"ISOHISTAMINE"

(2-(2-AMINOETHYL) IMIDAZOLE)

AND RELATED COMPOUNDS

by

MICHAEL EDWARD FOOTTIT

A Thesis submitted for the Degree of Doctor
of Philosophy of the University of Leicester

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789 East Eisenhower Parkway
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"It is not easy to design new structures having biological activity. If anyone tells you it is, do not listen to them....."

Robert Burns Woodward

4th November 1970

STATEMENT

The accompanying thesis, submitted for the degree of Doctor of Philosophy, is based on work conducted by the author at the Smith Kline & French Laboratories Ltd., Welwyn Garden City, Herts.

All the work recorded in this thesis is original, unless otherwise acknowledged in the text, or by references. None of this work has been submitted for another degree in this, or any other University.

Signed ..... October 1971

(M.E. Foottit)

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Abstract

"Isohistamine", (2-(2-aminoethyl)imidazole), and Related Compounds

As part of a programme to prepare structural analogues of histamine for pharmacological examination, the positional isomer, 2-(2-aminoethyl)-imidazole, (isohistamine) was required.

The synthesis of this compound, published in 1949, involved the nucleophilic displacement of chlorine by cyanide ion in 1-benzyl-2-chloromethylimidazole. Repetition of this reaction has shown that a previously undetected rearrangement occurs and that a mixture of nitriles is obtained. The subsequent stages of the published synthesis led to 4(5)-aminomethyl-2-methylimidazole, and not isohistamine. This reformulation explains the anomalous properties of the compound previously thought to be isohistamine. A similar published synthesis of 2-(2-aminoethyl)-1-methylimidazole has been investigated and shown to be in error.

When the cyanide ion displacement reaction on 1-benzyl-2-chloromethyl-imidazole was carried out in dimethylformamide, the expected 2-cyano-methyl compound was obtained together with a novel type of stable primary enamine, 1-amino-2-(1-benzylimidazol-2-yl)acrylonitrile.

The homologues of isohistamine, 2-(3-aminopropyl)imidazole and 2-(4-aminobutyl)imidazole have been synthesised and the isothioureas and guanidines related to these amines have also been made for

pharmacological examination.

In order to provide alternative syntheses of the foregoing compounds, the preparation of 2-substituted imidazoles by cyclisation of the appropriate iminoethers has been investigated.

The metalation of 1-substituted imidazoles with organo-lithium compounds, as another route to 2-substituted imidazoles, is discussed, and the reaction of these lithio derivatives has been investigated. The anomalous behaviour of ethylene oxide, which reacts with the lithio derivative of 1-benzylimidazole at the benzylic methylene group has been studied.

The biological rationale for the synthesis of the compounds described in this work is briefly discussed.

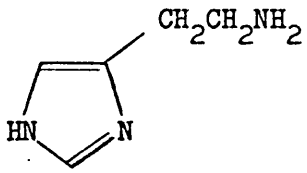
CONTENTS

A SUMMARY OF REACTIONS IS INSERTED AT THE END OF THIS THESIS.

SECTION I

INTRODUCTION

It has for long been recognised that histamine, namely 4(5)-(2-aminoethyl) imidazole (I.1), exerts marked physiological effects upon mammalian tissue.



(I.1)

The first correlation between the chemical structure of histamine and its action upon smooth muscle and blood pressure was reported as early as 1910 by Barger and Dale,[1] who isolated histamine from ergot,[2] and showed that it was identical with a synthetic sample. Later, the same authors were to demonstrate the occurrence of histamine in intestinal mucosa.[3] Abel and Kubota showed histamine to be a normal constituent of many, if not all, tissues.[4]

Histamine is known to cause contraction in smooth muscle and it has a profound effect on the circulatory apparatus. Intravenous injections of the substance cause a sharp fall in arterial blood pressure. Comparatively large doses cause a profuse secretion from the salivary glands and produce a stimulating effect on the adrenal medulla, causing liberation of catecholamines. Release of histamine is known to be associated with allergic reactions. It also exerts a powerful effect as a stimulant of gastric acid secretion,[5] and the histamine-induced

secretion of hydrochloric acid has been extensively studied.

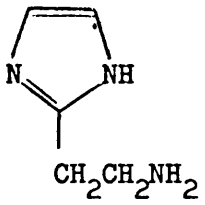
It has been postulated that many of the physiologically active substances within the body, in the course of their actions, combine with specific sites known as receptors. Histamine is a compound believed to act in such a way, but in addition, it has been proposed that it acts at two different receptor sites. Ash and Schild[6] defined H-1 receptors as those which are specifically antagonised by low concentrations of conventional antihistamine drugs, e.g. mepyramine. Such receptors may be typically demonstrated in the isolated uterus and ileum of the guinea pig and in the guinea pig bronchi.

Certain actions of histamine such as the stimulation of gastric acid secretion, the relaxation of spasm in the isolated rat uterus, the production of tachycardia in the isolated heart and atrium are not antagonised by mepyramine and other antihistamines. The histamine-like activity of certain histamine analogues on gastric secretion was in agreement with that found in the relaxation of spasm in the isolated rat uterus, but differed markedly from that found in the guinea pig ileum, which led to the suggestion[6] that in the rat gastric secretion, and in the isolated rat uterus, histamine acts through another class of receptor, which has been termed the H-2 receptor.[7]

The mechanism of the histamine induced secretion of acid by the stomach presents one of the unsolved problems in pharmacology. This phenomenon may be important in the development and persistence of peptic ulcers.

Such ulceration is a major medical problem and the objective of a current research programme in these laboratories is to produce a specific H-2 receptor antagonist. As part of this programme a wide variety of analogues of histamine have been synthesised.

The work to be described in this thesis deals with some aspects of the chemistry of 2-substituted imidazoles. Most of the compounds to be discussed were obtained in the course of preparing the positional isomer of histamine (I.1) namely 2-(2-aminoethyl)imidazole (I.2) and related compounds. We have previously called compound (I.2) isohistamine.[8]



(I.2)

This study deals with the synthesis of 2-substituted imidazoles by the following routes:

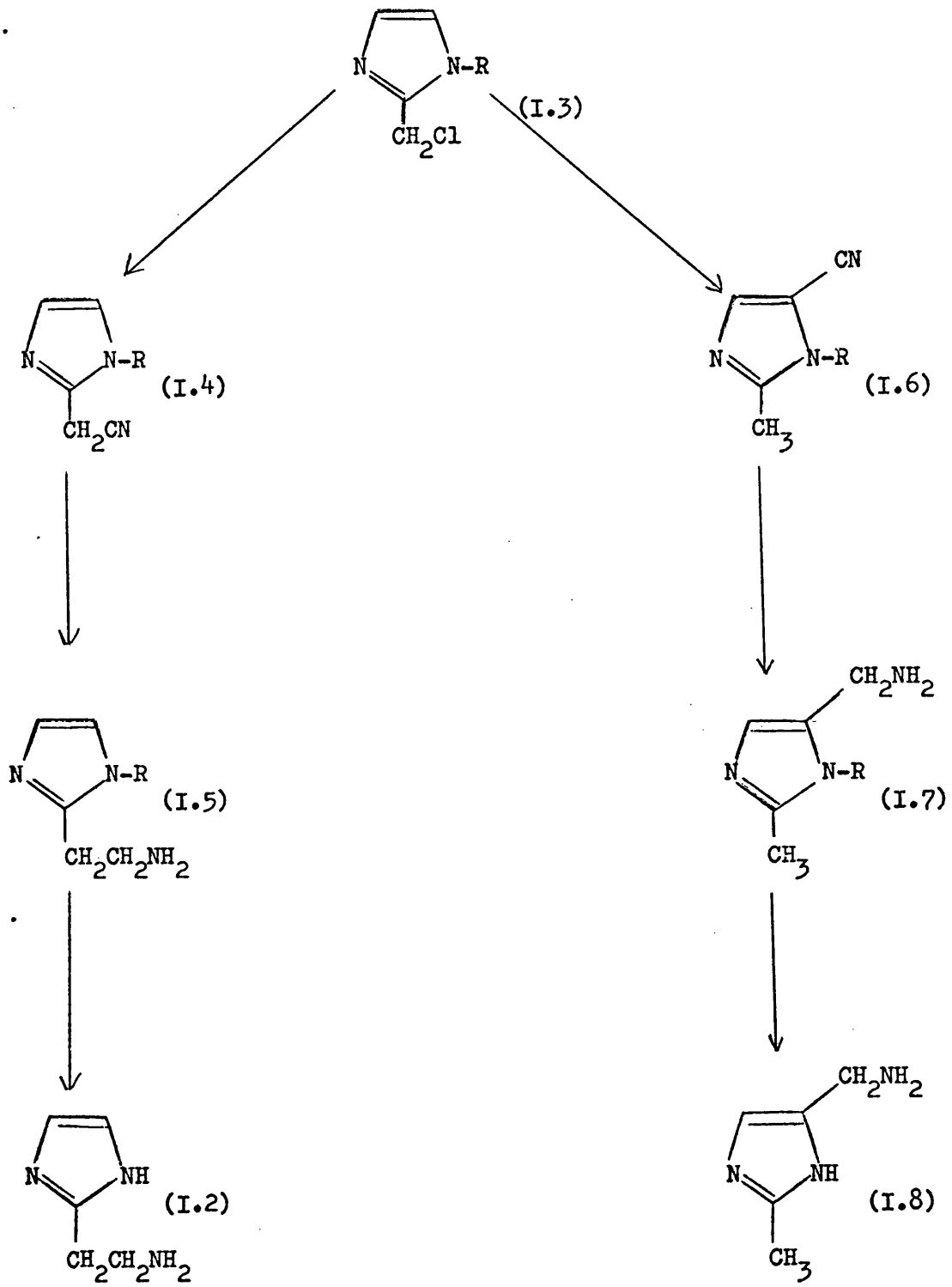
1. Chain extension by nucleophilic displacement of halogen in 2-chloromethyl imidazole derivatives.
2. Formation of the imidazole ring by cyclisation reactions.
3. Metalation of imidazoles with organolithium compounds.

1. Chain extension by nucleophilic displacement of halogen in 2-chloromethylimidazole derivatives

Isohistamine (I.2) was first reported in 1949 by Jones,[9] who used a conventional synthesis starting from 1-benzyl-2-chloromethylimidazole (I.3a) by the route shown in Scheme I.1. Treatment of the chloromethyl compound (I.3a) with aqueous ethanolic potassium cyanide was reported to give 1-benzyl-2-cyanomethylimidazole (I.4a) which was reduced with lithium aluminium hydride to the aminoethyl compound (I.5a). Debenzylation of this material using sodium in liquid ammonia gave an amine formulated as (I.2), which surprisingly had no histamine-like activity.

This absence of activity has been commented upon.[10-12] In contrast to histamine, this material was inactive on the guinea pig ileum and did not affect the blood pressure of the cat. It did not stimulate the secretion of acid by the stomach, nor cause any skin reaction, and it was not a substrate for amine oxidase.

Our investigation of this synthetic route, which will be discussed in detail later, showed that a rearrangement had occurred. The n.m.r. spectrum of the final product showed that it was not the aminoethyl compound (I.2), but an aminomethyl compound (I.8). Similarly the n.m.r. spectra of the intermediates were incompatible with the cyanomethyl (I.4a) and aminoethyl structures (I.5a) and support their reformulation as the cyano- (I.6a) and aminomethyl-



a, R = $-CH_2Ph$; b, R = -Me

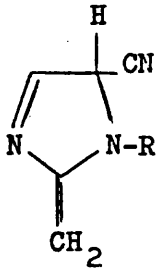
Scheme I.1

compounds (I.7a). After we had discovered this previously undetected rearrangement,[8] it was disclosed[13] that Gutche and Gitel had also observed it (unpublished work).

The reformulation of (I.2) as (I.8) explains the lack of histamine like properties mentioned above and it also explains the observations which led Holmes and Jones[14] to adumbrate that the compound formed a 5-membered chelate ring with metal ions.

