- and 2-alkylated tetrazoles was formed. The isomeric alcohols were easily separated by chromatography, on silica gel for the 5-phenyltetrazoles, and on alumina for the 5-methyl and 5-unsubstituted derivatives. As noted previously[95] the 1-alkylated isomers were the more polar, *i.e.*, they had lower R_f values on t.l.c., and they were also distinguished by several features in their n.m.r. spectra. Thus, (i) the chemical shifts of the protons α to the tetrazole were *ca.* δ 0.3 lower in the 1-alkylated isomers,[105(b),113] (ii) the ring proton resonated at *ca.* δ 0.4 lower field in the 1-alkylated isomers in the 5-unsubstituted series,[113] and (iii) the *ortho* protons were at *ca.*

δ 0.2 lower field than the *meta* and *para* protons in the 1-alkylated isomers but at *ca.* δ 0.5 lower field in the 2-alkylated isomers, in the 5-phenyl series. For the 5-phenyl (26c) and 5-methyltetrazoles (26b) the regioselectivity was quite good, the ratio of 1- to 2-alkylation being greater than 4:1 in most cases and the combined yields were good to excellent. In the reaction of (26c) with cyclohexene oxide the regioselectivity improved when the reaction was carried out in ether at room temperature rather than in refluxing benzene. For this reason most of the alkylations were done under the former, milder conditions even though several days were required for complete reaction in some cases.

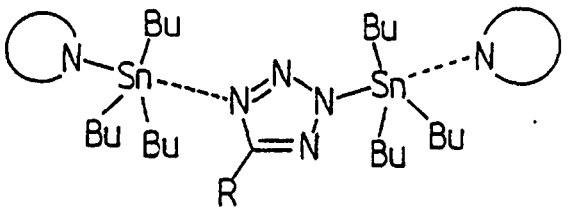
However, the 5-unsubstituted tetrazole (26a) gave almost equal proportions of 1- and 2-alkylation and in poor overall yields. The yields were improved significantly by using the tributylstannyltetrazoles catalytically. Thus, the use of (25) with 10 mol % of (26) gave an appreciable increase in yields (Table 2.1, Procedure B). This improvement



was probably due to the fact that less acid was needed to quench the reactions and there was less tributylstannyl compound contaminating the products so that separation was more efficient and the recovery was higher. N.m.r. spectra of the crude product mixtures indicate that there

was essentially no change in the regioselectivity, the apparent changes on isolation being due to the improvement in recovery referred to above. This is also consistent with the observation that tetrazole (25a) did not react with ethylene oxide under the conditions of Procedure B and thus no change in regioselectivity would be expected. A variation of the catalytic method in which the tributylstannyltetrazole was formed *in situ* by adding 5 mol % of $(Bu_3Sn)_2O$ to a mixture of the tetrazole (25) and the epoxide (Procedure C) gave very similar results to Procedure B (Table 2.1). Of the three procedures this is the method of choice because it is the most convenient to carry out.

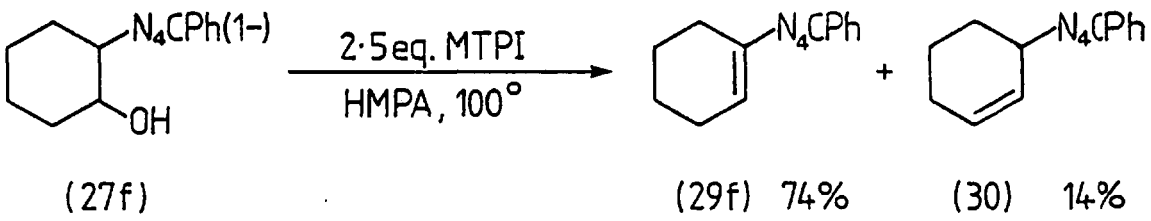
The poor regioselectivity shown by (26a) is puzzling. Sterically, the absence of a substituent at C-5 would be expected to favour 1-alkylation and electronically the 5-unsubstituted derivative would be expected to be intermediate between the 5-methyl and 5-phenyltetrazoles (*c.f.*, relative acidities[95(b)]). Indeed, previous reports show that sodium and ammonium salts have a relatively high preference for 1-alkylation.[108,113] A possible explanation for the amomalous behaviour of the stannyl derivative (26a) is suggested by consideration of the structures of the tributylstannyltetrazoles in concentrated solution in non-polar solvents, *i.e.*, the conditions of the epoxide ring-opening reactions. Under these conditions viscosity measurements showed that the stannyltetrazoles were polymeric and it was proposed that this was due to coordination of N-5 to the tin as shown.[112] The aggregated structure was thought not to be involved in the reactions with alkyl halides because addition of methanol which disrupts this kind of association, did not affect the regioselect-



ivity.[111] However, in the present alkylations using epoxides, the use of methanol rather than ether as the solvent causes a pronounced reduction in the rate of reaction, suggesting that the polymeric form is involved in these reactions. The size of the substituent R would be expected to strongly affect the strength of the coordination of N-5 to the highly hindered tin atom. This is borne out by the observation that 5-alkyltetrazoles are more strongly associated than 5-aryl derivatives,[112] and leads to the prediction that the N-5-Sn bond would be strongest for R = H. The effect of the strong coordination at N-5 might be to suppress alkylation at that site and this may explain the low selectivity in the case of the 5-unsubstituted tetrazole (26b).

2.2.1.2. Dehydration. The first alcohol which was dehydrated was the cyclohexanol (27f). Reaction with phosphorus oxychloride in pyridine[114] gave no identifiable products and a blank experiment showed that the alcohol was unstable in pyridine solution. The alcohol was unchanged after refluxing with *p*-toluenesulphonic acid (PTSA) in xylene[115] for 70 h, and treatment with triphenylphosphine and carbon tetrachloride in refluxing acetonitrile[116] for 70 h gave only 6% of dehydrated product. An attempt to prepare the cyclohexyl chloride by reaction with refluxing thionyl chloride was also unsuccessful, the alcohol surviving unchanged. Dehydration was finally accomplished by treatment with methyltriphenoxy-

phosphonium iodide (MTPI) in hexamethylphosphoramide (HMPA) at 100° for 41h, and gave a mixture of vinyl (29f) and allyl (30) tetrazoles. This reagent system[117] converts alcohols to the iodides, which are then

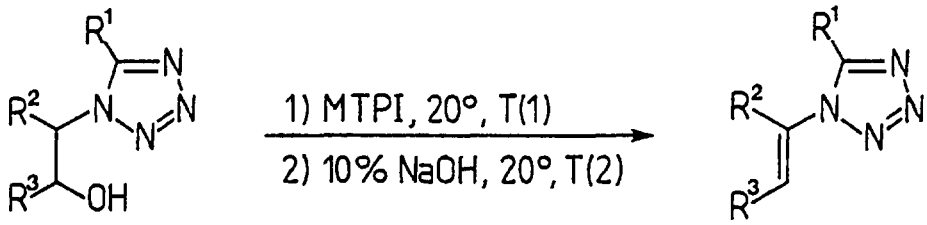


(27f) (29f) 74% (30) 14%

dehydroiodinated by excess of MTPI, iodide being a good base in dipolar aprotic solvents such as HMPA.

It was later found that better results are obtained by using one equivalent of MTPI in HMPA at room temperature to form the iodides and pouring the reaction mixture into 10% aqueous sodium hydroxide to effect elimination. This variation was successfully employed to dehydrate a series of 1-(2-hydroxyalkyl)tetrazoles (27) (Table 2.2). The method is very simple and gave good yields in all but one case.

The yields were excellent for the 5-phenyltetrazoles but were lower for the 5-methyl and 5-unsubstituted compounds because these alkenes were water soluble and in extracting them from the aqueous phase, the HMPA was also extracted and could not then be separated without considerable loss of the product. However, replacement of the HMPA with DMF improved the yields considerably because it could be distilled from the alkenes without significant losses. Trial experiments using DMF in the 5-phenyl series suggest that it is not quite as good as HMPA because in the second stage some reversion of the iodide to the alcohol occurred in addition to the elimination. This problem caused only a small decrease in yield for a secondary alcohol (27e) but was more acute for a primary one (27d) (Table 2.2).



(27) (28)

TABLE 2.2. Dehydrations using MTPI.

(27),(29)	R^1	R^2	R^3	Solvent	T(1)/h	T(2)/h	Yield (29) (%)
a	H	H	H	DMF	4	27	69
b	H	H	Me	DMF	4	15	67
c	Me	H	Me	DMF	6	5	73
d	Ph	H	H	HMPA	3	1	93
d	Ph	H	H	DMF	4	14	76
e	Ph	H	Me	HMPA	26	2	86
e	Ph	H	Me	DMF	22	2	83
f	Ph	$-(CH_2)_4-$		HMPA	24	3	79
g	Ph	H	Ph	HMPA	19	1	85
h	Ph	Ph	H	HMPA	19	1	89
i	Ph	Ph	CO_2Et	HMPA	10	0.75[c]	0

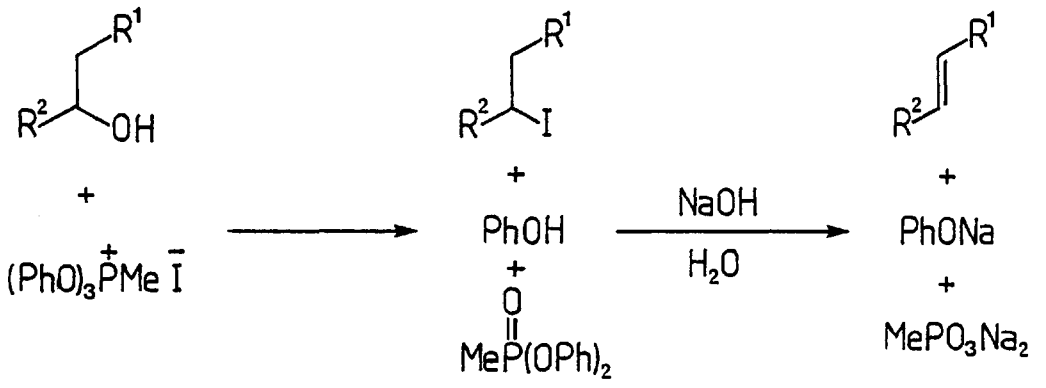
[a] 1-10 h was sufficient, some times are much longer than necessary

[b] 1-2 h was sufficient, some times are much longer than necessary

[c] NaOEt/EtOH was used as the base in order to prevent hydrolysis of the ester.

The coupling constants of the olefinic protons in the n.m.r. spectra of the products showed them to be the *trans* isomers but very small amounts of the *cis* alkenes were present in the products from the dehydrations carried out in DMF. Excellent regioselectivity was observed. The propanols gave the prop-1-enyltetrazoles exclusively and in the case of the cyclohexanol (27f), the n.m.r. of the crude product showed that less than 5% of the cyclohex-2-enyl isomer (30) was formed (*c.f.*, 15% in the original procedure described above).

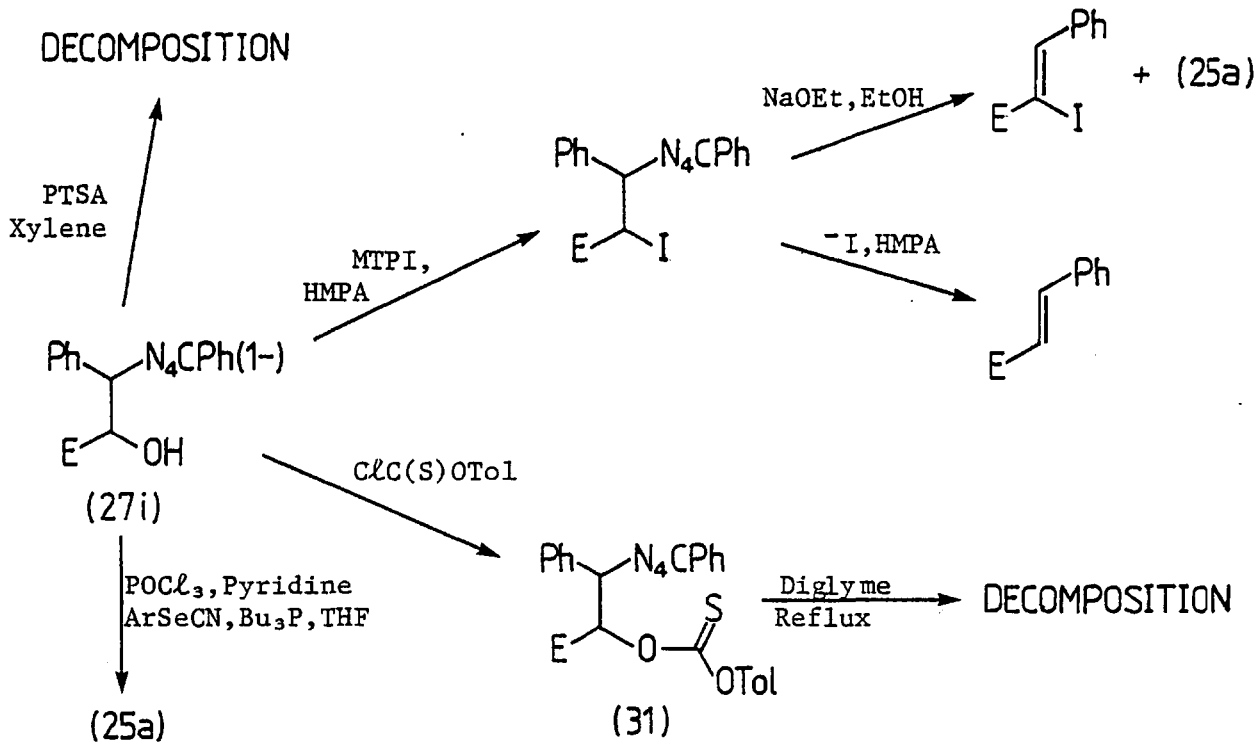
This modified dehydration procedure offers several advantages over the original method.[117] Only a small excess of MTPI is required as opposed to over 2 equivalents needed previously. Milder conditions are used and the method, which was applicable only to secondary alcohols, is extended to include primary alcohols also. This is because primary alkyl iodides are dehydroiodinated by the aqueous base whereas they are inert to the original conditions. The work-up is greatly facilitated because the by-product, diphenyl methyl phosphonate, which proved very difficult to remove chromatographically, is hydrolysed and does not contaminate the products (Scheme 2.3.). In many cases isolation of the



SCHEME 2.3

alkene simply by filtration gives very pure product. The chief problems are the difficulties in handling MTPI, which is very moisture sensitive, and the limitations imposed by the use of a relatively strongly basic solution in the second step, *e.g.*, side reactions such as hydrolysis of esters.

The method failed completely for the β-tetrazolyl ester (27i) because elimination of 5-phenyltetrazole was favoured over loss of hydrogen iodide. The elimination of tetrazoles from β-tetrazolyl esters is well documented[118,119] and it also frustrated several other attempts to dehydrate (27i) (Scheme 2.4.). Use of the original MTPI method, *i.e.*,

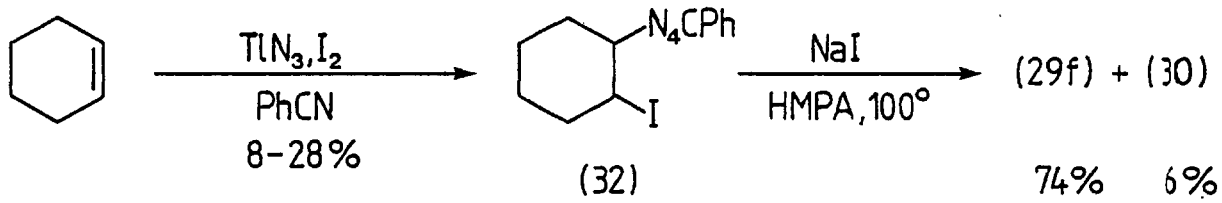


SCHEME 2.4

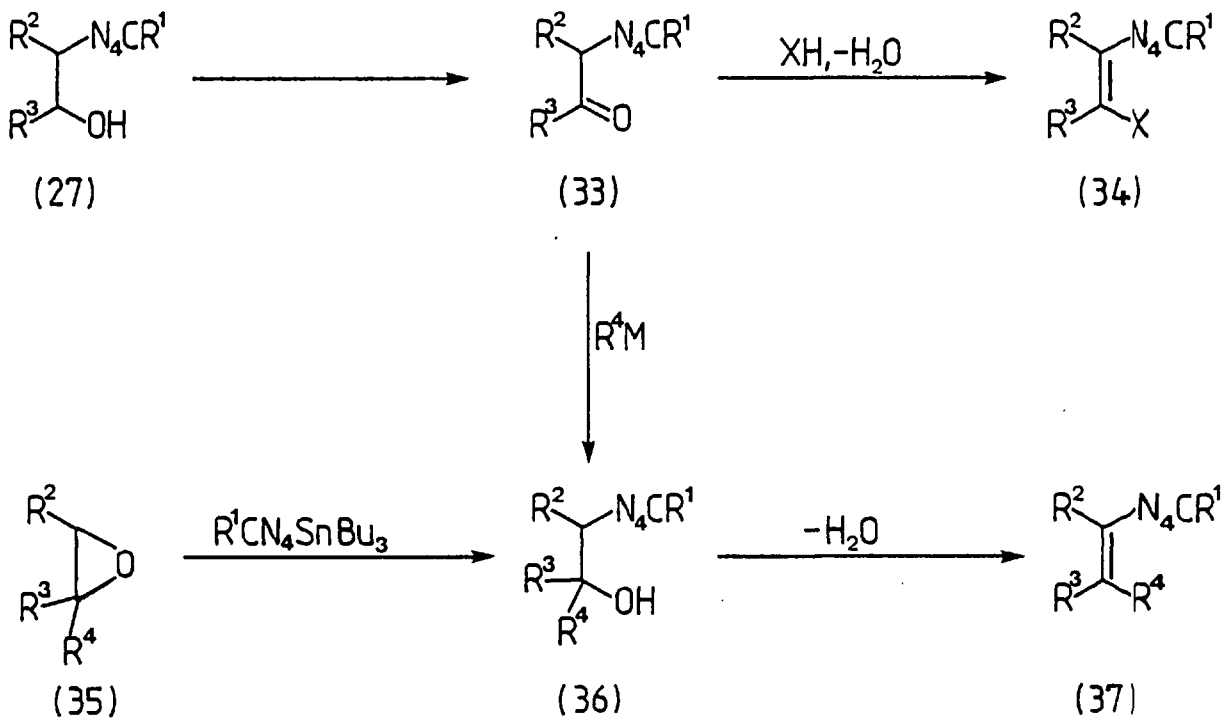
MTPI in HMPA, gave ethyl cinammate presumably by reductive elimination to form iodine and 5-phenyltetrazole anion. Reaction with 2-nitrophenylselenocyanate and tributylphosphine[120] also caused elimination of

5-phenyltetrazole, probably because relatively basic intermediates, *e.g.* $ArSe^-$, are formed. The thiocarbonate ester (31) was prepared but an attempted pyrolytic elimination[121] gave a mixture containing none of the desired alkene. Reaction with PTSA in refluxing xylene[115] gave an intractable mixture and phosphorus oxychloride in pyridine gave 5-phenyltetrazole as the only isolated product. The desired tetrazolylacrylates were subsequently prepared by a different route (2.2.3).

The cyclohexenyltetrazole (29f) was also prepared by an alternative two-step route. Reaction of cyclohexene with iodine and thallous azide in benzonitrile[122] gave the iodocyclohexyltetrazole (32) but the yields were low and irreproducible and although elimination using sodium iodide in HMPA did give the vinyltetrazole this route was abandoned in favour of the epoxide method.



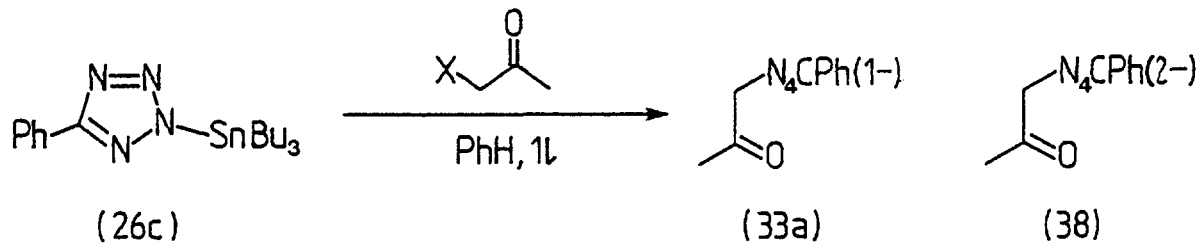
2.2.1.3. Extension to 2,2-Disubstituted Vinyltetrazoles. As outlined in the introduction, it was hoped to obtain 4*H*-imidazoles by photolysis of 1-(2,2-disubstitutedvinyl)tetrazoles (37). These could be obtained *via* the epoxide route either by using 1,1-disubstituted epoxides (35) in the alkylation or by converting the secondary alcohols (27) into tertiary ones (36) by oxidation to the ketones (33) followed by addition of organometallic compounds (Scheme 2.5.). Initially it was decided to investigate the ketone method because it was anticipated that the tetra-



SCHEME 2.5

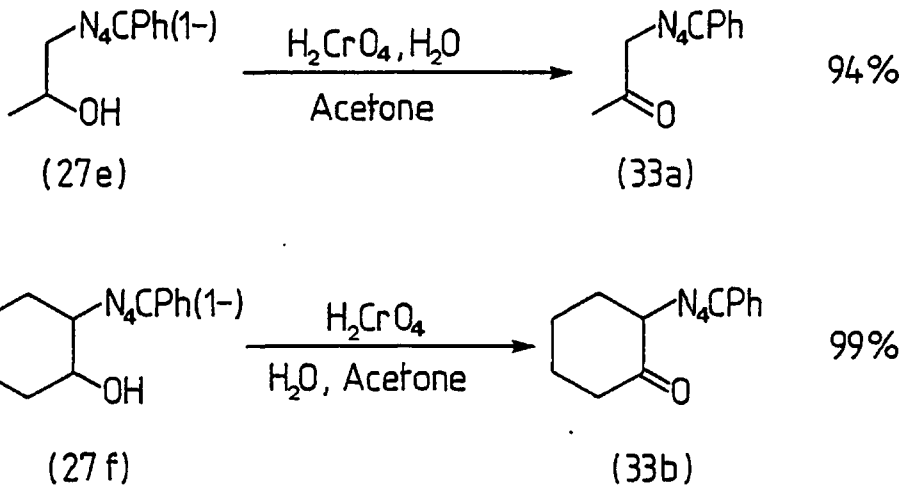
zolyl ketones (33) would be versatile precursors for a variety of heterosubstituted alkenyltetrazoles (34).

Since it was reported that 2-tributylstannyltetrazoles reacted with ethyl bromoacetate to give α-tetrazol-1-ylesters in high yield[111] it was decided to attempt to make the ketones (33) by alkylation with α-halo ketones. However, reaction of 5-phenyl-2-tributylstannyltetrazole with α-bromoacetone gave the 2-alkylated isomer (38) predominantly, and although the use of α-chloroacetone favoured 1-alkylation the yield of

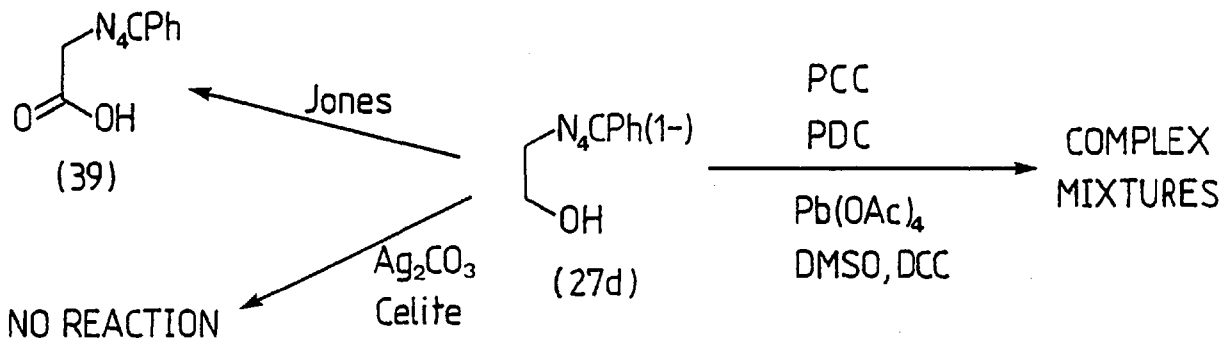


(33a) was only 31%. Moreover, attempts to reproduce the reported reaction with ethyl bromoacetate gave only 34% of the tetrazol-1-ylester as opposed to the 90% yield claimed in the literature. In view of the low yields and regioselectivity found in these reactions it was decided not to pursue this approach.

Oxidation of the propanol (27e) and the cyclohexanol (27f) with Jones' reagent[123] gave the corresponding ketones (33a) and (33b) in high yields and this two-step route is much superior to the one-step method discussed



above. However, the tetrazolylethanol (27d) did not give the corresponding aldehyde using a variety of reagents (Scheme 2.6.). Jones' reagent

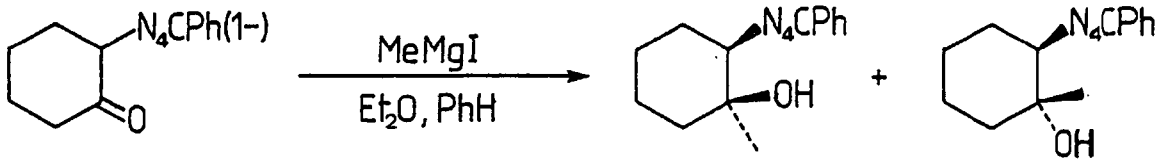


SCHEME 2.6

oxidised it to the acid (39); pyridinium chlorochromate,[124] pyridinium

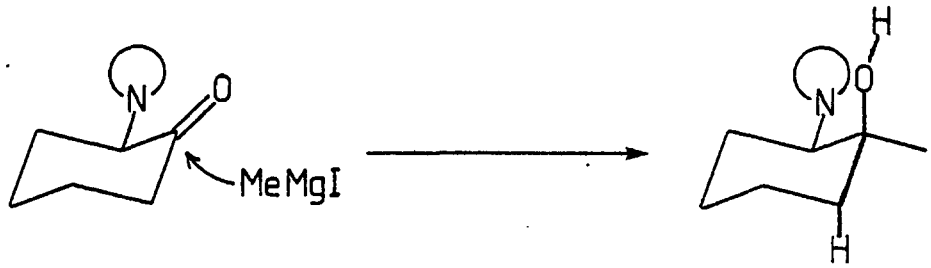
dichromate[125] and lead tetraacetate in pyridine[126] gave complex mixtures containing no aldehyde; Moffatt oxidation using dicyclohexylcarbodiimide, dichloroacetic acid and DMSO in ethyl acetate[127] also gave an intractable mixture but a small amount of aldehyde was formed (n.m.r.). The alcohol was inert to silver carbonate on Celite in refluxing benzene.[128]

Of the ketones, only the cyclohexanone (33b) was further elaborated. Reaction with methyl magnesium iodide gave a mixture of diastereomeric alcohols (36a) and (36b) whose stereochemistries were tentatively assigned on the basis of " W" coupling of the hydroxyl proton in the n.m.r. of (36a).

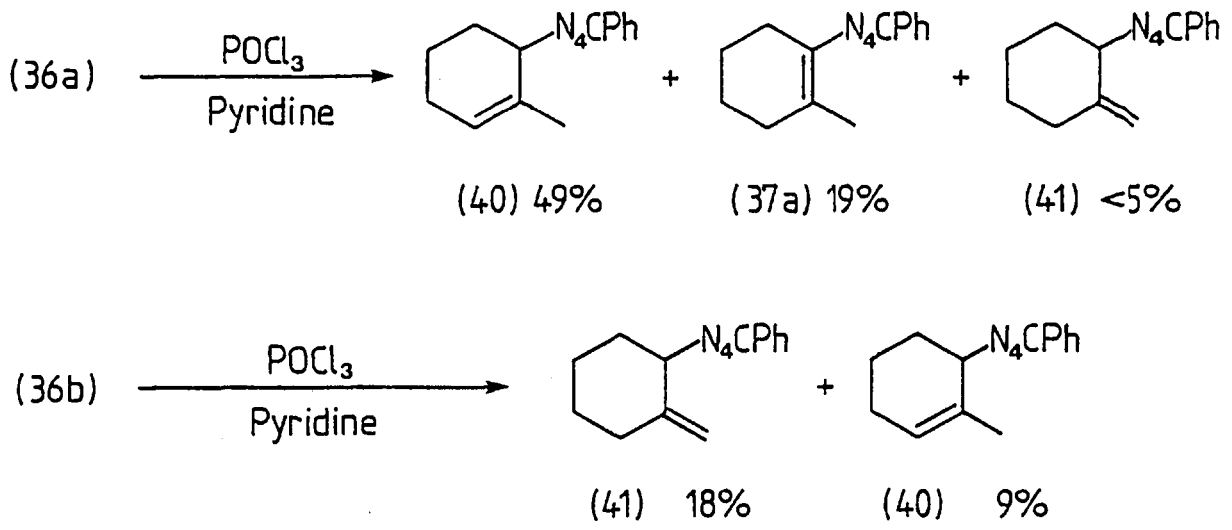


(33b) (36a) 77% (36b) 10%

As expected the major product is the result of pseudo-equatorial attack of the Grignard reagent on a conformation of the ketone in which the tetra-

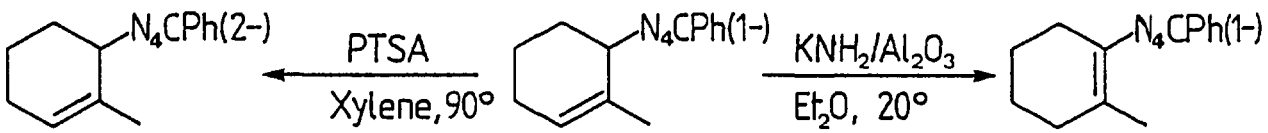


zolyl group is equatorial. Dehydration of the alcohols with phosphorus oxychloride in pyridine at room temperature gives mixtures of the three possible alkenes, (37a), (40) and (41). The major alcohol (26a) gave an approximately two to one mixture of the cyclohex-2-enyl- (40) and the cyclohex-1-enyl- (37a) tetrazoles, together with a small amount of the *exo*-methylene compound (41), in good total yield. The diastereomeric



alcohol (36b) gave a mixture of alkenyltetrazoles in only 27% yield. The mixture could not be separated by chromatography but n.m.r. showed it to consist of (41) and (40) in a ratio of *ca.* two to one. That the two diastereomers gave different product mixtures rules out a carbonium ion mechanism and it appears that the product ratios are the result of E2 elimination with a preference for tri- over tetra- and tetra- over di-substituted alkenes.

Unfortunately, the desired vinyltetrazole (37a) was a minor product. Since it was considered that this might be the most stable isomer several attempts were made to convert the unwanted allyltetrazoles into it. The isomerisation of alkenes[129] has been used to prepare vinylcarbazoles[130] and vinylpurines [131] from the allyl isomers. Heating (40) at 90° in xylene containing a catalytic quantity of *p*-toluenesulphonic acid caused rearrangement to the 2-allyltetrazole (42). The rearrangement of 1-alkyl to 2-alkyl 5-phenyltetrazoles in the presence of excess of alkylating agent has been observed and shown to proceed *via* an alkylation-dealkylation



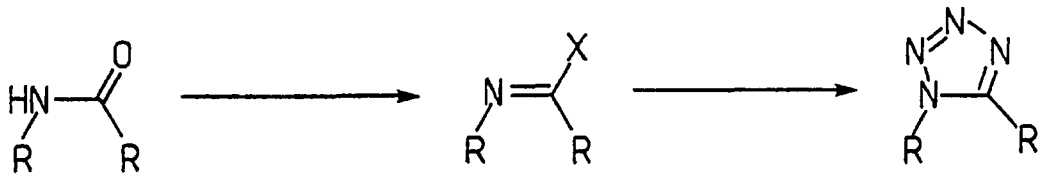
(42) (40) (37a)

sequence to give the more stable isomer.[132,133] The rearrangement of (40) to (42) may have a similar mechanism with the alkyltetrazole itself, or a protonated derivative, acting as the alkylating agent. An alternative mechanism involving a [3,3]sigmatropic shift is unlikely for stereochemical reasons. Treatment of (40) with rhodium(III) chloride and triethylamine in refluxing aqueous ethanol[134] caused slow isomerisation to (42). Conversion of a mixture of (40) and (41) into the vinyltetrazole (37a) was finally accomplished (73%) using potassium amide on alumina as the " catalyst" .[130] It was found that, on the small scale employed, an excess of potassium was required to bring about complete isomerisation.