Recently Kornfeld[15] and his co-workers reported that 1-benzyl-2-chloromethylimidazole and sodium cyanide react in aprotic media (dimethyl sulphoxide) without rearrangement and they corrected the structural assignments of their colleague Jones.[9]

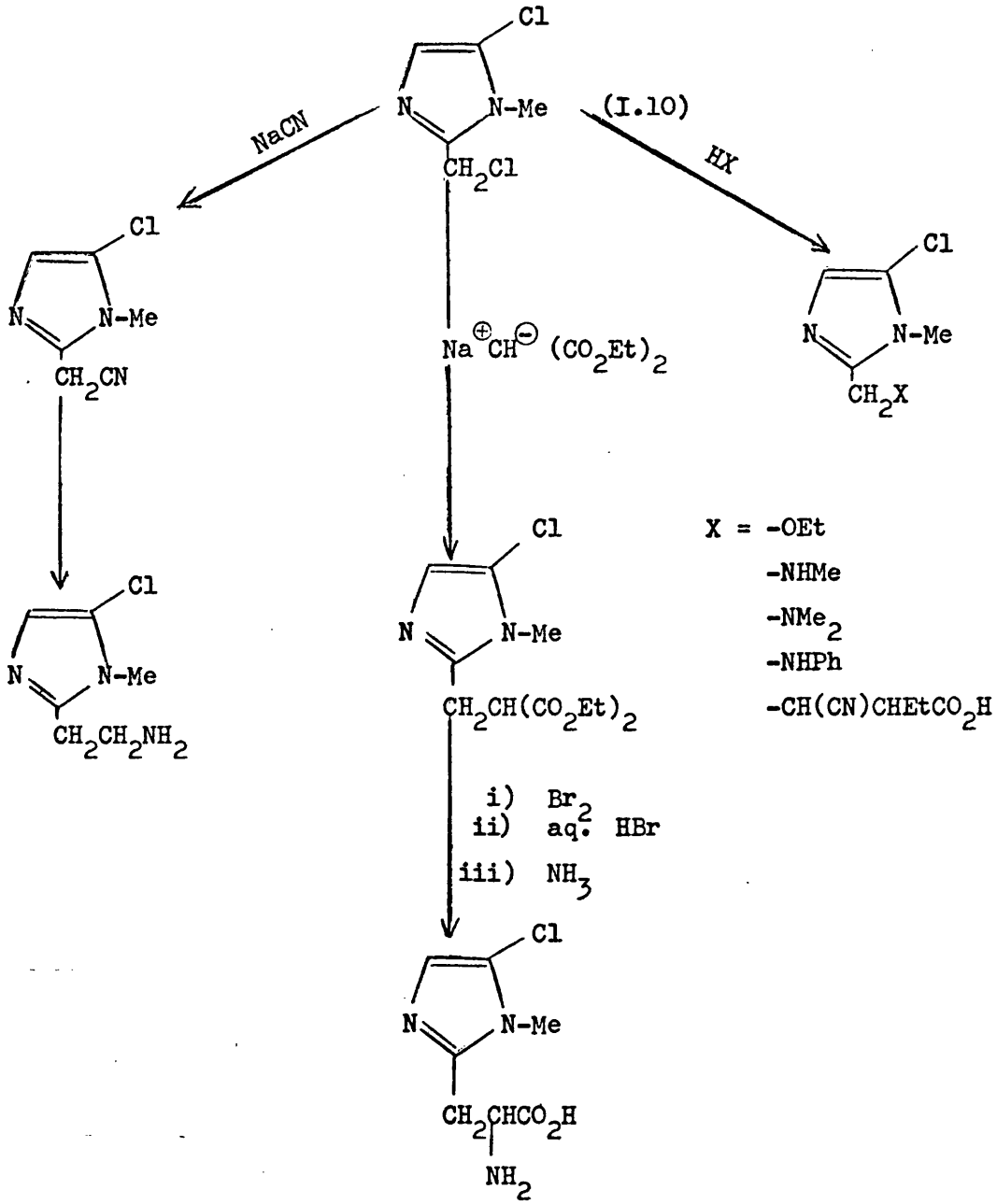
Following these findings we decided to investigate the claim of Jocelyn[16] to have obtained 1-methylisohistamine (I.5b), by a route analogous to that used by Jones. It became clear that the rearranged product (I.7b) was also obtained in this series. Presumably in



(I.9)

both these syntheses the reaction proceeds via the exocyclic methylene intermediate (I.9). This mechanism provides evidence for the structure of the cyano- and aminomethyl compounds (I.6) and (I.7).

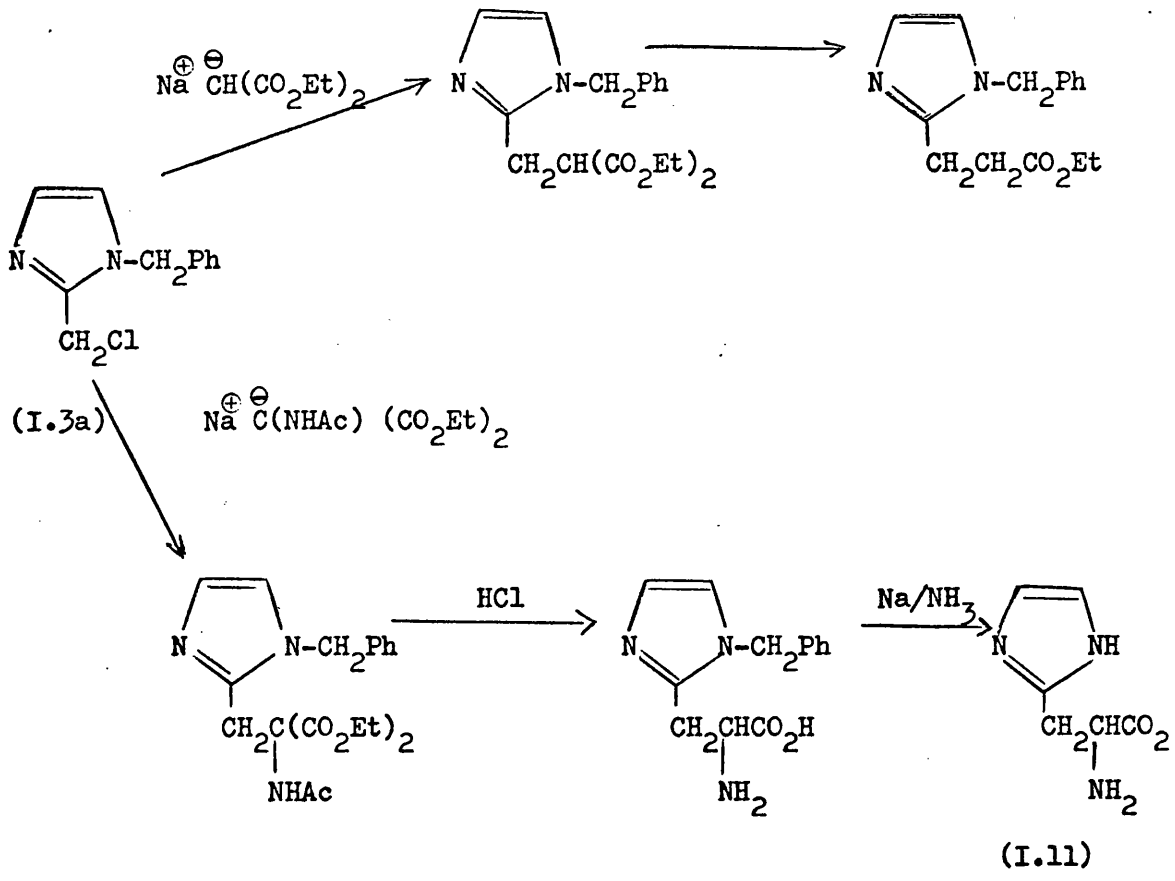
The only other report[17] of the reaction of a 2-chloromethylimidazole with cyanide ion is shown below in Scheme I.2.



Scheme I.2

However in this instance rearrangement is highly unlikely since the 5-position of the imidazole ring is effectively blocked by an aromatic chlorine atom, which is considerably less labile than the aliphatic chlorine atom also present in the molecule. Other transformations carried out on the chloromethyl compound (I.10) are shown in Scheme I.2.

Jones[8] also treated the chloromethyl compound (I.3a) with the sodium salt of diethyl malonate in ethanol (Scheme I.3). He also



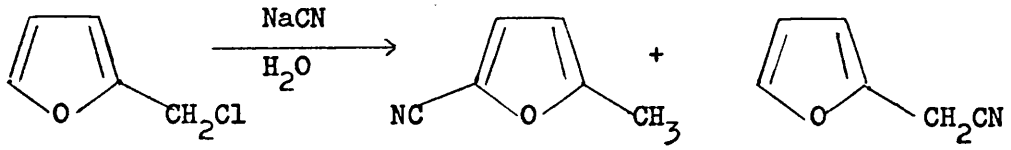
Scheme I.3

prepared the positional isomer of histidine, i.e. isohistidine (I.11), by the condensation of sodioacetamidomalonic ester with

the chloromethyl compound (I.3a) in ethanol (Scheme I.3). In neither of the above instances did Jones, or Schneider[18] who repeated the latter reaction, obtain any evidence for abnormal products. Schneider also reported the reaction between potassium phthalimide and the chloromethyl compound (I.3a) which appeared to give only normal products.

Substitution with rearrangement (SN') which occurs via an ambident electrophilic species is rarely observed in heterocyclic systems. Most of the known examples occur in five membered π-electron-rich systems such as the furans and thiophenes, with cyanide ion as the most frequently observed nucleophile. The subject of ambident electrophiles has been reviewed.[19]

Reichstein observed that nucleophilic displacement of chlorine in 2-chloromethylfuran (I.12) by aqueous sodium cyanide (Scheme I.4) led to a mixture of products.[20] Similar rearrangements



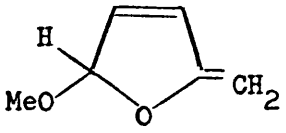
(I.12) 85% 15%

Scheme I.4

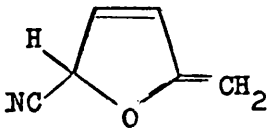
with 2-α-chloropropylfuran[21] and 3-chloromethylfuran[22] are also known. Other work[23, 24] indicated that if the 5-position of the furan ring was blocked with a methyl group, no rearranged product was obtained. Extensive studies have been made on the rearrangement of 2-chloromethylfuran.[21, 25 - 32]

Generally in reactions of this type aprotic solvents favour the formation of normal products while rearrangement usually occurs in protic solvents.

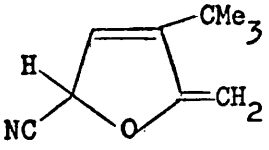
The following exocyclic methylene intermediates, (I.13) and (I.14), derived from the rearrangement with methoxide and cyanide ions have actually been isolated.[31] Compounds (I.15) and (I.16) were detected[33] but not isolated.



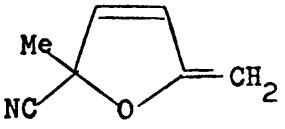
(I.13)



(I.14)

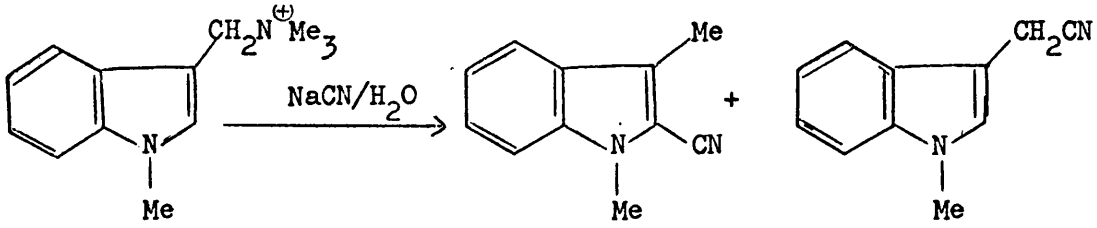


(I.15)



(I.16)

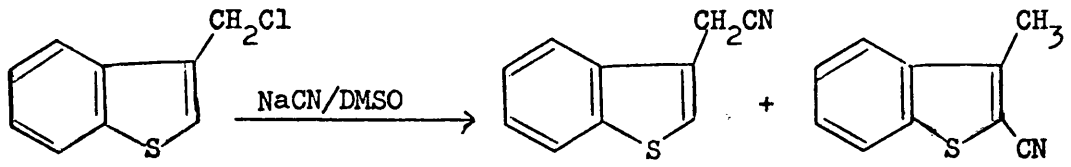
Simple pyrroles are not known to give rise to rearranged products. However the 3-trimethylammoniummethylindole (I.17) does give a



(I.17) 4% 96%

Scheme I.5

small quantity of the rearranged product on treatment with aqueous sodium cyanide.[34] No simple thiophenes are known to act as ambident electrophiles, but Campaigne[35, 36] obtained a small quantity of 2-cyano-3-methylbenzo[b]thiophene (I.19) on treatment of the chloromethylthiophene (I.18) with sodium cyanide in dimethyl

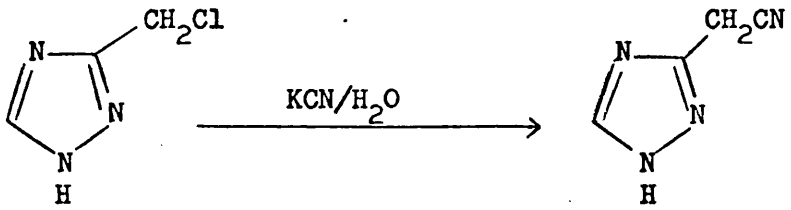


(I.18) 98% (I.19)

sulphoxide. It was also shown[37] that the related 5-benzoyloxy-3-bromomethylbenzo[b]thiophene affords the rearranged product analogous to the nitrile (I.19) on treatment with sodium cyanide in aprotic solvents. No rearrangement was detected in ethanol.[36] This observation that rearrangement can occur in dipolar aprotic

solvents is in contrast to findings with other heterocycles where rearrangement occurs exclusively in protic media. Examples of rearrangement in the related non-aromatic thiophene -1,1-dioxides are also known[38] and have been studied.[39]

No examples of anomalous nucleophilic displacements are known in the 1,2,4-triazole series and 3-chloromethyl-1,2,4-triazole (I.20) does not undergo rearrangement on treatment with aqueous potassium cyanide.[40] Novitskii[41] has recently reported on studies involving



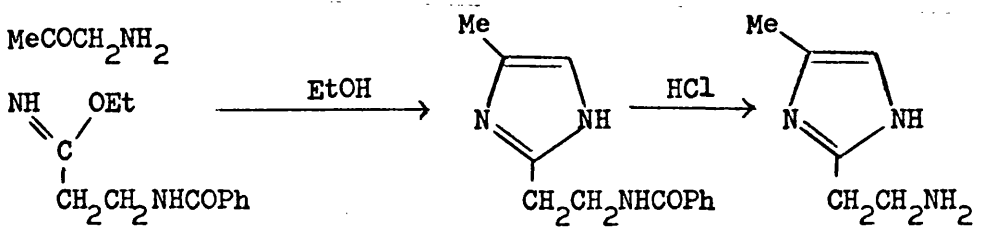
(I.20)

3-chloromethyl pyridazine where no rearrangement was detected.[41] However, rearranged products have been observed from the reaction of 2-chloro-3-dichloromethylpyridazine with alkoxide ions.[42] No further examples are known of similar nucleophilic displacements in heterocyclic systems leading to abnormal products. Rearrangements in the imidazole series will be discussed in Section II with reference to the present work.