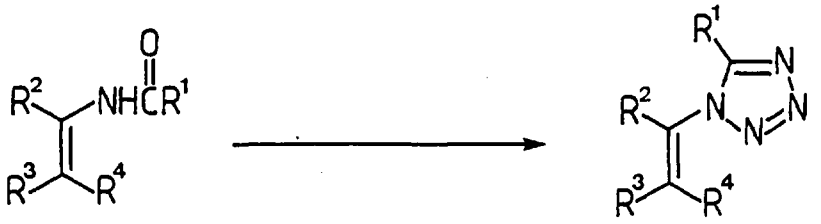
The unfavourable regiochemistry in the dehydration of the tertiary alcohols (36) is a serious limitation on this approach to 2,2-disubstituted vinyltetrazoles. Although the unwanted allyl isomers were successfully isomerised to the required vinyltetrazole the necessity of an extra step considerably reduces the efficiency of this route.

2.2.2. Preparation of 1-Alkenyltetrazoles using Enamides.

One of the most general methods of preparing 1,5-disubstituted tetrazoles is the conversion of secondary amides into imidoyl derivatives such as imidoyl chlorides followed by reaction with azide ion.[95] This



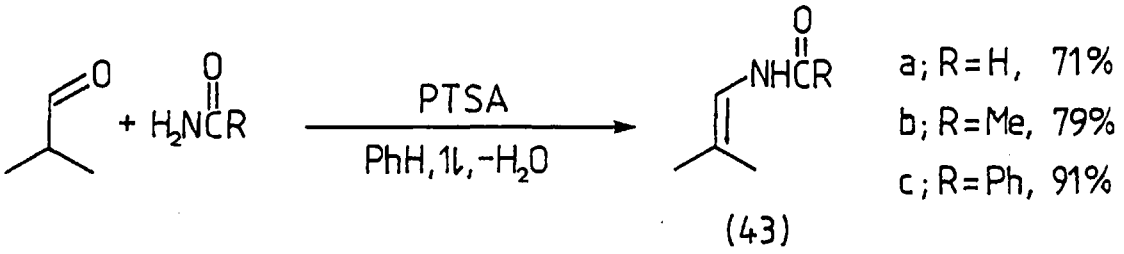
works well for *N*-alkyl and *N*-aryl amides and would provide 1-alkenyl-tetrazoles if enamides (43) were employed. If successful, this method



(43) (37)

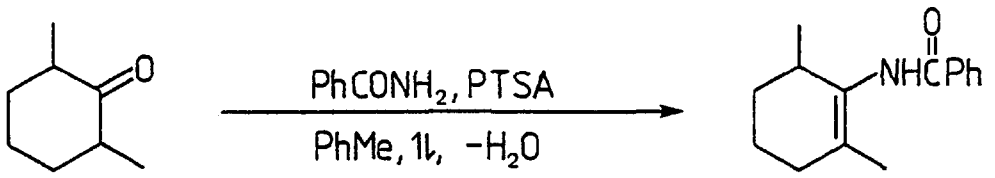
would overcome two of the chief limitations of the epoxide route, (i) only 1-substituted tetrazoles would be formed, and (ii) only alk-1-enyltetrazoles would be formed. Although enamides have been widely used in synthesis, especially in photocyclisation reactions,[135] most of those reported are tertiary amides and relatively little attention has been devoted to secondary derivatives. They have been prepared by the condensation of primary amides with aldehydes,[136] but the reaction with ketones is less well described and there are only a few isolated examples.[137,138] They have also been made by the reaction of nitriles with ketones in the presence of aluminium chloride.[139] Enamides were converted into enimidoyl chlorides by phosphorus pentachloride[140] and to enimidates by triethyloxonium tetrafluoroborate,[141] and enimidoyl halides and esters were formed by indirect methods.[142] However, there has been no report of the conversion of enamides into tetrazoles.

Formamide, acetamide and benzamide condensed with *iso*-butyraldehyde in refluxing benzene containing a catalytic amount of *p*-toluenesulphonic acid to give the enamides (43a-c) in good yields. It was important



(43)

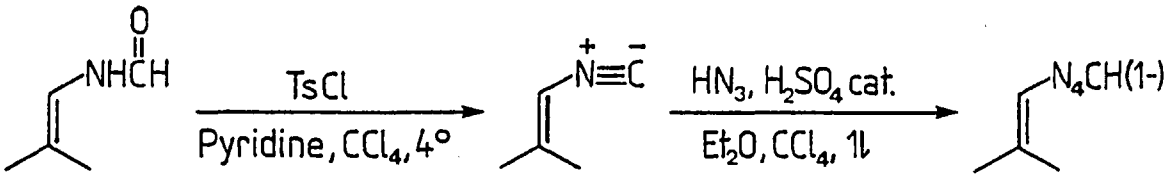
to use dilute reaction mixtures in order to suppress formation of *iso*-butyrylidene-bis-amides. Benzamide condensed with 2,6-dimethylcyclohexanone in refluxing toluene to give the enamide (43d) in 54% yield. No



(43d)

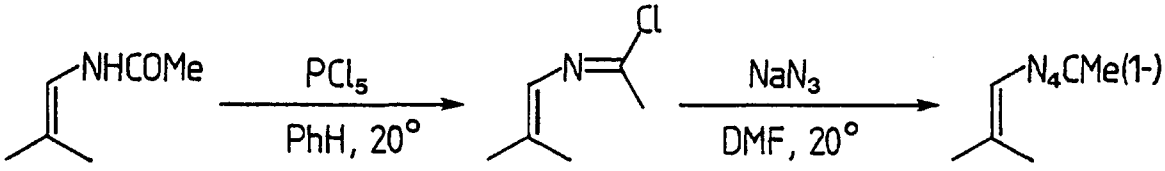
other ketones were tried but the success of this hindered example indicates that some generality may be expected.

Great differences in reactivity were found in the conversion of the enamides (43a-d) into tetrazoles. Treatment of the formamide (43a) with one mol of tosyl chloride and two mol of pyridine in carbon tetrachloride at 4° gave the alkenylisonitrile (44) which was not isolated because it was very volatile. After removal of the pyridinium salts an ethereal solution of hydrogen azide was added, and refluxing the mixture gave the tetrazole (37b) in 41% yield.[107]



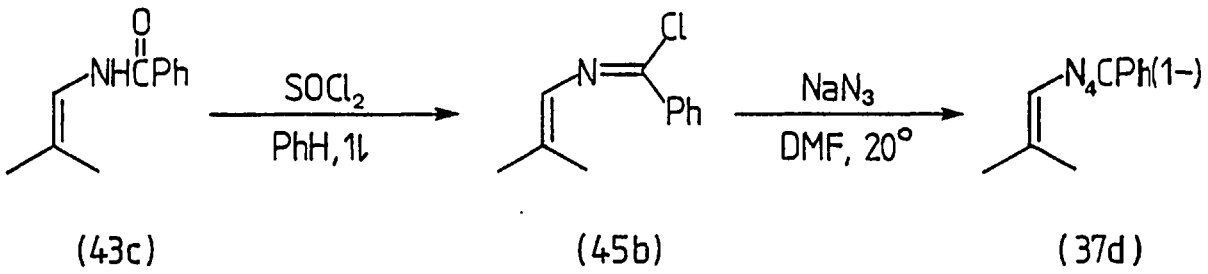
(43a) (44) (37b)

The acetamide (43b) was decomposed by thionyl chloride in refluxing benzene.[143] It reacted immediately at room temperature with phosphorus pentachloride-quinoline complex[144] but formed an unstable intermediate rather than the expected imidoyl chloride and attempts to convert this intermediate to the imidate or the tetrazole were unsuccessful. However, reaction of (43b) with phosphorus pentachloride in benzene at room temperature gave the imidoyl chloride (45a). The solvent was removed on the water pump at room temperature to prevent loss of the volatile imidoyl chloride, and reaction with sodium azide in DMF gave the tetrazole (37c), in 50% yield. The benzamide (43c) was inert to phosgene in refluxing



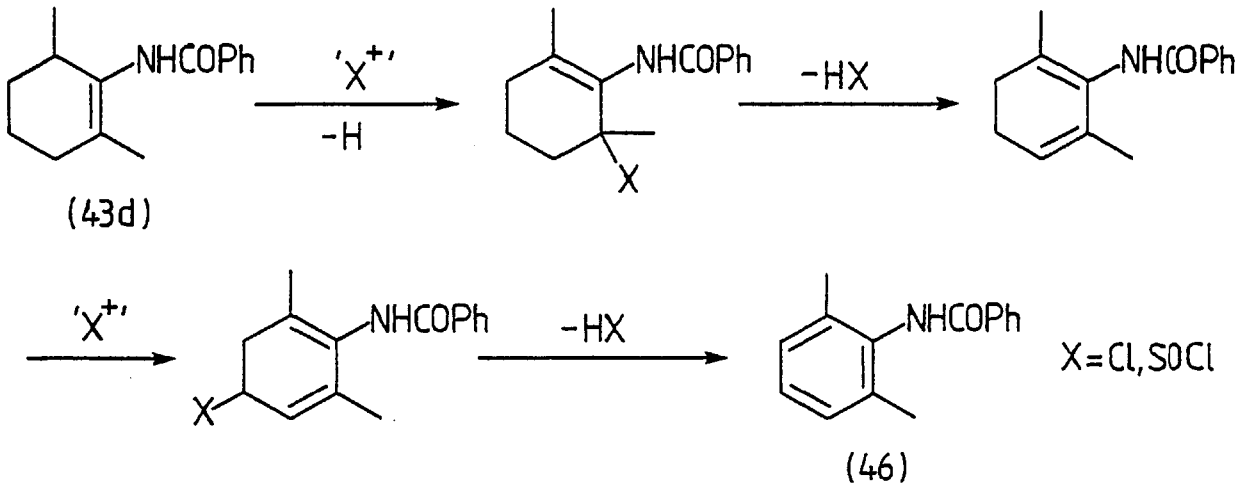
(43b) (45a) (37c)

benzene and reacted rapidly with phosphorus pentachloride-quinoline complex and with oxalyl chloride in acetonitrile[145] to give unstable intermediates which could not be converted into the tetrazole. Treatment with thionyl chloride in refluxing benzene gave the imidoyl chloride (45b) which yielded the tetrazole (37d) on addition to sodium azide in DMF. Surprisingly, addition of a catalytic amount of DMF to the thionyl chloride reaction caused extensive decomposition.



(43c) (45b) (37d)

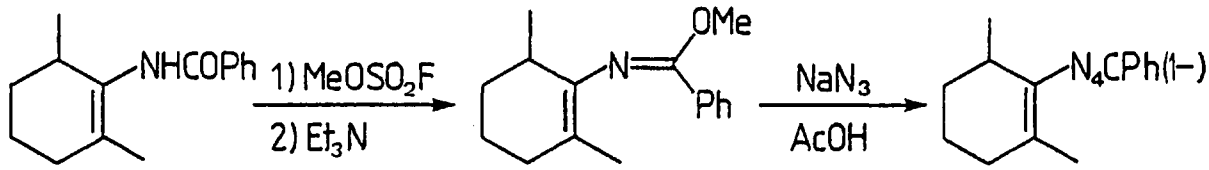
The dimethylcyclohexenylbenzamide (43d) was inert to phosphorus pentachloride in refluxing benzene and gave a complex mixture on heating at 50° with thionyl chloride and catalytic DMF in benzene. It reacted rapidly with oxalyl chloride in acetonitrile at -20° but addition of sodium azide did not give the tetrazole. Reaction with thionyl chloride alone in refluxing benzene gave a mixture which did not contain any imidoyl chloride and from which only a benzanilide (46) could be isolated. Enamides are known to undergo electrophilic substitution at carbon[146] so the dehydrogenation probably occurred *via* a sequence of substitution and elimination reactions (Scheme 2.7). Because of the failure to form an



SCHEME 2.7

imidoyl chloride it was decided to attempt to use the imidate instead. The amide (43d) was not alkylated by dimethyl sulphate, but reaction with methyl fluorosulphonate in benzene followed by a non-aqueous work-up

and flash chromatography on silica gave the imidate (47) in 66% yield. Azidolysis of the imidate (47)[147] with sodium azide in acetic acid at room temperature gave the tetrazole (37e) in only 13% yield and the yield was not improved by conducting the reaction at 50°. The major



(43d) (47) 66% (37e) 13%

product in the azidolysis reactions was the enamide (43d) indicating that O-alkyl cleavage was occurring in preference to O-acyl cleavage. This has been observed in the acidic hydrolysis of hindered imidates,[147] and indicates that the enamide route is inefficient in these cases.

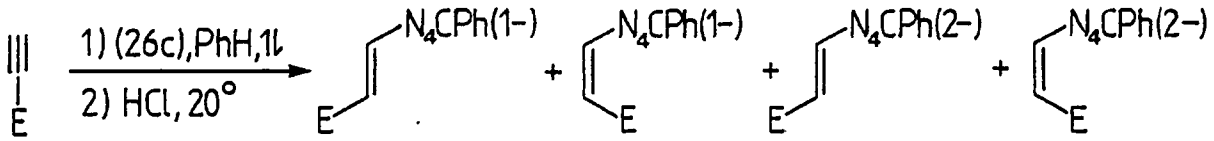
The yields of tetrazoles from the *iso*-butenylamides (43a-c) were only moderate but might improve with optimisation. This approach is unlikely to be competitive with the epoxide route for the synthesis of 1-(2-monosubstitutedvinyl)tetrazoles but for 2,2-disubstituted vinyl derivatives it is attractive because it is short and easy to carry out. Also, it complements the epoxide method in that it is based on ketones rather than alkenes so that two different classes of readily available compounds can be easily converted into 1-alkenyltetrazoles.

2.2.3. Preparation of 1-Alkenyltetrazoles using Acetylenic Esters.

As described in Section 2.2.1., the epoxide route failed in the case of a tetrazolylacrylate. The formation of *N*-acryloyl heterocycles by conjugate addition to activated acetylenes is well known[149] and although

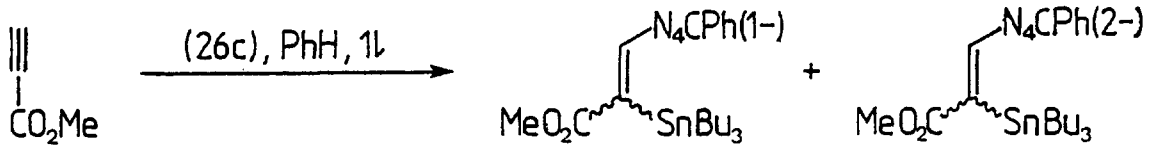
tetrazoles have not been reacted with acetylenes they are reported to undergo conjugate addition to α,β-unsaturated esters,[119] ketones,[150] and nitriles.[151] The yields in these reactions were low and the major products were the 2-alkylated derivatives. It was hoped that the use of 2-tri-*n*-butylstannyl tetrazoles would overcome these problems.

Reaction of 5-phenyl-2-tributylstannyltetrazole (26c) with an excess of methyl propiolate in refluxing benzene followed by cleavage of the intermediate vinylstannanes with hydrogen chloride gave the desired acrylates (29i) and (29j) in good yields and with high regioselectivity. As in the epoxide alkylations the 1-substituted products



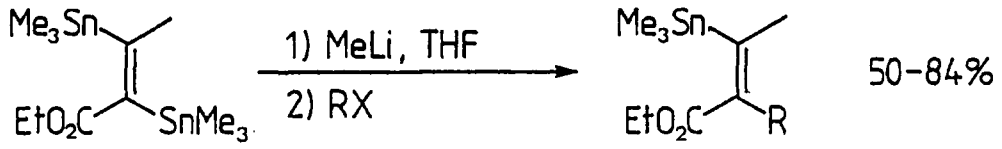
E=CO_2Me (29i) 35% (29j) 36% (48a) 14% (48b) 12%

were readily distinguished and separated from the 2-substituted isomers (48a) and (48b). When the stannyltetrazole (26c) was used catalytically, the 2-substituted derivatives predominated by a factor of two, possibly because of competing conjugate addition of the N-H compound (25c). The alkenylstannanes were relatively stable and were isolated and separated by chromatography on silica gel. They were cleaved by acetic acid only



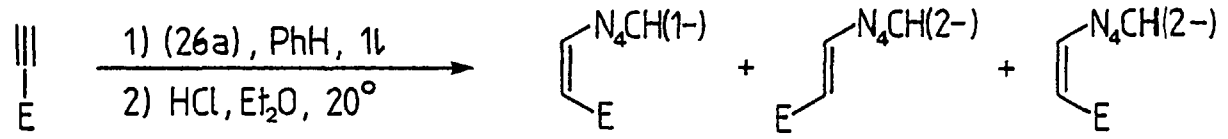
after prolonged refluxing in benzene, but were protonolysed in a few hours at room temperature by hydrogen chloride in benzene. These

stannanes could be useful in the preparation of 2,2-disubstituted vinyltetrazoles because similar compounds have been shown to undergo efficient transmetallation and alkylation.[152] The ratio of *cis* to *trans* alkenes



formed in the conjugate additions varied quite considerably but no attempt was made to study the factors influencing this ratio because it was (correctly) anticipated that both isomers would give the same imidazole on photolysis.

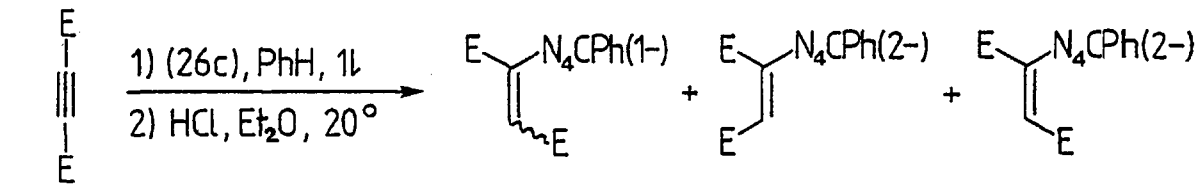
However, in the case of the 5-unsubstituted tetrazole (26a) the yield of the conjugate addition was low and the undesired isomers (48c) and (48d) predominated. When the reaction was carried out in refluxing



E=CO2Me (29k) 17% (48c) 20% (48d) 21%

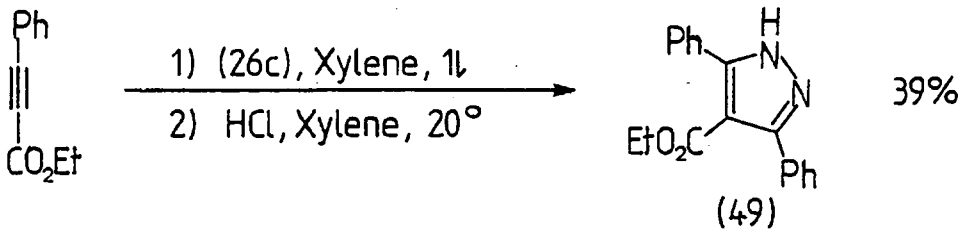
acetonitrile the isomer ratio and the yield were even lower and refluxing ethanol gave no conjugate addition.

Tetrazole (26c) reacted with dimethyl acetylenedicarboxylate (DMAD) to give a *cis/trans* mixture of 1-alkenyltetrazoles (29*l*) in good yield.



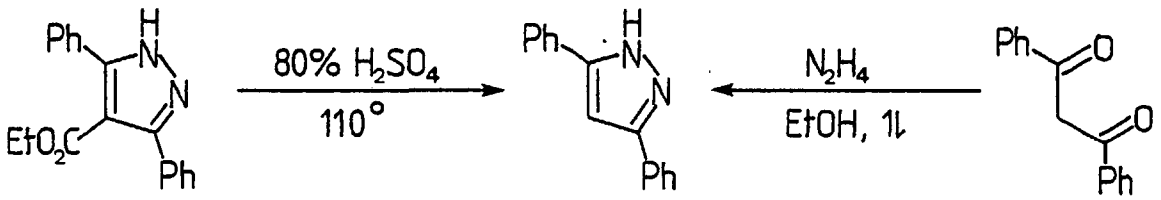
E=CO2Me (29l) 79% (48e) 8% (48f) 12%

However, reaction of (26c) with methyl tetrolate in xylene at reflux caused decomposition of the tetrolate and no more than traces of addition products were formed. Ethyl phenylpropiolate reacted slowly with (26c) in refluxing xylene to give, after protonolysis with hydrogen chloride, one major product. This was isolated by chromatography and its spectral data showed that it was not an alkenyltetrazole but a



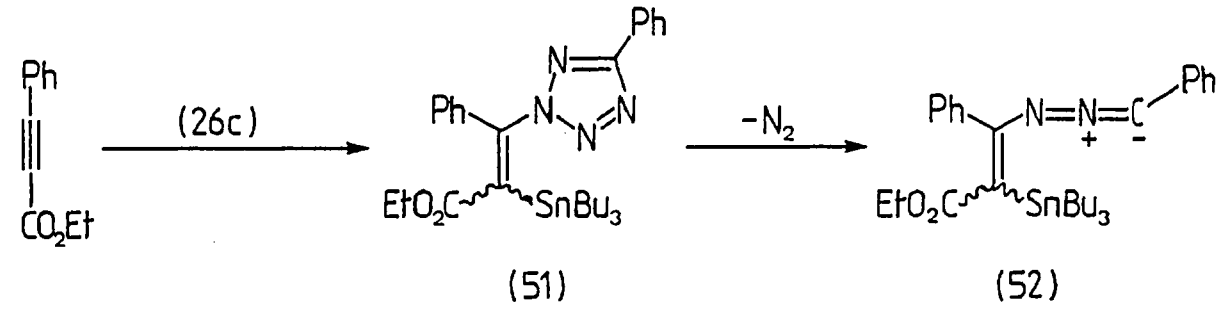
(49)

pyrazole (49). The structure was confirmed by hydrolysis and decarboxylation to give 2,4-diphenylpyrazole (50). In contrast to the literature[153] treatment of (49) with 80% sulphuric acid at 110° gave the decarboxylated product (50) directly and this was identical with a sample prepared

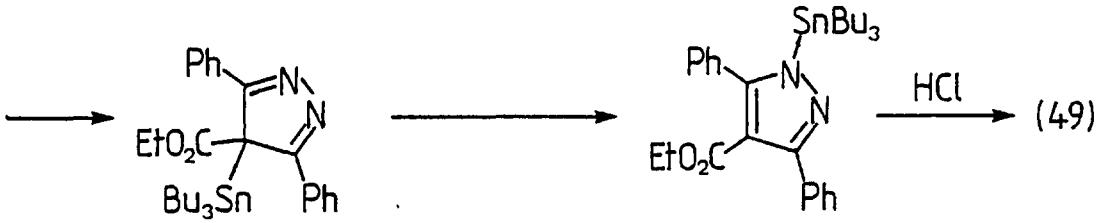


(49) (50)

from hydrazine and dibenzoylmethane. It is likely that the pyrazole (49) was formed by conjugate addition of (26c) to give the tetrazol-2-ylacrylate (51), formed in preference to the tetrazol-1-yl isomer for steric reasons, followed by loss of nitrogen, cyclisation of the nitrile imine (52) to give a 4*H*-pyrazole (53) and rapid migration of the stannyl group to give the 1*H*-isomer (54). The formation of nitrile imines from 2,5-disubstituted tetrazoles is well known and intramolecular cyclisation has been observed

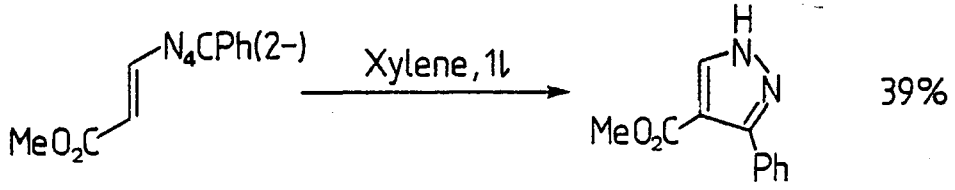


(51) (52)



(53) (54)

in 2,5-diaryl derivatives.[154] Thermolysis of a tetrazol-2-ylacrylate (48a) in refluxing xylene gave the corresponding pyrazole (55) consistent with the proposed mechanism. This new route to pyrazoles parallels the



(48a) (55)

formation of imidazoles from 1-alkenyltetrazoles.

In summary the conjugate addition of tributylstannyltetrazoles to acetylenic esters works well only for 5-phenyltetrazoles and for more reactive acetylenes such as methyl propiolate and DMAD and in these cases it provides a high yielding one-step synthesis of tetrazolylacrylates. The use of *N*-stannylheterocyclics in conjugate addition is new and offers

some advantages over that of the NH compounds, (i) the reactivity is increased, (ii) because the electron rich alkenylstannanes are stable, addition of a second molecule of heterocyclic does not occur, and (iii) the alkenylstannanes may be useful intermediates.

2.3. SPECTROSCOPIC PROPERTIES OF 1-ALKENYLTETRAZOLES.

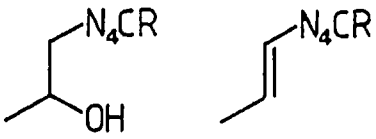
2.3.1. Infrared.

The 1-alkenyltetrazoles have C=C stretching absorbtions in the regions expected of non-conjugated olefins indicating that the interaction between the C=C and the heterocyclic nucleus is not very substantial. The absorbtions are of weak to medium intensity except for the acrylates which have strong bands, as expected. Strong CH out of plane deformation absorbtions at 940-950 cm^{-1} in the propenyl and 2-phenylethenyl derivatives confirm that they are the *trans* isomers.

2.3.2. Ultraviolet.

The u.v. absorbtions show bathochromic shifts on dehydration of the alcohols (27) to give alkenyltetrazoles (29) (Table 2.3) indicating that there is significant conjugation of the alkenes with the tetrazole rings. This shift was accompanied by an increase in extinction coefficients (ε) and it was more marked in the 5-unsubstituted and 5-methyl series than in

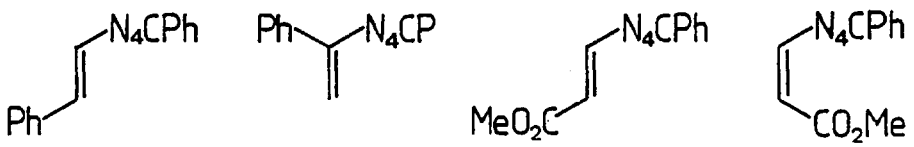
TABLE 2.3. U.v. data of 1-propenyltetrazoles.



(27) (29)

R	H	Me	Ph
λ_{max} (ε) of (27)	< 200	< 200	230(9600)
λ_{max} (ε) of (29)	229(7350)	226(7150)	240(1200)

the 5-phenyltetrazoles. All of the other derivatives absorbed in the same regions as the propenyl compounds except for the styryl (29g) and acryloyl (29i) tetrazoles which had higher λ_{max} and ε values as expected.



(29g) (29h) (29i) (29j)

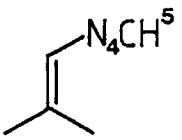
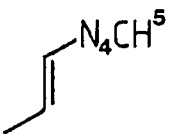
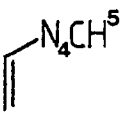
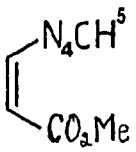
	(29g)	(29h)	(29i)	(29j)
λ_{max} (nm)	284	243	253	239
ε	17700	20300	16600	14400

2.3.3. Nuclear Magnetic Resonance.

The ^{1}H n.m.r. spectra conform to a fairly predictable pattern. In the vinyl compounds, the α protons are strongly deshielded, occurring at δ 7.14 in the 5-phenyltetrazole (29d) and at δ 7.65 in the 5-unsubstituted tetrazole (27a) and the *cis* [δ 6.22 in (29d) and δ 6.32 in (29a)] and *trans* [δ 5.5 in (29d) and δ 6.5 in (29a)] β protons are also substantially deshielded indicating that there is no enamine type electron donation by the tetrazole ring. The chemical shifts in the substituted derivatives were close to those predicted by the usual substituent effects. In all of the 5-phenyl derivatives the phenyl protons occurred as two multiplets

with the *ortho* protons *ca.* δ 0.3 downfield of the *meta* and *para* protons indicating that the presence of the substituent on N-1 causes loss of coplanarity of the phenyl and tetrazolyl rings. In the 5-unsubstituted tetrazoles the chemical shift of the nuclear proton was very sensitive to the nature of the 1-substituent.[113] It moved δ 0.4 downfield on introduction of the double bond and moved downfield with increasing electron demand in the alkene (Table 2.4).

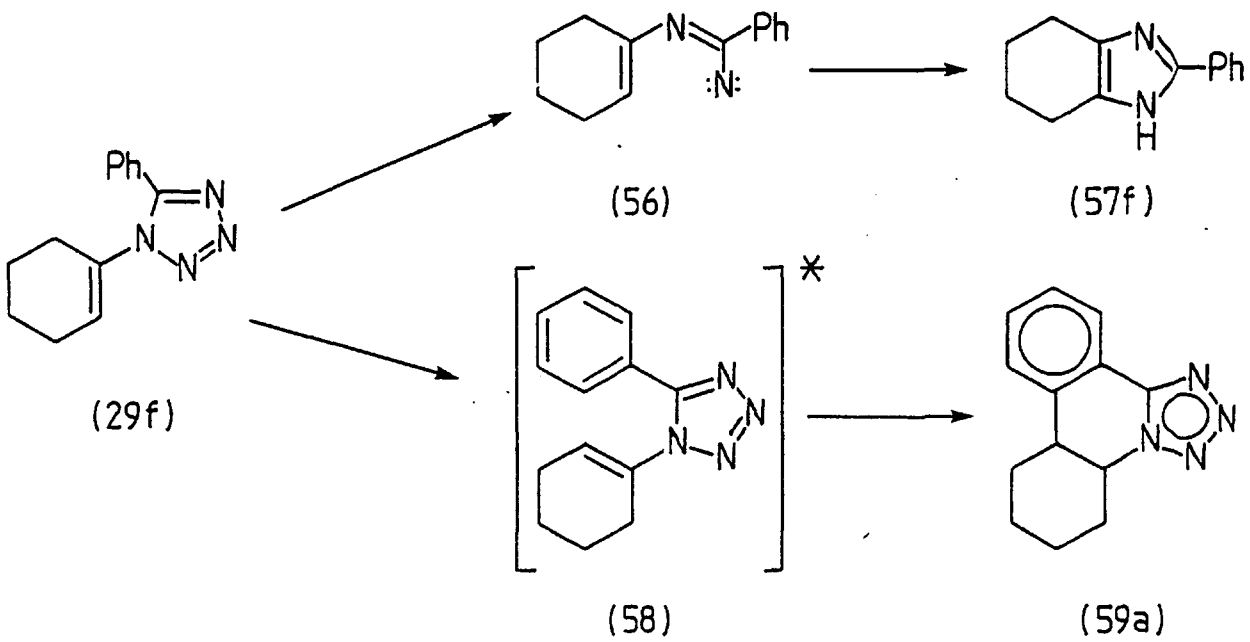
TABLE 2.4. Variation of the chemical shift of H^5

Tetrazole				
$\delta(H^5)$	8·93	9·24	9·52	10·12

2.4. PHOTOLYSIS OF 1-ALKENYLTETRAZOLES.

2.4.1. Formation of 1*H*-Imidazoles.

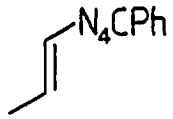
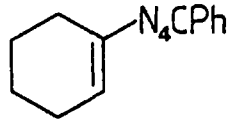
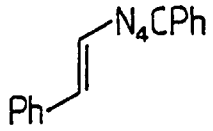
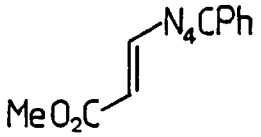
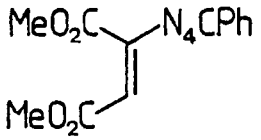
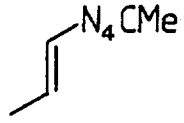
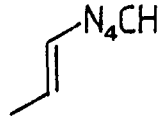
Early experiments showed that the photolysis of 1-alkenyl-5-phenyltetrazoles did give the required imidazoles but that other products were also formed. For example, irradiation of the cyclohexenyltetrazole (29f) at 254 nm in acetonitrile solution gave the imidazole (57f) (30%) and an isomer of the starting material (43%) which was assigned structure (59a) on the basis of its spectral data. The imidazole probably arises *via* cyclisation of the imidoyl nitrene (56) as expected and the fused tetrazole (59) was probably formed by a hexatriene ring closure in an excited state (58) followed by a [1,5] hydrogen shift (Scheme 2.8). It was found that



SCHEME 2.8

the yields of imidazoles varied greatly with the conditions so the effects of solvent, wavelength, and additives were studied in some detail. The results, mostly determined by analysis of the n.m.r. spectra of the crude photolysates, are listed in Table 2.5. The by-products in the photolyses

TABLE 2.5. Effect of photolysis conditions on yields of imidazoles.