2. Formation of the imidazole ring by cyclisation reactions

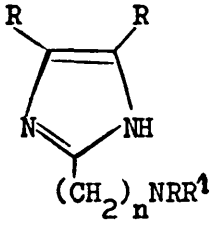
When we demonstrated that the structure of the compound which Jones[9] formulated as (I.2) was incorrect, it was necessary to synthesise (I.2), isohistamine, by an unambiguous method. A survey of possible methods revealed that potentially useful synthetic routes to isohistamine and related 2-substituted imidazoles involved a cyclisation reaction to form the heterocyclic ring.

The earliest synthesis of this type is that described by Ellinger and Goldberg,[43-45] who prepared 4-methylisohistamine (I.22) as shown in Scheme I.6. A process for preparing compounds of the general structure (I.23) was described,[44-46] and the method was exemplified by the



(I.21) (I.22)

Scheme I.6



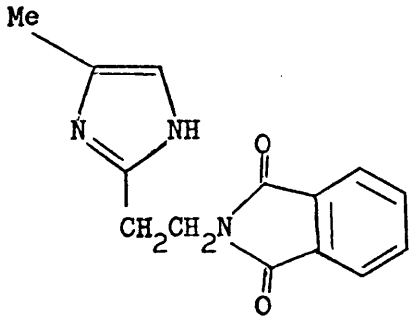
(I.23)

R = H, alkyl, aryl or aralkyl

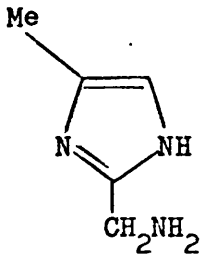
R^1 = H or acyl

n = any integer

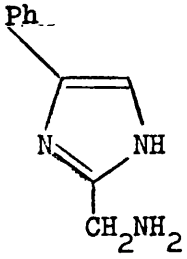
preparation of the following compounds, 4(5)-methyl-2-(2-N-phthalimidoethyl)imidazole (I.24), 4(5)-methyl-2-aminomethylimidazole (I.25) and 4(5)-phenyl-2-aminomethylimidazole (I.26).



(I.24)

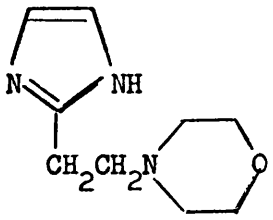


(I.25)

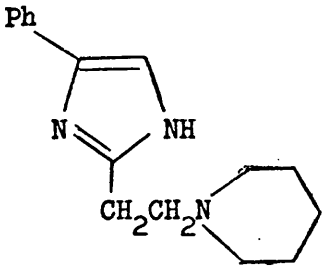


(I.26)

2-(2-N-Morpholinoethyl)imidazole (I.27) and 4(5)-phenyl-2-(2--N-piperidinoethyl)imidazole (I.28) were reported among a series of Ciba compounds tested for histamine agonist and antagonist



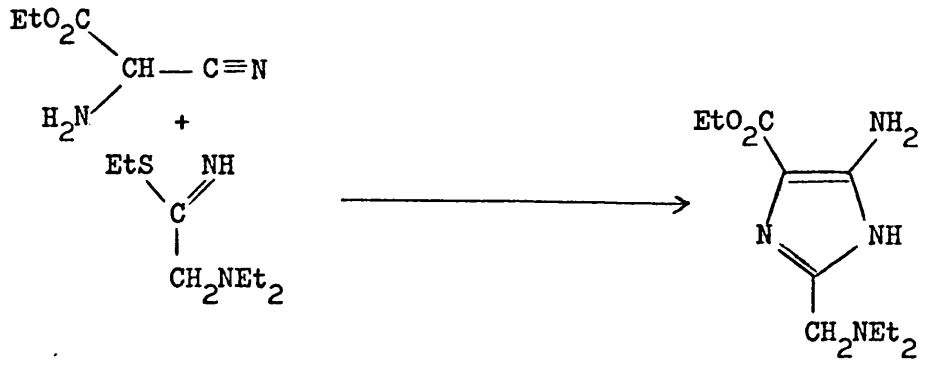
(I.27)



(I.28)

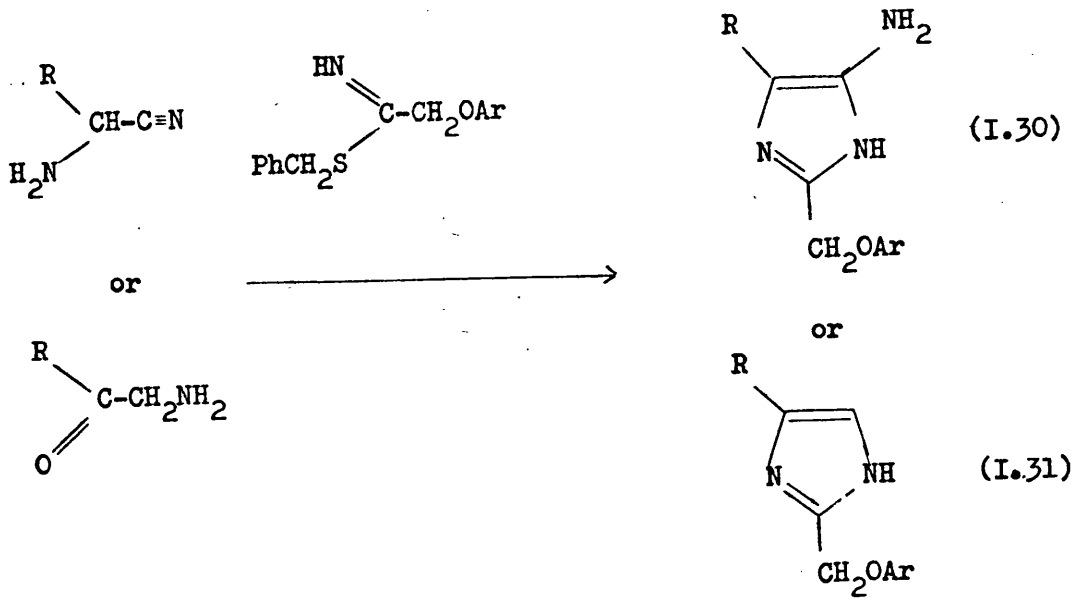
activity.[47] The method by which these compounds were prepared has not been reported, but it is conceivable that a cyclisation procedure was used.

Bader and his coworkers[48] have prepared 2-(diethylaminomethyl)-4-ethoxycarbonyl-5-aminoimidazole (I.29) as shown, and this work was extended[49] to the synthesis of other one-carbon side chain.



(I.29)

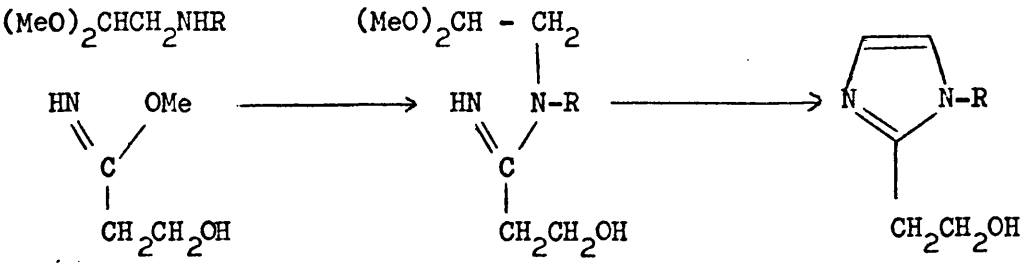
derivatives, namely 4-alkyl-5-aminoimidazol-2-ylmethyl aryl ethers (I.30) and 4-alkylimidazol-2-ylmethyl aryl ethers (I.31).



(I.30)

(I.31)

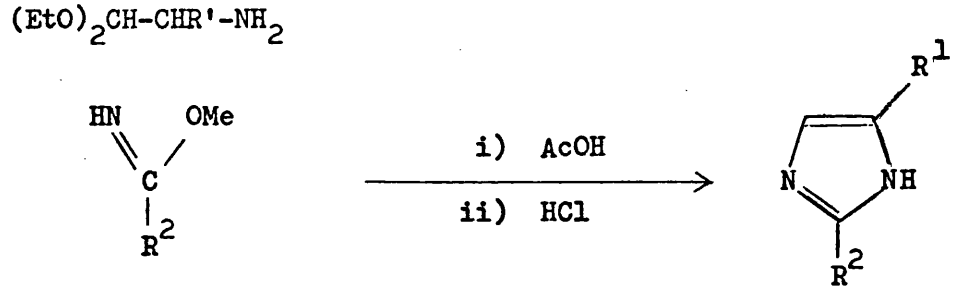
J.K. Lawson[50-51] overcame the difficulties associated with the use of the highly reactive α-amino carbonyl component. He extended the convenient synthetic method of Ellinger and Goldberg[43-45] to include the synthesis of imidazoles unsubstituted in the 4-position (I.33), by the use of suitable α-aminoacetals. The intermediate amidines



(I.32) (I.33)

R = -H or -Me

(I.32) were not isolated. Hydrolysis of the acetal was accompanied by cyclisation to the imidazole ring. A. Lawson[46] prepared the series of 2-aryl- and 2-pentyl-4(5)-substituted imidazoles shown below by a similar method.



R^1 = -H, -Me, $-CO_2Et$, -Et, $-CH_2CO_2Et$, $-CH_2OH$, -Ph, $-CH_2Ph$, $-CH_2C_6H_4$-4-OH, $-C_6H_4$-4-OH

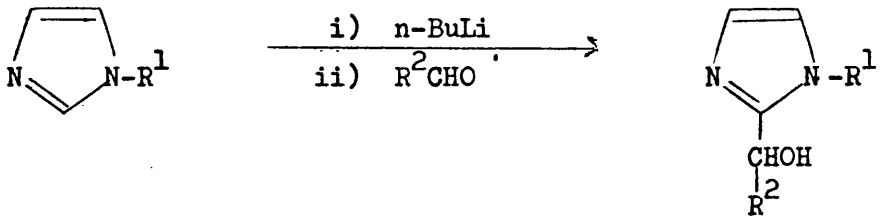
R^2 = -Ph or $-C_5H_{11}$

The use of a combination of the routes described by Ellinger and Goldberg[43-45] and J.K. Lawson[50,51] to prepare isohistamine[8] (I.2) and its analogues will be discussed in Section III.

3. Metalation of imidazoles with organolithium compounds

Metalation affords a convenient method of introducing functional groups into the 2-position of the imidazole nucleus. A recent review[52] describes the application of this method to imidazole and other heterocycles.

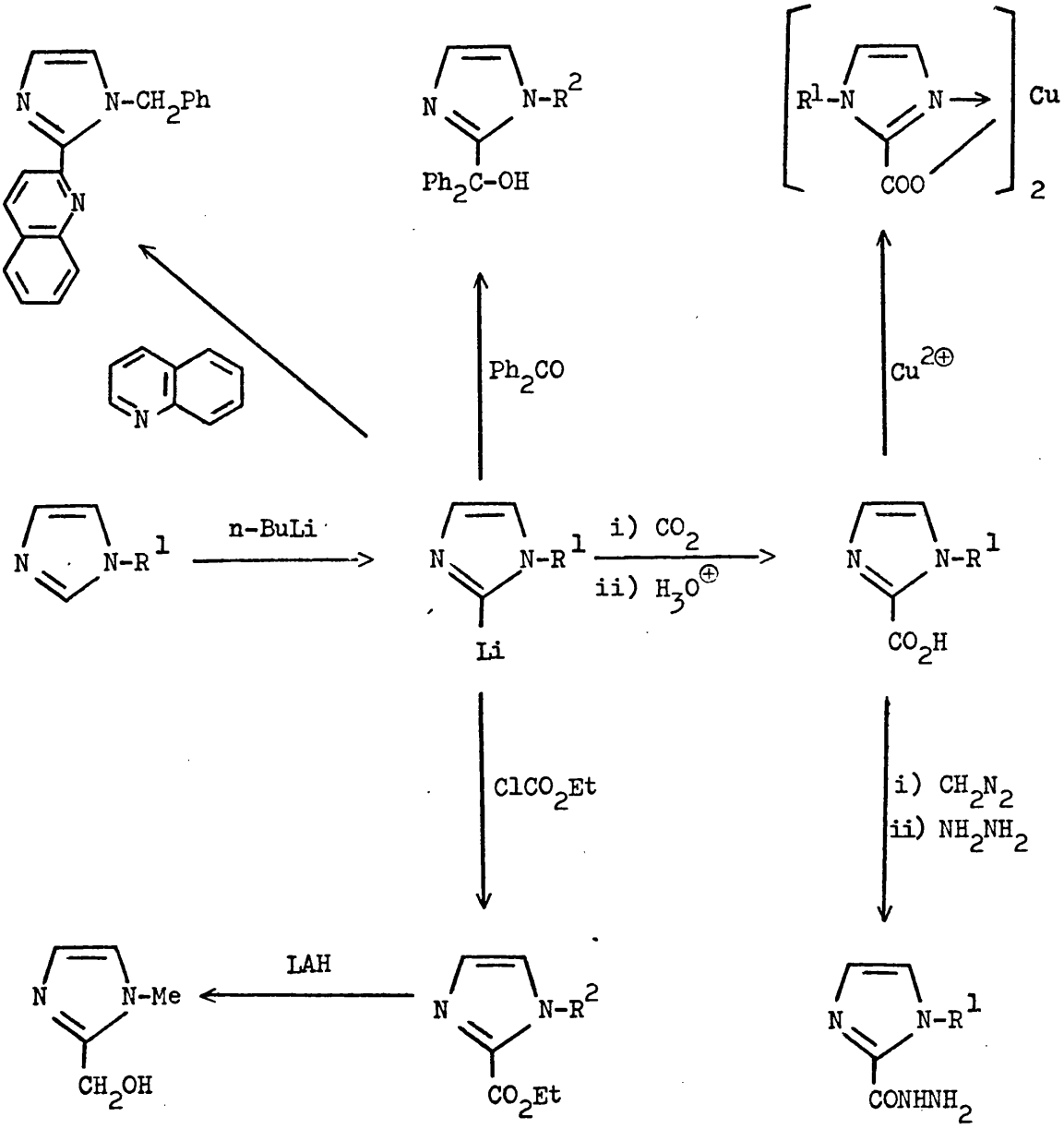
Shirley and Alley[53] demonstrated that 1-substituted imidazoles undergo metalation by n-butyllithium at low temperatures with the formation of 2-lithio derivatives, which are useful intermediates for the preparation of a range of 2-substituted imidazoles (Scheme I.7, p. 20). They also show that the 5-lithio derivative of 1-methylimidazole was formed in approximately 5% yield. Following this work, Roe[54] prepared a series of secondary alcohols (I.35) by the action of aldehydes on the lithio derivatives of 1-substituted imidazoles (Scheme I.8).



(I.35)

R^1 = -Me, $-CH_2Ph$, $-CH_2OMe$

R^2 = -Me, -Ph, $-CH_2Ph$, $-C_6H_4$-4-OMe, $-C_6H_4$-4-NMe_2, -2-C_5H_4N, -3-C_5H_4N, -n-C_6H_{13}.

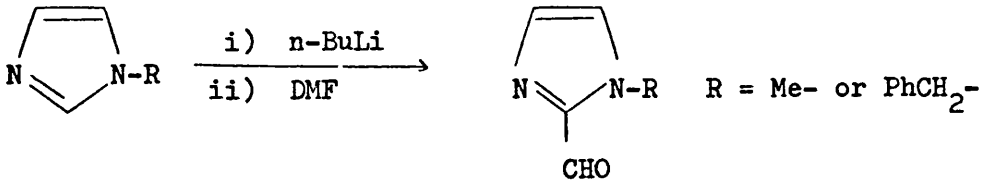


R^1 = -Me, -Ph or $-CH_2Ph$

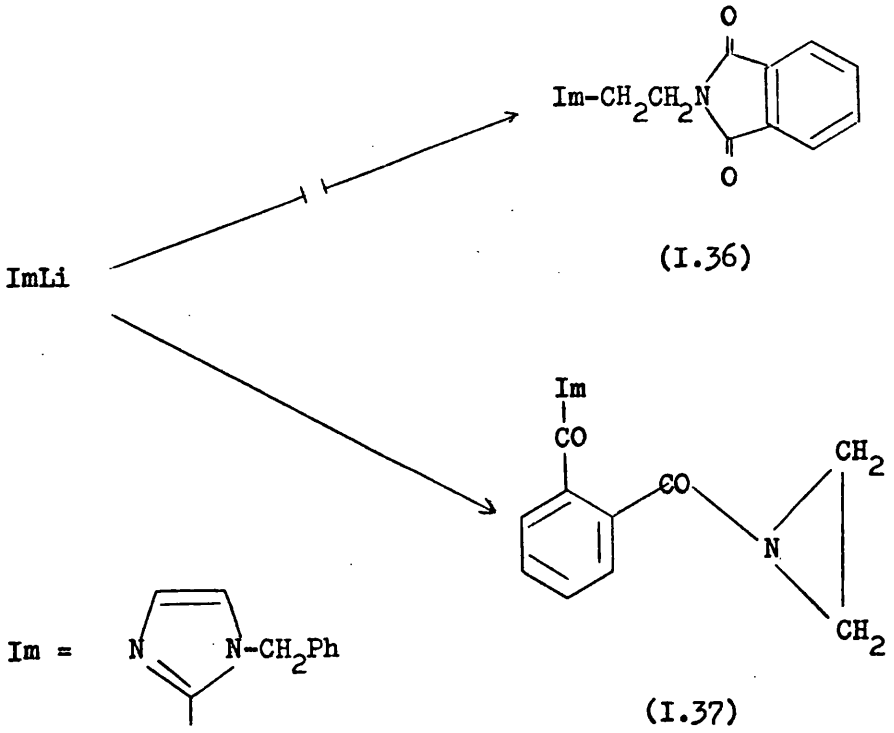
R^2 = -Me or -Ph

Scheme I.7

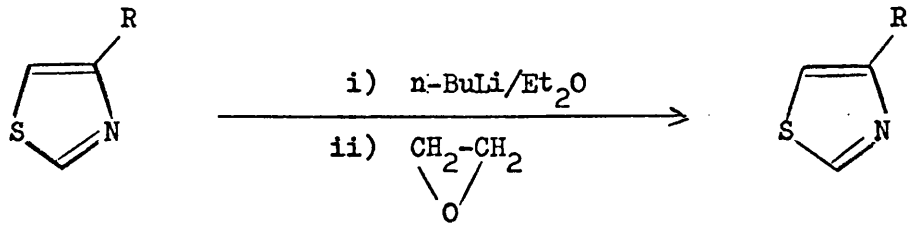
Iversen and Lund[55] have recently made a comparative study of the yields of 1-substituted imidazole-2-carboxaldehydes obtained using four different methods. These included metalation, oxidation of a 2-methyl group and oxidation of a 2-hydroxymethyl group with selenium dioxide or nitric acid. On the grounds of convenience and yield metalation procedures were preferable to the other methods.



Attempts have been made to prepare 1-benzyl-2-(2-N-phthalimidoethyl) imidazole by the reaction of bromoethylphthalimide with the lithio derivative of 1-benzylimidazole[15] (Scheme I.9). Instead of the desired product (I.36), the amide (I.37) was isolated, due to the reaction of the lithio derivative at the carbonyl group of the phthalimide, not at the halogen group as had been expected.



As far as is known a 2-substituted-ethyl side chain has not been successfully introduced into the 2-position of the imidazole nucleus by the use of lithio derivatives. However, the lithio derivatives of thiazole and 4-methylthiazole can be successfully hydroxyethylated using ethylene oxide[56] and, by analogy, this method



R = -H or -Me

could present an attractive route to isohistamine and its derivatives. Application of this type of reaction to imidazoles will be discussed in Section IV.

SECTION II

CHAIN EXTENSION BY NUCLEOPHILIC DISPLACEMENT OF HALOGEN IN 2-CHLOROMETHYLIMIDAZOLE DERIVATIVES

DISCUSSION

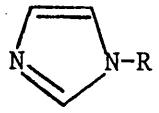
This section describes our investigation of the purported synthesis of isohistamine,2-(2-aminoethyl)imidazole,and it also describes the synthesis of related compounds by chain extension methods.

1-Substituted imidazoles

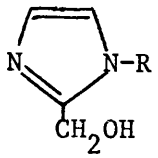
The starting materials used in this study were 1-methyl- and 1-benzyl-imidazole (II. 1a) and (II. 1b), which were obtained using established methods involving the alkylation of the sodio derivative of imidazole in liquid ammonia.[54] The use of a modified isolation procedure[55] in the preparation of 1-benzylimidazole (II. 1a) led to higher yields and a cleaner product.

Hydroxymethylation of 1-substituted imidazoles

Certain 1-methylimidazoles have for long been known to condense with formaldehyde to yield the corresponding 2-hydroxymethylimidazoles.[17,54,55,57,] In our hands, this condensation was found to be particularly dependent upon the temperature of reaction and the purity of the formaldehyde solution. Unless fresh AR 40% formalin was used, low yields of 1-methyl-2-hydroxymethylimidazole (II. 2b) were obtained.



(II. 1)



(II. 2)

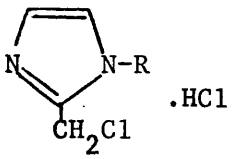
a, R = $-CH_2Ph$

b, R = -Me

The preparation of 1-benzyl-2-hydroxymethylimidazole (II. 2a) appeared to be less susceptible to changes in reaction conditions and proceeded in high yield as described.[9,54,55]

1-Substituted-2-chloromethylimidazoles

The conversion of a hydroxymethyl into a chloromethyl heterocycle can be accomplished by reaction with thionyl chloride, phosphorus chlorides or hydrogen chloride. On the grounds of convenience, thionyl chloride was preferred since volatile secondary products were formed and isolation of the chloromethyl compounds (II. 3a) and (II. 3b) as their hydrochlorides was readily accomplished. This method has been described.[9,16]



(II. 3)

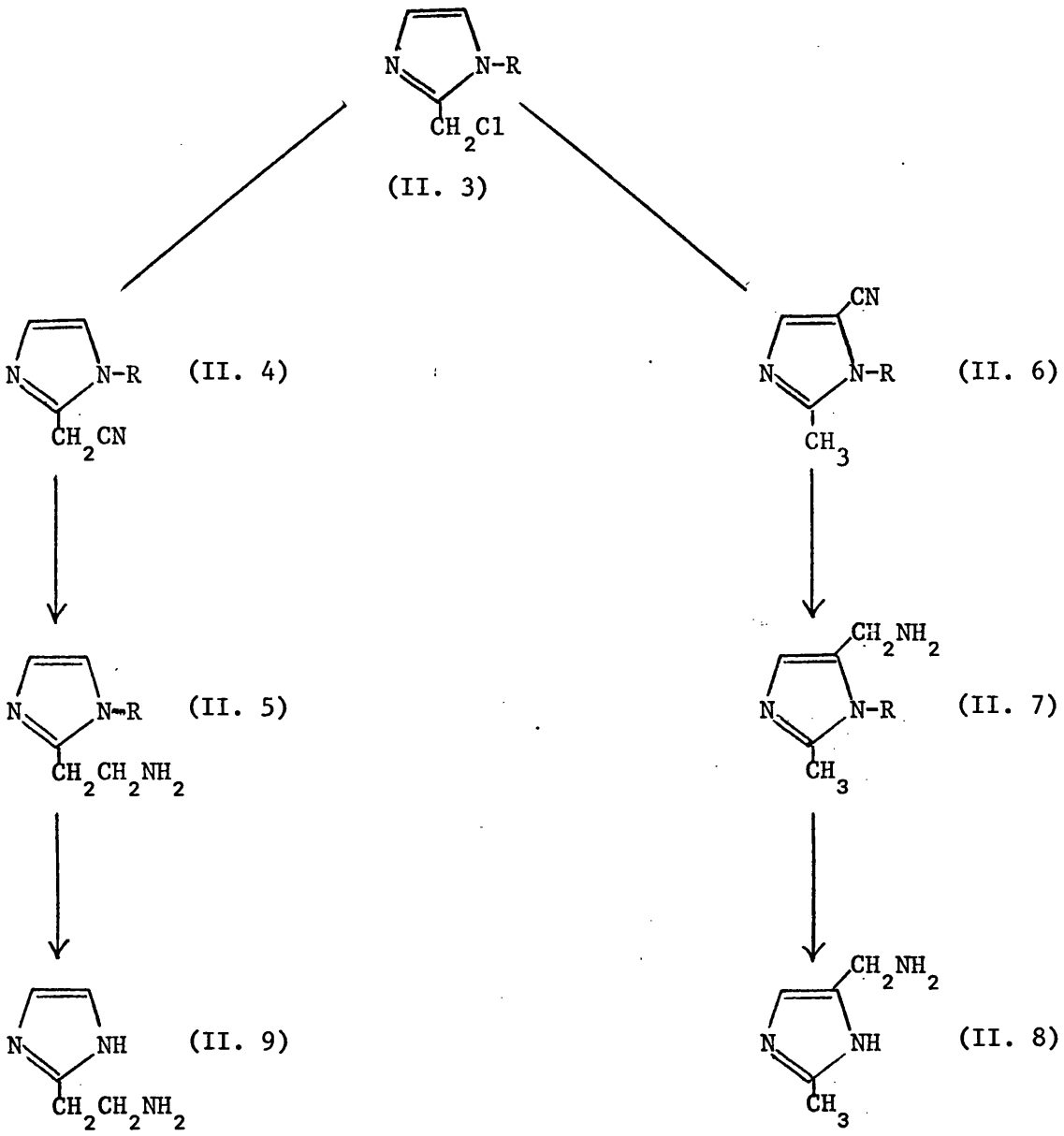
a, R = CH_2Ph

b, R = -Me

Displacement reactions with cyanide ion as nucleophile

Investigation of Jones' synthesis of isohistamine[9]

Description of this reaction is perhaps simplified by reference to Scheme I. in the Introduction which is reproduced here. (Scheme II. 1). The chloromethyl compound (II. 3a) was treated with potassium cyanide in aqueous ethanol.



a, R = $-CH_2Ph$

b, R = -Me

Scheme II.1

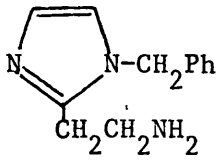
The major product, isolated as its picrate, was identical to that described as (II. 4a) by Jones. However, the n.m.r spectrum was incompatible with this structural assignment and supports its reformulation as (II. 6a). Thus it appears that the chloromethyl compound (II. 3a) had undergone nuclear substitution by cyanide ion with displacement of chloride ion, followed by rearrangement of a proton. The nitrile (II. 6a) was reduced by the action of lithium aluminium hydride in ether to give the aminomethyl compound (II. 7a) in good yield. Debenzylation of this material with sodium in liquid ammonia using the established method of du Vigneaud[59] afforded the amine (II. 8).