(29) Alkenyltetrazole	Yield of imidazole
e 	Petrol[a] > ethanol > benzene, acetone, dichloromethane, acetonitrile. TFA/ethanol[b] > PTSA/ethanol[c] > ethanol > $BF_3.OEt_2$/ethanol[d]. Insensitive to triplet sensitisers (acetone) or quencher (α-methylstyrene). 254 nm >> 300 nm.
f 	Petrol > THF/ethanol > ethanol > acetic acid, ethanol > acetonitrile >> acetone
g 	Petrol > cyclohexane 254 nm ∿ 300 nm
i 	Petrol > ethanol
l 	Petrol >> dioxan > methanol
c 	Water > methanol > ethanol > petrol
b 	Water > ethanol ∿ petrol

[a]B.p. 60-80°C. [b]2.5 molar equivalents of TFA. [c]4.3 molar equivalents of PTSA [d]12 molar equivalents of $BF_3.OEt_2$.

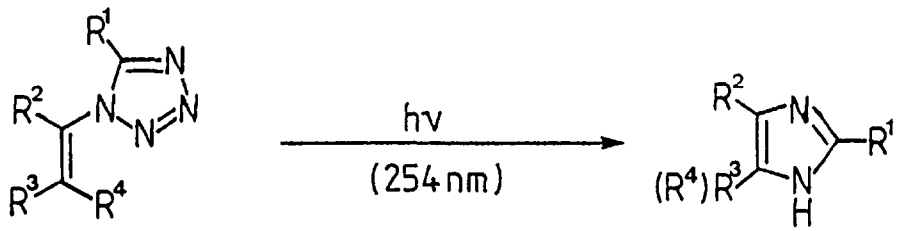
were photocyclisation products (see above) and many very minor products which were not isolated and identified. Several trends are discernible in these results.

(i) In the 5-phenyl series the yields of imidazole were generally best when the solvent was 60-80° petrol. Ethanol gave slightly poorer results but addition of an acid ($\geq$ 2 mol), *e.g.*, TFA or PTSA, gave cleaner products and made it competitive with petrol. Other solvents were much inferior, *e.g.*, in the case of the cyclohexenyltetrazole (29f) the ratio of imidazole to photocyclised tetrazole decreased in going from petrol (4:1) to ethanol (1.5:1) to acetonitrile (1:2) to acetone (1:4). The trend in the 5-methyltetrazole (29c) was also quite clear, water being significantly better than alcohols or petrol. The 5-unsubstituted tetrazole (29b) also gave the best yields in water but the results in petrol and ethanol were very similar.

(ii) The propenylphenyltetrazole (29e) (λ_{max} 240 nm) gave the imidazole quite cleanly when irradiated at 254 nm but irradiation at 300 nm in a Pyrex vessel gave a complex mixture. However, the styryltetrazole (29g) (λ_{max} 284 nm) gave similar yields from photolyses at 254 nm and 300 nm.

(iii) Photolysis of the propenyltetrazole (29e) in acetone, which is a triplet sensitiser, and in ethanol containing a large excess of α-methylstyrene, a triplet quencher, did not have a dramatic effect on the yield of imidazole.

With these factors in mind the tetrazoles were photolysed on a preparative scale (1-2 mmol in 75-100 ml of solvent) and the results are listed in Table 2.6. Because of the large number of variables, thorough optimisation was not attempted, and the yields could probably be improved. With a few exceptions the isolated yields were in the region of 60-73% and the method appears to be quite general for imidazoles bearing alkyl, aryl, and ester groups. It is particularly notable that considerable variation in the 5-substituent of the tetrazole is tolerated indicating that the photolysis of tetrazoles is a general route to imidoyl nitrenes. However,



(29) (57)

TABLE 2.6. Yields of imidazoles from photolysis of 1-alkenyltetrazoles.

(29), (57)	R^1	R^2	R^3	R^4	Solvent	Yield (57)(%)
a	H	H	H	H	EtOH	32
b	H	H	Me	H	EtOH	62
k	H	H	H	CO_2Me	EtOH	< 10[a]
c	Me	H	Me	H	H_2O	73
d	Ph	H	H	H	2.5 mol TFA/EtOH	61
e	Ph	H	Me	H	Petrol[b]	66
f	Ph	$-(CH_2)_4-$		H	Petrol[b]	64
g	Ph	H	Ph	H	Petrol[b]	66
h	Ph	Ph	H	H	EtOH	38
i	Ph	H	CO_2Me	H[c]	Petrol[b]	51
j	Ph	H	H	CO_2Me[c]	Petrol[b]	62
l	Ph	H	CO_2Me,	H[d]	Petrol[b]	24

[a] Small scale experiment and n.m.r. yield.

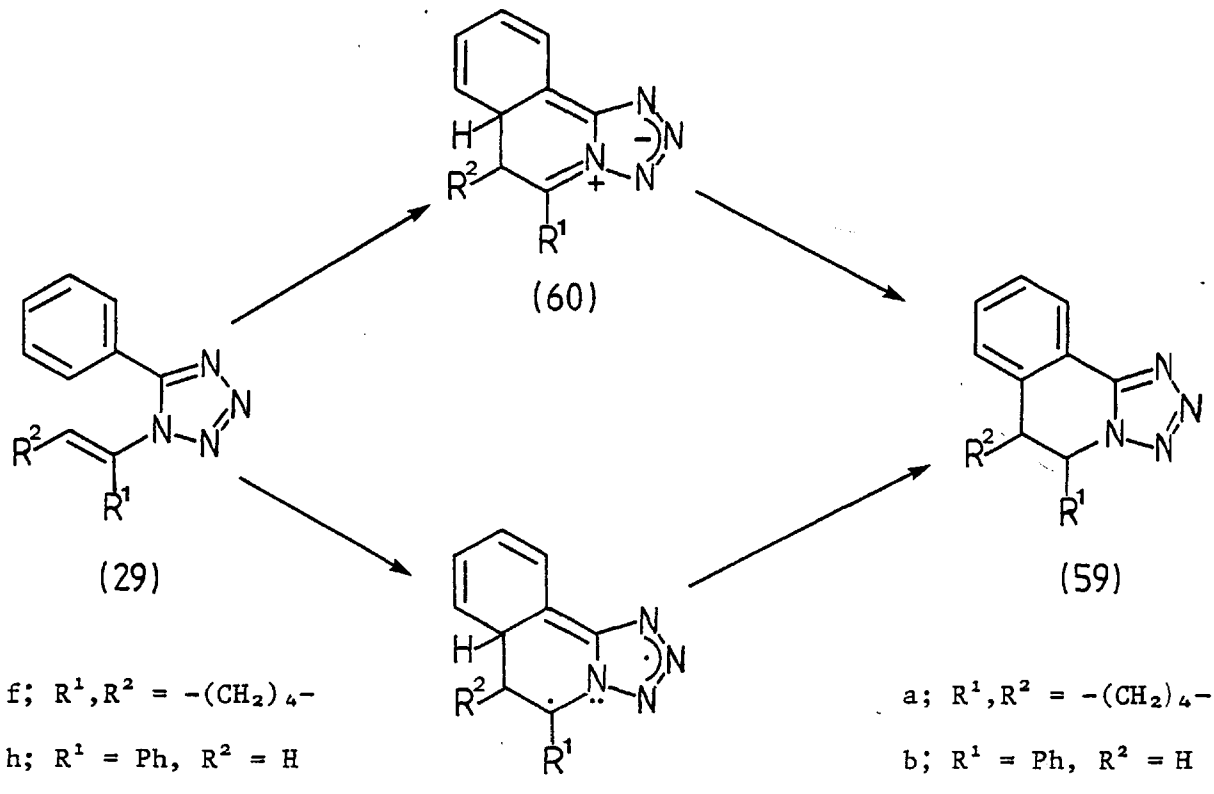
[b] B.p. 60-80°C

[c] *Cis, trans* isomerisation occurred during the photolysis

[d] A *cis, trans* mixture was photolysed.

the yields of 2-unsubstituted imidazoles were very variable and unless much improved conditions can be found this is a limitation on the method. There was no evidence of carbodiimide formation in these photolyses and this conforms with other authors' observations of little or no carbodiimide formation in the photolytic decomposition of tetrazoles.[93,94,164]

The photocyclisation was only a minor reaction except in the case of 1-substituted vinyl tetrazoles when it was a substantial, and in some conditions, the major pathway. The solvent dependence of the imidazole to photocyclisation ratios in the cyclohexenyltetrazole photolyses has already been described and as indicated the yield of the photocyclised tetrazole (59a) varied from 12% in 60-80° petrol to *ca.* 60% in acetone. The diester (29ℓ) gave 5% of the photocyclisation product (59c) even in



(29) (60) (61) (59)

f; $R^1,R^2 = -(CH_2)_4-$

h; R^1 = Ph, R^2 = H

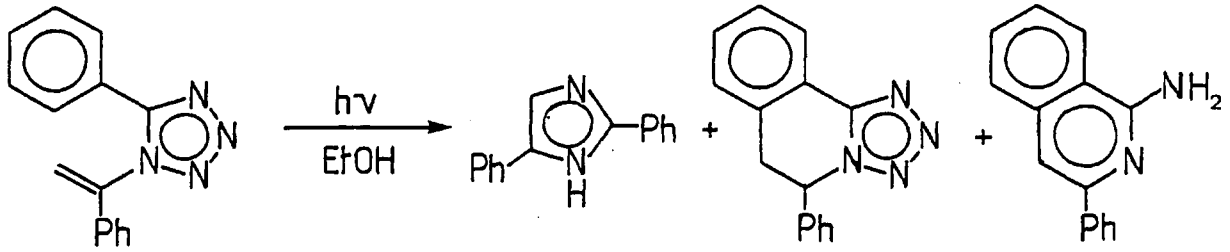
ℓ; $R^1 = R^2 = CO_2Me$

a; $R^1,R^2 = -(CH_2)_4-$

b; R^1 = Ph, R^2 = H

c; $R^1 = R^2 = CO_2Me$

petrol and (59c) was formed almost exclusively in methanol. The α-styryltetrazole (29h), on photolysis in ethanol, gave only 38% of the imidazole and it was accompanied by 7% of the photocyclised tetrazole (59b) and 21% of an isoquinoline (62) which has the skeleton of a photocyclised product.



(29h) (57h) 38% (59b) 7% (62) 21%

The mechanism by which (62) was formed is unclear, a blank experiment having ruled out the possibility that it arose by further photolysis of (59b).

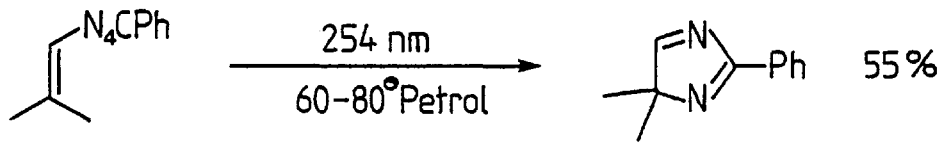
That having an α-substituent on the alkene promotes photocyclisation is clear but the reasons for this are less so. In the photocyclisation of enamides[135,155] and of other heterocyclics,[156] zwitterionic intermediates, *e.g.*, (60) in the present system, are thought to be involved and they have been intercepted by carrying out the photolysis in the presence of reducing agents.[155] However, since electron-withdrawing substituents (R^1 = CO_2Me) promote the reaction as well as electron-donating (R^1 = alkyl) and conjugating substituents (R^1 = Ph) it is unlikely that an intermediate such as (60) is involved. It is possible that diradicals (61), formed *via* triplet processes, are intermediates and this is consistent with the substituent effects.

Some exploratory thermolyses of the propenyltetrazole (29e) were carried out. Thermolysis at 240° without a solvent gave a complex mixture containing only a small amount of imidazole (57e) and although the use

of diphenyl ether as solvent gave a much cleaner product the yield of (57e) was only *ca.* 25%. Addition of catalytic quantities of copper powder and bis(acetylacetonato)copper(II) to the solution thermolyses did not lower the temperature required for decomposition and gave more complex product mixtures. Flash vacuum pyrolysis at 4 mbar and an oven temperature of 720° gave a complex mixture containing very little imidazole. It would appear that photolysis is much superior to thermolysis for the decomposition of 1-alkenyltetrazoles.

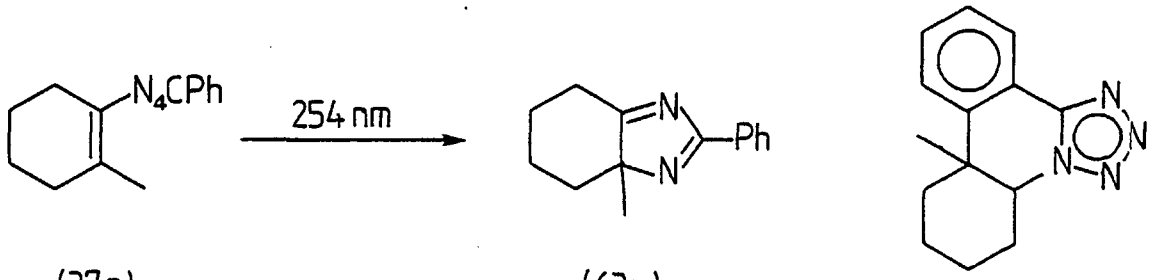
2.4.2. Formation of 4*H*-imidazoles.

Photolysis of the *i*-butenyltetrazole (37d) in 60-80° petrol gave the 4*H*-imidazole (63d) in 55% yield after sublimation. Best results were obtained when very dilute (7×10^{-3} M) solutions were used. The methyl-



(37d) (63d)

cyclohexenyl (37a) derivative also gave the 4*H*-imidazole (63a) but it was accompanied by some photocyclisation product (64) (6%) and the proportion of (64) was greater (35%) when the photolysis was carried out in

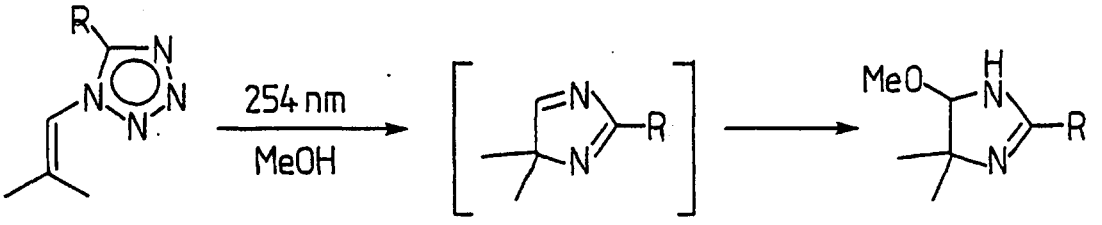


(37a) (63a) (64)

60-80° Petrol	55%	6%
MeCN	41%	35%

acetonitrile. The proportion of photocyclisation in these photolyses was reduced relative to those of the cyclohexenyltetrazole (29f) presumably because the extra methyl group hinders the electrocyclic ring closure. There was no indication of nitrene insertion into the *cis* methyl groups in these reactions and this is consistent with earlier reports that imidoylnitrenes do not insert into C-H bonds.[93,94,157]

Photolyses of the 5-unsubstituted (37b) and 5-methyl (37c) *iso*-butenyltetrazoles in 60-80° petrol gave complex mixtures containing no more than traces of the 4*H*-imidazoles. When the photolyses were carried out in methanol, n.m.r. indicated that the methanol adducts (65) were formed showing that the 4*H*-imidazoles (63) were generated but were rapidly



(37) b; R=H
c; R=Me

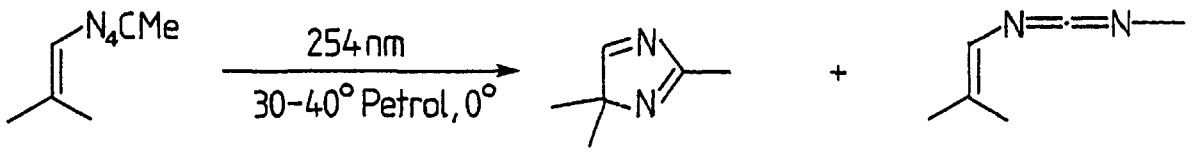
(63) b; R=H
c; R=Me

(65) a; R=H
b; R=Me

trapped by the solvent. In the case of the 2-methylimidazoline (65b) several attempts were made to regenerate the 4*H*-imidazole (63c) by elimination of methanol but all were unsuccessful. Thus, attempted azeotropic removal of the methanol by refluxing in 30-40° petrol gave no reaction, and refluxing in benzene containing a trace of PTSA caused loss of methanol but gave a complex mixture. Addition of 4Å molecular sieves to solutions of (65b) with and without PTSA, caused slow decomposition,

and an attempted sublimation at 75° and 0.3 mbar did not give any 4*H*-imidazole. The failure of these experiments was due to two main factors which emerged from subsequent work, (i) the 4*H*-imidazole is extremely labile and was probably decomposed under the conditions used to bring about elimination of methanol, and (ii) it is very volatile and even if it survived, it was probably lost in the work up, *e.g.*, it would have been lost in the high vacuum used in the sublimation.

2,4,4-Trimethyl-4*H*-imidazole (63c) was finally isolated by carrying out the photolysis in dilute solution in 30-40° petrol cooled to 0°, to minimise polymerisation and by evaporating the solvent on a water pump at 0°, to minimise losses due to volatility. This gave a yellow oil which was immediately distilled at room temperature and *ca.* 3 mbar into a receiver cooled to -78°, to yield a colourless liquid. Proton and ^{13}C n.m.r. of the product showed it to consist of a 3:1 mixture of the 4*H*-imidazole (63c) and an unknown which is tentatively identified as a carbodiimide (66). Attempted isolation of (63c) from the deuterochloro-



(37c) (63c) (66)

form solution used to record the spectra gave only decomposition products illustrating the reactivity of this system. The assignment of structure (66) to the contaminant is based on the proton n.m.r. spectrum which shows typical *iso*-butenyl signals and a three proton singlet at δ 3.01 and on the i.r. which contains a strong band at 2130 cm^{-1}. However, as mentioned earlier, carbodiimides were not detected in any of the other photolyses so this apparently anomalous result must be regarded as very tentative.

Unfortunately, when the 5-unsubstituted tetrazole (37b) was photolysed in the same way the crude product contained no more than a trace of the "parent" 4*H*-imidazole (63b). The reasons for this failure are not clear but the preliminary indications are that (63b) may be so volatile that it cannot be isolated even from 30-40° petrol. Although (63b) was probably formed in these photolyses and was certainly formed in the photolysis in methanol solution, it has not been isolated.

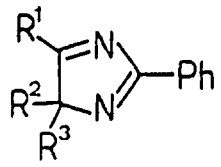
It is clear from the discussion above that the preparation of simple 4*H*-imidazoles presents considerable problems because of their reactivity and volatility. Although the photolytic method described above has not been completely successful, its mildness and generality are crucial in overcoming these problems, and it provides a very useful route to the 4*H*-imidazole ring system. It has made 2,4,4-trisubstituted 4*H*-imidazoles available for the first time and it is confidently anticipated that with further study it will give, the as yet unknown, 4,4-disubstituted derivatives.

2.5. PROPERTIES OF 4*H*-IMIDAZOLES.

2.5.1. Spectroscopic Properties.

The i.r. spectra of the 2-phenyl derivatives all have a strong band at 1610-20 cm^{-1} accompanied by one or two medium to strong bands in the 1560-1580 cm^{-1} region (Table 2.7). Their u.v. spectra (Table 2.7) show absorbtions at *ca.* 255 nm with pronounced shoulders at *ca.* 280 and 290 nm. This conforms well with the analysis suggested in the review (Section

TABLE 2.7. I.r. and u.v. spectra of 4*H*-imidazoles:

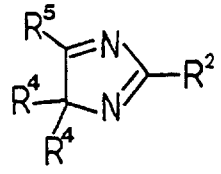


R^1	R^2	R^3	ν/cm^{-1} [Phase]	$\lambda(\varepsilon)/nm$ [Solvent]
H	Me	Me	1610(s), 1582(s) [Thin film]	257 (9000),282(3700),291(2400) [30-40° Petrol]
Me	Me	Me	1618(s), 1580(m), 1562(m) [Thin film]	253(8100),280(2700),289(1900) [30-40° Petrol]
$-(CH_2)_4-$		Me	1614(s), 1578(m), 1563(m) [Nujol mull]	255(9100),281,290 (shoulders) [Ethanol]

1.3.2), and indicates that a conjugating substituent in the 2-position has a smaller effect than one at C-5 as would be expected from a cross-conjugated rather than a linearly-conjugated group.

Since 5-unsubstituted 4*H*-imidazoles have not previously been reported the most interesting features of the proton n.m.r. spectra (Table 2.8) were

TABLE 2.8. ^1H and ^{13}C n.m.r. spectra of 4*H*-imidazoles[a]:



R^4,R^4	δ(H)	δ(C-4)	R^2	δ(H)	δ(C-2)	R^5	δ(H)	δ(C-5)
CH_3,CH_3	1.30	82.8	CH_3	2.43	171.7	H	8.64	193.5
CH_3,CH_3	1.41	83.1	C_6H_5	7.35-7.65, 8.20-8.47	170.3	H	8.77	193.1
CH_3,CH_3	1.36	82.5	C_6H_5	7.30-7.65, 8.15-8.45	170.3	CH_3	2.35	203.4
$CH_3,-(CH_2)_4-$	1.38	82.0	C_6H_5	7.30-7.55, 8.18-8.45	171.0	$-(CH_2)_4-$		205.8

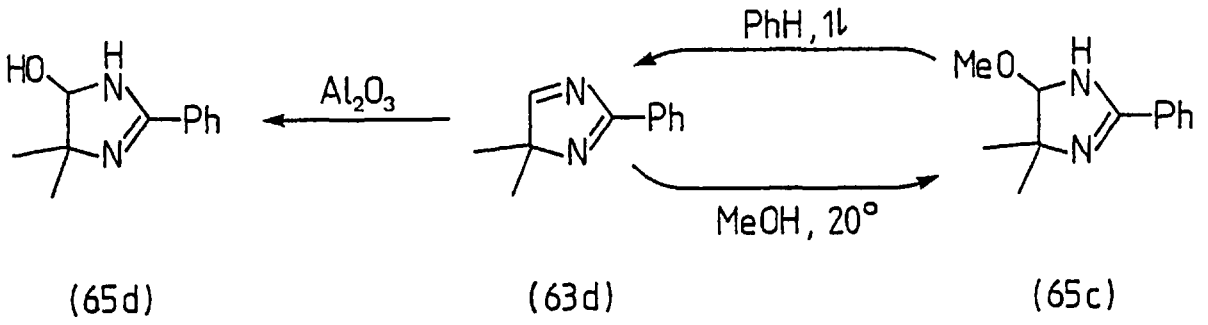
[a] All spectra recorded in $CDCl_3$ solution.

the chemical shifts of the protons at C-5. These resonated at δ8.6-8.8 which is reasonable for imino type protons. The ^{13}C n.m.r. spectra were consistent with the trends noted earlier (Section 1.3.4).

The mass spectra of the 2-phenyl derivatives are very similar each showing several characteristic features. (i) There is a weak peak at M^+-15. (ii) There is a strong loss of R^5-C≡N, together with a metastable for $M^+ \longrightarrow M^+ - R^5CN$. However, loss of PhCN is extremely weak. (iii) There is a weak loss of 15 from M^+-R^5CN. (iv) There is a strong peak at 104 corresponding to $[PhCNH]^+$, together with a metastable for M^+-$R^5CN \longrightarrow 104$.

2.5.2. Chemical Properties.

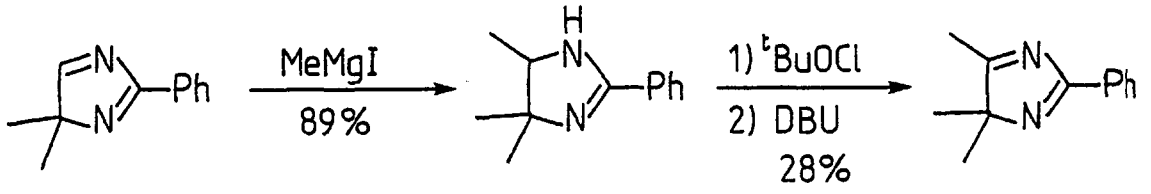
As expected the 4*H*-imidazoles were very sensitive to hydrolysis, especially under acidic conditions, and their reactivity varied greatly with the substitution pattern. All of the 4*H*-imidazoles gave low R_f streaky spots on t.l.c. on silica gel, presumably because of rapid hydrolysis. Those without a substituent at the 5-position were also hydrolysed on alumina, *e.g.*, elution of 4,4-dimethyl-2-phenyl-4*H*-imidazole (63d) on alumina with 10% methanol/90% ether gave the covalent hydrate (65d). However, (63a) and (63e), which do have a 5-substituent, had high R_f's on alumina t.l.c. and were readily purified by chromatography on alumina. All of the 4*H*-imidazoles were soluble in petrol and were quite volatile so those which could not be chromatographed were purified by sublimation/distillation. Those without 5-substituents reacted with methanol to give 5-methoxyimidazolines. As described in Section 2.4.2, the 2-unsubstituted (63b) and 2-methyl (63c) derivatives reacted very rapidly with methanol, and the 2-phenyl compound (63d) gave the corresponding 5-methoxyimidazoline (65c) after 40 h in methanol solution. The 4*H*-



(65d) (63d) (65c)

imidazole (63d) was regenerated in good yield by heating (65c) in benzene with azeotropic removal of methanol. It is apparent from the relative rates of methanol addition to (63c) and (63d) and from the failure to recover the 2-methyl derivative from its adduct that the 2-methyl-4*H*-imidazole is much more reactive than the 2-phenyl. The large difference in reactivity is slightly surprising but it is not unreasonable that the strained, sterically exposed, and highly electrophilic 4*H*-imidazoles (63b) and (63c) should be so labile.

Addition of methylmagnesium iodide to (63d) was very rapid and gave a 5-methylimidazoline (67) in high yield. Treatment of the product with

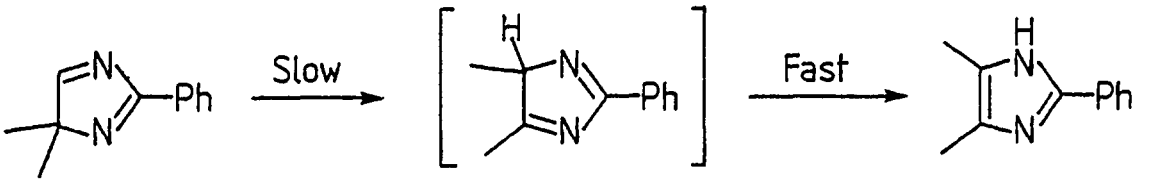


(63d) (67) (63e)

t-butyl hypochlorite to give the *N*-chloro derivative followed by elimination of hydrogen chloride using 1,5-diazabicyclo[5.4.0]undec-5-ene [DBU] gave the 5-methyl 4*H*-imidazole (63e) albeit in low yield. With optimisation

of the dehydrogenation method[158] this sequence could provide a general method for converting 5-unsubstituted into 5-substituted 4*H*-imidazoles.

On heating at 120° in dimethyl sulphoxide-d_6 the 4*H*-imidazole (63d) rearranged to 4,5-dimethyl-2-phenyl-1*H*-imidazole (69) in quantitative yield. The reaction had first order kinetics with a half-life of 30 min and no intermediates were detectable by n.m.r. This is consistent with



(63d) (68) (69)

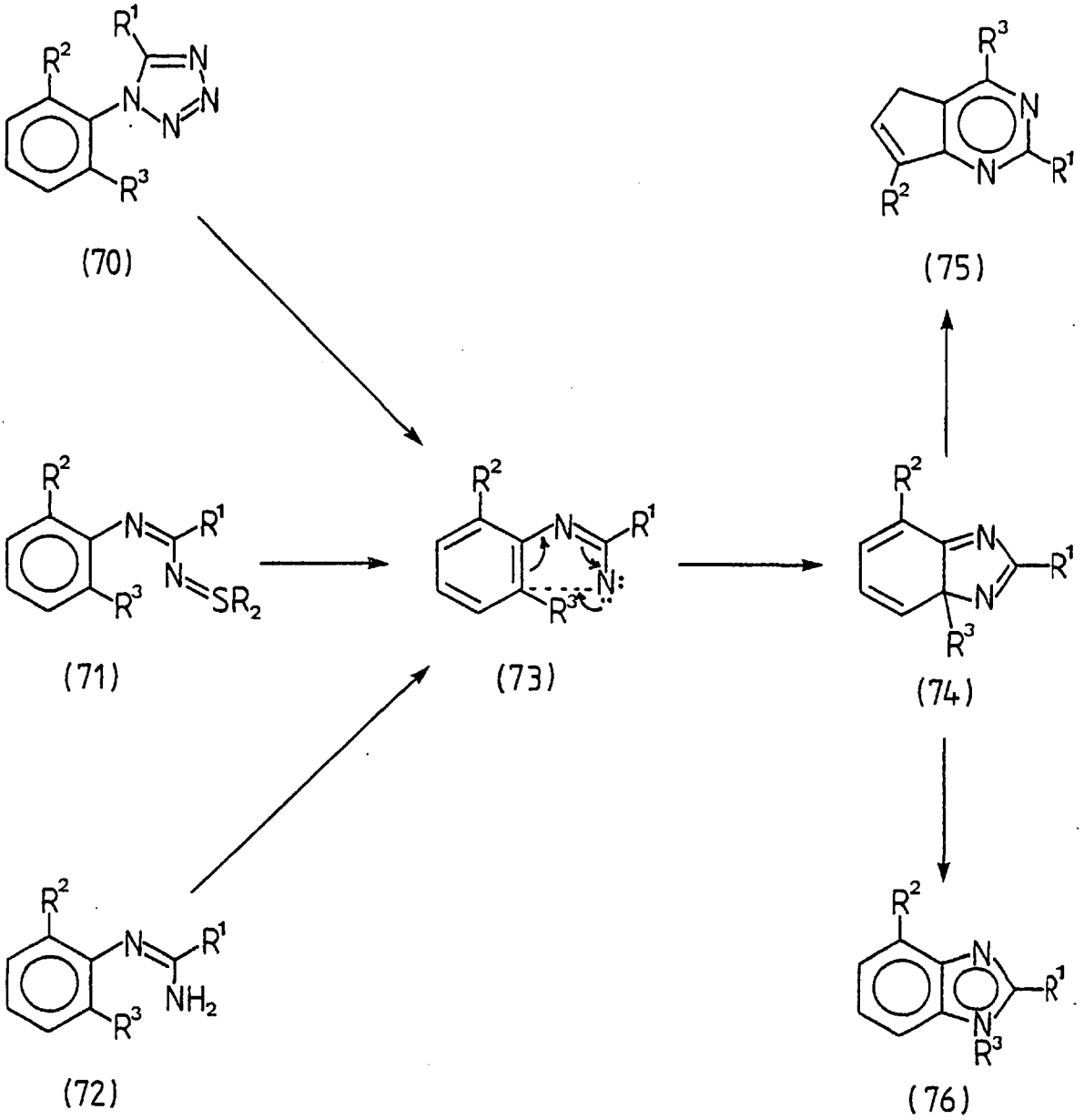
a rate-determining [1,5]methyl migration to C-5 to give a 4*H*-imidazole (68) followed by a rapid hydrogen shift to give (69). These results are in keeping with the relatively facile alkyl shifts[159] in other non-aromatic heterocyclics, *e.g.*, pyrazoles.[160] Also consistent with earlier work[160,161,162] is the observation that the methyl group migrated exclusively to carbon, to give another non-aromatic 4*H*-imidazole, rather than migrating to nitrogen and thus giving a 1*H*-imidazole directly. The preference for migration to carbon rather than nitrogen is very well documented and has been ascribed to better overlap in the transition state.[161]

It was hoped that the sterically exposed, electron deficient $C^5=N^1$ bond of (63d) would undergo cycloadditions. Nitrile oxides react well with azomethines[68] but surprisingly benzonitrile oxide did not react with the 4*H*-imidazole (63d) at room temperature, when generated *in situ* in dichloromethane or when preformed in ether solution. The strongly nucleophilic 1-diethylaminopropyne reacted rapidly with (63d) in acetonitrile solution to give a mixture which consisted (n.m.r.) mainly of two compounds. However, an attempt to isolate the components by chromatography on alumina gave only small amounts of decomposition products.

Unfortunately, it was not possible to examine the chemistry of the 4*H*-imidazoles in any depth and most of the questions raised in Section 1.4 remain unresolved. In particular, the problems of the relative electrophilicities of C-2 and C-5, the relative nucleophilicities of N-1 and N-3, and the rearrangement and cycloaddition reactions of 4*H*-imidazoles are still unexplored. However, with the development of an effective synthetic route and the emergence of a clearer pattern of reactivity and ease of handling, it is now possible to select and prepare model compounds which should yield the answers to these questions.