This finding of a hitherto undetected rearrangement indicated that Jones had not obtained authentic isohistamine (II. 9); the compounds formulated as the aminoethyl compounds (II. 5a) and (II. 9) have now been shown to be the aminomethyl compounds (II. 7a) and (II. 8). Table II. 1 (p. 34) shows the melting points of compounds whose structures have been confirmed by n.m.r. analysis, and the melting points recorded by Jones and other workers. These clearly illustrate the error of their structural arrangements.

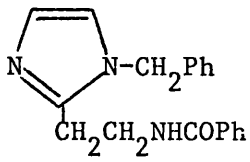
Initially, the normal substitution product (II. 4a) was not detected, but it was later isolated by fractional crystallisation of the mixed picrates, and its properties were found to differ considerably from those claimed by Jones. From n.m.r. data it was concluded that the "abnormal" and "normal" products were present in approximately equimolar proportions.

The n.m.r spectrum of the authentic cyanomethyl compound (II. 4a) hydrochloride in deuterium oxide exhibited no signal attributable to the 2-methylene protons, indicating rapid proton-deuteron exchange in this solvent. The finding that the methylene protons were acidic led us to believe that attempted reduction of this material with lithium aluminium hydride might give rise to complications due to the interaction of the $(AlH_4)^{\ominus}$ moiety with the methylene group. In these laboratories the reduction of the isomeric 4-cyanomethyl compound with lithium aluminium hydride was accomplished with difficulty and low yields of the aminoethyl compound were obtained.[60]

A survey of other reducing agents revealed that diborane or a catalytic method could offer advantages over lithium aluminium hydride. Catalytic methods might lead to reduction of the benzyl protecting group or even its cleavage. For these reasons diborane was chosen. In order to simplify the isolation procedure the diborane was generated externally[61] and the reduction of the nitrile (II. 4a) was carried out in tetrahydrofuran. The resulting boron complex was decomposed by heating under reflux in hydrochloric acid, which resulted in incomplete decomposition. Additional treatment with strong base was necessary to effect total breakdown of the boron complex. The reaction proceeded in high yield and the aminoethyl compound (II. 5a) was isolated as its dipricate in 62% yield. 1-Benzylisohistamine (II. 5a) was benzoylated under typical Schotten-Baumann conditions to yield the benzoyl derivative (II. 10).


(II. 5a)

PhCOCl/aq.NaOH

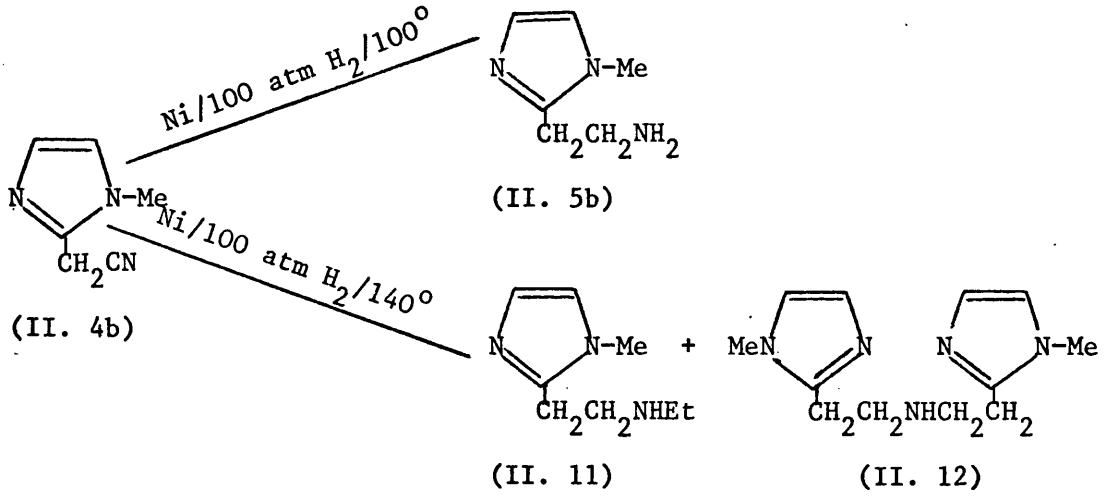

(II. 10)

After we had discovered this abnormal nucleophilic displacement, Gutche reported that he had also observed it.[13] Following the publication of our findings,[8] workers at the Eli Lilly Laboratories, led by Kornfeld,[15] corrected the earlier structural consignments of their colleague Jones.[9]

Investigation of Jocelyn's synthesis of 1-methylisohistamine[16]

In view of the rearrangement detected during the Jones' synthesis of isohistamine, it was decided to examine Jocelyn's reported synthesis of the 1-methyl analogue (II. 5b). In this case also the chloromethyl compound (II. 3b) afforded a mixture of nitriles on treatment with potassium cyanide in aqueous ethanol. We were not able to separate these isomers as claimed by Kornfeld's team, who reported[15] that "picrate salt formation gave only the normal isomer, therefore, Jocelyn's structure seems secure". This claim is entirely unsupported by experimental evidence and since Kornfeld does not record the melting points of these picrates, it is difficult to assess his work. As will be shown later we have conclusive evidence that Jocelyn's structure is incorrect, therefore we cannot allow Kornfeld's conclusions to remain unchallenged. In our hands a mixed picrate was isolated, m.p. 164-7°, comprising approximately 35% of the rearranged product (II. 6b) and 65% of the normal isomer (II. 4b). The physical properties of this mixture were identical to those claimed by Jocelyn (See Table II. 1). The nitriles (II. 4b) and (II. 6b) were separated by converting the mixed picrates into the free bases

and separating the mixture on an alumina column. The isomers were converted into their individual picrates, and mixed melting point determinations were carried out on these picrates using intimately ground mixtures of known composition. A graph of melting point against composition (Figure II. 1) showed that a compound with an incongruent melting point was formed, having a composition approximately 20% normal product (II. 4b) and 80% rearranged product (II. 6b). The melting point of a mixture of picrates with similar composition to that estimated from the n.m.r. spectrum to constitute the crude reaction product was identical to that observed. These mixed melting point determinations reinforce our conviction that the products cannot be separated by fractional crystallisation of the mixed picrates as claimed.[15] Reduction of the nitrile (II. 6b) with lithium aluminium hydride in ether afforded the aminomethyl compound (II. 7b). Like the benzyl analogue the methylene protons of the cyanomethyl compound (II. 4b) are acidic and exchange for deuterons in deuterium oxide. For this reason, attempts were not made to reduce the nitrile (II. 4b) with lithium aluminium hydride and instead a catalytic method was used. Reduction of the nitrile (II. 4b) was effected in ammoniacal methanol at 100° under 100



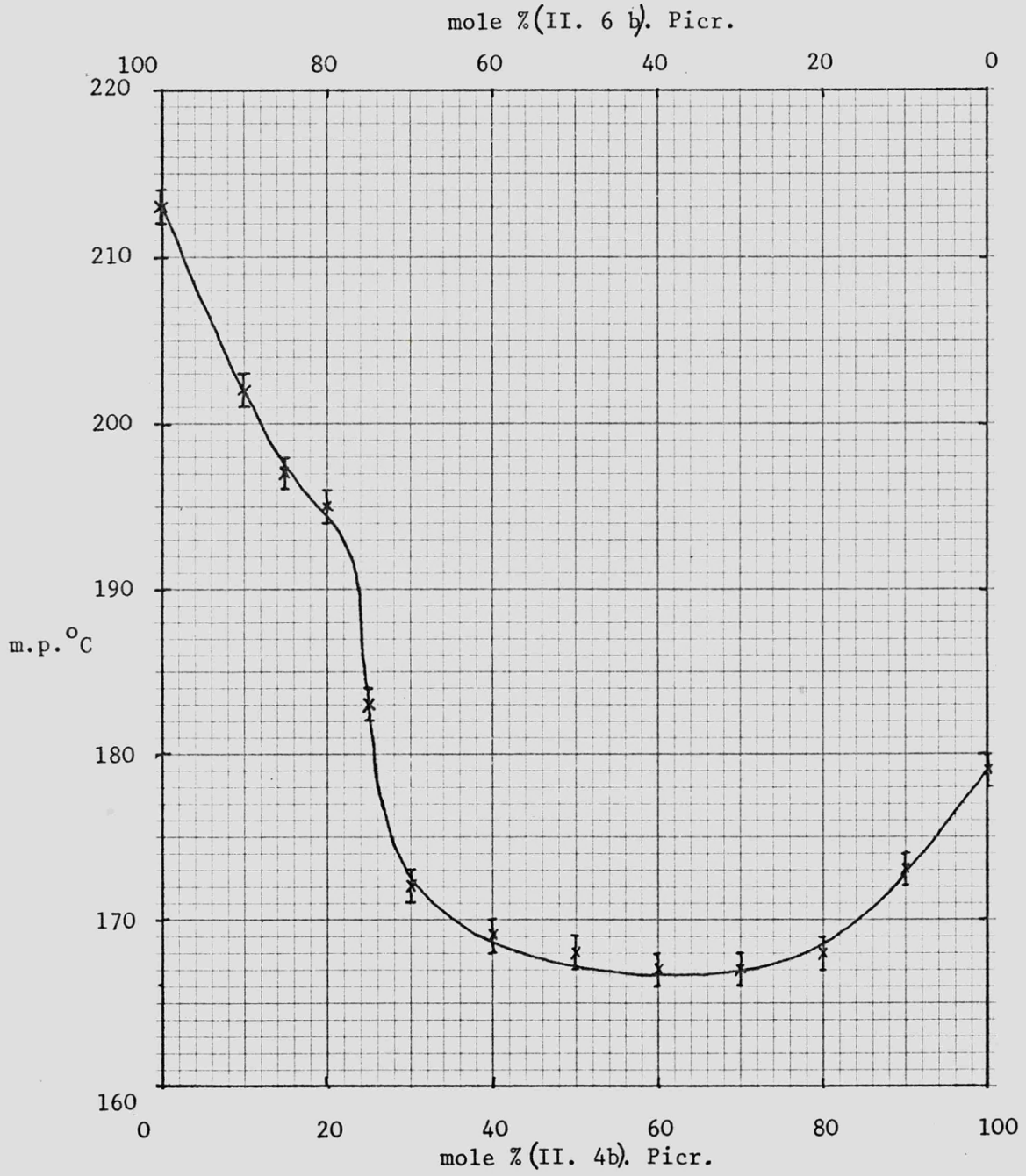


Fig. II. 1

Phase diagram of mixtures of picrates of 1-methyl-2-cyanomethylimidazole (II. 4b) and 1,2-dimethyl-5-cyanoimidazole (II. 6b)

atmospheres of hydrogen using Raney nickel as catalyst, and the amine (II. 5b) was isolated as its dipicrate. When the reduction was carried out in ethanol containing insufficient ammonia using Raney nickel as catalyst at 140° under 100 atmospheres of hydrogen, the N-ethyl compound (II. 11) and the bis amine (II. 12) were isolated as their di- and tri-picrates respectively. Alkylation by solvent ethanol is common in such reactions at temperatures above 150° [62] and this accounts for the formation of the N-alkyl compound (II. 11). The bis-amine (II. 12) arose due to insufficient ammonia being present in the reaction mixture. Examination of Table II. 1 shows that the melting points of the amine picrates (II. 5b) and (II. 7b) are very close, but, those of the dihydrochlorides differ by 70°. Jocelyn records a melting point very similar to that of the rearranged dihydrochloride and we concluded that he did not obtain 1-methylisohistamine. As has been mentioned, these findings differ from those of the Eli Lilly Laboratories.

We were fortunate to have obtained from Dr. P.C. Jocelyn a few milligrams of the product, which he formulated as 1-methylisohistamine (II. 5b) dipicrate. Owing to the very small amount of material available the n.m.r. spectrum was obtained only by the use of a computer of average transients. Two thousand scans were necessary in order to obtain an interpretable spectrum which clearly showed that the material comprised mainly the rearranged product (II. 7b) together with a small quantity of 1-methylisohistamine (II. 5b). The remainder of the material was subjected to a thin layer chromatographic examination on precoated silica gel plates, using methanol/35% aqueous ammonia, 6:1, as solvent system, and was compared with reference mixtures of dipricrates of the amines (II. 5b) and (II. 7b). Visualisation of the separated components with potassium iodoplatinate indicated that Jocelyn's sample contained approximately 5% of the normal product (II. 5b). (See Figure II.2. p. 33).

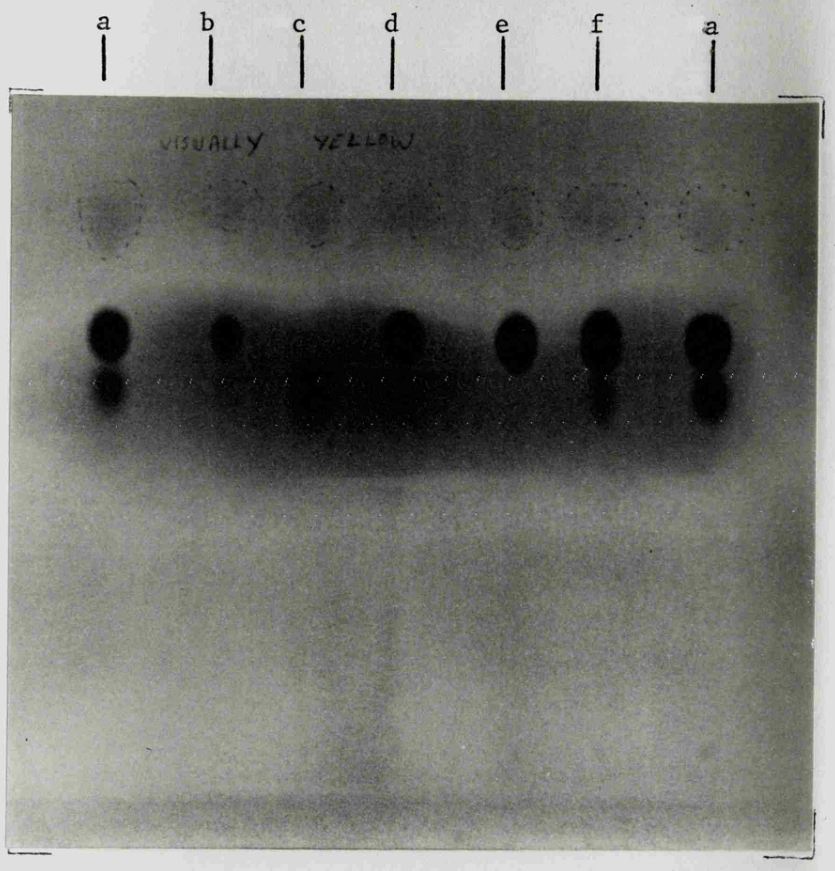


Fig. II. 2

Thin layer chromatogram of mixtures of picrates of 1-methyl-2-cyanomethylimidazole (II. 4b) and 1,2-dimethyl-5-cyanoimidazole (II. 6b)

Samples run on precoated silica gel plates using methanol/35% aqueous ammonia, 6:1 as solvent system and visualised with potassium iodoplatinate. The visually yellow spot is characteristic of picric acid run in this system.

Applications

a) 25 µg. (II. 4b) Picr.+25 µg. (II. 6b) Picr.

b) 10 µg. Jocelyn's sample.

c) 25 µg. (II. 4b) Picr.

d) 25 µg. Jocelyn's sample.

e) 25 µg. (II. 6b) Picr.

f) 50 µg. Jocelyn's sample.

Table II. 1

Physical properties of compounds obtained during the investigation of Jones' and Jocelyn's syntheses of isohistamines

COMPOUND[a]	M.p.	LITERATURE		CHEMICAL SHIFT (τ)[b]	MULTIPLICITY[c]	RELATIVE INTENSITY	ASSIGNMENT
		STRUCTURE	M.p.				
(II. 3a) HCl[d,e]	187°	(II. 3a)[9]	181-182	2.22 2.31	q[g]	2	4-H,5-H
				4.34	s	2	$-\underline{CH_2}Ph$
				4.74	s	2	$-\underline{CH_2}Cl$
(II. 6a) base	123-124	(II. 4a)[9]	114-115	1.63	s	1	4-H
HCl[d,e]	177-178.5			4.38	s	2	$-\underline{CH_2}Ph$
picr.	167-169		166-167	7.15	s	3	$-C\underline{CH_3}$
(II. 7a) base	61.5- 63.5	(II. 5a)[9]	59- 60	2.22	t	1	4-H
2HCl[d,e]	226-228		222-225	4.39	s	2	$-\underline{CH_2}Ph$
dipicr.	189-191 (decomp)		185-186	5.62	d	2	$-\underline{CH_2}N$
				7.26	s	3	$-C\underline{CH_3}$
(II. 8) 2HCl[d,e]	229.5-231 (decomp)	(II. 9)[9]	229-230	2.42	broad s	1	4-H
dipicr.	213-214 (decomp)		213-214 (decomp)	5.60	d	2	$-\underline{CH_2}N$
				7.31	s	3	$-C\underline{CH_3}$
(II. 4a) base	101-103	(II. 4a)[15]	102.5-103.5	2.17 2.24	q[g]	2	4-H,5-H
HCl[d,e]	188-189.5 (decomp)		196-202				
picr.	131-133			4.42	broad s	2	$-\underline{CH_2}Ph$
				5.10	s[h]	2	$-\underline{CH_2}CN$
(II. 5a) dipicr.[d,f]	191-193			2.28	broad s	2	$-\underline{CH_2}Ph$
2HCl		(II. 5a)[15]	158-160	4.53	s	2	$-\underline{CH_2}CN$
				Centred 198 c/s	broad s	2	4-H,5-H
(II. 9) 2HCl[d,e]	262-263 (decomp)	(II. 9)[15]	265-266	2.58	s	2	4-H,5-H
dipicr.	217-218 (decomp)			6.52	s	4	$-\underline{CH_2}\underline{CH_2}-$
(II. 6b) base	54-57	(II. 4b)[16]		1.53	s	1	4-H
picr.[d,f]	211-212		165-166	6.17	s	3	$-N\underline{CH_3}$
				7.35	s	3	$-C\underline{CH_3}$
(II. 7b) 2HCl	268-270 (decomp)	(II. 5b)[16]	262-263	2.40	t	1	4-H
dipicr.H_2O[d,f]	219-220 (decomp)		196	5.55	d	2	$-\underline{CH_2}-$
				6.17	s	3	$-N\underline{CH_3}$
				7.31	s	3	$-C\underline{CH_3}$
(II. 4b) HCl	236-238 (decomp)			2.24 2.31	q[g]	2	4-H,5-H
picr.[d,f]	179-180 (decomp)			5.31	s[h]	2	$-\underline{CH_2}CN$
				6.08	s	3	$-N\underline{CH_3}$
(II. 5b) 2HCl.$\frac{1}{2}H_2O$[d,e]	193-195 (decomp)			2.52	s	2	4-H,5-H
dipicr.	213.215 (decomp)			6.08	s	3	$-N\underline{CH_3}$
				6.68	s	4	$-\underline{CH_2}\underline{CH_2}-$

See p. 35 for footnotes.

Notes to Table II. 1

a) All compounds had satisfactory microanalysis; n.m.r. spectra were determined on a Varian A60A spectrometer using approximately 10% w/v solutions.

b) Signals from phenyl-, picryl and N-H protons are omitted from this Table.

c) s = singlet, d = doublet, t = triplet, q = quartet.

d) Compound used for n.m.r. determination.

e) Determination in D_2O using sodium 2,2-dimethyl-2-silopentane sulphonate as internal reference.

f) Determination in $(CD_3)_2SO$ using tetramethylsilane as internal reference

g) J(4-H, 5-H) = 2.0 c/s.

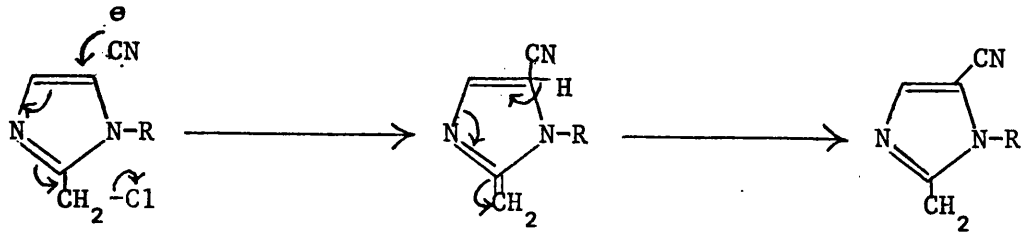
h) When the spectra of II. 4a and II. 4b as their hydrochloride salts were determined in D_2O, the $-\underline{CH_2}-$ signals were not observed, indicating rapid proton- deuteron exchange in this solvent.

Kornfeld[15] and his colleagues achieved a synthesis of isohistamine using essentially the same sequence as Jones,[9] except that displacement of chlorine by cyanide was carried out in a dipolar aprotic solvent (dimethyl sulphoxide) using sodium cyanide. Under these conditions only the normal nitrile (II. 4a) was obtained. They also stated that treatment of the 1-methyl analogue (II. 3b) with sodium cyanide in dimethyl sulphoxide afforded only the normal product (II. 4b). These findings, which have been repeated, were in agreement with our observations that displacement of chlorine by sodium cyanide in dimethyl formamide did not lead to formation of the abnormal nitrile (II. 6a).

As early as 1962 F. Holmes and F. Jones had studied the formation of complexes of copper and nickel ions with 2-(2-aminoethyl) imidazole,[14,63] which they had prepared by the method of R.G. Jones.[9] They found that the formation constants were anomalous, and were more like those to be expected for a 5-membered ring chelated complex. This anomaly is now removed since they were in fact studying complexes of the aminomethyl compound (II. 8). Holmes and his coworkers have now studied[64,65] the formation of these complexes with authentic isohistamine (II. 9) which we supplied as the dihydrochloride in a high state of purity.

Both the acid dissociation constants (pKa's) of Jones' compound are unexpectedly close to those of histamine, and in order to rationalise these facts, several pKa's of relevant compounds have been measured. The pKa's of the ring protons are listed in Table II 2. It will be seen that substitution of a 2-methyl group in imidazole, 4(5)-aminomethyl-imidazole and 4(5)-aminoethylimidazole, increases the basicity of the ring by 0.9-1.2 units. It will also be seen that there is a decrease in the basicity of the ring on going from a protonated aminoethylimidazole to a protonated 4(5)-aminomethylimidazole of about 1.1-1.4 units, which accounts for this coincidence. Furthermore the pKa's of authentic isohistamine (9.37 and 6.08) are also very close to the values for histamine itself, (9.815 and 6.07), which we have determined.

We have provided no evidence to aid a discussion of the mechanism by which a 5-cyanoimidazole is obtained from a 2-chloromethylimidazole. Gutche and Voges claim that the mechanism is S_N2', but present no evidence to support this claim.[13] Suschitzky has discussed the mechanisms by which such reactions can occur and has discussed the effect of solvent.[19] We recognise that a mechanism cannot be defined until kinetic studies have been carried out, but we can only postulate that the formation of the abnormal nitrile (II. 6) occurs via the intermediate (II. 13).



(II. 13) (II. 6)

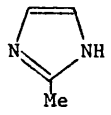
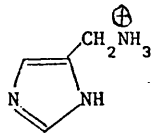
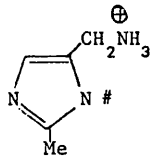
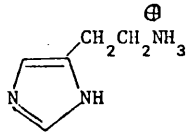
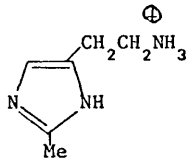
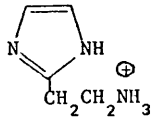
COMPOUND	pKa
	7.06 [a]
	7.97 [a]
	4.71 [b]
	5.95 [b]
	6.07 [a]
	7.03 [a]
	6.08 [a]

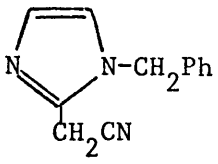
Table II. 2

The data given above are the apparent pKa's in water for the imidazole ring and were obtained by treatment of the protonated imidazoles with 0.1M sodium hydroxide against a "background" of similar ions to those of the protonated species.

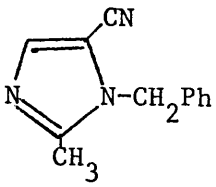
a Determined in our laboratories by Mr. M.J. Graham and relate to the hydrochloride sales in 0.1M potassium chloride. The determination was carried out using Radiometer equipment, comprising an Autoburette with titration assembly and a pH52 meter, with microglass and calomel electrodes.

b Determined by Holmes and Jones.[14,63] The percholorate salts were used against a background of perchlorate ions.

As a necessary prelude to a study of the effects of solvent on the cyanide replacement reaction, a simple method of determining the proportions of the normal and abnormal nitriles (II. 4a) and (II. 6a) would have been a decided advantage. For our purposes gas-liquid chromatographic techniques would have been ideal. Although conditions were established



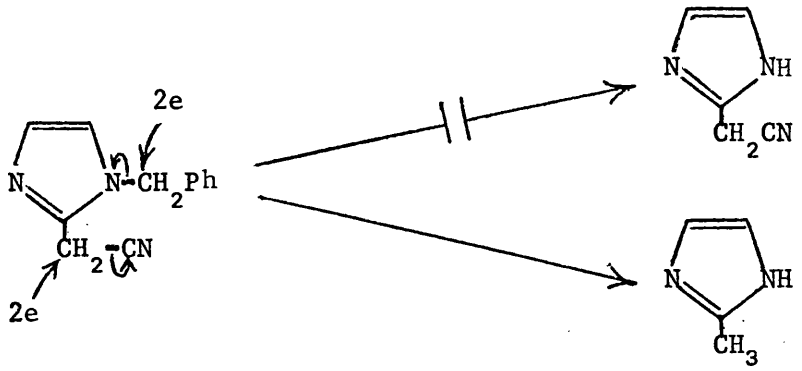
(II. 4a)



(II. 6a)

for the separation of the nitriles, it was not found possible to determine the proportion of each isomer present in a mixture because the response of a flame ionisation detector to the normal nitrile (II. 4a) is approximately 20% that of the rearranged material (II. 6a). This phenomenon possibly arises from the acidity of the 2-methylene protons which has been discussed earlier. A solution to this dilemma would have been to use a gas density balance as detector. Although not available in our laboratories we had access to such an instrument, but unfortunately the separation of the isomers was not accomplished with this apparatus. It would have been possible to estimate the proportions of products using n.m.r techniques but a much lower order of accuracy would have been obtained by such a method. This line of enquiry was therefore discontinued.

Attempts were made to debenzylate the nitrile (II. 4a) using sodium in liquid ammonia. As was usual for such debenzylation reactions, sodium metal was added to the nitrile in ammonia mixture until a blue colour persisted, hence an excess of sodium was usually present.