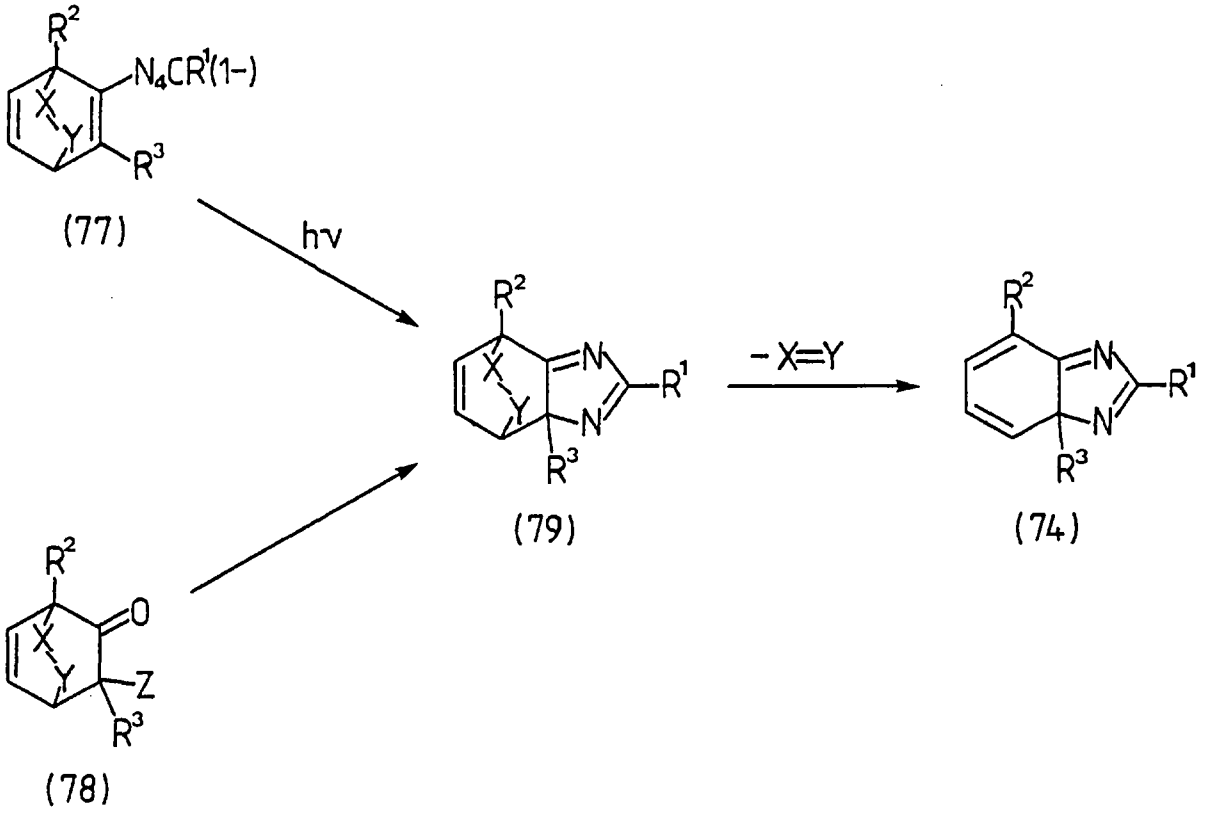
2.6. SYNTHETIC APPROACHES TO 3a*H*-BENZIMIDAZOLES.

N-Arylimidoyl nitrenes (73) have been generated from a variety of precursors,[163] including 1,5-diaryltetrazoles (70) arylimidoylsulphimides (71)[93,94] and *N*-arylamidines (72)[157,165] and in all cases the final products are benzimidazoles (76) or cyclopentapyrimidines (75), which are presumed to arise *via* electrocyclisation to give 3a*H*-benzimidazoles (74) followed by rearrangement (Scheme 2.9). It was hoped that generation of a 3a*H*-benzimidazole (74) by a non-nitrene method would provide confirmation of its intermediacy in these reactions and that a study of its chemistry would provide useful comparisons with that of several related systems currently under investigation.[95,96,97] It was envisaged that (74) could be formed by a retrocycloaddition[166] in the flash vacuum



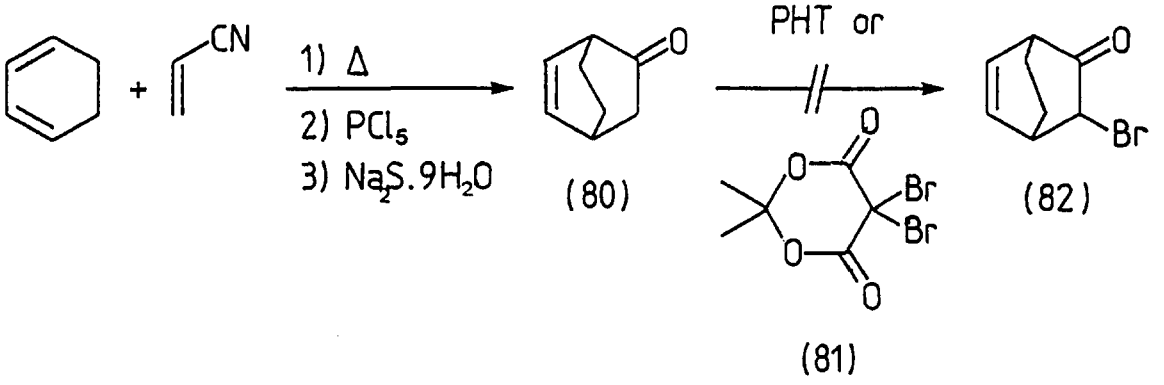
SCHEME 2.9

pyrolysis of compounds of type (79) and that possible precursors for (79) are (77) and (78) from which the 4*H*-imidazole ring of (79) could be formed by photolytic or " wet" methods respectively (Scheme 2.10). Several attempts were made to synthesise compounds of type (79).

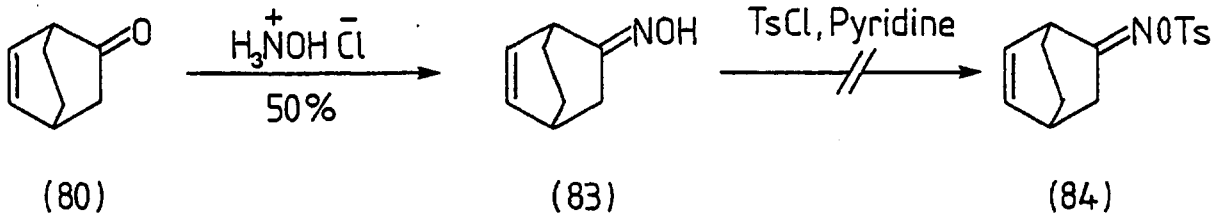


SCHEME 2.10

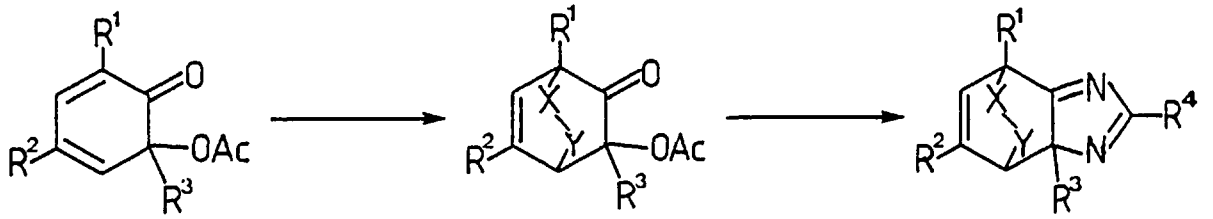
During the investigation of the reaction of 5-phenyl-2-tributyl-stannyltetrazole (26c) with α-halo ketones it was decided to attempt to prepare 2-bromobicyclo[2.2.2.]oct-5-enone (82)[167] in the hope that it could be used as an alkylating agent as outlined in Scheme 5. Bicyclo-[2.2.2.]oct-5-en-2-one (80) was prepared by literature methods[168] (the yield was much lower than reported) but attempts to selectively α-brominate this ketone using pyrrolidone hydrotribromide (PHT)[169] and 5,5-dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane (81)[170] gave inseparable mixtures of brominated products. In view of these failures and of the disappointing yields in the alkylations using α-halo acetones this approach was abandoned. Attempts to make the α-amino derivative by a Neber rearrange-



ment[171] of the ketoxime tosylate (84) also failed, because treatment of the oxime (83) with tosyl chloride in pyridine gave no identifiable products.

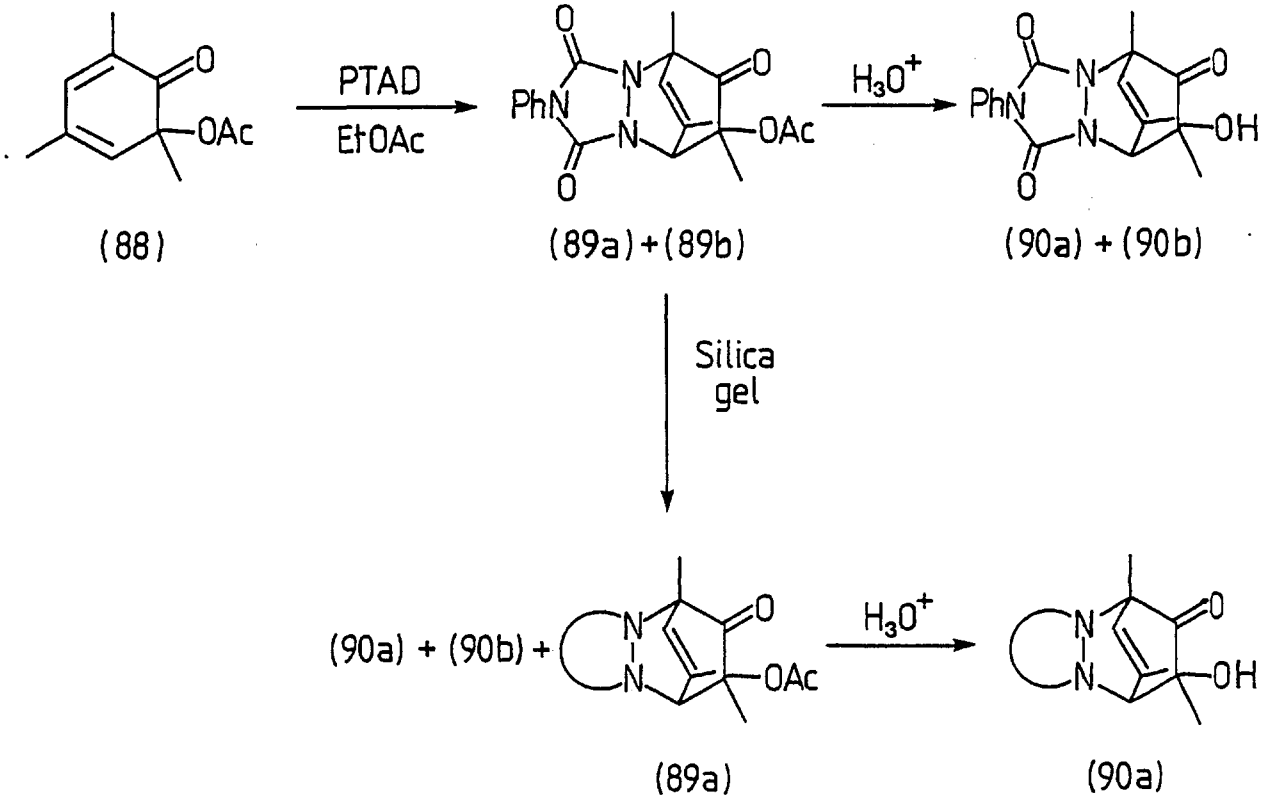


Cyclohexadienone acetates (85) are readily available[172] and it was decided to prepare one, protect it by a cycloaddition, attempt to condense the adduct (86) with an amidine to give 4*H*-imidazole (87), and then do a retro-Diels-Alder reaction[166] to give a 3a*H*-benzimidazole (74). 6-Acetoxy-2,4,6-trimethylcyclohexadienone (88) was prepared in 91% yield by lead tetraacetate oxidation of mesitol.[173] 4-Phenyl-1,2,4-triazol-3,5-dione (PTAD)[174] reacted rapidly with the quinol acetate (88) to give a mixture of two products. The major one was obtained in 60% yield by fractional crystallisation and its spectral data indicated that it was the



(85) (86) (87)

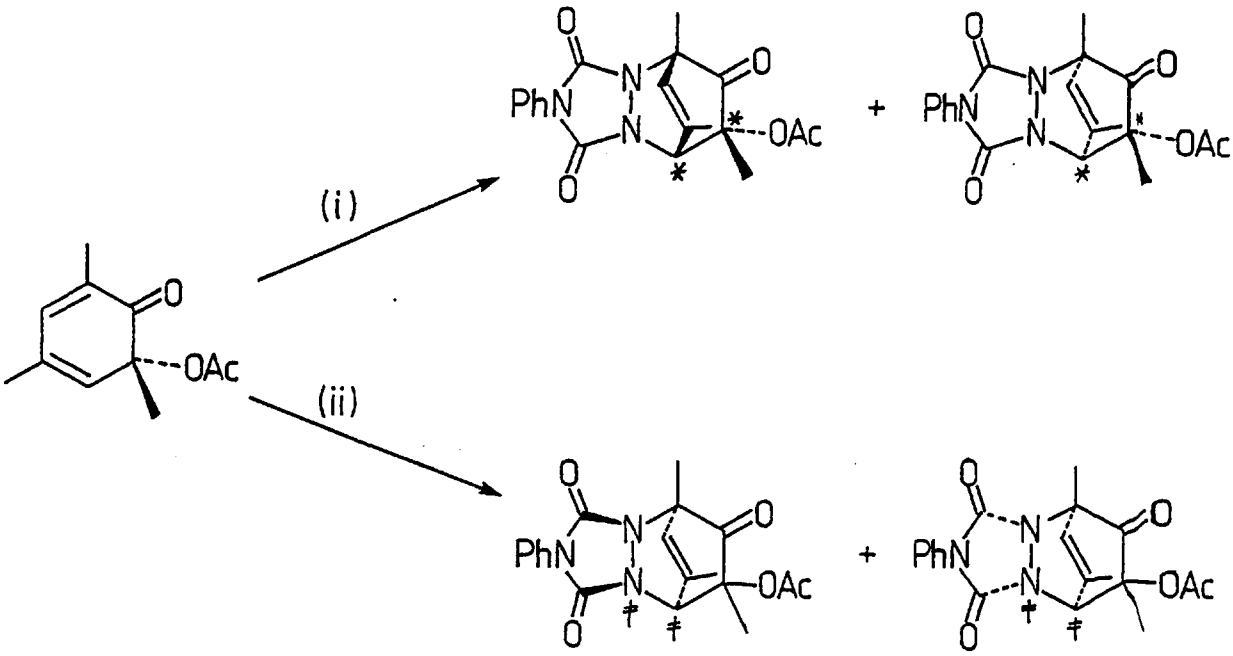
expected adduct (89a). Proton n.m.r. indicated that the minor component was an isomer of this adduct but it did not survive chromatography and has not been characterised. When the crude mixture (4:1 ratio by n.m.r.) of cycloadducts was hydrolysed using aqueous methanolic hydrochloric acid a mixture of isomeric alcohols (90a) and (90b) was obtained in 81% yield



SCHEME 2.11

(Scheme 2.11). The ester (89a) was hydrolysed to (90a) in 98% yield in ethanolic hydrochloric acid but surprisingly, attempts to hydrolyse the acetate using aqueous ethanolic sodium hydroxide appeared to result in cleavage of the urazole ring.

The formation of two isomers in the cycloaddition could be explained in two ways (Scheme 2.12). (i) Addition of the PTAD to both diastereotopic faces of the cyclohexadienone (88) would give rise to a pair of diastereomers

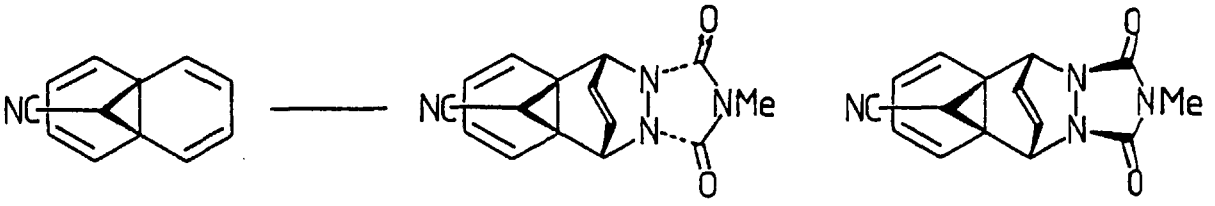


SCHEME 2.12

differing in the relative sterochemistry of the centres marked with an asterisk [Type (i) isomerism]. In this case it is assumed that the bridgehead nitrogens are either planar or are rapidly inverting in solution. (ii) If it is assumed that the nitrogen atoms are not planar and that they do not invert in solution, then two isomeric adducts could arise by addition of the PTAD to just one face of the diene but with formation of

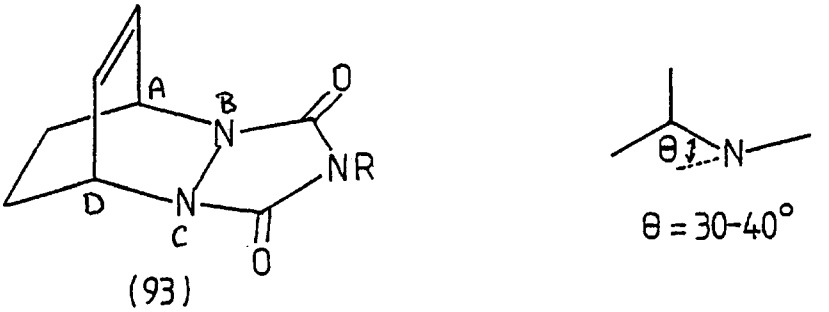
exo and *endo* adducts. The isomers would then have different relative stereochemistries at the centres marked with a dagger [Type (ii) isomerism).

A search of the Cambridge Crystallographic Database revealed that in the addition of 4-methyltriazoldione (MTAD) to a propelladiene (91) two crystalline products were isolated and shown by *X*-ray structure determinations to be the *exo* (92a) and *endo* (92b) adducts.[175] In common



(91) (92a) (92b)

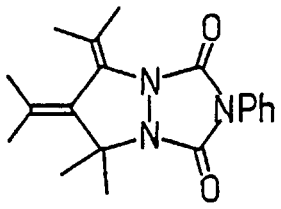
with those of all the other TAD adducts whose structures have been determined, the bridgehead nitrogens in these compounds are pyramidal and the plane of the urazole ring is generally at an angle of 30-40° to that defined by atoms A to D in (93). However, these workers found that



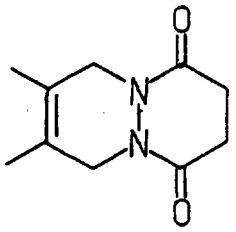
(93)

while nitrogen inversion in the solid state occurred only above 175°C, the two isomers had identical spectra in solution down to -30°C at least,

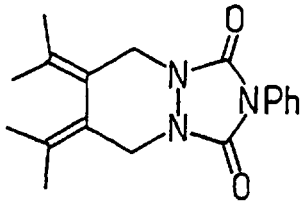
indicating that inversion was rapid in solution. Calculations on model compounds suggested a barrier to inversion of 7-9 kcal mol^{-1}. This is in accord with variable temperature n.m.r. studies of compounds (94)[176] and (95)[177] which led to estimates of 11.9 and <10.4 kcal mol^{-1} respectively for the barriers to inversion in these systems. Other workers ruled out fast inversion from the n.m.r. of (96)[178] but a reappraisal[176]



(94)

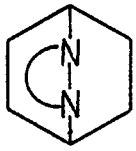


(95)

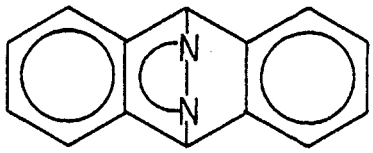


(96)

suggests that their conclusion is incorrect and that nitrogen inversion is rapid even at -60°C. Finally the PTAD adducts (97) and (98), with structures similar to those in the present work, were symmetrical (by n.m.r.)



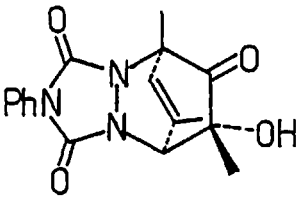
(97)



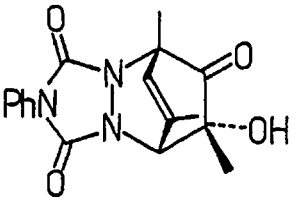
(98)

down to -90°C and although the authors interpreted this as evidence that the nitrogens were planar, the *X*-ray structures rule out that possibility and force the conclusion that here too *exo/endo* interconversion is extremely rapid in solution.[179]

Since the isomers (90a) and (90b) were not interconverted in solution, even at 140°C, the evidence presented above precludes *exo/endo* isomerism. Proof that Type (i) isomerism was involved was provided by *X*-ray structure determinations (details are provided in the Experimental Section).[189] The minor alcohol was shown to have structure (90b) (Figure 2.1) and the



(90b)



(90a)

determination of a derivative (see below) established that the isomeric alcohol had the stereochemistry shown in (90a). The adduct (90b) crystallised in the *endo* form as have the majority of TAD adducts. Thus, the major isomer (89a) is formed by addition of the PTAD *syn* to the acetoxy group, *i.e.*, to the more hindered face of the diene. This may be due to secondary orbital overlap with the π^* orbitals of the ester carbonyl, such interactions are well described,[180,181] but no directing effect was observed in the case of another acetoxy diene,[182] so no firm conclusion can be drawn.

Attempted condensations of the acetoxy ketone (89a) with benzamidine in refluxing ethanol and with thiourea in refluxing acetic acid gave only the alcohol (90a) indicating that cleavage of the ester was occurring in preference to condensation with the ketone. When treated with thiourea in refluxing acetic acid the hydroxy ketone (90a) reacted slowly to give a mixture of several products which were not identified. Reaction with hydroxylammonium chloride in standard oximation conditions gave

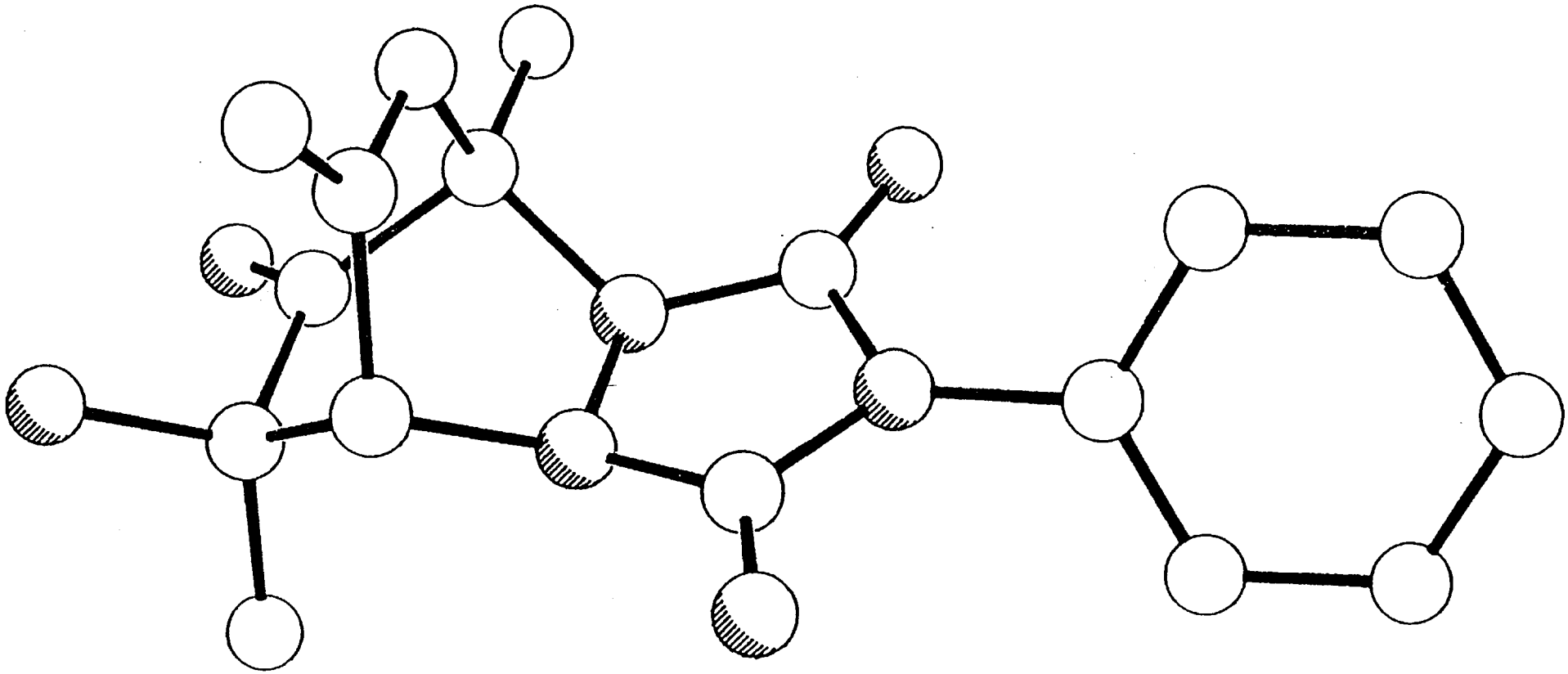
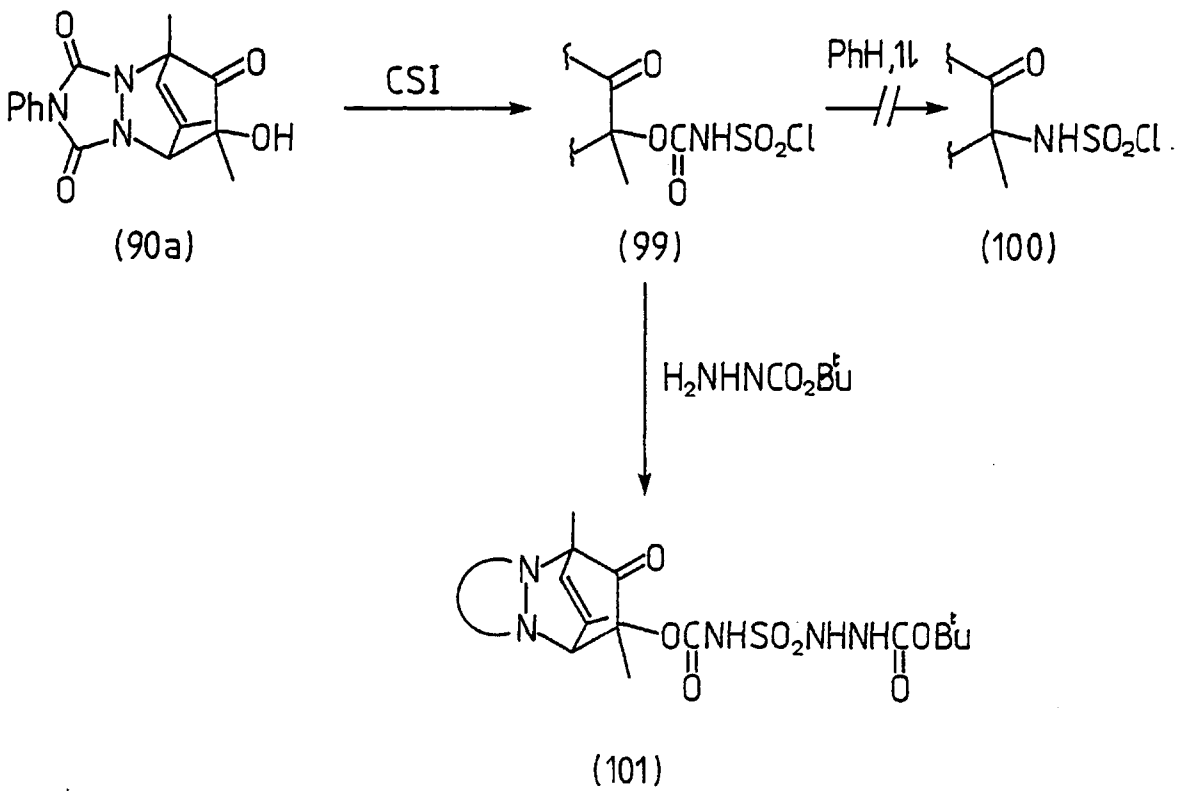


FIGURE 2.1

only starting ketone after four hours in refluxing alcohol. The failure of this reaction indicated that it was most unlikely that condensation with relatively weak nucleophiles such as amidines would succeed, so this approach was not pursued.

An α-amino derivative was required and two possibilities for transforming the alcohol into an amine were investigated. Alcohols have been converted into amines by elimination of carbon dioxide in the thermolysis of urethane derivatives.[183,184] The fragmentation of sulphonylurethanes proceeds under very mild conditions (refluxing hexane) so this method was applied.[184] The alcohol was treated with chlorosulphonyl isocyanate (CSI) at room temperature in benzene but when the solution was warmed no evolution of carbon dioxide was observed. The product (99) was treated with *t*-butyl carbazate and gave, after chromatography, a material (101) whose structure could not be determined from its spectra. When the



(90a) (99) (100)

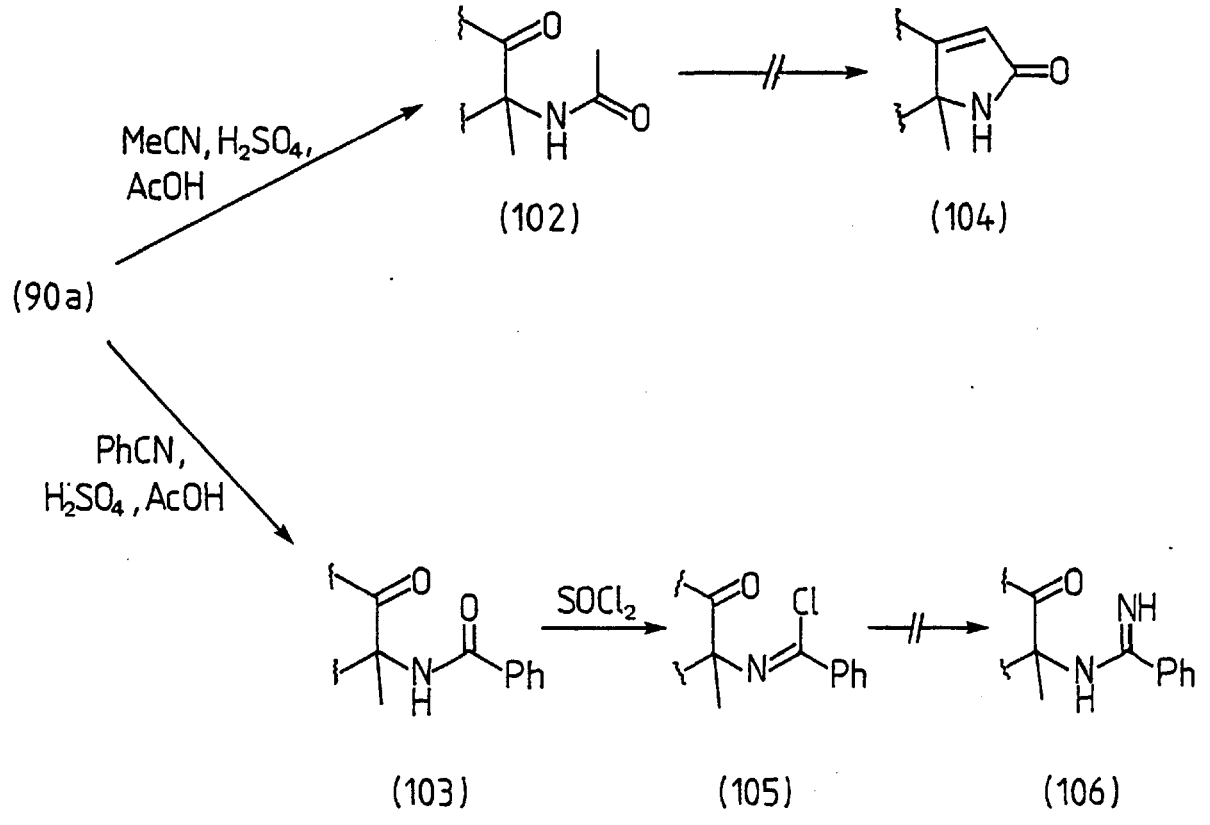
(101)

sequence was repeated without heating the intermediates, the product was identical with that previously obtained, indicating that loss of carbon dioxide had not occurred. This result and the observation that (101) evolved a gas on heating to 150-160° shows that the product was the urethane derivative (99) and not the desired sulphonamide (100). No further work was carried out on this method but the evolution of a gas at 150-160° indicates that an amide might be obtained in this way.