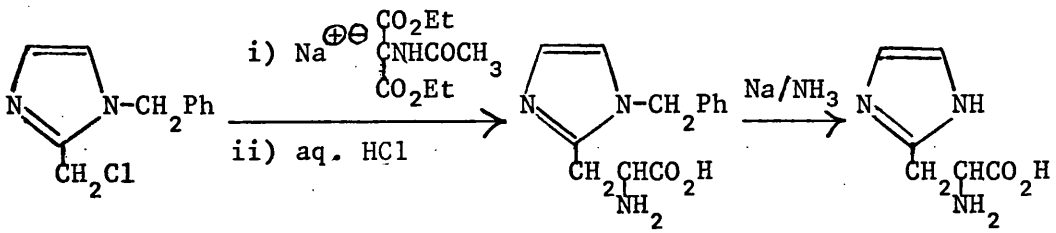
(II. 14)

(II. 15)

The product, isolated as its picrate, was identified as 2-methylimidazole (II. 15) and not the cyanomethyl compound (II, 14). There are some analogies for the cleavage of cyano groups from arylacetonitriles by sodium in liquid ammonia.[66] Essentially we have two debenzylation reactions taking place. The first is the normal debenzylation which has been observed by Kornfeld and his coworkers,[15] when the cyanomethyl compound (II. 14) was obtained. This is followed by a further cleavage in which the imidazol-2-yl group reacts like a benzyl group, and 2-methylimidazole (II. 15) is formed.

Displacement reactions with other nucleophiles

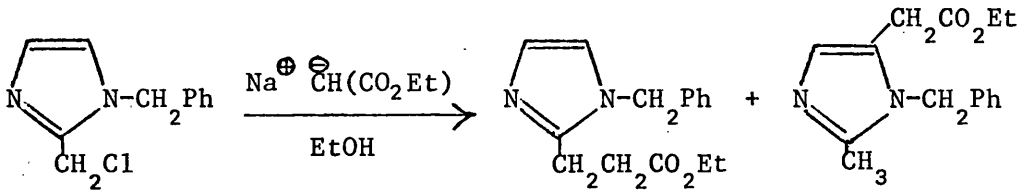
The anomalous nucleophilic displacement of chlorine by cyanide ion prompted us to investigate other nucleophilic displacements carried out on the chloromethyl compound (II. 3a) by R.G. Jones.[9] In particular the synthesis of isohistidine was investigated.



(II. 3a) (II. 16) (II. 17)

The displacement of chlorine by sodioacetamidomalonic ester in ethanol proceeded as described. The benzyl compound (II. 16) was isolated as its hydrate, and debenzylation was carried out under the usual conditions with sodium in liquid ammonia to give isohistidine (II. 17).

Similarly the chloromethyl compound (II. 3a) was condensed with sodiomalonic ester. The product from this reaction was examined by



(II. 3a) (II. 18) (II. 19)

n.m.r. and gas-liquid chromatographic techniques. The n.m.r. spectrum (Table II. 3) indicated that the material comprised mainly the normal product (II. 18). Gas-liquid chromatography supported these findings. Attempts were made to separate the isomers using preparative gas-liquid chromatography but an n.m.r. spectrum of the material obtained indicated that decomposition of the material had occurred at the high temperature necessary to achieve separation. This is the first example of this type of rearrangement occurring with a carbanion as nucleophile.

Compound	Chemical Shift	Multiplicity	Assignment
II. 18	3.06 } 3.20 }	d	4-H, 5-H
	4.92	s	$-\underline{CH_2}Ph$
	5.90	q	$-O\underline{CH_2}CH_3$
	180-155	broad s	$-\underline{CH_2}\underline{CH_2}-$
	8.33	t	$-OCH_2\underline{CH_3}$
II. 19	3.27	d	4-H
	4.97	s	$-\underline{CH_2}Ph$
	6.40	s	$-CH_2CO_2-$
	8.03	s	$-C\underline{CH_3}$

Table II. 3

N.m.r. spectrum of the ester mixture comprising (II. 18) and (II. 19)

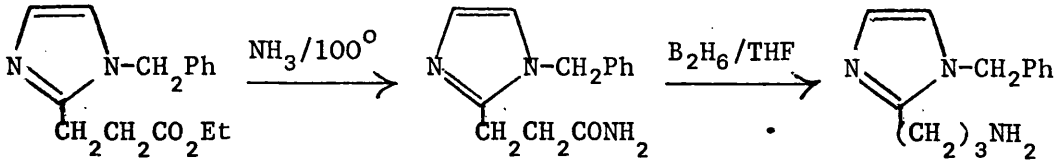
The spectrum was run in deuterochloroform using tetramethylsilane as internal reference. The above peaks are the only definitely assignable signals in the spectrum. From the ratio of the signals it was concluded that the mixture comprised mainly the "normal" product (II. 18) together with approximately 5% of the rearranged material (II. 19).

Synthesis of compounds related to isohistamine

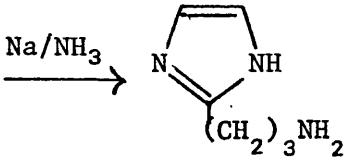
In view of the pharmacological interest aroused by our findings concerning the synthesis of isohistamine, using routes involving the displacement of chlorine by cyanide ion, homologues of isohistamine were prepared for pharmacological evaluation. (See Section V).

2-(3-Aminopropyl)imidazole (II. 22)

As mentioned earlier, the ester (II. 18) was obtained by treatment of the chloromethyl compound (II. 3a) with sodiomalonic ester. The following sequence was utilised to obtain the isohistamine homologue (II. 22). Treatment of the purified ester (II. 18) with liquid



(II. 18) (II. 20) (II. 21)

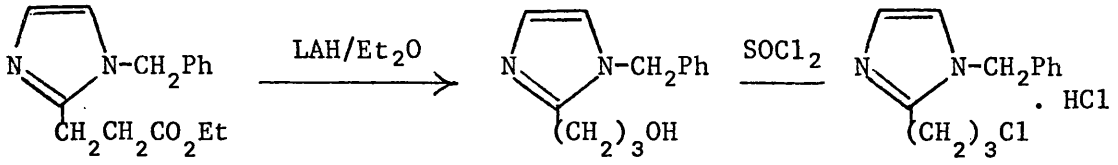


(II. 22)

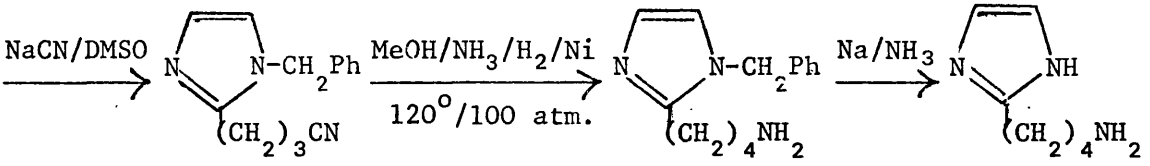
ammonia in an autoclave at 100° afforded the amide (II. 20) in 80% yield, which was reduced with externally generated diborane to give a 70% yield of the amine (II. 21), isolated as its dipricate. After conversion into its dihydrochloride this material was debenzylated to give the aminopropyl compound (II. 22) which was characterised both as its dipicrate and dihydrochloride.

2-(4-Aminobutyl)imidazole (II. 27)

The ester (II. 16) also offered a convenient route to the four-carbon side chain analogue of isohistamine. The following route was used.



(II. 16) (II. 23) (II. 24)



(II. 25) (II. 26) (II. 27)

Reduction of the ester (II. 16) with lithium aluminium hydride occurred in almost quantitative yield to give the alcohol (II. 23). The alcohol (II. 23) was treated with thionyl chloride and a small quantity of water to ensure hydrochloride formation, to give the chloro compound (II. 24).

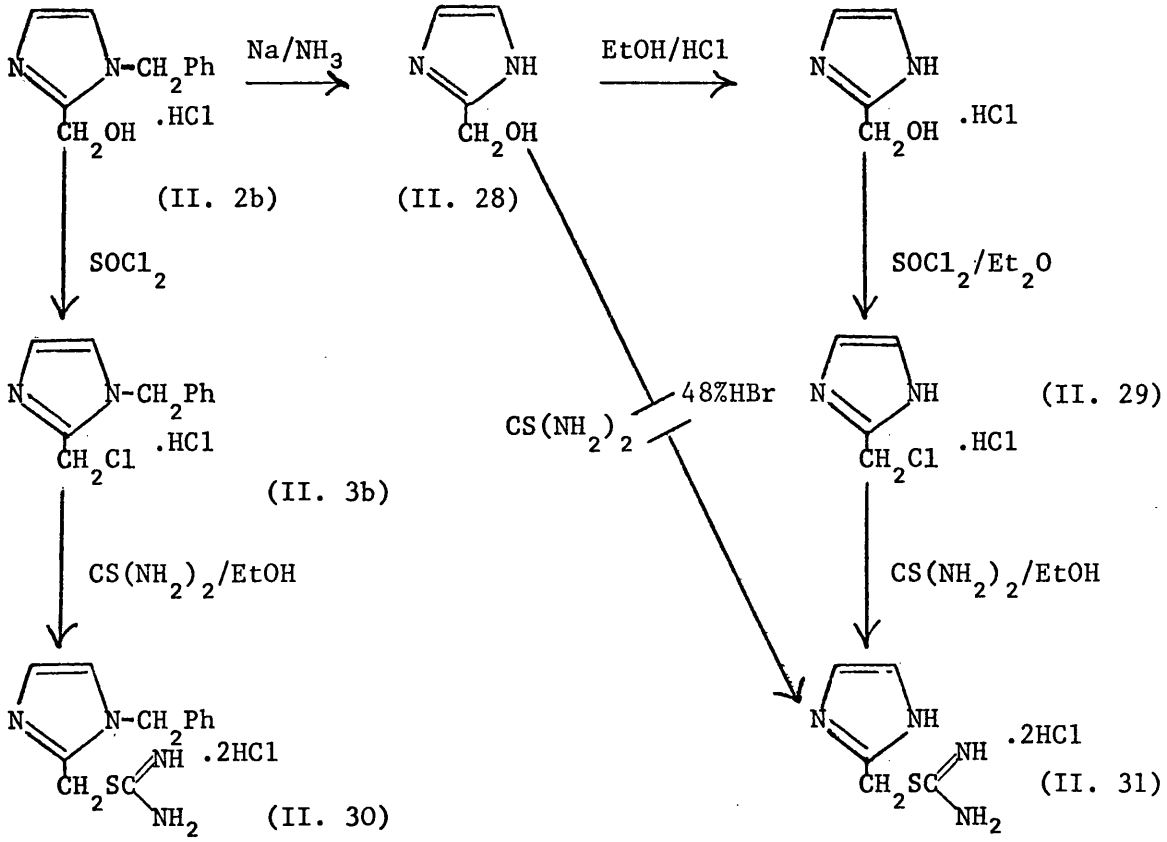
Generally the conversion of an alcohol to a chloro compound occurred more readily when the hydrochloride salt was used. When this was not available precautions to ensure an excess of hydrogen chloride were necessary. In addition, specially pure thionyl chloride occasionally had to be employed. In view of our earlier findings, the displacement of chlorine in (II. 24) was carried out using

sodium cyanide in a dipolar aprotic solvent (dimethyl sulphoxide) and approximately 80% conversion was attained. Reduction of the nitrile (II. 25) using Raney nickel and hydrogen under pressure, gave the amine (II. 26) which was characterised as its dipicrate. The dihydrochloride of this material was extremely hygroscopic and could not be characterised. Debenzylation of the crude dihydrochloride of the aminobutyl compound (II. 26) was carried out under the usual conditions with sodium in liquid ammonia and the required amine (II. 27) was characterised both as its dihydrochloride and dipicrate salts.

Isothioureas

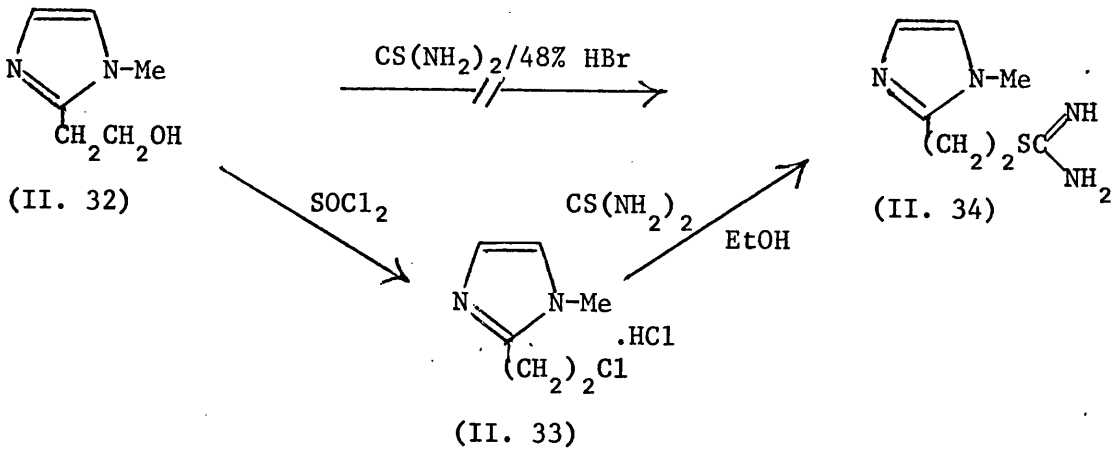
In these laboratories the preparation of isothioureas of potential pharmacological interest has been carried out using two general methods. Where the chloroalkyl compounds could be conveniently obtained as hydrochlorides, reaction with an ethanolic solution of thiourea was the method of choice and the isothioureas were obtained as their dihydrochlorides. Generally, these reactions proceeded in high yield and few difficulties were encountered. In other cases, where only the corresponding alcohols were available, the isothioureas were prepared by heating with thiourea in constant boiling hydrobromic acid. Presumably the bromoalkyl compound is first formed which then reacts with the thiourea to form the isothioureas as their dihydrobromides.