The Ritter reaction has been widely used for the conversion of alcohols into amides.[185] A careful literature search did not uncover any examples of the use of α-hydroxy ketones in Ritter reactions, but α-chloro ketones[186] and α-azido derivatives[187] have been used in modified versions. The Ritter reaction would involve generation of α-keto carbonium ions and although these cations are destabilised by the carbonyl group, recent studies have shown that they are readily accessible by the solvolysis of sulphonates and are surprisingly stable due to resonance stabilisation by the carbonyl group which almost offsets the destabilising inductive effect.[188]

Treatment of a suspension of the alcohol (90a) in a mixture of acetonitrile and acetic acid with concentrated sulphuric acid gave a product (102) (62%) whose spectral data seemed consistent with the desired acetamide. Mass spectroscopy and micro-analysis indicated that it had the correct molecular formula, the n.m.r. spectrum contained a new methyl signal at the expected chemical shift, and the i.r. spectrum showed a new carbonyl absorption at 1655 cm^{-1}. The ketone C=O stretch was no longer visible but it was assumed that it was just obscured by the higher frequency C=O stretch of the triazolidinedione system. When benzonitrile was used in similar conditions the corresponding benzamide (103)(62%) was obtained.

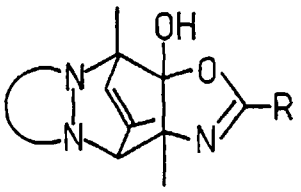
It was hoped that the " acetamide" (102) could be cyclised to give a pyrrolone (104) (Scheme 2.13) but attempts to effect this using several acids and bases gave only starting material. Difficulties were encountered with the " benzamide" too. It was hoped to convert it into the benzamidine (106) and to cyclise this to give a 4*H*-imidazole (87) (Scheme 2.13). The " amide" (103) reacted with thionyl chloride in refluxing benzene to give a product (95%) (105) whose spectral data



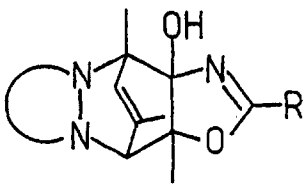
SCHEME 2.13

indicated that it was the benzimidoyl chloride. However, this " imidoyl chloride" was inert to several attempts to displace the chloride with ammonia. It did react when heated at 100° in a sealed tube with a solution of ammonia in DMF to give a product which seemed by n.m.r. to be the required amidine (106), but this material was not conclusively identified.

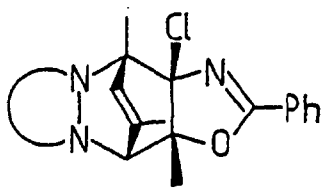
The failure of these reactions was disquieting and prompted a reappraisal of the structural assignments. The ^{13}C n.m.r. spectra of compounds (102) (103) and (105) were recorded and clearly showed that they did not contain ketonic carbons. This and the previously noted absence of the ketone C=O stretch in the i.r. spectra suggested that the " amides" were in fact oxazolines with structures (107) or (108). It was found that both " amides" were hydrolysed by aqueous acetic acid to give the alcohol (90a) in good yields indicating that the 4-hydroxyoxazoline structures (108) were correct. This assignment was confirmed by an *X*-ray



(107)



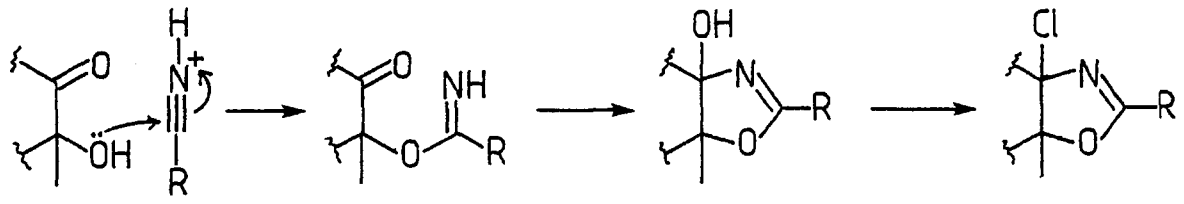
(108)



(110)

crystal structure determination of the " imidoyl chloride" which showed it to be a 4-chlorooxazoline (110) (Figure 2.2).[189]

It is likely that the oxazolines are formed by a Pinner reaction to give imidates (111) followed by tautomeric ring closure. With hindsight it is not surprising that the attempted Ritter reactions were diverted in this way and this reaction is well precedented, having been used as



(90a) (111) (108) (110)

an oxazole synthesis.[190] In addition to revealing the skeletal structure of the " amides" the structure determination provided the final piece

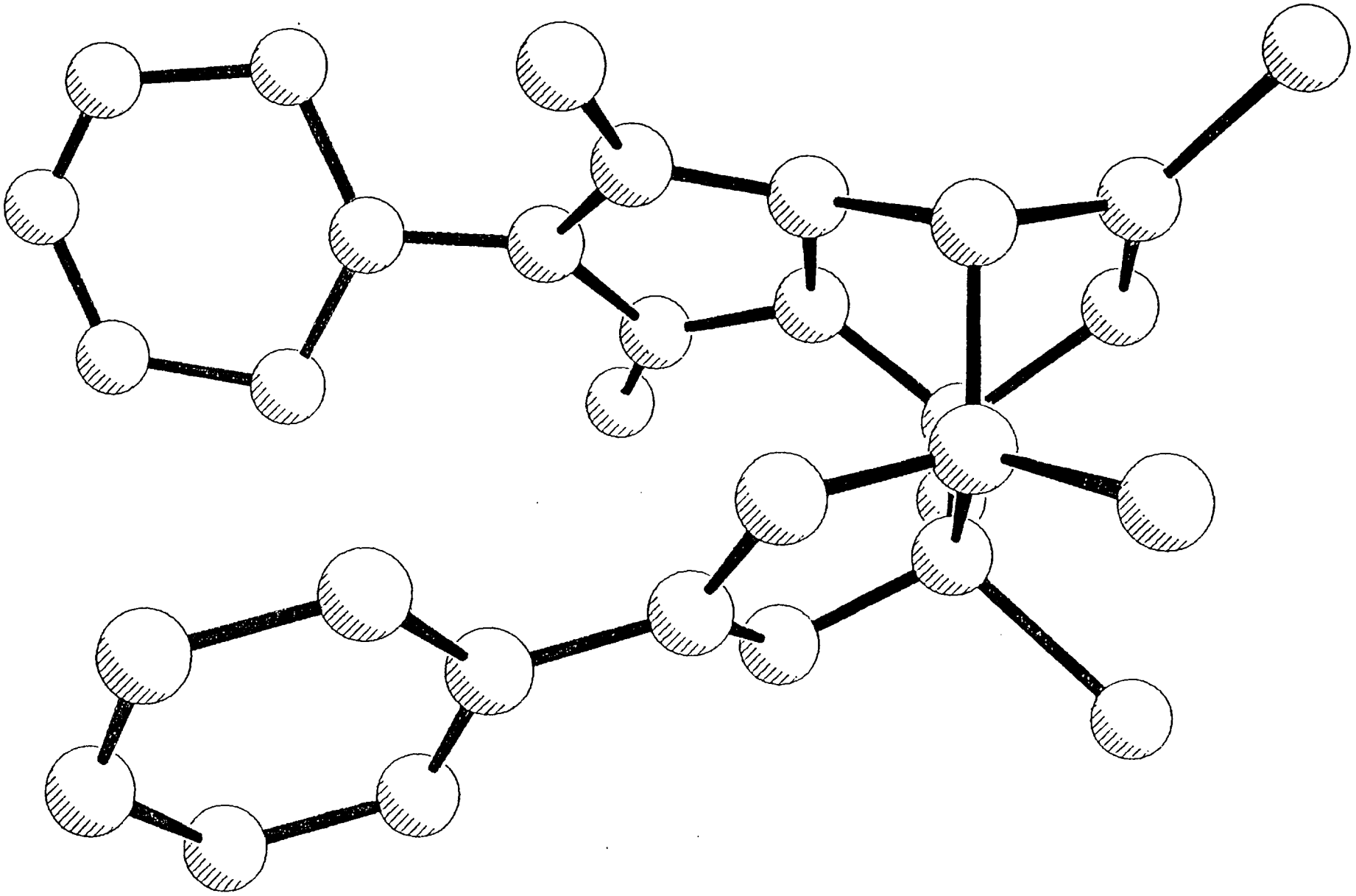


FIGURE 2.2

of evidence that the isomerism in the acetoxy and hydroxy ketones was of Type (i). The chlorooxazoline (110) was formed from the acetate (89a) by a sequence which could not have led to inversion at any of the chiral centres so the stereochemistry of (110) shows that (89a) was formed by addition of the PTAD *syn* to the acetoxy group. Interestingly, the urazole ring in (110) is *exo* in the solid state although this is almost certainly the contrathermodynamic configuration in solution.

It was thought that the carbonium ion might be formed in more forcing conditions because oxazoline formation is reversible. However, heating the alcohol in strong acid gave mixtures of products in which the olefinic bridge was no longer present. This shows that protonation of the tri-substituted double bond is more favourable than generation of the α-keto carbonium ion and that a nitrogen function cannot be introduced α to the ketone simply by treatment with strong acid. Other possiblities include generation of the required carbonium ion by solvolysis of a chloroformate[191] or sulphonate[188] ester and the use of a cyclohexadienone which already contains a nitrogen function *e.g.*, 6-nitro derivatives.[192]

VI. CONCLUSIONS.

The alkenyltetrazole route to 1*H*-imidazoles differs from the great majority of imidazole syntheses[1] in that it is not based on α-substituted carbonyl compounds. Instead its starting materials are alkenes, epoxides, and alkynes, and these are converted into imidazoles in two to four steps under very mild conditions. It is also unusual in that it appears to be quite general for imidazoles bearing alkyl, aryl, or ester groups. The sequence gives acceptable overall yields of 2-methyl and 2-phenyl-imidazoles (29-45%) and further optimisation should be possible. In cases where a sensitive imidazole was required and the corresponding alkene was accessible this photochemical route could be quite attractive.

Its major weakness is the poor results obtained for 2-unsubstituted imidazoles. The majority of the naturally occurring and the pharmacologically active imidazoles do not have a substituent on C-2 so the poor yields (0-17%) of such compounds are particularly disappointing. The key problem is the photolysis of 5-unsubstituted tetrazoles and if good yields of imidazoles could be obtained from this reaction the flaw in the method would be overcome. Since the study of the photolysis conditions was far from exhaustive an improvement is feasible, and indeed likely.

2,2-Disubstituted vinyl tetrazoles are easily prepared from ketones *via* enamides in moderate (but unoptimised) yields. The photolysis of these tetrazoles provides the first general route to 4*H*-imidazoles and this mild method is especially useful for the preparation of lightly substituted derivatives, which are very sensitive. Preliminary results indicate that these simple systems are very reactive and it is hoped that the study of their chemistry will be continued.

An attempt to prepare 3a*H*-benzimidazoles *via* quinol acetate-PTAD adducts was unsuccessful. Although this approach remains viable, several alternative routes have been devised, and methods involving photolytic preparation of a 4*H*-imidazole to give a suitably protected benzimidazole might be more rewarding.

3. EXPERIMENTAL

3.1. GENERAL

Starting materials. Starting materials were prepared according to literature procedures as indicated, and if no reference is quoted are available commercially.

Solvents. Petroleum ether, b.p. 30-40°, 40-60°, and 60-80° were distilled before use. In the text, petrol refers to petroleum ether, b.p. 60-80°. Benzene, ether and THF were dried over sodium wire or over potassium-benzophenone as required. Chloroform was purified when necessary, by passing through a column of alumina (Brockmann Grade 1). Acetonitrile and DMF were dried by distillation from phosphorus pentoxide. DMSO and HMPA were dried by distillation from calcium hydride at water pump pressure. All dried solvents were stored under nitrogen over 4Å molecular sieves.

Chromatography. Column chromatography was carried out using Silica gel H (type 60) (Merck or Rose Chemicals) or Aluminium oxide 60 H basic (Type E) at 5-10 p.s.i. Extensive use was made of t.l.c. on commercial plates of Silica gel 60 F_{254} coated on aluminium sheets.

Photolyses. Photolyses were carried out in a Rayonet photochemical reactor using lamps emitting at 254 or 300 nm as specified. Quartz vessels were used, nitrogen was passed through the solution continuously during the photolyses, and no cooling was provided unless otherwise stated.

Melting Points. Melting points were determined on a Kofler Hot Stage apparatus and are uncorrected.

Spectra. Infra red (i.r.) spectra were recorded in the range 600-4000 cm^{-1} using Perkin-Elmer 257 and 298 spectrophotometers and calibrated against polystyrene. Unless otherwise specified the spectra of oils were recorded as thin films between sodium chloride plates and those of solids as Nujol mulls.

Ultraviolet (u.v.) spectra were recorded in the range 200-450 nm using a Pye Unicam SP 800 spectrophotometer. Cells of 0.5 cm pathlength were used and the solvent was ethanol unless otherwise stated. Extinction coefficients (ε) are quoted in parenthesis.

Proton n.m.r. spectra were recorded on a Perkin-Elmer R32 spectrometer operating at 90 MHz unless otherwise stated. Other instruments used were the Varian T60 (60 MHz) and EM 360 (60 MHz) and Bruker WM 250 (250 MHz) spectrometers. Tetramethylsilane (TMS) was used as an internal reference and the solvent is specified only if other than deuterochloroform. Signals are indicated to be singlets (s), doublets (d), triplets (t), quartets (q), or multiplets (m) and values of coupling constants (J) are quoted in Hz. Broad signals are listed as (br.) and those which underwent proton-deuterium exchange on treatment with D_2O as (exch. D_2O). ^{13}C spectra were recorded on a Bruker WM 250 operating at 62.9 MHz, using deuterochloform as solvent and TMS as an internal reference, unless otherwise stated.

Low and high resolution mass spectra were recorded on A.E.I. MS 12 and VG Micromass 7070 B instruments, at 70 or 12 eV, using a direct insertion probe or a septum inlet. Relative intensities are quoted in parentheses and metastable peaks at mass m^1 for the decay of fragments of mass m^2 to fragments of mass m^3 are indicated by; $m^*\ m^1\ (m^2 \rightarrow m^3)$.

3.2. PREPARATION OF 1-ALKENYLTETRAZOLES.

3.2.1. Preparation of 2-Tri-*n*-butylstannyltetrazoles.

2-Tri-n-butylstannyltetrazole (26a). A mixture of 1*H*-tetrazole (212 mg, 3.03 mmol) and tri-*n*-butylstannyl oxide (902 mg, 1.51 mmol) in ethanol (2.5 ml) was refluxed under nitrogen for 2h. The solvent was removed to give the *tetrazole* (26a) as an oil; ν_{max} 1488, 1301, 1141, 1036, 880 and 868 cm^{-1}; δ 0.67-2.45 (27H, m), 8.51 (1H, s). It was used without purification.

5-Methyl-2-tri-*n*-butylstannyltetrazole (26b)[112] was prepared from acetonitrile and tri-*n*-butylstannyl azide,[193] in 83% yield after distillation, m.p., 49-55° (lit.,[112] 49-50°).

5-Phenyl-2-tri-*n*-butylstannyltetrazole (26c)[112] was prepared from 5-phenyltetrazole[194] and tri-*n*-butylstannyl oxide, in 98% yield after recrystallisation, m.p. 66-71° (lit.,[112] 66-7°).

Methyl 2-tri-n-butylstannyltetrazole-5-carboxylate (26d). Methyl cyanoformate[195] (0.77 ml, 9.03 mmol) was added with stirring to tri-*n*-butylstannyl azide[193] (2.0 g, 6.02 mmol) and an exothermic reaction occurred. After 2h, the excess of cyanoformate was removed *in vacuo* to give the crude *tetrazole* (26d); ν_{max} 2925, 1724, 1460, 1373, 1230, 1070, 778 and 680 cm^{-1}. It was used without purification.

3.2.2. Reaction of 2-Tri-*n*-butylstannyltetrazoles with Epoxides.

General Procedure A. A solution of the stannyltetrazole (26) and the epoxide (1.0 to 2.5 molar equivalents) in ether or benzene [1-2 ml per 1 mmol of (26)] was stirred at room temperature (when the solvent was ether) or refluxed under nitrogen (when the solvent was benzene) until no (26) remained (t.l.c., ^{1}H n.m.r.). Excess of hydrogen chloride, excess of hydrochloric acid (1M), or one molar equivalent of acetic acid was added and the mixture was stirred for 1-2h. In some cases the crude products crystallised at this stage and separation of the isomeric tetrazoles was achieved by recrystallisation of the major product followed by chromatography of the residues on silica gel. Otherwise the solvent was removed and the products were isolated by chromatography, immediately, or after washing with cold 60-80° petrol to remove stannyl salts. Preparations carried out using Procedure A are as follows:

1-(2-Hydroxyethyl)tetrazole (27a). Reaction of (26a) (4.60 g, 12.8 mmol) and ethylene oxide (1.6 ml, 32 mmol) in ether (10 ml) for 43h followed by quenching with acetic acid (0.73 ml, 12.8 mmol), washing with petrol, and chromatography on alumina gave 2-(2-*hydroxyethyl*)*tetrazole* (28a) (415 mg, 28%) as an oil; ν_{max} 3400, 2960, 1370, 1290, 1195, 1140, 1075, 875 and 705 cm^{-1}; δ 4.17 (2H, t, *J* 5), 4.47 (1H, br.s), 4.83 (2H, t, *J* 5), and 8.57 (1H, s); *m/e* 115 (M^+), 71 and 55; which was characterised as the 3,5-*dinitrobenzoate ester*,[196] m.p. 117-9° (from chloroform/petrol) (Found: C, 38.98; H, 2.52; N, 26.99. $C_{10}H_8N_4O_6$ requires C, 38.97; H, 2.62; N, 27.27%), and 1-(2-*hydroxyethyl*)*tetrazole* (27a) (531 mg, 36%)

as an oil; ν_{max} 3380, 2960, 1484, 1430, 1172, 1104, 1065, 972, and 869 cm^{-1}; δ [$(CD_3)_2CO$] 4.04 (2H, t, *J* 6), 4.48 (1H, br s), 4.68 (2H, t, *J* 6) and 9.07 (1H, s); *m/e* 115 (M^+ + 1), 84, 83, 71, and 55; which was characterised as the 3,5-*dinitrobenzoate* ester,[196] m.p., 178-80° (from acetone/petrol) (Found: C, 39.04; H, 2.53; N, 27.07. $C_{10}H_8N_6O_6$ requires C, 38.97; H, 2.62; N, 27.27%).

1-(2-Hydroxypropyl)tetrazole (27b). (26a) (2.75 g, 7.66 mmol) and propylene oxide (0.804 ml, 11.5 mmol) reacted in ether (7 ml) for 36h, the reaction was quenched with acetic acid (0.44 ml, 7.66 mmol) and the product was chromatographed on alumina, to give 2-(2-*hydroxypropyl*)*tetrazole* (28b) (361 mg, 37%) as an oil; ν_{max} 3400, 2980, 1362, 1283, 1143, 1027, 944 and 712 cm^{-1}; δ 1.29 (3H, d, *J* 6), 3.78 (1H, br d, *J* 5), 4.25-4.60 (1H, m), 4.70 (2H, d, *J* 6), and 8.54 (1H, s); *m/e* 113, 84, 55, and 45, which was characterised as the 3,5-*dinitrobenzoate ester*,[196] m.p. 114-6° (from chloroform/petrol)(Found: C, 40.88; H, 3.04; N, 25.81. $C_{11}H_{10}N_6O_6$ requires C, 41.00; H, 3.13; N, 26.08%), and 1-(2-*hydroxypropyl*)*tetrazole* (27b) (325 mg, 33%) as an oil; ν_{max} 3380, 2980, 1429, 1175, 1108, 958, 847, 754, and 668 cm^{-1}; δ 1.28 (3H, d, *J* 7), 4.10-4.80 (4H, m), and 8.89 (1H, s); *m/e* 129 (M^+ + 1), 84, 69, 55, and 45, which was characterised as the 3,5-*dinitrobenzoate ester*,[196] m.p. 167-70° (from acetone/petrol) (Found: C, 41.06; H, 3.07; N, 25.96. $C_{11}H_{10}N_6O_6$ requires C, 41.00; H, 3.13; N, 26.08%).

1-(2-Hydroxyethyl)-5-phenyltetrazole (27d). (26c) (4.14 g, 9.74 mol) was reacted with ethylene oxide (0.73 ml, 14.6 mmol) in ether (15 ml) for 3 days, the reaction was quenched with hydrogen chloride, and the products

were chromatographed on silica gel, to give 2-(2-*hydroxyethyl*)-5-*phenyl-tetrazole* (28d) (139 mg, 8%), m.p. 65-65° (from chloroform/petrol) (Found: C, 56.84; H, 5.27; N, 29.57. $C_9H_{10}N_4O$ requires C, 56.83; H, 5.30; N, 29.46%); ν_{max} 3320, 1528, 1450, 1149, 1074, 862, 793, 736, 720 and 695 cm^{-1}; δ 3.55 (1H, t, *J* 6), 4.07-4.37 (2H, m), 4.77 (2H, t, *J* 5), 7.35-7.63 (3H, m), and 7.90-8.23 (2H, m); *m/e* 190 (M^+), 162, 131, 104 (base), and 77, and 1-(2-*hydroxyethyl*)-5-*phenyltetrazole* (27d) (1.473 g, 80%), m.p. 79-80° (from chloroform/petrol) (Found: C, 57.00; H, 5.28; N, 29.60. $C_9H_{10}N_4O$ requires C, 46.83; H, 5.30; N, 29.46%); ν_{max} 3290, 1439, 1232, 1129, 1080, 953, 864, 785, 742, 711 and 696 cm^{-1}; δ 4.0-4.3 (2H, m), 4.3-4.6 (3H, m, 1H exch. D_2O), 7.45-7.65 (3H, m), and 7.65-7.9 (2H, m); *m/e* 190 (M^+), 147, 131, 118, 104, 90, 77 (base), and 45 .

1-(2-Hydroxypropyl)-5-phenyltetrazole (27e). (26c) (10.59 g, 24.9 mmol) was reacted with propylene oxide (1.92 ml, 27.4 mmol) in ether (30 ml) for 90h, the reaction was quenched with hydrogen chloride, and the products were purified by fractional recrystallisation from ethanol/water followed by chromatography on silica gel, to give 2-(2-*hydroxypropyl*)-5-*phenyl-tetrazole* (28e) (356 mg, 7%), m.p. 52-5° (from chloroform/petrol) (Found: C, 58.56; H, 5.90; N, 27.31. $C_{10}H_{12}N_4O$ requires C, 58.81; H, 5.92; N, 27.42%); ν_{max} 3320, 1533, 1396, 1130, 1066, 940, 845, 782, 730 and 689 cm^{-1}; δ 1.28 (3H, d, *J* 7), 3.52 (1H, d, *J* 5), 4.20-4.75 (3H, m), 7.25-7.60 (3H, m), and 7.95-8.25 (2H, m); *m/e* 204 (M^+), 176, 131 (base), 104, and 77, and 1-(2-*hydroxypropyl*)-5-*phenyltetrazole* (27c) (3.52 g, 69%), m.p. 90-2° (from chloroform/petrol) (Found: C, 58.80; H, 5.89; N, 27.36. $C_{10}H_{12}N_4O$ requires C, 58.81; H, 5,92; N, 27.43%); ν_{max} 3340, 1409, 1301, 1131, 944, 850, 785, 773, 742, and 711 cm^{-1}; λ_{max} 240 (9600); δ 1.29 (3H, d, *J* 8), 4.15-4.70 (4H, m), and 7.35-7.95 (5H, m); *m/e* 205, 204 (M^+), 160, 147, 131, 118, 117, 104 (base), and 77.

1-(2-Hydroxycyclohexyl)-5-phenyltetrazole (27f). (i) (26c) (17.35 g, 40.8 mmol) was reacted with cyclohexene oxide (4.0 g, 40.8 mmol) in ether (40 ml) for 140h. The reaction was quenched by washing with hydrochloric acid (1M; 50 ml), the solution was washed with aqueous sodium hydroxide and with water, dried with sodium sulphate and concentrated, and the products were isolated by fractional crystallisation from dichloromethane/petrol followed by chromatography on silica gel, to give 2-(2-*hydroxycyclohexyl*)-5-*phenyltetrazole* (28f) (1.53 g, 15%), m.p. 107-8.5° (from dichloromethane/petrol) (Found: C, 64.16; H, 6.62; N, 23.07. $C_{13}H_{16}N_4O$ requires C, 63.92 ; H, 6.60; N, 22.93%); ν_{max} 3375, 1074, 962, 802, 734 and 694 cm^{-1}; δ 1.1-2.4 (8H, m), 3.71 (1H, d, *J* 7, exch. D_2O), 4.18 (1H, m), 4.58 (1H, ddd, *J* 6, 11, 12), 7.45 (3H, m), and 8.04 (2H, m); *m/e* 244 (M^+), 216, 104 (base), 103, 57, 56, and 43, and 1-(2-*hydroxycyclohexyl*)-5-*phenyltetrazole* (27f) (5.67 g, 57%), m.p. 156-8° (from dichloromethane/petrol) (Found: C, 63.75; H, 6.66; N, 22.64. $C_{13}H_{16}N_4O$ requires C, 63.92; H, 6.60; N, 22.93%); ν_{max} 3355, 1069, 959, 778, 740, and 700 cm^{-1}; δ 1.0-2.4 (8H, m), 4.0-4.4 (2H, m), 4.66 (1H, br s, exch. D_2O), 7.56 (3H, m), and 7.77 (2H, m); *m/e* 244 (M^+), 216, 173 (base), 147, 118, 104, 88, 81 and 77. (ii) (26c) (2.17 g, 5.1 mmol) was reacted with cyclohexene oxide (0.5 g, 5.1 mmol) in refluxing benzene (20 ml) for 10h, the reaction was worked up as in (i), and the products chromatographed on silica gel, to give (28f) (441 mg, 36%) and (27f) (627 mg, 51%).

1-(2-Hydroxy-2-phenylethyl)-5-phenyltetrazole (27g). (26c) (5.19 g, 12.21 mmol) was reacted with styrene oxide (1.67 ml, 14.65 mmol) in benzene (15 ml) at reflux for 10h, the reaction was quenched with hydrogen chloride and the products were washed with petrol and chromatographed on silica gel, to give 2-(2-*hydroxy*-2-*phenylethyl*)-5-*phenyltetrazole* (28g) (184 mg, 6%), m.p. 100.5-102° (from chloroform/petrol) (Found: C, 67.36; H, 5.26;

N, 21.04%); ν_{max} 3245, 3155, 1206, 1062, 744, 731, and 691 cm^{-1}; δ 3.87 (1H, d, *J* 4, exch. D_2O), 4.08-4.98 (2H, m), 5.37 (1H, ddd, *J* 4,5,6), 7.25-7.55 (8H, m), and 7.95-8.18 (2H, m); *m/e* 266 (M^+), 238, 210, 160, 132, 131, 107, 104, 79 and 77, and 2-(2-*hydroxy*-1-*phenylethyl*)-5-*phenyltetrazole* (28h) (232 mg, 7%), m.p. 92-5° (from chloroform/petrol)(Found: C, 67.53; H, 5.29; N, 20.87. $C_{15}H_{14}N_4O$ requires C, 67.65; H, 5.30; N, 21.04%); ν_{max} 3285, 1341, 1070, 791, 741, 733, 702, and 693 cm^{-1}; δ 3.79 (1H, t, *J* 6, exch. D_2O), 4.06-4.42 (1H, m), 4.52-4.88 (1H, m), 6.12 (1H, dd, *J* 4, 9), 7.25-7.65 (8H, m), and 8.0-8.23 (2H, m); *m/e* 266 (M^+), 238, 207, 131, 104, 103, 91 and 77, and 1-(2-*hydroxy*-2-*phenylethyl*)-5-*phenyltetrazole* (27g) (1.465 g, 45%), m.p. 108-18° (from chloroform/petrol) (Found: C, 67.92; H, 5.26; N, 21.11. $C_{15}H_{14}N_4O$ requires C, 67.65; H, 5.30; N, 21.04%); ν_{max} 3240, 1413, 1304, 1068, 941, 781, 746, 735, 706 and 700 cm^{-1}; δ 4.33-4.70 (2H, m), 4.74 (1H, d, *J* 4), 5.21-5.54 (1H, m), 7.28 (5H, br s), and 7.35-7.75 (5H, m); *m/e* 267, 266 (M^+), 160 (base), 159, 107, 104, 79, and 77, and 1-(2-*hydroxy*-1-*phenylethyl*)-5-*phenyltetrazole* (27h)(1.107 g, 34%), m.p. 130-2° (from chloroform/petrol) (Found: C, 67.39; H, 5.28; N, 20.92. $C_{15}G_{14}N_4O$ requires C, 67.65; H, 5.30; N, 21.04%); ν_{max} 3370, 1543, 1068, 864, 774, 735, 722, 712, and 701 cm^{-1}; δ 3.3-3.65 (1H, br, exch. D_2O), 3.95-4.05 (1H, m), 4.50-4.90 (1H, m), 5.72 (1H, dd, *J* 4, 10), and 7.2-7.75 (10H, m); *m/e* 267, 266 (M^+), 236 (base), 207, 193, 160, 105, 104, 103 and 77.

1-(2-Ethoxycarbonyl-2-hydroxy-1-phenylethyl)-5-phenyltetrazole (27i). (26c) (2.02 g, 4.75 mmol) was reacted with ethyl 3-phenylglycidate[197] (1.10 g, 5.70 mmol) in benzene (5 ml) at reflux for 22h, the reaction was quenched with hydrogen chloride, and the products were washed with petrol and chromatographed on silica gel, to give 2-(2-*ethoxycarbonyl*-2-*hydroxy*-1-

phenylethyl)-5-*phenyltetrazole* (28j) (164 mg, 10%), m.p. 103-5° (from chloroform/petrol) (Found: C, 63.93; H, 5.32; N, 16.57. $C_{18}H_{18}N_4O_3$ requires C, 63.89; H, 5.36; N, 16.56%); ν_{max} 3490, 1722, 1238, 1162, 1105, 842, 733, 727, 706, and 688 cm^{-1}; δ 1.07 (3H, t, *J* 7.5), 3.68 (1H, br d, *J* 4.5), 4.14 (2H, q, *J* 7.5), 5.14-5.36 (1H, m), 6.30 (1H, d, *J* 6), 7.25-7.67 (8H, m), and 8.0-8.3 (2H, m); *m/e* 338 (M^+), 236, 207, 146, 118, 104, 91 and 77, and 1-(2-*ethoxycarbonyl*-2-*hydroxy*-1-*phenylethyl*)-5-*phenyltetrazole* (27j) (1.162 g, 72%), m.p. 119-23° (from chloroform/petrol) (Found: C, 63.58; H, 5.27; N, 17.67. $C_{18}H_{18}N_4O_3$ requires C, 63.89; H, 5.36; N, 16.56%); ν_{max} 3370, 1744, 1293, 1240, 1217, 1111, 796, 746, 711, 700, and 692 cm^{-1}; δ 1.06 (3H, t, *J* 7), 4.09 (2H, q, *J* 7), 4.75 (1H, br s), 5.16 (1H, d, *J* 7), 5.89 (1H, d, *J* 7), 7.36 (5H, s), and 7.53 (5H, s); *m/e* 338 (M^+), 236, 207, 146, 118, 104, 91, and 77.

General Procedure B. A suspension of the 5-substituted tetrazole (25) in a solution of the stannyltetrazole (26) (0.1 molar equivalents) and the epoxide (1.5-2.5 molar equivalents) in ether [1-10 ml per 1 mmol of (26)] was stirred at room temperature until no (25) remained. As the reaction approached completion the tetrazole (25) was seen to disappear and in some cases the alkylated products oiled out of the reaction mixture. When carried out on a very small scale (< 1 mmol) no acid was added and the crude product was chromatographed directly. On a larger scale acetic acid (0.1 molar equivalents) or hydrogen chloride (excess) were added to the mixture and stirring was continued for 1h. The solvent was removed and the products were chromatographed. Prepared according to this procedure were the following:

1-(2-Hydroxyethyl)tetrazole (27a). Reaction of tetrazole (316 mg, 4.51 mol) and the stannyl derivative (26a) (181 mg, 0.505 mmol) with ethylene oxide (0.643 ml, 12.9 mmol) in ether (2 ml) for 25h, followed by quenching with hydrogen chloride and chromatography on alumina gave the 2-*alkyltetrazole* (27b) (254 mg, 44%).

1-(2-Hydroxypropyl)tetrazole (27b). Reaction of tetrazole (1.00 g, 14.3 mmol) and the stannyl derivatve (26a) (569 mg, 1.585 mmol) with propylene oxide (1.50 ml, 21.4 mmol) in ether (2 ml) for 23h, followed by quenching with acetic acid (91 μℓ, 1.59 mmol) and chromatography on alumina gave the 2-*alkyltetrazole* (28b) (777 mg, 38%) and the 1-*alkyltetrazole* (27b) (849 mg, 42%).

1-(2-Hydroxypropyl)-5-phenyltetrazole (27c). Reaction of 5-phenyltetrazole (139 mg, 0.953 mmol) and the stannyl derivative (26c) (40 mg, 0.0953 mmol) with propylene oxide (100 μℓ, 1.43 mmol) in ether (1 ml) for 90h, followed by chromatography on silica gel, gave the 2-*alkyltetrazole* (28e) (34 mg, 18%) and the 1-*alkyltetrazole* (27e) (153 mg, 78%).

General Procedure C. A suspension of the 5-substituted tetrazole (25) in a solution of tri-*n*-butylstannyl oxide (0.05 molar equivalents) and the epoxide (1.5-2.5 molar equivalents) in ether (2-5 ml per 1 mmol of stannyl oxide) was stirred at room temperature until no (25) remained. Work up and separation are as described for Procedure B. Prepared according to this procedure were the following:

1-(2-Hydroxyethyl)tetrazole (27a). Reaction of tetrazole (360 mg, 5.14 mmol) with tri-*n*-butylstannyl oxide (153 mg, 0.257 mmol) and ethylene oxide (0.642 ml, 12.8 mmol) in ether (2 ml) for 25h, followed by quenching with hydrogen chloride and chromatography on alumina, gave the 2-*alkyltetrazole* (28a) (93 mg, 16%) and the 1-*alkyltetrazole* (27a) (254 mg, 43%).

1-(2-Hydroxypropyl)-5-methyltetrazole (27c). Reaction of 5-methyltetrazole[112] (705 mg, 8.38 mmol) with tri-*n*-butylstannyl oxide (500 mg, 0.838 mmol) and propylene oxide (0.88 ml, 12.6 mmol)in ether (2 ml) for 39h, followed by quenching with acetic acid (96.2 μℓ, 1.68 mmol) and chromatography on alumina, gave 2-(2-*hydroxypropyl*)-5-*methyltetrazole* (28c) (242 mg, 20%) as an oil; ν_{max} 3420, 2985, 1503, 1135, 1071, 943, 847, and 795 cm^{-1}; δ 1.27 (3H, d, *J* 6), 2.49 (3H, s), and 4.2-4.8 (4H, m); *m/e* 143 (M^+ + 1), 127, 114, 98, 83, 69, 45 and 42 (base), and 1-(2-*hydroxypropyl*)-5-*methyl-tetrazole* (27c) (839 mg, 70%), as an oil; ν_{max} 3380, 2985, 1527, 1409, 1134, 1057, 941, 845, and 773 cm^{-1}; δ 1.29 (3H, d, *J* 6), 2.54 (3H, s), and 3.83-4.83 (4H, m); *m/e* 143 (M^+ + 1), 127, 112, 99, 98 and 69.

Reaction of methyl 2-tri-*n*-butylstannyltetrazole-5-carboxylate (26d) with propylene oxide.

A solution of the stannyltetrazole (26d) (236 mg, 0.566 mmol) and propylene oxide (120 μℓ, 1.6 mmol) in ether (2 ml) was allowed to stand at room temperature for 17 days. The solvent and exess of epoxide were removed, the residue was dissolved in ether (3 ml) and hydrogen chloride was passed through the solution. The solvent was removed and the residue was washed with petrol to leave an oil which was identical by t.l.c. and ^1H n.m.r. with 1-(2-*hydroxypropyl*)*tetrazole* (27b).

Alkylations in solvents other than ether and benzene.

(i) Dichloromethane. A solution of 5-phenyl-2-tri-*n*-butylstannyltetrazole (26c) (490 mg, 1.15 mmol) and cyclohexene oxide (0.128 ml, 1.27 mmol) in dichloromethane (2 ml) was allowed to stand at room temperature for 3 days. T.l.c. on silica gel showed that the rate and regioselectivity of the reaction were comparable to those carried out in ether.

(ii) Ethanol. As in (i) but the reaction was carried out in ethanol (2 ml) for 5 days. T.l.c. showed that the reaction was rapid but that 2-alkylation was favoured over 1-alkylation.

(iii) DMF. As in (i) but the reaction was carried out in DMF (2 ml) for 5 days. T.l.c. showed that alkylation was slow and that 2-alkylation predominanated.

(iv) Methanol. Propylene oxide (74 μℓ, 1.06 mmol) was added to a stirred solution of tetrazole (49.5 mg, 0.707 mmol) and tri-*n*-butylstannyl oxide (21 mg, 0.035 mmol) in methanol (2 ml), and stirring was continued for 50h. The solvent was removed and deuterochloroform (0.5 ml) and excess of acetic acid were added causing precipitation of a considerable quantity of tetrazole. ^{1}H n.m.r. showed that very little alkylation had occurred and that the ratio of 2- to 1-alkylation was very similar to that for the reaction in ether.

3.2.3. Dehydration of the 2-Hydroxyalkyltetrazoles

Attempted dehydrations of 1-(2-hydroxycyclohexyl)-5-phenyltetrazole (27f).

(i) Phosphorus oxychloride in pyridine.[114] A solution of phosphorus oxychloride (0.5 ml) in dry pyridine (2 ml) was added dropwise to a stirred solution of the alcohol (27f) (100 mg, 0.409 mmol) in pyridine (2 ml).

The solution was stirred for 5.5h and refluxed for 0.5h, and after cooling was poured carefully into water (30 ml). It was extracted with ether, washed with hydrochloric acid (1M), sodium bicarbonate (1M), and water, dried over sodium sulphate and concentrated. T.l.c. showed three products in very small amounts.

(ii) PTSA.[115] A solution of the alcohol (27f) (100 mg) and PTSA monohydrate (50 mg) in toluene (5 ml) was refluxed in a Dean and Stark apparatus for 5 days. T.l.c. showed the product to consist predominantly of starting material and baseline products. A similar result was obtained after refluxing under nitrogen in xylene for 3 days.

(iii) Triphenylphosphine - carbon tetrachloride.[116] A solution of the alcohol (27f) (100 mg, 0.409 mmol), triphenylphosphine (129 mg, 0.491 mmol), and carbon tetrachloride (86.4 μℓ, 0.818 mmol) in dry acetonitrile (10 ml) was refluxed under nitrogen for 75h. The solution was concentrated and chromatographed on silica gel to give the alcohol (27f) (82 mg, 82%) and 1-(cyclohex-2-enyl)-5-phenyltetrazole (30) (6 mg, 6%).

(iv) Thionyl chloride. A solution of the alcohol (27f) (100 mg) in thionyl chloride (2 ml) was refluxed for 20h. T.l.c. showed that only starting material was present.

(v) Methyltriphenoxyphosphonium iodide in HMPA.[117] A solution of the alcohol (27f) (142 mg, 0.581 mmol) and MTPI[198] (0.656 g, 1.45 mmol) in HMPA (4 ml) was stirred at 100° for 41h. Water (40 ml) was added and the solution was extracted with ether (3 x 30 ml). The extracts were washed with saturated sodium chloride solution (2 x 40 ml) and dried over sodium sulphate. The solvent was removed and the residue chromatographed on silica gel, to give 1-(*cyclohex-1-enyl*)-5-*phenyltetrazole* (29f) (96 mg, 74%), m.p. 102.5-4.5° (from chloroform/petrol) (Found: C, 69.32; H, 6.22;

N, 24.54. $C_{13}H_{14}N_4$ requires C, 69.00; H, 6.24; N, 24.78%); ν_{max} ($CC\ell_4$) 2945, 1675, 1458, 1402, 1124, 922 and 693 cm^{-1}; λ_{max} 236 (10900) nm; δ 1.4-2.5 (8H, m), 6.06 (1H, m), 7.06 (3H, m), and 7.78 (2H, m); *m/e* 227, 226 (M^+), 198, 197, 144, 130 (base), 117, and 103, and 1-(*cyclohex-2-enyl*)-5-*phenyltetrazole* (30) (19 mg, 14%), m.p. 95-8° (from chloroform/petrol)(Found: C, 68.89; H, 6.26; N, 24.72. $C_{13}H_{14}N_4$ requires C, 69.00; H, 6.24; N, 24.78%); ν_{max} 1390, 1152, 939, 836, 784, 728 and 701 cm^{-1}; δ 1.5-2.4 (6H, m), 5.05-5.35 (1H, m), 5.62-5.85 (1H, m), 5.98-6.30 (1H, m), and 7.50-7.80 (5H, m); *m/e* 226 (M^+), 169, 155, 142, 129, 103, 91, 90, 81 (base) and 79.

Preparation of methyltriphenoxyphosphonium iodide (MTPI). MTPI was prepared according to the method of Verheyden and Moffatt[198] but rather than inducing the crude oil to crystallise in the reaction flask, it was poured into rapidly stirring dry ethyl acetate and seeded, to give a finely divided pale yellow solid. It was washed with one portion of ethyl acetate and stored under ethyl acetate. All subsequent manipulation was carried out in a dry-box under nitrogen.

General Procedure for dehydrations using MTPI. A solution of the tetrazolylalcohol (27) and MTPI (1.2-2.0 molar equivalents) in dry HMPA or dry DMF (2-4 ml per 1 g of MTPI) was stirred at room temperature until t.l.c. indicated that no alcohol remained. The solution was poured into 10% aqueous sodium hydroxide solution (10 ml per 1 ml of HMPA/DMF) and stirred at room temperature until t.l.c. showed that no iodide or phosphonate remained. The products were then isolated by filtration or by extraction with ether, and purified by recrystallisation or chromatography. Prepared according to this procedure were the following:

1-Vinyltetrazole (29a).[105(a)] 1-(2-Hydroxyethyl)tetrazole (27a) (690 mg, 6.05 mmol) was reacted with MTPI (3.42 g, 7.56 mmol) in DMF (10 ml) for 4h and with aqueous hydroxide for 27h, and the product was isolated by continuous extraction with ether and chromatography on silica gel, to give the alkenyltetrazole (29a) (400 mg, 69%),[105(a)]; ν_{max} 3117, 1648, 1473, 1094, 958, 920 and 668 cm^{-1}; λ_{max} 224 (6100) nm; δ 5.60 (1H, dd, *J* 2.9), 6.22 (1H, dd, *J* 2, 18), 7.65 (1H, dd, *J* 9, 18), and 9.52 (1H, s); *m/e* 96 (M^+), 68, 67, 53, 42, 41, 40, and 39.

Trans-1-(*prop-1-enyl*)*tetrazole* (29b). 1-(2-Hydroxypropyl)tetrazole (27b) (273 mg, 5.64 mmol) was reacted with MTPI (3.19 g, 7.05 mmol) in DMF (10 ml) for 4h and with aqueous hydroxide for 15h, and the product was isolated by continuous extraction with ether followed by chromatography on silica gel, to give the *alkenyltetrazole* (29b) (418 mg, 67%), m.p. 57-8°(from chloroform/petrol)(Found: C, 43.89; H,5.49; N, 50.93. $C_4H_6N_4$ requires C, 43.62; H, 5.45; N; 50.88%); ν_{max} 3125, 1674, 1664, 1549, 1406, 1200, 1173, 1106, 949, and 770 cm^{-1}; λ_{max} 229 (7350) nm; δ 1.98 (3H, dd, *J* 2,7), 6.66 (1H, dq, *J* 7, 14), 7.32 (1H, dq, *J* 2, 14), and 9.24 (1H, s); *m/e* 111, 110 (M^+), 81, 55, 54, 41, 39, and 28.

Trans-1-(*prop-1-enyl*)-5-*methyltetrazole* (29c). 1-(2-Hydroxypropyl)-5-methyltetrazole (27c) (1.953 g, 13.74 mmol) was treated with MTPI (7.82 g, 17.29 mmol) in DMF (25 ml) for 6h and aqueous hydroxide for 5h, and the product was isolated by continuous extraction with ether followed by chromatography on silica gel, to give the *alkenyltetrazole* (29c) (1.240 g, 73%), m.p. 40-2° (from benzene/petrol) (Found: C, 48.53; H, 6.48; N, 45.17. $C_5H_8N_4$ requires C, 48.37; H, 6.50; N, 45.13%); ν_{max} 1680, 1516, 1408, 1258, 1123, 1074, 947, 806 and 672 cm^{-1}; λ_{max} 226 (7100) nm; δ 1.97 (3H, dq, *J* 1,7), 2.62 (3H, s), 6.55 (1H, dq, *J* 7, 14), and 6.88 (1H,

dq, *J* 1, 14); *m/e* 125, 124 (M^+), 95, 81, 69, 68, 55, 54, 42, 41 and 28.

1-*Vinyl*-5-*phenyltetrazole* (29d). (i) In HMPA. 1-(2-Hydroxyethyl)-5-phenyltetrazole (27d) (660 mg, 3.47 mmol) was treated with MTPI (2.51 g, 5.55 mmol) in HMPA (10 ml) for 3h and with aqueous hydroxide for 1h, and the product was isolated by filtration, to give pure *alkenyltetrazole* (29d) (554 mg, 93%), m.p. 104-6° (from chloroform/petrol) (Found: C, 62.82; H, 4.72; N, 32.34. $C_9H_8N_4$ requires C, 62.78; H, 4.68; N, 32.54%); ν_{max} 1641, 1413, 1162, 959, 919, 781, 751, 700, and 663 cm^{-1}; λ_{max} 239 (11800) nm; δ 5.50 (1H, dd, *J* 2, 9), 6.22 (1H, dd, *J* 2, 16), 7.14 (1H, dd, *J* 9, 16), and 7.52-7.87 (5H, m); *m/e* 173, 172 (M^+), 117 (base), and 77.
(ii) In DMF. The alcohol (27d) (186 mg, 0.978 mmol) was treated with MTPI (550 mg, 1.22 mmol) in DMF (1 ml) for 4h and with aqueous hydroxide for 14h, and the product was isolated by filtration to give the *alkenyltetrazole* 128 mg, 76%), m.p. 103-5°.

Trans-1-(*prop*-1-*enyl*)-5-*phenyltetrazole* (29c). (i) In HMPA. 1-(2-Hydroxypropyl)-5-phenyltetrazole (27e) (3.44 mg, 16.86 mmol) was treated with MTPI (10.15 g, 22.4 mmol) in HMPA (40 ml) at room temperature for 20h and at 50° for 6h and with aqueous hydroxide for 2h, and the product was isolated by extraction with ether and Kugelrohr distillation at 125°/0.05 mbar, to give pure *alkenyltetrazole* (27e) (2.70 g, 86%), m.p. 60-3° (from chloroform/petrol) (Found: C, 64.79; H, 5.42; N, 30.33. $C_{10}H_{10}N_4$ requires C, 64.50; H, 5.41; N, 30.09%); ν_{max} 1412, 942, 785, 739, 708, and 689 cm^{-1}; λ_{max} 240 (12000) nm; δ 1.96 (3H, d, *J* 5), 6.50-7.05 (2H, m), and 7.05-7.9 (5H, m); *m/e* 187, 186 (M^+), 158, 157, 131, 130, 104, 103 and 77.

(ii) In DMF. The alcohol (27e) (145 mg, 0.712 mmol) was treated with MTPI (550 mg, 1.22 mmol) in DMF (2 ml) for 22h and with aqueous hydroxide for 2h, and the product was isolated by extraction with chloroform to give the *alkenyltetrazole* (29e) (110 mg, 83%).

1-(*Cyclohex-1-enyl*)-5-*phenyltetrazole* (29f). A solution of the cyclohexanol (27f) (74 mg, 0.30 mmol) was treated with MTPI (250 mg, 0.553 mmol) in HMPA (1 ml) for 24h and with aqueous hydroxide for 3h, and the product was isolated by filtration, to give the *alkenyltetrazole* (29f) (54 mg, 79%), m.p. 94-100°.

Trans-1-(2-phenylethenyl)-5-phenyltetrazole (29g).[101] The phenylethanol (27g) (1.272 g, 4.78 mmol) was treated with MTPI (3.78 g, 8.36 mmol) in HMPA (15 ml) for 19h and with aqueous hydroxide for 1h, and the product was isolated by extraction with ether and recrystallisation from chloroform/petrol, to give the alkenyltetrazole (29g) (1.015 g, 85%), m.p. 147-9° (from chloroform/petrol) (lit.,[101] 75-7°) (Found: C, 72.36; H, 5.02; N, 22.59. $C_{15}H_{12}N_4$ requires C, 72.56; H, 4.87; N, 22.57%); ν_{max} 1407, 1133, 947, 775, 759, 733 and 699 cm^{-1}; λ_{max} 284 (17700) and 243 (13100) nm; δ 7.4-8.0 (m); *m/e* 249, 248 (M^+), 219, 193, 117, 90, and 87.

1-(1-*Phenylethenyl*)-5-*phenyltetrazole* (29h). The phenylethanol (27h) (780 mg, 2.93 mmol) was treated with MTPI (2.65 g, 5.86 mmol) in HMPA (10 ml) for 19h and with aqueous hydroxide for 2h, and the product was isolated by extraction with ether and recrystallisation from chloroform/petrol, to give the *alkenyltetrazole* (29h) (647 mg, 89%), m.p. 89.5-90.5 (from chloroform/petrol) (Found: C, 72.26; H, 4.91; N, 22.53. $C_{15}H_{12}N_4$ requires C, 72.56; H, 4.87; N, 22.57%); ν_{max} 1643, 1465, 1405, 914, 781, 776, 737, 702, 696, and 632 cm^{-1}; λ_{max} 243 (20,300); δ 5.63 (1H, d, *J* 1),

6.09 (1H, d, *J* 1), 7.05-7.77 (8H, m), and 7.7-7.95 (2H, m); *m/e* 249, 248 (M^+), 220, 219, 180, 129, 118, 117 (base), 103, 85 and 77.

Attempted dehydrations of 1-(2-ethoxycarbonyl-2-hydroxy-1-phenylethyl)-5-phenyltetrazole (27i).

(i) MTPI/Sodium ethoxide. A solution of the alcohol (27i) (157 mg, 0.464 mmol) and MTPI (440 mg, 0.973 mmol) in HMPA (2 ml) was stirred for 10h, and poured into water (25 ml). After 12h the precipitated crystals were filtered off, to give 1-(2-*ethoxycarbonyl*-2-*iodo*-1-*phenylethyl*)-5-*phenyltetrazole* (55 mg, 26%), m.p. 170-2° (from chloroform/petrol) (Found: C, 48.00; H, 3.79; N, 12.22. $C_{18}H_{17}IN_4O_2$ requires C, 48.23; H, 3.82; N, 12.50%); ν_{max} 1723, 1265, 1182, 1138, 782, 755, 725 and 702 cm^{-1}; δ 1.02 (3H, t, *J* 7), 4.02 (2H, q, *J* 7), 5.54 (1H, d, *J* 12), 5.89 (1H, d, *J* 12), 7.27-7.75 (5H, m), and 7.64 (5H, s); *m/e* 488 (M^+), 247, 219, 207, 176, 148, 147, 132, 131, 104, 103, 77 and 76. Extraction of the aqueous phase with ether and concentration yielded a further crop of the *iodoalkyltetrazole* (26 mg, 13%) and the residue contained further iodide and ethyl cinnamate (by ^1H n.m.r.). A solution of sodium ethoxide (33 mg, 0.48 mmol) in ethanol (0.5 ml) was added dropwise to a stirred suspension of the *iodoalkyltetrazole* (40 mg, 0.0892 mmol) in ethanol (1 ml) and stirring was continued for 45 min. The mixture was poured into hydrochloric acid (1M; 10 ml) and extracted with ether (3 x 5 ml). The extract was washed with water, dried and concentrated, to give a mixture of ethyl 2-iodocinnamate and 5-phenyltetrazole (25a) (^1H n.m.r.). Recrystallisation from methanol/chloroform/petrol gave (25a), m.p. 215-8° (lit.,[194] 213-5°)

(ii) Excess of MTPI. A solution of the alcohol (27i) (110 mg, 0.325 mmol) and MTPI (580 mg, 1.28 mmol) in HMPA (2 ml) was heated at 100° for 1h, and then poured into water (30 ml). It was extracted with ether, washed with aqueous base and chromatographed on silica gel to give ethyl cinnamate (42 mg, 73%); δ ($CC\ell_4$) 1.31 (3H, t, *J* 7), 4.22 (2H, q, *J* 7), 6.38 (1H, d, *J* 17), 7.23-7.63 (5H, m), and 7.61 (1H, d, *J* 17).

(iii) 2-Nitrophenylselenocyanate. Treatment of the alcohol (27i) with 2-nitrophenylselenocyanate[199] and tributylphosphine according to the method of Grieco, *et. al.*[120] gave an immediate precipitate which was filtered off and recrystallised from ethanol/chloroform/petrol, to give 5-phenyltetrazole, m.p. 212-5°.

(iv) Pyrolysis of the thiocarbonate. A solution of the alcohol (27i) (59 mg, 0.175 mmol), p-tolylchlorothioformate[200] (36 mg, 0.193 mmol) and pyridine (15.6 μℓ, 0.193 mmol) in dichloromethane (1 ml) was stirred for 29h. Ether (10 ml) was added and the mixture was washed with hydrochloric acid (1M; 4 ml), aqueous sodium hydroxide (1M; 4 ml) and water (4 ml) and dried with magnesium sulphate. The solvent was removed and the residue was chromatographed on silica gel, to give the *thiocarbonate* (31) (36 mg, 42%); δ 1.12 (3H, t, *J* 16), 2.34 (3H, s), 4.15 (2H, q, *J* 16), 6.14 (1H, d, *J* 8), 6.70 (1H, d, *J* 8), 6.75-7.30 (4H, m), 7.44 (5H, br s), and 7.57 (5H, s); *m/e* 488 (M^+), 462, 365, 342, 321, 219, 145, 131, 122, 108, 107, 104 and 103, and the starting alcohol (18 mg, 30%).

A solution of the *thiocarbonate* (35 mg, 0.0716 mmol) in diglyme (0.5 ml) was refluxed for 16h. Although t.l.c. indicated that considerable starting material remained, ^{1}H n.m.r. showed that the product was a complex mixture with one major component.

(v) PTSA. A solution of the alcohol (27i) (58 mg) and PTSA (*ca.* 5 mg) in xylene (2 ml) was refluxed for 3 days. T.l.c. showed complete decomposition.

(vi) Phosphorus oxychloride. Phosphorus oxychloride (0.2 ml) was added dropwise to a stirred solution of the alcohol (27i) (107 mg, 0.316 mmol) in pyridine (2 ml) and stirring was continued for 1h. The solution was poured carefully into water (20 ml) and the aqueous solution was acidified and extracted with ether, to give crude product (21 mg) which consisted of a mixture of 5-phenyltetrazole and a small amount of what was probably the chloroethyltetrazole (^{1}H n.m.r.).

Preparation of 1-(cyclohex-1-enyl)5-phenyltetrazole (29f) from cyclohexene.

(i) Cyclohexene (2.09 g, 25.5 mmol) was treated with iodine (8.10 g, 31.9 mmol) and thallous azide[201] (15.72 g, 63.8 mmol) in benzonitrile (75 ml) according to a literature method,[122] to give 1-(2-*iodocyclohexyl*)-5-*phenyltetrazole* (32) (0.757 g, 8%), m.p. 154-5° (from ethanol) (Found: C, 43.85; H, 4.20; N, 15.71. $C_{13}H_{15}IN_4$ requires C, 44.08; H, 4.27; N, 15.82%); ν_{max} 1174, 971, 782, 773, 727, 686, and 661 cm^{-1}; δ 1.2-2.9 (8H, m), 4.3-4.9 (2H, m), and 7.5-7.8 (5H, m); *m/e* 354 (M^+), 227, 199, 147, 131, and 81 (base).

(ii) A solution of the iodide (32) (100 mg, 0.284 mmol) and sodium iodide (43 mg, 0.284 mmol) in HMPA (2.5 ml) was heated at 100° for 24h. Water (20 ml) was added and the solution was extracted with ether (3 x 20 ml). The extracts were washed with water (30 ml), dried with sodium sulphate and concentrated to give 1-(*cyclohex-1-enyl*)-5-*phenyltetrazole* (64 mg, 74%).

3.2.4. Preparation of 2,2-Disubstituted Vinyltetrazoles using Epoxides.

1-(2-*Oxopropyl*)-5-*phenyltetrazole* (33a).

(i) By alkylation with α-chloroacetone. A solution of 5-phenyl-2-tri-*n*-butylstannyltetrazole (26c) (1.06 g, 2.5 mmol) and α-chloroacetone (0.944 g, 10.2 mmol) in benzene (15 ml) was refluxed for 95h. The solution was washed with hydrochloric acid (1M; 10 ml), aqueous sodium hydroxide (1M; 10 ml) and saturated sodium chloride solution (10 ml), dried with magnesium sulphate and evaporated, and the residue was chromatographed on silica gel, to give 2-(2-*oxopropyl*)-5-*phenyltetrazole* (38) (101 mg, 20%), m.p. 133-6° (from dichloromethane/petrol) (Found: C, 59.07; H, 4.91; N, 27.61. $C_{10}H_{10}N_4O$ requires C, 59.40; H, 4.98; N, 27.71%); ν_{max} 1722, 1185, 801, 730, and 688 cm^{-1}; δ 2.23 (3H, s), 5.50 (2H, s), 7.5 (3H, m), and 8.17 (2H, m); *m/e* 202 (M^+), 174, 146, 131 (base), 105, 104, 103, 77, 51 and 43, and 1-(2-*oxopropyl*)-5-*phenyltetrazole* (33a) (158 mg, 31%), m.p. 110.5-2.5° (from dichloromethane) (Found: C, 59.30; H, 4.93; N, 27.69. $C_{10}H_{10}N_4O$ requires C, 59.40; H, 4.98; N, 27.91%); ν_{max} 1727, 1421, 1182, 783, 740, 709, and 700 cm^{-1}; δ 2.26 (3H, s), 5.31 (2H, s), and 7.57 (5H, s); *m/e* 202 (M^+), 160, 104 (base), and 43.

(ii) By alkylation with α-bromoacetone. A solution of the stannyltetrazole (26c) (4.0 g, 9.4 mmol) and bromoacetone[202] (2.58 g, 18.8 mmol) in benzene (50 ml) was refluxed under nitrogen for 26h. The solvent was evaporated and fractional crystallisation from dichloromethane followed by chromatography on silica gel gave 2-(2-*oxopropyl*)-5-*phenyltetrazole* (38) (0.85 g, 50%) and 1-(2-*oxopropyl*)-5-*phenyltetrazole* (33a) (0.29 g, 15%).

(iii) By oxidation of the alcohol (27e). A solution of Jones reagent was prepared by dissolving chromium trioxide (3.5 g, 0.035 mol) in water (25 ml) and cautiously adding concentrated sulphuric acid (3.05 ml).

This chromic acid solution (25.4 ml, 29 mmol) was added dropwise to a stirred solution of 1-(2-hydroxypropyl)-5-phenyltetrazole (27e) (5.93 g, 29.0 mmol) in acetone (150 ml) and stirring was continued for 13h. Water (150 ml) was added and the mixture was extracted with dichloromethane (3 x 70 ml). The extract was washed with a solution of sodium thiosulphate (2 g) in water (50 ml) and with water (50 ml). Drying over magnesium sulphate and evaporation gave 1-(2-*oxopropyl*)-5-*phenyltetrazole* (33a) (5.51 g, 94%), m.p. 105-11°.

1(2-*Oxocyclohexyl*)-5-*phenyltetrazole* (33b). A solution of chromic acid 1.14 M; 5.5 ml) was added dropwise to a stirred solution of the alcohol (27f) (1.80 g, 7.37 mmol) in acetone (40 ml) and stirring was continued for 24h. Water (20 ml) and dichloromethane (40 ml) were added and the layers were separated. The aqueous phase was extracted with chloroform (2 x 20 ml) and the combined extracts were washed with a solution of sodium thiosulphate (2 g) in water (30 ml), and with saturated sodium chloride solution (30 ml), and dried with magnesium sulphate. The solvent was removed to give the *ketone* (33b) (1.77 g, 99%), m.p. 135-8° (from chloroform/petrol) (Found: C, 64.78; H, 5.84; N, 23.44. $C_{13}H_{14}NO$ requires C, 64.45; H, 5.82; N, 23.12%); ν_{max} 1717, 1069, 788, 773, 740, and 690 cm^{-1}; δ 1.6-2.9 (8H, m), 5.16 (1H, dd, *J* 9, 13) and 7.54 (2H,s); *m/e* 242 (M^+), 202, 171, 118, 104 (base), and 103.

Attempted oxidations of tetrazol-1-ethanol (37d).

(i) Jones Reagent. Chromic acid solution (1.14 M; 0.27 ml) was added dropwise to a stirred solution of the alcohol (27d) (54 mg, 0.284 mmol) in acetone (2 ml) and stirring was continued for 40h. Dilution with

water and extraction with chloroform yielded tetrazole-1-acetic acid (45 mg); δ 5.19 (2H, s), 7.60 (5h, br s), and 8.50 (1H, br s), contaminated with some starting material.

(ii) Pyridinium chlorochromate (PCC). A solution of the alcohol (27d) (47 mg, 0.246 mmol) in dichloromethane (0.5 ml) was added to a suspension of pyridinium chlorochromate[124] (80 mg, 0.369 mmol) in dichloromethane (1 ml). After 1 day considerable starting material remained (t.l.c.) and PCC (80 mg, 0.369 mmol) was added. After 3 days, ether (5 ml) was added, the solvent was decanted, and the residue was washed with ether (3 x 2 ml). The solvent was removed to give a product containing many compounds but no aldehyde (^{1}H n.m.r.).

(iii) Pyridinium dichromate (PDC). PDC[125] (600 mg, 1.62 mmol) was added to a stirred solution of the alcohol (27d) (41 mg, 0.216 mmol) in dichloromethane (3 ml) and stirring was continued for 48h. The mixture was filtered through Celite and the solvent was removed to give an oil consisting of a complex mixture (^{1}H n.m.r.).

(iv) Lead tetraacetate (LTA).[126] LTA (222 mg, 0.5 mmol) was added to a stirred solution of the alcohol (27d) (95 mg, 0.5 mmol) in pyridine (2.5 ml) and stirring was continued for 21h. The mixture was poured into hydrochloric acid (1M) and extracted with ether, and the solvent was removed to give a complex mixture possibly containing some acetyl ester of the starting alcohol (^{1}H n.m.r.).

(v) Moffatt oxidation.[127] The alcohol (27d) (50.5 mg, 0.266 mmol) was treated with DMSO (0.4 ml), dicyclohexylcarbodiimide (164.5 mg, 0.797 mmol) and dichloroacetic acid (11 μℓ, 0.133 mmol) according to a literature procedure[127] to give a complex mixture which may have contained a small amount of the desired aldehyde (^{1}H n.m.r.).

(vi) Silver carbonate on Celite. Silver carbonate on Celite[128] (*ca.* 5 mmol) was suspended in a solution of the alcohol (27d) (94 mg, 0.50 mmol) in benzene (30 ml), benzene (*ca.* 3 ml) was distilled off, and the mixture was refluxed for 24h. The reagent was filtered off and the solvent was removed, to give starting material (99 mg).

1-(2-Hydroxy-2-methylcyclohexyl)-5-phenyltetrazole (36). A solution of the Grignard reagent was made from iodomethane (2.10 g, 14.8 mmol) and magnesium turnings (300 mg, 12.3 mmol) in ether (14 ml) in the usual way. A solution of 1-(2-oxocyclohexyl)-5-phenyltetrazole (33b) (1.50 g, 6.19 mmol) in benzene (80 ml) was added dropwise to the stirred solution of the Grignard reagent and the solution was refluxed for 3h. It was poured into water (100 ml) and acidified with hydrochloric acid (1M). The organic layer was separated and the aqueous was extracted with dichloromethane (3 x 50 ml). The extract was washed with water (50 ml) dried over sodium sulphate, evaporated, and chromatographed on silica gel to give 1-(2-(R,S)-*hydroxy*-2-*methylcyclohex*-1(S,R)-*yl*)*phenyltetrazole* (36a) (1.318 g, 77%), m.p. 99-101° (from chloroform/petrol)(Found: C, 65.00; H, 7.04; N, 21.83. $C_{14}H_{18}N_4O$ requires C, 65.09; H, 7.02; N, 21.69%); ν_{max} 3480, 1283, 1176, 1099, 1008, 963, 784, 703, and 699 cm^{-1}; δ 0.84 (3H, s), 1.1-2.7 (8H, m), 3.73 (1H, d, *J* 3), 4.32 (1H, dd, *J* 4, 15) and 7.63 (5H, s); *m/e* 258 (M^+), 243, 215, 173 (base), 160, 147, 104, and 43, and 1-(2(R,S)-*hydroxy*-2-*methylcyclohex*-1(R,S))-5-*phenyltetrazole* (36b) (233 mg, 10%), m.p. 155-8° (from chloroform/petrol)(Found: C, 64.83; H, 6.99; N, 21.69. $C_{14}H_{18}N_4O$ requires C, 65.09; H, 7.02; N, 21.69%); ν_{max} 3360, 1398, 1168, 936, 883, 783, 741, and 700 cm^{-1}; δ 1.15-2.43

(8H, m), 1.55 (3H, s), 3.76 (1H, br s), 4.41 (1H, dd, *J* 3,12), 7.31-7.64 (3H, m), and 7.67-7.95 (2H, m); *m/e* 258 (M^+), 229, 215, 173 (base), 160, and 104, and starting material (69 mg, 5%).

Dehydration of 1-(2-hydroxy-2-methylcyclohexyl)-5-phenyltetrazole (36).

(i) (36a). Phosphorus oxychloride (5 ml) was added to a well-stirred solution of the alcohol (36a) (741 mg, 2.87 mmol) in pyridine (10 ml) and stirring was continued for 1.5h. The mixture was poured CAREFULLY into ice-water (100 ml) and extracted with ether (3 x 30 ml). The extracts were washed with water (30 ml) and dried over magnesium sulphate. The solvent was removed and the residue was chromatographed on silica gel, to give 1-(2-*methylcyclohex*-1-*enyl*)-5-*phenyltetrazole* (37a) (132 mg, 19%), m.p. 81-2.5° (from chloroform/petrol) (Found: C, 70.03; H, 6.70; N, 23.35. $C_{14}H_{16}N_4$ requires C, 69.97; H, 6.70; N, 23.35%); ν_{max} 1400, 1283, 1187, 788, 736 and 702 cm^{-1}; λ_{max} 237 (12000) nm; δ 1.36 (3H, s), 1.6-2.15 (8H, m), 7.48-7.75 (3H, m), and 7.79-8.05 (2H, m); *m/e* 240 (M^+), 212, 211, 197, 184, 144 (base), 118, 117, 104, 95 and 77, and 1-(2-*methylcyclohex*-2-*enyl*)-5-*phenyltetrazole* (40) (337 mg, 49%), m.p. 65-8° (from chloroform/petrol)(Found: C, 69.78; H, 6.71; N, 23.25. $C_{14}H_{16}N_4$ requires C, 69.97; H, 6.71; N, 23.31%); ν_{max} 1394, 1157, 970, 799, 779, 738, and 703 cm^{-1}; δ 1.37 (3H, s), 1.5-2.45 (6H, m), 4.93-5.20 (1H, m), 5.87 (1H, m), and 7.65 (5H, s); *m/e* 241, 240 (M^+), 169, 156, 147, 95, 94 (base) and 79, which was contaminated with a small amount of 1-(2-*methylenecyclohexyl*)-5-*phenyltetrazole* (41).

(ii) (36b). Phosphorus oxychloride (1.5 ml) was added to a stirred solution of the alcohol (36b) (234 mg, 0.905 mmol) in pyridine (3 ml) and stirring was continued for 3h. The mixture was poured CAREFULLY into ice-water (50 ml) and extracted with ether (3 x 15 ml). The extracts were washed with water (15 ml) and dried over magnesium sulphate. The solvent was removed and the residue was chromatographed on silica gel, to give an oil (59 mg, 27%), which consisted of a mixture of (41) and (40) in the ratio of *ca.* 2:1 as determined by the integration of the multiplets at δ 4.05 and δ 4.97 relative to those at δ 4.85 and δ 5.87.

Isomerisation of the allyltetrazoles (40) and (41).

(i) PTSA. A solution of the allyltetrazole (40) (66 mg, 0.275 mmol) and PTSA (*ca.* 50 mg) in xylene (3 ml) was heated at 90°, under nitrogen for 12h. T.l.c. showed clean conversion into one higher R_f product. The solvent was removed to give 2-(2-*methylcyclohex*-2-*enyl*)-5-*phenyltetrazole* (42), as an oil; δ 1.2-2.5 (6H, m), 1.54 (3H, s), 5.43 (1H, m), 5.93 (1H, m), 7.4-7.7 (3H, m), 8.1-8.35 (2H, m).

(ii) Rhodium(III) chloride.[134] A solution of the allyltetrazole (40) (48.5 mg, 0.202 mmol), triethylamine (14.6 μℓ, 0.202 mmol) and rhodium(III) chloride trihydrate (3.7 mg, 0.014 mmol) in a mixture of water (0.1 ml) and ethanol (0.9 ml) was refluxed for 12h. The solvent was removed. T.l.c. and ^{1}H n.m.r. showed the product to consist of starting material and a small amount of the 2-allyltetrazole (42).

(iii) Potassium amide on alumina.[130] Ammonia (5 ml) was condensed, at -78° under nitrogen into a flask containing dried alumina H (600 mg). Potassium (80 mg) was added with stirring to give a deep blue solution.

After 5 min a few crystals of ferric nitrate nonahydrate were added and the suspension became colourless. The ammonia was evaporated by stirring at room temperature under nitrogen. A solution of the allyltetrazoles (40) and (41) (in the ratio of *ca.* 4:1) (186 mg, 0.773 mmol) in dry ether (3 ml) was added with stirring, causing the alumina to become brown, and the mixture was stirred for 5h. The catalyst was filtered off and washed with ether. The solvent was evaporated to give 1-(2-*methyl*-*cyclohex*-1-*enyl*)-5-*phenyltetrazole* (37a) (136 mg, 73%) as a colourless solid.

3.2.5. Preparation of enamides.

N-(i-*But*-1-*enyl*) *formamide* (43a). A solution of *iso*-butyraldehyde (4.60 ml, 50 mmol), formamide (1.0 ml, 25 mmol) and PTSA (*ca.* 250 mg) in benzene (300 ml) was refluxed in a Dean and Stark apparatus for 21h. The mixture was filtered, the solvent was removed, and the residue was chromatographed on alumina, to give the *enamide* (43a) (1.77 g, 71%) as a liquid (Found: M^+, 99.0683. C_5H_9NO requires M 99.0684); ν_{max} 3280, 1654, 1416, 1386, 1035 and 847 cm^{-1}; δ 1.67 (6H, br s), 6.09 (0.17H, br d, J 11), 6.50 (0.83H, br d, J 11), 8.02 (0.83H, d, J 2), 8.16 (0.13H, d, J 11) 9.05 (1H, br d, J 11); *m/e* 99 (M^+, base), 70, 56, and 43.

N-(*i*-But-1-enyl)acetamide (43b).[136] Acetamide (2.96 g, 50 mmol) was condensed with *iso*-butyraldehyde (9.19 ml, 100 mmol) as for (43a), to give the enamide (43b) (4.45 g, 79%).

N-(*i*-But-1-enyl)benzamide (43c).[136] Benzamide (8.40 g, 69.3 mmol) was condensed with *iso*-butyraldehyde (12.7 ml, 139 mmol) as for (43a), to give the enamide (11.1 g, 91%) after chromatography on silica gel.

N-(*2,6-Dimethylcyclohex-1-enyl)benzamide* (43d). A solution of 2,6-dimethylcyclohexanone (5.0 g, 39.6 mmol), benzamide (12.0 g, 99 mmol), and PTSA (500 mg) in toluene (50 ml) was refluxed, under nitrogen, in a Dean and Stark apparatus, for 27h. The solvent was removed and the residue was washed with hot ether until all of the enamide had been extracted. The ether was evaporated and the product was chromatographed on silica gel and then recrystallised from benzene/petrol, to give the *enamide* (4.87 g, 54%), m.p. 159-61° (from benzene/petrol) (Found: C, 78.36; H, 8.38; N, 6.08. $C_{15}H_{19}NO$ requires, C, 78.56; H, 8.35; N, 6.11%); ν_{max} 3295, 1641, 1480, 1522, 1488, 1292, 709, and 692 cm^{-1}; δ 1.02 (3H, d, *J* 8), 1.2-1.8 (7H, m), 1.64 (3H, s), 7.13 (1H, br s, exch. D_2O), 7.3-7.6 (3H, m), and 7.75-8.0 (2H, m); *m/e* 229 (M^+), 214, 187, 124, 105 (base), 77.

3.2.6. Preparation of alkenyltetrazoles from enamides.

1-(i-*But-1-enyl)tetrazole* (37b). A solution of *p*-toluenesulphonyl chloride (3.71 g, 19.5 mmol) in carbon tetrachloride (25 ml) was added slowly to a stirred solution of the enamide (43a) (1.931 g, 19.48 mmol) and pyridine (3.15 ml, 39 mmol) in carbon tetrachloride (25 ml) at 4° under nitrogen, and stirring at 4° was continued for 15h. The mixture was filtered and an ethereal solution of hydrazoic acid [prepared from sodium azide (7.60 g, 117 mmol) and concentrated sulphuric acid (20 ml) in water (75 ml) and ether (150 ml) according to a literature procedure[160]] was added to the

solution of isonitrile. After refluxing for 30h, hydrochloric acid (4M, 30 ml) was added and the mixture was stirred vigorously for 6h in order to hydrolyse the enamide. The layers were separated, the aqueous was extracted with chloroform (4 x 30 ml), the extracts were dried with magnesium sulphate, the solvent was removed, and the residue was chromatographed on silica gel to give the *tetrazole* (37b) (994 mg, 41%), b.p. 90° at 0.5 mbar (Found: M^+, 124.0749. $C_5H_8N_4$ requires M 124.0749); ν_{max} 3135, 1474, 1183, 1092, 1012, 962, 803, and 663 cm^{-1}; λ_{max} 228 (5000) nm; δ ($CC\ell_4$) 1.82 (3H, d, J 1), 1.97 (3H, d, J 1), 6.89 (1H, m), and 8.93 (1H, s); *m/e* 124 (M^+), 95, 81, 69, 68, 55, 54, 42 (base), 41 and 39.

1-(i-*But*-1-*enyl*)-5-*methyltetrazole* (37c).

(i) Thionyl chloride in refluxing benzene. A solution of the enamide (43b) (161 mg, 0.42 mmol) and thionyl chloride (0.206 ml, 2.84 mmol) in benzene (2 ml) was refluxed for 12h. The solvent was removed to give a complex mixture (^{1}H n.m.r.).

(ii) Phosphorus pentachloride - quinoline complex.[144] Phosphorus pentachloride (229 mg, 1.1 mmol) was dissolved in warm, ethanol free, chloroform (3 ml) and quinoline (02.59 ml, 2.2 mmol) was added causing rapid precipitation of a colourless solid complex. After cooling the mixture, the enamide (43b) (95 mg, 0.84 mmol) was added with stirring, and the mixture rapidly became homogeneous. After stirring for 4h the solvent was removed and ^{1}H n.m.r. showed the product to consist mostly of one product. THF (4 ml) was added and the suspension was filtered. The solvent was removed but only starting material was present (^{1}H n.m.r.).

The procedure was repeated in deuterochlorofom and ^{1}H n.m.r. showed that the same intermediate as before was formed rapidly, but an attempt to convert it to the imidate by adding methanol gave an unstable product which was not the imidate and was not identified.

(iii) Phosphorus pentachloride. Phosphorus pentachloride (6.76 g, 32.5 mmol) was added over 10 min to a stirred solution of the enamide (43b) (3.34 g, 29.5 mmol) in benzene (30 ml) and stirring was continued for 30 min. The solvent was removed on a water pump at room temperature and the enimidoyl chloride was dissolved in DMF (20 ml). The solution was added dropwise to a well-stirred, ice-cooled, suspension of sodium azide (3.42 g, 52.6 mmol) in DMF (20 ml), and stirring was continued for 1h. Water (200 ml) was added and the mixture was extracted with chloroform (4 x 50 ml). The extracts were dried over magnesium sulphate, the solvent was removed, and the crude was chromatographed on silica gel to give the *alkenyltetrazole* (37c) (2.04 g, 50%), m.p. 41-3° (from benzene/petrol)(Found: C, 51.98; H, 7.27; N, 41.07. $C_6H_{10}N_4$ requires C, 52.16; H, 7.29; N, 40.55%); ν_{max} 1522, 1419, 1343, 1274, 1266, 1124, 1087, 1063, 819, 810, 704, and 680 cm^{-1}; λ_{max} 215 (3400) nm; δ 1.77 (3H, d, *J* 2), 2.08 (3H, d, *J* 2), 2.59 (3H, s), and 6.65 (1H, m); *m/e* 139,138 (M^+), 109, 95, 83, 69, 68, 55, 42 (base), and 41.

1-(i-*But*-1-*enyl*)-5-*phenyl tetrazole* (37d).

(i) Phosphorus oxychloride-quinoline complex.[144] Phosphorus pentachloride (256 mg, 1.23 mmol) was dissolved in chloroform (3.5 ml) and quinoline (0.29 ml, 2.46 mmol) was added to form the complex which precipitated. The enamide (43c) (196 mg, 1.12 mmol) was added with stirring and the complex dissolved immediately. T.l.c. indicated that only starting material was present after stirring at room temperature for 47h and at

50° for 24h. The solvent was removed, THF (4 ml) was added, and the suspension was filtered. The solvent was removed to give a mixture which did not contain any imidoyl chloride (^{1}H n.m.r.).

(ii) Oxalyl Chloride.[145] Oxalyl chloride (65 μℓ, 0.74 mmol) was added dropwise to a stirred solution of the enamide (43c) (118 mg, 0.673) in acetonitrile (2 ml), gas evolution occurred immediately. Stirring was continued for 1.5h and the solvent was removed. ^{1}H n.m.r. showed the residue to consist mostly of one unknown compound. Treatment with sodium azide in DMF gave no tetrazole by t.l.c.

(iii) Thionyl chloride. A solution of the enamide (43c) (2.67 g, 15.2 mmol) and thionyl chloride (2.21 ml, 30.5 mmol) in benzene (10 ml) was refluxed for 30h. The solvent was removed, and the residue was dissolved in DMF (10 ml) and added dropwise to a well-stirred, ice-cooled suspension of sodium azide (2.96 g, 45.6 mmol) in DMF (10 ml). Stirring was continued at room temperature for 4h and the mixture was poured into water (200 ml). It was extracted with ether (3 x 50 ml) and dried over magnesium sulphate. The solvent was removed and the residue chromatographed on silica gel, to give the *alkenyltetrazole* (37d) (1.36 g, 45%), m.p. 66–7° (from chloroform/petrol) (Found: C, 66.16; H, 6.04; N, 28.18. $C_{11}H_{12}N_4$ requires C, 65.98; H, 6.04; N, 27.98%); ν_{max} 1413, 1278, 1107, 814, 809, 775, 729 and 698 cm^{-1}; λ_{max} 238 (12300) nm; δ 1.65 (3H, d, *J* 2), 1.99 (3H, d, *J* 2), 6.69 (1H, m), 7.4–7.75 (3H, m), and 7.75–8.05 (2H, m); *m/e* 201 (M^+ + 1), 172, 145, 130, 104, 103, 85, 83, 77, 76, and 47 (base).

Attempted conversion of *N*-2,6-dimethylcyclohex-1-enylbenzamide into the tetrazole.

(i) Using oxalyl chloride.[145] Oxalyl chloride (30 μℓ, 0.336 mmol) was added dropwise to a stirred suspension of the enamide (43d) (70 mg, 0.301 mmol) in acetonitrile (2 ml) at -20°. After stirring for 10 min the mixture became homogeneous and gas evolution ceased, and sodium azide (60 mg, 0.923 mmol) was added. The mixture was stirred at room temperature for 2h but t.l.c. showed that no tetrazole was formed.

(ii) Using thionyl chloride. A solution of the enamide (43d) (203 mg, 0.885 mmol) and thionyl chloride (0.385 ml, 5.31 mmol) in benzene (4 ml) was refluxed under nitrogen for 2.25h. The solvent and excess of thionyl chloride were removed and the residue was chromatographed on silica gel to give *N*-(2,6-dimethylphenyl) benzamide (50 mg, 25%), m.p. 160-2° (from benzene) (lit.,[203] 163-4°), identical by i.r. with an authentic sample.

1-(2,6-Dimethylcyclohex-1-enyl)-5-phenyltetrazole (37e).

(i) A suspension of the enamide (43d) (2.26 g, 9.86 mmol) in a solution of methyl fluorosulphonate (2.39 ml, 29.6 mmol) in benzene (30 ml) was stirred at room temperature for 105h. Triethylamine (5.5 ml, 39.4 mmol) was added dropwise and the mixture was stirred for 30 min. The benzene layer was separated and concentrated and the residue was chromatographed on silica gel to give *methyl* N-(2,6-*dimethylcyclohex*-1-*enyl*)*benzimidate* (47) (1.59 g, 66%), as an oil; ν_{max} 1676, 1447, 1274, 1109, 977 and 695 cm^{-1}; δ ($CC\ell_4$) 1.00 (3H, d, *J* 7), 1.2-2.2 (7H, m), 1.36 (3H, s), 3.82 (3H, s), 7.08-7.4 (3H, m), and 7.46-7.68 (2H, m).

(ii) A suspension of sodium azide (0.93 g, 14.3 mmol) in a solution of the imidate (47) (1.16 g, 4.77 mmol) in acetic acid (10 ml) was stirred at room temperature for 48h. It was basified by addition of aqueous sodium hydroxide (4M) and was extracted with dichloromethane (3 x 30 ml). The extracts were washed with saturated aqueous sodium chloride solution (30 ml) and dried with magnesium sulphate. The solvent was removed and the residue was chromatographed on silica gel, to give 1-(2,6-*dimethylcyclohex-1-enyl*)-5-*phenyltetrazole* (37e) (158 mg, 13%), m.p. 83-5° (from chloroform petrol) (Found: C, 71.24; H, 7.20; N, 22.18. $C_{15}H_{18}N_4$ requires (C, 70.84; H, 7.13; N, 22.03%); ν_{max} 1401, 1272, 1093, 972, 781, 739 and 697 cm^{-1}; λ_{max} 238 (12300) nm; δ 0.80 (3H, d, *J* 7), 1.2-1.8 (10H, m), 7.4-7.7 (3H, m), and 7.81-8.1 (2H, m); *m/e* 255, 254 (M^+), 226, 211, 144 (base), and 104, and starting enamide (43d) (320 mg, 28%).

3.2.7. Reaction of stannyltetrazoles (26) with acetylenic esters. Reaction of (26c) with methyl propiolate. (i) A solution of 5-phenyl-2-tributylstannyltetrazole (26c) (3.04 g, 7.15 mmol) and methyl propiolate (0.954 ml, 10.7 mmol) in benzene (9 ml) was refluxed under nitrogen for 30h. The solvent and excess of propiolate were removed and the residue was dissolved in ether (25 ml). The solution was saturated with hydrogen chloride, after 3h the solvent was removed, and the residue was chromatographed on silica gel, to give trans-*methyl* 2-(5-*phenyltetrazol-2-yl*)*acrylate* (48a) (222 mg, 14%), m.p. 144.5-5.5° (from chloroform/petrol) (Found: C, 57.13; H, 4.34; N, 24.18. $C_{11}H_{10}N_4O_2$ requires C, 57.39; H, 4.38; N, 24.34%); ν_{max} 1712, 1644, 1311, 1174, 938, 837 and 737 cm^{-1}; δ 3.88 (3H, s), 6.94 (1H, d, *J* 14), 7.44-7.64 (3H, m), 8.08-8.30 (2H, m),

and 8.40 (1H, d, *J* 14); *m/e* 202 (M^+ - 28), 171, and 104, cis-*methyl* 2-(5-*phenyltetrazol*-2-*yl*)*acrylate* (48b) (195 mg, 12%), m.p. 73-5° (from chloroform/petrol) (Found: C, 57.42; H, 4.33; N, 24.34. $C_{11}H_{10}N_4O_2$ requires C, 57.39; H, 4.38; N, 24.34%); ν_{max} 1727, 1668, 1252, 1223, 1204, 989, 923, 833, 732, and 693 cm^{-1}; δ 3.88 (3H, s), 6.12 (1H, d, *J* 12), 7.42-7.65 (4H, m), and 8.07-8.30 (2H, m); *m/e* 230 (M^+), 202, 171, 104 and 103, trans-*methyl* 2-(5-*phenyltetrazol*-1-*yl*)*acrylate* (29i) (577 mg, 35%), m.p. 94.5-6° (from chloroform/petrol) (Found: C, 57.21; H, 4.33; N, 24.20. $C_{11}H_{10}N_4O_2$ requires C, 57.39; H, 4.38; N, 24.34%); ν_{max} 1706, 1661, 1326, 1269, 1202, 953, 777 and 702 cm^{-1}; λ_{max} 253 (16600), 218 (13500) nm; δ 3.87 (3H, s), 7.01 (1H, d, *J* 13), 7.55-7.85 (5H, m), and 7.99 (1H, d, *J* 13); *m/e* 230 (M^+), 201, 171 (base), 144, 133, 104, 103 and 77, and cis-*methyl* 2-(5-*phenyltetrazol*-1-*yl*)*acrylate* (29j), as an oil (Found: M^+, 230.0807. $C_{11}H_{10}N_4O_2$ requires *M*, 230.0804); ν_{max} 1725, 1662, 1457, 1437, 1228, 1175, 829, 778 and 697 cm^{-1}; λ_{max} 239 (14400), 223 (14200) nm; δ 3.66 (3H, s), 6.32 (1H, d, *J* 9), 7.27 (1H, d, *J* 9), and 7.4-8.0 (5H, m); *m/e* 230 (M^+), 201, 171, 144, 104, 103, and 77 (base).

(ii) In a similar reaction of (26c) (561 mg, 1.32 mmol) and methyl propiolate (111 mg, 1.32 mmol) the protonolysis with hydrogen chloride was stopped after *ca.* 10 min and chromatography on silica gel then yielded, in addition to (29i), (29j), (48a), and (48b), *methyl* 2-(5-*phenyltetrazol*-2-*yl*)-1-*tri*-n-*butylstannylacrylate*, δ ($CC\ell_4$) 0.6-2.0 (27H, m), 3.85 (3H, s), 7.43-7.66 (3H, m), 8.07-8.36 (2H, m), and 8.56 (1H, s), and *methyl* 2-(5-*phenyltetrazol*-1-*yl*)-1-*tri*-n-*butylstannylacrylate*, δ ($CC\ell_4$) 0.6-2.1 (27H, m), 3.82 (3H, s), 7.45-7.95 (5H, m), and 8.13 (1H, s).

Reaction of (26a) with methyl propiolate. A solution of tetrazole (500 mg, 7.14 mmol) and tri-*n*-butylstannyl oxide (2.13 g, 3.57 mmol) in ethanol (5 ml) was refluxed for 1h. The solvent was removed and the stannyl-tetrazole (26a) was dissolved in benzene (10 ml). Methyl propiolate (0.953 ml, 10.71 mmol) was added and the solution was refluxed under nitrogen for 23h. The solvent and excess of acetylene were removed and the residue was dissolved in ether (10 ml). The solution was saturated with hydrogen chloride, and after 2h the solvent was removed. The residue was washed with petrol (30 ml) at -20° and the crude product was chromatographed on silica gel, to give trans-*methyl 2-(tetrazol-2-yl)acrylate* (48c) (223 mg, 20%), m.p. 111.5-2.5° (from chloroform/petrol)(Found: C, 39.04; H, 3.88; N, 36.44. $C_5H_6N_4O_2$ requires C, 38.96; H, 3.92; N, 36.35%); ν_{max} 1720, 1666, 1332, 1182, 980, 939 and 707 cm^{-1}; δ 3.93 (3H, s), 7.01 (1H, d, *J* 14), 8.48 (1H, d, *J* 14), and 8.72 (1H, s); *m/e* 154 (M^+), 125, 99, 95 and 68 (base), and cis-*methyl 2-(tetrazol-2-yl)acrylate* (48d) (227 mg, 21%), m.p. 45-6° (from chloroform/petrol) (Found: C, 38.95; H, 3.89; N, 36.37. $C_5H_6N_4O_2$ requires C, 38.96; H, 3.92; N, 36.35%); ν_{max} 1727, 1672, 1246, 1223, 1199, 1124, 1024, 990, 907, 839, 768 and 707 cm^{-1}; δ 3.87 (3H, s), 6.24 (1H, d, *J* 10), 7.63 (1H, d, *J* 10) and 8.67 (1H, s); *m/e* 155 ($M^+ + 1$) 126, 122, 99, 95, and 68 (base), and cis-*methyl 2-(tetrazol-1-yl)acrylate* (29k), m.p. 35-7° (from chloroform/petrol) (Found: C, 39.08; H, 3.89; N, 35.91. $C_5H_6N_4O_2$ requires C, 38.96; H, 3.92; N, 36.35%); ν_{max} 237 (8900) nm; δ 3.88 (3H, s), 6.16 (1H, d, *J* 11), 7.75 (1H, d, *J* 11), and 10.12 (1H, s); *m/e* 155 ($M^+ + 1$), 122, 95 (base), 94, 68, 67, 59, 53 and 40.

Reaction of (26c) with DMAD. A solution of (26c) (4.25 g, 10 mmol) and DMAD (1.85 g, 13 mmol) in benzene (30 ml) was refluxed under nitrogen for 38h. The solvent and excess of DMAD were removed and the residue was dissolved in a saturated solution of hydrogen chloride in ether (25 ml). After 1h the mixture was filtered to give 5-phenyltetrazole (230 mg, 16%). The solvent was removed and the product was chromatographed on silica gel, to give *dimethyl 5-phenyltetrazol-2-ylfumarate* (48f) (281 mg, 12%), m.p. 92-94° (from chloroform/petrol)(Found: C, 54.51; H, 4.19; N, 19.57. $C_{13}H_{12}N_4O_4$ requires C, 54.17; H, 4.20; N, 19.44%); ν_{max} 1749, 1717, 1650, 1208, 1161, 981, 886, 742, 733, 721, and 703 cm^{-1}; δ 3.88 (3H, s), 4.12 (3H, s), 7.04 (1H, s), 7.45-7.63 (3H, m), and 8.1-8.35 (2H, m); *m/e* 288 (M^+), 260 (base), 229, 197, 172, 129, 118, 103, and 82, and *dimethyl 5-phenyltetrazol-2-ylmaleate* (48) (193 mg, 8%); δ 3.67 (3H, s), 3.92 (3H, s), 7.36 (1H, s), 7.4-7.64 (3H, m), and 8.1-8.35 (2H, m), which was contaminated with some by-products and could not be purified, and an inseparable mixture of *dimethyl 5-phenyltetrazol-1-ylmaleate* and *dimethyl 5-phenyltetrazol-1-ylfumarate* (29ℓ) (1.919 g, 79%) (Found: M^+, 288.0850 $C_{13}H_{12}N_4O_4$ requires *M*, 288.0858); ν_{max} 1736, 1655, 1437, 1260, 1202, 1014, 892, 778, 727, and 697 cm^{-1}; λ_{max} 231 nm; the ^1H n.m.r. spectrum consisted of the superimposition of two spectra: δ 3.57 (3H, s), 3.91 (3H, s), 6.92 (1H, s), and 7.45-7.85 (5H, m) [ascribed to the *fumarate*] and δ 3.66 (3H, s), 3.78 (3H, s), 7.37 (1H, s), and 7.45-7.85 (5H, m) [ascribed to the *maleate*]; *m/e* 288 (M^+), 260, 259, 229, 202, 201, 145, 134 (base), 133, 104 and 103.

Reaction of (26c) with ethyl phenylpropiolate. A solution of (26c) (5.10 g, 12 mmol) and ethyl phenylpropiolate (3.14 g, 18 mmol) in xylene (15 ml) was refluxed under nitrogen for 3 days. The solvent was removed and the residue was dissolved in chloroform (25 ml). The solution was saturated with hydrogen chloride and after 12h the precipitate was filtered off and recrystallised twice from ethanol/water to give ethyl 3,5-diphenylpyrazole-4-carboxylate (49) (450 mg, 13%), m.p. 139-41° (lit.,[153] 141-2°); ν_{max} 3220, 1703, 1376, 1136, 971, 763, and 698 cm^{-1}; δ 1.01 (3H, t, *J* 1), 4.11 (2H, q, *J* 7) and 7.17-7.62 (5H, m); *m/e* 292 (M^+), 247 (base), 220, 105 and 77. The filtrate and the mother liquors were combined, washed with aqueous hydroxide, concentrated, washed with petrol, and chromatographed on silica gel, to give further pyrazole (49) (900 mg, 26%).

Hydrolysis and decarboxylation of (49).[153] A solution of the pyrazole-carboxylate (49) (150 mg, 0.51 mmol) in 80% sulphuric acid (0.5 ml) was heated at 110° for 6h. After cooling it was added to water (10 ml) and stirred for 30 min to give a suspension of a colourless solid. The precipitate was filtered off, washed with water and extracted with chloroform. The extracts were dried over magnesium sulphate and the solvent was removed, to give 3,5-diphenylpyrazole (50) (100 mg, 90%), m.p. 198-202° (from methanol/chloroform/petrol) (lit.,[153] 199-200°); ν_{max} 971, 750 and 685 cm^{-1}, which was identical with a sample prepared by independent synthesis.

Independent synthesis of 3,5-diphenylpyrazole (50). A solution of dibenzoylmethane (200 mg, 0.89 mmol) and hydrazine hydrate (600 mg, 12 mmol) in ethanol (4 ml) was refluxed for 5 min, during which it changed

from red to colourless. Water (5 ml) was added, the mixture was allowed to cool, and the precipitate was filtered off and dried, to give 3,5-diphenylpyrazole, m.p., 199-201°.

Thermolysis of *trans*-methyl 2-(5-phenyltetrazol-1-yl)acrylate (48a). A solution of the acrylate (48a) (56 mg, 0.24 mmol) in xylene (1 ml) was refluxed under nitrogen for 1.5h. The solvent was removed and the residue was chromatographed on silica gel, to give methyl 2-phenylpyrazole-3-carboxylate (55) (19.4 mg, 39%) m.p. 113-5° (from chloroform/petrol) (lit.,[204] 111.5-2.5°); δ 3.80 (3H, s), 7.30-7.85 (6H, m), and 7.98 (1H,s).

3.3. Photolysis of 1-Alkenyltetrazoles.

General Procedure. Solutions of the tetrazoles in the solvents specified (75-150 ml per 1 mmol of tetrazole) were irradiated with light of 254 nm wavelength, in quartz vessels, with nitrogen passing through the solution as described in Section 3.1. Irradiation was continued until no tetrazole remained (t.l.c.) (the durations are given for comparison purposes) and the imidazoles were isolated as described below. No attempt was made to identify minor (< 5%) by-products.

1-Vinyltetrazole (29a). A solution of (29a) (191 mg, 1.99 mmol) in ethanol (150 ml) was irradiated for 40 min. The solvent was removed and the residue was distilled at 75° at 0.33 mmHg to give imidazole (57a) (43.6 g, 32%), m.p. 86-9° (lit.,[205] 88-9°).

trans-1-(Prop-1-enyl)tetrazole (29b). A solution of (29b) (222 mg, 2.02 mmol) in ethanol (150 ml) was irradiated for 1h. The solvent was removed and the residue was chromatographed on alumina, to give 4-methylimidazole (57b) (103 mg, 62%), m.p. 53-5° (after distillation) (lit.,[206] 56°).

cis-1-(2-Ethoxycarbonylethenyl)tetrazole (29k). A solution of (29k) (54 mg, 0.35 mmol) in ethanol (25 ml) was irradiated for 2.5h. The solvent was removed and ^{1}H n.m.r. of the residue showed it to be a complex mixture containing only a small amount (< 10%) of the imidazole (57k).

trans-1-(Prop-1-enyl)-5-methyltetrazole (29c). A solution of (29c) (293 mg, 2.36 mmol) in water (10 ml) was irradiated for 3.5h. The solvent was evaporated and the residue was chromatographed on alumina, to give 2,4-dimethylimidazole (57c) (165.5 mg, 73%), m.p. 88-91° (from chloroform/petrol) (lit.,[206] 92°).

5-Phenyl-1-vinyltetrazole (29d). A solution of (29d) (102 mg, 0.592 mmol) and TFA (0.114 ml, 1.48 mmol) in ethanol (40 ml) was irradiated for 2.5h. The solvent was removed and the residue was chromatographed on alumina, to give 2-phenylimidazole (57d) (52 mg, 61%), m.p. 138-48° (lit.,[207] 148-9°).

trans-1-(Prop-1-enyl)-5-phenyltetrazole (29e). A solution of (29e) (408 mg, 2.19 mmol) in petrol (175 ml) was irradiated for 4.25h. The precipitate was filtered off, washed with petrol, and sublimed at 140° at 2 mmHg, to give 4-methyl-2-phenylimidazole (57e) (229 mg, 66%), m.p., 180-3° (lit.,[208] 181-2°).

1-(Cyclohex-1-enyl)-5-phenyltetrazole (29f). A solution of (29f) (71 mg, 0.312 mmol) in petrol (40 ml) was irradiated for 6h. The precipitate was filtered off and washed with petrol to give 2-phenyl-4,5-tetramethyleneimidazole (57f) (40 mg, 64%), m.p. 295-7° (lit.,[209] 298°). The petrol was evaporated and the residue was chromatographed on alumina, to give 1a,1,2,3,4,4a-*hexahydro-tetrazolo*[1,5-d]*phenanthridine* (59a) (8.5 mg, 12%), m.p. 148-50° (from chloroform/petrol) (Found: C, 68.74; H, 6.26; N, 24.71. $C_{13}H_{14}N_4$ requires C, 69.00; H, 6.24; N, 24.76%); ν_{max} 1611, 1544, 785, 771, 744, 724 and 700 cm^{-1}; δ (250 MHz), 1.45-1.7 (3H, m), 1.7-1.95 (1H, m), 1.95-2.17 (2H, m), 2.5-2.7 (2H, m), 2.7-2.9 (1H, m), 2.2-3.1 (2H, m), 2.92 (1H, ddd, *J* 3.8, 11.3, 12.7), 7.3-7.6 (3H, m), and 8.04-8.12 (1H, m); δ_c 23.8 (t), 25.0 (t), 26.6 (t), 29.2(t), 42.4 (d), 59.5 (d), 121.4 (s), 124.6 (d), 125.8 (d), 127.9 (d), 131.9 (d), 137.5 (s), and 150.6 (s); *m/e* 226 (M^+, base), 197, 169, 141, 129 and 115.

trans-1-(2-Phenylethenyl)-5-phenyltetrazole (29g). A solution of (29g) (256 mg, 1.03 mmol) in petrol (350 ml) was irradiated for 3h. The solvent was removed and the residue was chromatographed on silica gel, to give 2,4-diphenylimidazole (57h) (150 mg, 66%), as noted previously[210,211] the m.p. varied with the solvent of recrystallisation but a good correlation with the literature values could not be obtained. A sample was prepared according to the literature method,[210] and was identical with the photolysate by i.r.

1-(2-Phenylethenyl)-5-phenyltetrazole (29h). A solution of the tetrazole (248 mg, 1.00 mmol) in ethanol (75 ml) was irradiated for 3h. The solvent was removed and the residue was dissolved in chloroform (20 ml) and

extracted with hydrochloric acid (1M, 2 x 10 ml). The insoluble hydrochloride was filtered off and washed with water. It was suspended in water (10 ml) and the solution was basified by addition of 10% aqueous sodium hydroxide. It was extracted with chloroform (3 x 10 ml) and the extracts were washed with water (10 ml) and dried over magnesium sulphate. The solvent was removed to give 2,4-diphenylimidazole (57g) (83 mg, 38%). The chloroform solution was evaporated to dryness, the residue was dissolved in ether (5 ml), and a saturated solution of hydrogen chloride in ether (5 ml) was added to give a precipitate which was filtered off and washed with ether. It was dissolved by shaking with a mixture of chloroform (10 ml) and sodium hydroxide solution (1M, 5 ml). The extract was washed with water (5 ml) and dried with magnesium sulphate, and the solvent was removed to give 1-amino-3-phenylisoquinoline (62) (47 mg, 21%), m.p. 97.5-9° (from chloroform/petrol) (lit.,[212] 99.0-99.5°); ν_{max} ($CHC\ell_3$) 3520, 3410, 2935, 1623, 1612, 1567, and 1414; δ (250 MHz) 5.23 (1H, br s, exch. D_2O), 7.33-7.43 (1H, approx. t), 7.43-7.56 (3H, approx. t), 5.51 (1H, s), 7.58-7.69 (1H, approx. t), 7.74-7.86 (2H, approx. t), and 8.03-8.13 (2H, approx. d); δ_c 108.9, 117.1, 122.6, 125.9, 126.8, 127.6, 128.2, 128.6, 130.2, 138.4, 140.0, 149.8 and 155.9;[213] *m/e* 220 (M^+, base), 194, 165, 110, 109.5, and 69. The ether solution of non basic components was evaporated to give 3-*phenyl*-3,4-*dihydrotetrazolo*[1,5-a]*isoquinoline* (59b) (17 mg, 7%) (Found: M^+, 248.1068. $C_{15}H_{12}N_4$ requires *M*, 248.1062); δ (250 MHz) 3.52 (1H, dd, *J* 5,16), 4.76 (1H, dd, *J* 5,16), 5.98 (1H, t, *J* 5), 6.05-6.13 (2H, m), 7.2-7.4 (4H, m), 7.4-7.54 (2H, m), and 8.16-8.24 (2H, m); *m/e* 248(M^+), 219, 147, 122, 105 (base), 77 and 57.

trans-1-(2-Ethoxycarbonylethenyl)-5-phenyltetrazole (29i). A solution of (29i) (172 mg, 0.745 mmol) in petrol (100 ml) was irradiated for 24h, transferred to a clean vessel and irradiated for a further 12h. The solvent was removed and the residue was chromatographed on silica gel, to give 4-ethoxycarbonyl-2-phenylimidazole (59i) (79 mg, 52%), m.p., 218-20° (from chloroform/petrol) (lit.,[214] 219-21°).

cis-1-(2-Ethoxycarbonyl)-5-phenyltetrazole (29j). A solution of (29j) (98.5 mg, 0.428 mmol) in petrol (150 ml) was irradiated for 20h. The solvent was removed and the residue was chromatographed on silica gel to give (59i) (52.5 mg, 61%), m.p., 218-20° (from chloroform/petrol).

1-(1,2-Bisethoxycarbonylethenyl)-5-phenyltetrazole (29ℓ). A solution of (29ℓ) (193.5 mg, 0.671 mmol) in petrol (600 ml) was irradiated for 7h. The solvent was removed and the residue was chromatographed on silica gel, to give 3,4-*bisethoxycarbonyl*-3,4-*dihydrotetrazolo*[1,5-a]*isoquinoline* (59c) (10 mg, 5%), m.p., 168-70° (from chloroform/petrol) (Found: C, 53.95; H, 4.13; N, 19.30. $C_{13}H_{12}N_4O_4$ requires C, 54.17; H, 4.20; N, 19.44%); ν_{max} 1736, 1616, 1453, 1439, 1304, 1270, 1222, 992, 781 and 734 cm^{-1}; δ (250 MHz) 3.66 (3H, s), 3.68 (3H, s), 4.67 (1H, d, *J* 1), 6.19 (1H, d, *J*1), 7.55-7.6 (3H, m), and 8.18-8.26 (2H, m); *m/e* 288 (M^+), 229 (base), 173, 169, 142, 128, 115, and 59, and 4,5-bisethoxycarbonyl-2-phenylimidazole (42 mg, 24%), m.p. 157-60° (from chloroform/petrol) (lit.,[215] 157°).

1-(*i*-But-1-enyl)-5-phenyltetrazole (37d). A solution of (37d) (980 mg, 4.89 mmol) in petrol (800 ml) was irradiated for 6h. The solvent was removed and the crude product was sublimed at 50° at 5 mmHg, to give 4,4-*dimethyl*-2-*phenyl*-4H-*imidazole* (63d) (464 mg, 55%), m.p. 40-4° (from 30-40° petrol at -78°) (Found: M^+, 172.1006. $C_{11}H_{12}N_2$ requires *M*, 172.1000); ν_{max} (thin film) 2980, 1611, 1602, 1574, 1450, 1320, 1281, 1022, 914, 718 and 677 cm^{-1}; λ_{max} (30-40° petrol) 257 (9000), 282 (3700) and 291 (2400); δ 1.41 (6H, s), 7.35-7.65 (3H, m), 8.20-8.47 (2H, m), and 8.77 (1H, s); δ_c 20.7, 83.1, 128.2, 130.8, 131.5, 170.3 and 193.1; *m/e* 172 (M^+, 25), 157 (6), 145 (100), m* 122.2 (172 → 145), 104 (79), m* 74.6 (145 → 104), 77 (16) and m* 57.0 (104 → 77).

1-(2-Methylcyclohex-1-enyl)-5-phenyltetrazole (37a).

(i) In petrol. A solution of (37a) (303 mg, 1.26 mmol) in petrol (200 ml) was irradiated for 3h. The solution was filtered, the solvent was removed, and the residue was chromatographed on alumina, to give 4-*methyl*-2-*phenyl*-4,5-*tetramethylene*-4H-*imidazole* (63a) (147 mg, 55%), m.p. 110-13° (from petrol) (Found: C, 78.99; H, 7.63; N, 13.22. $C_{14}H_{16}N_2$ requries C, 79.21; H, 7.60; N, 13.20%); ν_{max} 1614, 1276, 1145, 1046, 1023, 732, 726 and 699 cm^{-1}; λ_{max} 255 (9140), 281 (sh), and 290 (sh); δ (250 MHz), 1.18-1.25 (1H, m), 1.38 (3H, s), 1.60-1.86 (2H, m), 2.20-2.34 (1H, m), 2.43-2.68 (2H, m), 3.02-3.12 (1H, m), 7.43-7.54 (3H, m), and 8.24-8.34 (2H, m); δ_c 19.6 (q), 21.9 (t), 29.3 (t), 29.9 (t), 40.8 (t), 82.0 (s), 128.4 (d), 128.8 (d), 130.8 (d), 132.3 (s), 171.0 (s), and 205.8 (s); *m/e* 212 (M^+, 32), 717 (12), 144 (29), m* 137.9 (212 → 171), 131 (7), 104 (100), m* 97.8 (212 → 144), 77 (15), m* 75.1 (144 → 104), and m* 59.0 (104 → 77), and 1a-*methyl*-1a,1,2,3,4,4a-*hexahydrotetrazolo*-[1,5-*d*]-*phenanthridine* (64) (17 mg, 6%), as an oil, (Found: M^+, 240.1381. $C_{14}H_{16}N_4$ requires *M*, 240.1374); ν_{max} 1484, 1446, 1101, 1037, 778, 765,

733 and 701 cm^{-1}; δ 0.95 (3H, s), 1.3-3.0 (8H, m), 4.14 (1H, dd, *J* 4, 12), 7.30-7.67 (3H, m), and 8.05-8.20 (2H, m); *m/e* 240 (M^+), 212, 211, 197, 169, 145, 141, 85, 83, 74 and 59.

(ii) In acetonitrile. A solution of (37a) (130.5 mg, 0.543 mmol) in acetonitrile (50 ml) was irradiated for 2.5h. The solvent was removed and the residue was chromatographed on alumina, to give the 4H-*imidazole* (63a) (47 mg, 41%), and the *tetrazolophenanthridine* (64) (46 mg, 35%).

1-(*i*-But-1-enyl)-5-methyltetrazole (37c).

(i) In methanol. A solution of (37c) (55 mg, 0.40 mmol) in methanol (40 ml) was irradiated for 1h. The solvent was removed to give 5-*methoxy*-2,4,5-*trimethyl*-1,5-*dihydro*-4H-*imidazole* (65b), δ 1.18 (3H, s), 1.24 (3H, s), 1.97 (3H, s), 3.39 (3H, s), 4.49 (1H, s), and 5.93 (1H, br s). As detailed in Section 2.4.2 several attempts to eliminate methanol from this adduct were unsuccessful.

(ii) In 30-40° petrol. A solution of (37c) (241 mg, 1.74 mmol) in redistilled petrol (b.p. 30-40°) (250 ml), cooled at 0°, was irradiated for 1h. The solvent was removed at *ca.* 5° at water pump pressure and the residue was distilled at 18° at 3 mbar into a receiver cooled at -78°, to give 2,4,4-*trimethyl*-4H-*imidazole* (63c) as a colourless oil; δ 1.33 (6H, s), 2.43 (3H, s), and 8.56 (1H, d); δ_C 18.0, 20.7, 82.8, 171.7 and 193.5, which was contaminated with a minor product tentatively identified as (*i*-*But*-1-*enyl*) *methylcarbodiimide* (66), δ 1.64 (3H, m), 1.69 (3H, m), 3.01 (3H, s), and 5.96 (1H, m). Evaporation of the deuterochloroform at 5° at water pump pressure gave an oil, whose u.v. (30-40° petrol) had no abosorption maximum above 220 nm and whose i.r. (thin film) showed many very broad bands, the only well resolved peak being a strong one at 2130 cm^{-1} which might have been due to (66).

1-(*i*-But-1-enyl)tetrazole (37b).

(i) In methanol. A solution of (37b) (106 mg, 0.854 mmol) in methanol (40 ml) was irradiated for 80 min. The solvent was removed and n.m.r. of the product showed it to contain 4,4-*dimethyl*-5-*methoxy*-1,5-*dihydro*-4H-*imidazole* (65a), δ 1.21 (3H, s), 1.28 (3H, s), 3.38 (3H, s), 4.50 (1H, s), and 6.85 (1H, br s), along with many minor components.

(ii) In 30-40° petrol. A solution of (37b) (64.5 mg, 0.520 mmol) in redistilled petrol (b.p. 30-40°) (100 ml) at 0° was irradiated for 1h. The solvent was removed at 0° at water pump pressure, but the n.m.r. spectrum of the residue showed it to consist of a very complex mixture, with possibly a trace amount of 4,4-*dimethyl*-4H-*imidazole* as indicated by small peaks at δ 8.06 and δ 8.74.

3.4. Chemistry of 4*H*-Imidazoles.

Addition of methanol to 4,4-dimethyl-2-phenyl-4*H*-imidazole (63d). (63d) (58 mg, 0.34 mmol) was dissolved in methanol (1 ml). After 40h at room temperature the solvent was removed to give 4,4-*dimethyl*-5-*methoxy*-2-*phenyl*-1,5-*dihydro*-4H-*imidazole* (65c), δ (CCl_4) 1.13 (3H, s), 1.22 (3H, s), 3.27 (3H, s), 4.44 (1H, s), 6.88 (1H, br s), 7.01-7.44 (3H, m), and 7.72-7.98 (2H, m). The crude product was dissolved in benzene (4 ml) and the solution was refluxed with slow distillation for 2h. The solvent was removed to give a 1:1 mixture of (65c) and (63d) (^{1}H n.m.r.). This mixture was dissolved in benzene (4 ml), PTSA (5 mg) was added, and the solution was refluxed with slow distillation for 1h. The solvent was removed to give (63d) (^{1}H n.m.r.).

Hydration of (63d) on alumina. A crude sample of (63d) was chromatographed on alumina using 20% methanol/80% ether as eluent to give 4,4-*dimethyl*-5-*hydroxy*-2-*phenyl*-1,5-*dihyro*-4H-*imidazole* (65d), δ 1.16 (3H, s), 1.27 (3H, s), 4.96 (1H, s), 5.0 (2H, br s), 7.33-7.67 (3H, m), and 7.69-8.12 (2H, m); *m/e* 190 (M^+), 172, 145 (base), 104 and 77.

Addition of methylmagnesium iodide to (63d). A solution of (63d) (87 mg, 0.505 mmol) in ether (1 ml) was added dropwise to a stirred solution of methylmagnesium iodide, prepared from iodomethane (0.12 ml, 1.25 mmol) in ether (1 ml) and magnesium turnings (25.3 mg, 1.04 mmol) in ether (1 ml) according to the usual procedure, and stirring was continued for 30 min during which an oil precipitated. Hydrochloric acid (1M) was added until all of the solids were dissolved, water (10 ml) was added, and the ether layer was separated. The aqueous was basified by addition of 10% aqueous sodium hydroxide and was extracted with dichloromethane (3 x 4 ml). The extracts were dried with magnesium sulphate and the solvent was removed to give clean 2-*phenyl*-4,4,5-*trimethyl*-1,5-*dihyro*-4H-*imidazole* (67) (85 mg, 89%), m.p. 120-2° (from petrol) (Found: C, 76.78; H, 8.69; N, 14.91. $C_{12}G_{16}N_2$ requires C, 76.56; H, 8.57; N, 14.88%); ν_{max} 3160, 1597, 1567, 1513, 1320, 963, 790, and 701 cm^{-1}; δ 1.19 (3H, s), 1.26 (3H, d, *J* 7), 1.37 (3H, s), 3.72 (1H, q, *J* 7), 4.05 (1H, br s), 7.25-7.48 (3H, m), and 7.60-7.86 (2H, m); *m/e* 188 (M^+), 163, 145 (base), 131, 104 and 77.

2-*Phenyl*-4,4,5-*trimethyl*-4H-*imidazole* (63e). A solution of t-butyl hypochlorite[216] (0.28 ml, 2.34 mmol) in ether (2 ml) was added dropwise to a stirred suspension of the imidazoline (67) (220 mg, 1.17 mmol) in ether (5 ml) and stirring was continued for 4h. DBU (0.35 ml, 2.34 mmol)

was added and the mixture was stirred for 1h, and then filtered. After cooling at -20° for 2h the ether solution was decanted from the precipitated oil, the ether was removed, and the residue was chromatographed on alumina to give the 4H-*imidazole* (63e) (62 mg, 28%), m.p. 57-60 (after sublimation at 60° at 0.5 mbar) (Found: M^+, 186.1157. $C_{12}H_{14}N_2$ requires *M*, 186.1157); ν_{max} (thin film) 2980, 1620, 1581, 1563, 1461, 1327, 1275, 1065, 719 and 698 cm^{-1}; λ_{max} (30-40° petrol) 253 (8100), 280 (2700), and 298 (1800); δ 1.36 (6H, s), 2.35 (3H, s), 7.30-7.65 (3H, m), and 8.15-8.45 (2H, m); δ_c 15.4, 22.7, 82.5, 128.5, 128.9, 130.9, 132.3, 170.3, and 203.4; *m/e* 186 (M^+, 9), 171 (1), 145 (100), m* 113.0 (186 ⟶ 145) 104 (73), 77 (16) and m* 74.6 (145 ⟶ 104).

Thermal rearrangement of (63d). A solution of (63d) (20 mg) in dimethyl sulphoxide-d_6 (0.5 ml) was heated at 120° in a Bruker WM 250 n.m.r. spectrometer and the rearrangement was monitored by recording the spectrum at intervals of 100s. A clean and quantitative conversion into 4,5-dimethyl-2-phenylimidazole was observed and a plot of the logarithm of the concentration of (63d) against time was linear and gave a half-life of 30 min for the rearrangement.

3.5. Synthetic Approaches to 3a*H*-Benzimidazoles.

Bicyclo[2.2.2]oct-5-en-2-one (80).

(i) Cycloaddition of cyclohexadiene and acrylonitrile according to the method of Freeman, *et al.*[168] gave bicyclo[2.2.2]oct-5-en-2-carbonitrile in 21% yield (lit.,[168] 89%).

(ii) Chlorination of the nitrile with phosphorus pentachloride according to Freeman *et al.*[168] gave 2-chlorobicyclo[2.2.2]oct-5-en-2-carbonitrile in almost quantitaitive yield and it was used without purification

(iii) Hydrolysis of the chloro nitrile using sodium sulphide according to the method of Gregson and Mirrington[217] gave the ketone (80) in 24% yield from the nitrile.

Bicyclo[2.2.2]*oct-5-en-2-one, oxime* (83). A solution of hydroxylammonium chloride (480 mg, 6.93 mmol) and sodium acetate (610 mg, 7.45 mmol) in water (3 ml) was added to a solution of the ketore (80) (650 mg, 5.32 mmol) in ethanol (10 ml) and the mixture was heated on a water bath for 45 min. Water (25 ml) was added and the solution was extracted with dichloromethane (3 x 20 ml). The extracts were dried with magnesium sulphate, the solvent was removed, and the crude product was recrystallised twice from petrol to give the *oxime* (83) (358 mg, 50%), m.p. 133-6° (Found: C, 70.02; H, 8.11; N, 10.21. $C_8H_{11}NO$ requires C, 70.04; H, 8.08; N, 10.21%); ν_{max} ($CC\ell_4$) 3270, 1676, 926, 853, and 702 cm^{-1}; δ ($CC\ell_4$) 1.2-1.9 (4H, m), 2.22 (2H, m), 2.84 (1H, m), 3.23 (1H, m), 6.84 (2H, m), and 9.62 (1H, br s); *m/e* 137 (M^+), 109 (base), 91, 79 and 39.

Attempted preparation of the oxime tosylate (84). A solution of (83) (100 mg, 0.729 mmol) in pyridine (2 ml) was added over 10 min to an ice-cooled solution of tosyl chloride (280 mg, 1.46 mmol) in pyridine (2 ml) and the mixture was stirred at room temperature for 1.5h. It was poured into ice-water and extracted with dichloromethane (3 x 20 ml). The extracts were washed with hydrochloric acid (1M, 20 ml) and with water (20 ml) and dried over magnesium sulphate. The solvent was evaporated but the residue consisted of only a few milligrams of an unidentified oil.

6-Acetoxy-2,4,6-trimethylcyclohexadienone (88). This was prepared according to a literature procedure[173] in 91% crude yield. N.m.r. indicated that it was very clean (> 95%) so it was used without recrystallisation.

Cycloaddition of (88) with PTAD. A solutionof PTAD[218] (2.5 g, 14.3 mmol) in ethyl acetate (30 ml) was added dropwise over 1h to a stirred solution of the dienone (88) (2.37 g, 12.2 mmol) in ethyl acetate (11 ml) keeping the internal temperature at -23°. The addition was stopped when the pink colour was no longer discharged and the reaction mixture was stirred at -23° for 2h and at room temperature overnight. Methanol was added and most of the solvent was removed. The precipitate which formed was filtered off to give 8(R,S)-*acetoxy*-4-*phenyl*-1(S,R),8,11-*trimethyl*-2,4,6-*triaza*-*tricyclo*[5.2.2.$0^{2,6}$]*undec*-10-*en*-3,5,9-*trione* (89a) (2.72 g, 60%) m.p. 157-9° (from dichloromethane/methanol) (Found: C, 61.66; H, 5.15; N, 11.36. $C_{19}H_{14}N_3O_5$ requires C, 61.78; H, 5.18; N, 11.38%); ν_{max} 1750, 1711, 1411, 1017, 825, 753, and 689 cm^{-1}; δ 1.58 (3H, s), 1.96 (3H, s), 2.01 (3H, s), 2.03 (3H, d, *J* 2), 5.49 (1H, d, *J* 4), 5.94 (1H, m), and 7.47 (5H, br s); δ_c [$(CD_3)_2SO$] 14.0, 19.8, 20.1, 20.5, 60.0, 65.4, 76.0, 126.3, 126.5, 128.4, 128.9, 131.0, 144.0, 150.9, 151.7, 169.2 and 194.8; *m/e* 369 (M^+) 341, 299, 256, 255, 137 and 123. The residue was chromatographed on silica gel to give 8(S,R)-*hydroxy*-4-*phenyl*-1(S,R),8,11-*trimethyl*-2,4,6-*triaza*-*tricyclo*[5.2.2.$0^{2,6}$]*undec*-10-*en*-3,5,9-*trione* (90b) (189 mg, 5%), m.p. 203-7° (from benzene/petrol) (Found: C, 63.04; J, 5.29; N, 12.67. $C_{17}H_{17}N_3O_4$ requires C, 62.38; H, 5.23; N, 12.84%); ν_{max} 3385, 1760, 1745, 1701, 1416, 1260, 1160, 855, 777, 746, and 691 cm^{-1}; δ [$(CD_3)_2SO$] 1.42 (3H, s), 1.75 (3H, s), 1.97 (3H, d, *J* 2), 4.68 (1H, d, *J* 2), 6.02 (1H, m),

6.4 (1H, br s), and 7.47 (5H, br s); *m/e* 237 (M^+), 299, 256, 137 and 123 (base), and the 8(R,S)-*isomer* (90a) (488 mg, 12%), m.p. 212-3.5° (from acetic acid) (Found: C, 62.17; H, 5.18; N, 12.79. $C_{17}H_{17}N_3O_4$ requires C, 62.38; H, 5.23; N, 12.84%); ν_{max} 3370, 1761, 1742, 1692, 1500, 1425, 1289, 1135, 851, 759, 746, 692 and 647 cm^{-1}; δ [$(CD_3)_2SO$] 1.30 (3H, s), 1.78 (3H, s), 2.01 (3H, d, *J* 1), 4.74 (1H, d, *J* 1.5), 5.99 (1H, m), 6.68 (1H, s, exch. D_2O), and 7.30-7.75 (5H, m); δ_c [$(CD_3)_2$ SO] 14.4, 19.7, 21.2, 64.3, 64.9, 70.3, 125.5, 126.3, 128.9, 131.5, 146.1, 152.6, 154.1 and 198.8; *m/e* 327 (M^+), 299, 256, 137 and 123 (base), and a mixture of (90a) and (80b) (346 mg, 9%), which was not separated.

Cycloaddition of (88) with PTAD followed by hydrolysis. A solution of PTAD[218] in ethyl acetate was added dropwise to a stirred solution of (88) (5.35 g, 27.5 mmol) in ethyl acetate (25 ml) until the pink colour was no longer discharged. The solvent was removed, the crude product was suspended in a mixture of ethanol (50 ml) and hydrochloric acid (1M, 20 ml) and the mixture was stirred for 4h. Water (75 ml) was added and after cooling at 4° for 1h the precipitate was filtered off and dried *in vacuo*. Recrystallisation from acetic acid/water gave a mixture (*ca.* 4:1) of (90a) and (90b) (7.28 g, 81%).

Hydrolysis of (89a). A suspension of (89a) (1.0 g, 2.71 mmol) in a mixture of ethanol (15 ml) and hydrochloric acid (2M, 2 ml) was stirred for 2.75h. Water (50 ml) was added, the suspension was cooled, and the precipitate was filtered off and dried *in vacuo*, to give (90a) (0.861 g, 97%).

X-Ray crystal structure determination of (90b).[189] Crystals of (90b) are monoclinic; space group $P2_1/c$, a = 12.537(2), b = 9.728(2), c = 14.284(3)Å; β = 112.36(1)°, U = 1611 Å^3, Z = 4.

X-ray crystal structure determination of (110).[189] Crystals of (110) are orthorhombic; space group $Pbca$, a = 8.404(2), b = 17.464(4), c = 28.990(5)Å; U = 4255Å^3, Z = 8.

Reaction of (90a) with CSI and t-butyl carbazate.[184]

(i) CSI (23.4 μℓ, 0.268 mmol) was added to a stirred suspension of the alcohol (90a) (44 mg, 0.134 mmol) in a mixture of benzene (5 ml) and dichloromethane (2 ml) and stirring was continued until the mixture became homogeneous. The solution was refluxed for 5 min but no gas evolution was observed. The solvent was removed and the residue was dissolved in pyridine (0.5 ml). A solution of t-butyl carbazate (35 mg, 0.268 mmol) in pyridine (0.5 ml) was added. After 21h at room temperature the mixture was poured into hydrochloric acid (1M, 15 ml) and extracted with chloroform (3 x 10 ml). The extracts were washed with saturated sodium chloride solution and dried over magnesium sulphate. The solvent was removed and the residue was chromatographed on silica gel, to give the *urethane* (101) (38 mg, 50%); ν_{max} 3280, 1770, 1590, 1400, 1280, 1150, 1090, 840 and 745 cm^{-1}; δ 1.40 (12H, s), 1.87 (3H, s), 2.06 (3H, d), 4.80 (1H, d), 5.40 (3H, br s, exch. D_2O), 5.86 (1H, m), and 7.44 (5H, br s).

(ii) The alcohol (90a) (57 mg, 0.174 mmol) was reacted wtih CSI and t-butyl carbazate in the same way as in (i), but care was taken to avoid heating the intermediates at any stage, to give the urethane (101) (106 mg, 107%) without purification. This material was identical with that

obtained from (i) by ^{1}H n.m.r. and i.r. It was recrystallised from chloroform/petrol to give a yellow solid. m.p. 280-5° (decomposition). In determining the melting point, evolution of gas was observed at 150-60°.

12(R,S)*Hydroxy*-4-*phenyl*-1(S,R),8(R,S),10,14-*tetramethyl*-9-*oxa*-2,4,6,11-*tetrazatetracyclo*[5.5.2.$0^{2,6}0^{8,12}$]*tetradec*-10,13-*dien*-3,5-*dione* (102).

Concentrated sulphuric acid (7 ml) was added dropwise to a stirred, ice-cooled, suspension of a mixture of (90a) and (90b) (*ca.* 8:1) (4.0 g, 12.2 mmol) in a mixture of acetonitrile (3.83 ml, 73.7 mmol) and acetic acid (5 ml) and stirring was continued at room temperature for 2.5h. The mixture was poured into water (30 ml) and aqueous sodium hydroxide (4M, 110 ml) was added. It was extracted with chloroform (3 x 120 ml) and the extracts were washed with saturated sodium chloride solution (150 ml) and dried with magnesium sulphate. The solvent was removed and the crude product was washed with two portions of warm benzene to give the *oxazoline* (102) (2.77 g, 62%), m.p. 242.5-5.5° (from methanol/chloroform/petrol) (Found: C, 62.04; H, 5.47; N, 15.32. $C_{19}H_{20}N_4O_4$ requires C, 61.95; H, 5.47; N, 15.21%); ν_{max} 3300-3000 (br), 1763, 1710, 1654, 1401, 1070, 810, 762, and 642 cm^{-1}; δ [$(CD_3)_2SO$] 1.19 (3H, s), 1.83 (3H, s), 1.92 (3H, s), 1.93 (3H, d, *J* 3), 4.91 (1H, d, *J* 3), 6.04 (1H, m), 6.45 (1H, s), and 7.3-7.6 (5H, m); δ_c [$(CD_3)_2SO$] 13.6, 14.2, 18.0, 19.1, 59.0, 64.3, 86.9, 100.1, 125.8, 127.8, 128.8, 129.2, 131.5, 136.3, 150.6, 151.2 and 165.1; *m/e* 328, 299, 256, 177, 137, and 123 (base).

4,10-Diphenyl-12(R,S)-hydroxy-1(S,R),8(R,S),14-trimethyl-9-oxa-2,4,6,11-tetrazatetracyclo[5.5.2.0.^{2,6}0^{8,12}]*tetradec-10,13-dien-3,5-dione* (103). Concentrated sulphuric acid (5 ml) was added dropwise to a stirred, ice-cooled, suspension of a mixture of (90a) and (90b) (*ca.* 8.1) (2.61 g, 7.97 mmol) in a mixture of benzonitrile (4.9 ml, 47.8 mmol) and acetic acid (4 ml) and stirring was continued at room temperature for 2.5h. The mixture was poured into water (50 ml) and aqueous sodium hydroxide (4M, 80 ml) was added. It was extracted with chloroform (3 x 100 ml) and the extracts were washed with saturated sodium chloride solution (150 ml) and dried with magnesium sulphate. The solvent and excess of benzonitrile were removed and the crude product was washed with hot benzene to give the *oxazoline* (103) (2.11 g, 62%), m.p. 273-5° (from benzene) (Found: C, 66.60; H, 5.13; N, 12.81. $C_{24}H_{22}N_4O_4$ requires C, 66.97; H, 5.15; H, 13.02%); ν_{max} 3350-3000 (br), 1760, 1702, 1629, 1405, 1284, 1203, 765, and 701 cm^{-1}; δ [$(CD_3)_2SO$] 1.32 (3H, s), 1.93 (3H, s), 1.99 (3H, d, *J* 2), 5.07 (1H, d, *J* 2), 6.08 (1H, m), 6.09-6.29 (3H, m ; 1H, exch. D_2O), and 7.1-7.95 (8H, m); δ_c [$(CD_3)_2SO$] 15.2, 18.0, 58.7, 64.3, 87.8, 100.8, 125.9, 126.6, 127.6, 128.18, 128.24, 128.7, 129.9, 131.1, 132.3, 136.7, 150.0, 150.4, and 162.9; *m/e* 431 (M^+ + 1), 256, 255, 175, 135, 119, 109, 108, 104, 79, and 77.

12(R,S)-Chloro-4,10-diphenyl-1(S,R),8(R,S),14-trimethyl-9-oxa-2,4,6,11-tetrazatetracyclo[5.5.2.0.^{2,6}0.^{8,12}]*tetradec-10,13-dien-3,5-dione* (110). A suspension of the hydroxy oxazoline (103) (488 mg, 1.13 mmol) in a solution of thionyl chloride (0.165 ml, 2.27 mmol) in benzene (20 ml) was refluxed for 3.25h. The solvent and excess of thionyl chloride were removed to give the *chloro oxazoline* (110) (491 mg, 96%), m.p. 208-10° (from chloroform/ether) (Found: C, 64.01; H, 4.68; N, 12.35. $C_{24}H_{21}C\ell N_4O_3$ requires C, 64.21; H, 4.72; N, 12.48%); ν_{max} 1763, 1609, 1630, 1405, 1283

760, 719, and 697 cm^{-1}; δ [$(CD_3)_2SO$] 1.61 (3H, s), 2.07 (3H, d, *J* 1), 2.14 (3H, s), 5.38 (1H, d, *J* 1), 6.25 (1H, m), 6.53-6.72 (2H, m), 7.05-7.33 (3H, m), 7.40-7.75 (3H, m), and 7.92-8.02 (3H, m); δ [$(CD_3)_2SO$] 16.9, 19.1, 22.3 , 58.0, 65.2, 90.2, 101.9, 125.1, 125.9, 127.8, 128.3, 128.6, 128.9, 130.7, 133.4, 138.5, 149.6, 149.7 and 165.2; *m/e* 413, 255, and 108.

Hydrolysis of (102) and (103). A suspension of (103) (155 mg, 0.36 mmol) in a mixture of acetic acid (1 ml) and water (1 ml) was refluxed for 1h. After cooling water (3 ml) was added and the precipitate was filtered off and dried *in vacuo* to give (90a) (98 mg, 83%).

Similar treatment of (102) also gave (90a) in good yield.

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