S-(1-Benzylimidazol-2-yl)methylisothiourea (II. 30) and S-(Imidazol-2-yl)-methylisothiourea (II. 31) were obtained as their dihydrochlorides using the following reaction sequence. The benzyl-substituted isothiourea (II. 30) was prepared without difficulty from the chloro-methyl compound (II. 3b) under the usual conditions.



The alcohol (II. 2b) was debenzylated under similar conditions to those employed by Iversen and Lund.[55] Treatment of the alcohol (II. 28) with thiourea in hydrobromic acid did not furnish the required compound (II. 31). The chloromethyl compound (II. 29) was obtained from the hydrochloride of the alcohol (II. 28) by treatment with purified thionyl chloride. Purification of the thionyl chloride was effected by distillation from boiled linseed oil.[67] The chloromethyl compound (II. 29) was converted into its isothiourea (II. 31) by the usual method.

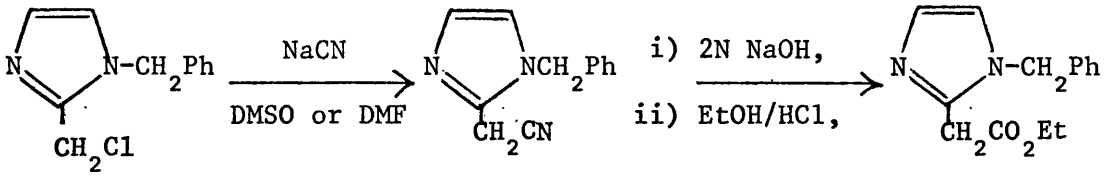
Attempts were then made to prepare several imidazolylethylisothioureas. 1-Methyl-2-(2-hydroxyethyl)imidazole (II. 32), prepared by reaction of the lithio-derivative of 1-methylimidazole with ethylene oxide (Section IV, p. 142) was treated with thiourea in 48% hydrobromic acid.



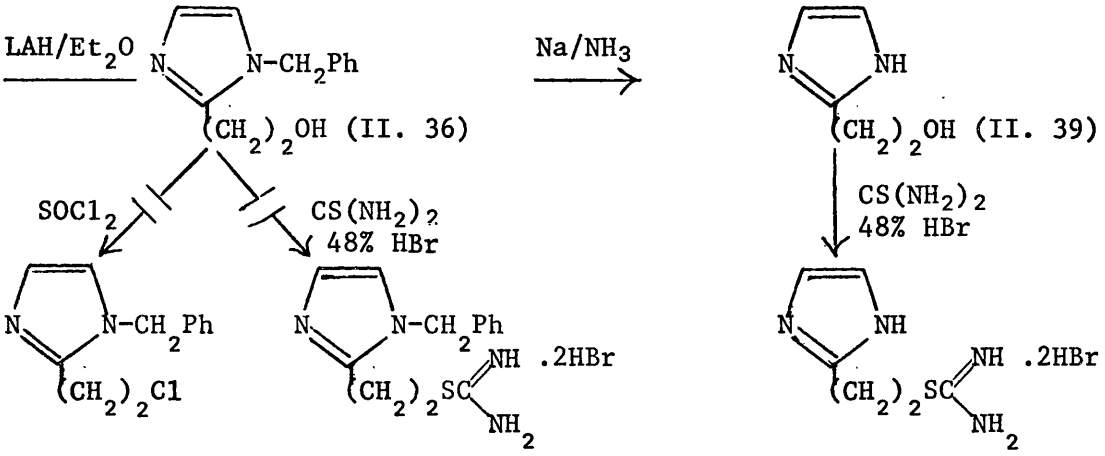
None of the required product (II. 34) was obtained. However, when the alcohol (II. 32) was converted into the chloro compound (II. 33) by treatment with thionyl chloride, reaction with ethanolic thiourea afforded a low yield (20%) of S-2-(1-methylimidazol-2-yl)ethyl-isothiourea (II. 34) as the dihydrochloride monohydrate.

Attempts to obtain 1-benzyl-2-(2-hydroxyethyl)imidazole via the hydroxyethylation of the lithio-derivative of 1-benzylimidazole using n-butyl lithium were not entirely successful. (See Section IV, p. 143) A satisfactory route to the alcohol (II. 36) was therefore required. The nitrile (II. 4b) could be conveniently obtained in high yield by the action of sodium cyanide on the chloromethyl compound (II. 3b) in dimethyl formamide or dimethyl sulphoxide as described (See p. 88)

Hydrolysis of the nitrile (II. 4b) with 2N sodium hydroxide followed by acidification, gave the free acid which was esterified with 5% ethanolic hydrogen chloride. The ester (II. 35) was isolated in 70% yield as a high boiling liquid. Reduction with lithium aluminium hydride in ether gave a quantitative yield of the crude alcohol (II. 36). Unsuccessful attempts were made to obtain both the chloroethyl compound (II. 37) by reaction with thionyl chloride and the isothiourea (II. 38)



(II. 3b) (II. 4b) (II. 35)

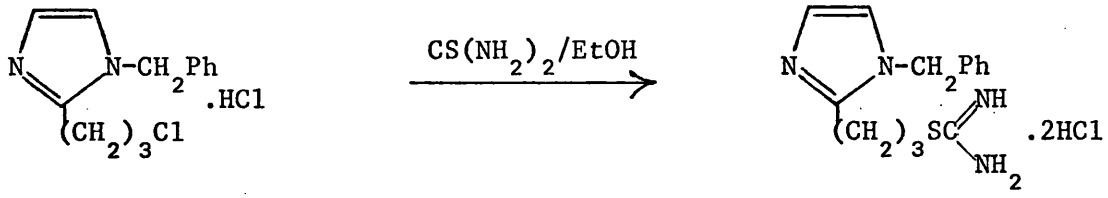


(II. 37) (II. 38) (II.40)

by reaction with thiourea in constant boiling hydrobromic acid.

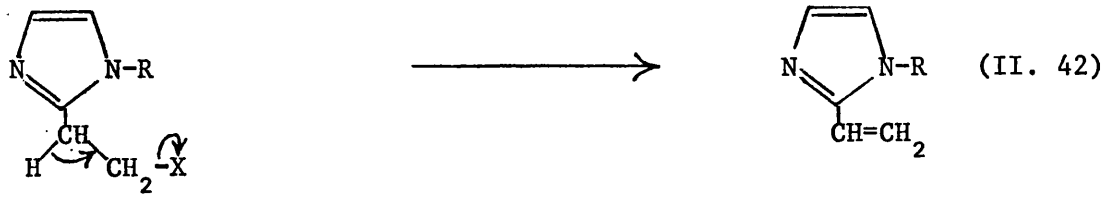
Debenzylation of the alcohol (II. 36) gave the hydroxyethyl compound (II. 39) which was identical with a sample of the material obtained from the hydroxyethylation reaction (See Section IV, p. 145). Treatment of this alcohol with thiourea in constant boiling hydrobromic acid afforded S-(imidazol-2-yl)ethylisothiourea (II. 40) as its dihydrobromide in 40% yield.

The imidazolylpropylisothiourea (II. 41) was made as its dihydrochloride in 65% yield by treatment of the chloro compound (II. 24) with ethanolic thiourea.



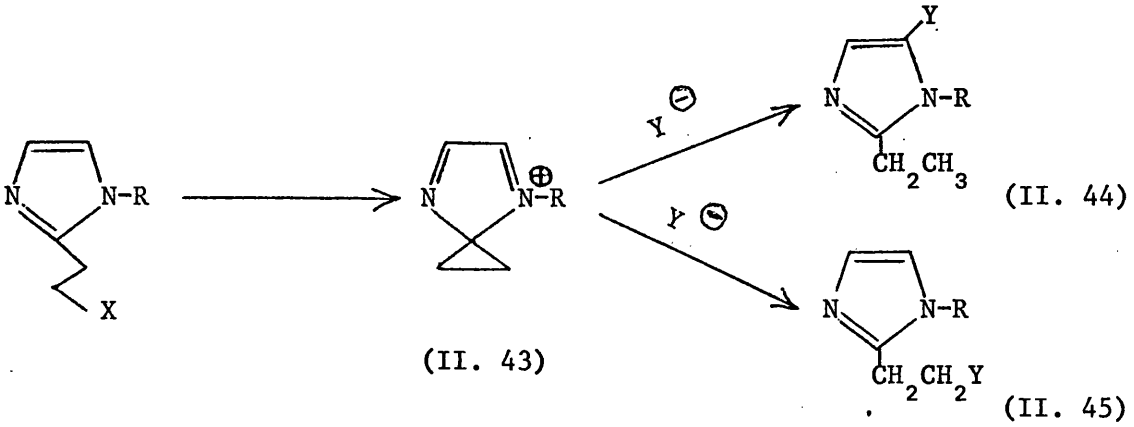
(II. 24) (II. 41)

It will have been noted that preparation of the isothioureas described in this section generally took place without difficulty. However a notable exception was the failure of 1-benzyl-2-(2-hydroxyethyl)imidazole (II. 36) to form either a chloro derivative (II. 37) or its isothiourea (II. 38). In addition, the other 2-carbon side chain compounds gave only moderate yields of products. This may be explained with reference to the three possible reactions which can occur. As well as the normal displacement reaction, which could lead to the formation of the required product, elimination can occur, which would give rise to vinylic products (II. 42). The third and



(II. 42)

much more intriguing possibility is that of homoallylic substitution. A unimolecular mechanism is depicted, however the reaction could proceed by a bimolecular process.



(II. 43)

(II. 44)

(II. 45)

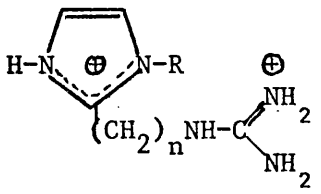
Nucleophilic attack on the spiro intermediate (II. 43) could lead to the formation of normal (II. 45) or abnormal (II. 44) products. There is also a possibility that thiourea could give rise to abnormal products, however no evidence was found for the formation of compounds of the type (II. 44).

Guanidines

Extensive work has been carried out in these laboratories on the preparation of guanidines. A wide variety of synthetic methods are available; however two routes have assumed a much greater importance than others. These are the addition of amines to cyanamides and the displacement of an alkylmercaptan by an amine from an alkylisothiouroniun salt.[68]

The guanidines described in this study were obtained by treatment of the amine with aqueous S-methylisothiouroniun sulphate. Where the amine dihydrochlorides were available these were first

converted into their free bases using ion-exchange techniques. This method was used to prepare the following guanidines which were usually isolated as their sulphates.



(II. 46)

a, R = -H , n = 2

b, R = -Me , n = 2

c, R = -H , n = 3

d, R = $-CH_2Ph$, n = 3

e, R = -H , n = 4

f, R = $-CH_2Ph$, n = 4

Unsuccessful attempts were made to characterise the guanidinobutyl compound (II. 46e) as its sulphate. This material was converted into its dipicrate which was characterised. The dihydrochloride obtained by treatment of the picrate salt with nitrobenzene/hydrochloric acid was also characterised.

One of the major difficulties with reactions of this type is the separation of the required guanidine from unreacted S-methylisothiouronium sulphate. This is usually overcome by the use of long reaction times (often several days) and the choice of appropriate conditions during the isolation procedure.

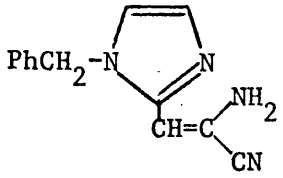
Synthesis of α-aminoacrylonitriles

During the course of our work on the synthesis of cyanomethylimidazoles, the reaction between sodium cyanide and 1-benzyl-2-chloromethyl-imidazole (II. 3a) in dipolar aprotic solvents was found to proceed without rearrangement. However, in all reactions a low yield (approximately 10%) of an unusual nitrile was also isolated using dry column chromatographic techniques.[69] Elemental analysis suggested that the cyanomethyl compound (II. 4a) formed as the major product in the reaction, had combined with a further molecule of hydrogen cyanide.

The spectral data of this new compound are given below,

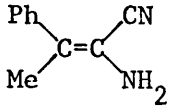
$\nu_{max.}$, (CCl_4) ;	2231 cm^{-1}	-C≡N	
	3488, 3260 (broad) cm^{-1}	$-NH_2$----	
$\lambda_{max.}$, (EtOH) ;	322 mμ	($\varepsilon_{max.}$ 17,600)	
τ, ($CDCl_3$);	2.85, 3.15	(2H, q),	4-H, 5-H
	3.90	(2H, broad s)	$-\underline{NH}_2$
	4.40	(1H, s)	$-\underline{CH}=$
	4.94	(2H, s)	$-\underline{CH}_2Ph$
m/e ;	224	M^+	
	91	$PhCH_2^+$	

and from these we deduced that 1-amino-2-(1-benzylimidazol-2-yl)-acrylonitrile (II. 47) had been formed. As far as we are aware, this is only the second α-aminoacrylonitrile to have been described.

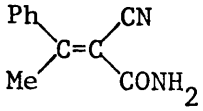


(II. 47)

Robert and Foucaud describe the aromatic α-aminoacrylonitrile (II. 48), which was prepared by a typical Hofmann reaction on the amide (II. 49).[70] The aminoacrylonitrile (II.48) was required for an



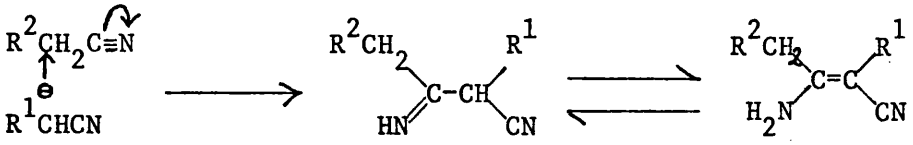
(II. 48)



(II. 49)

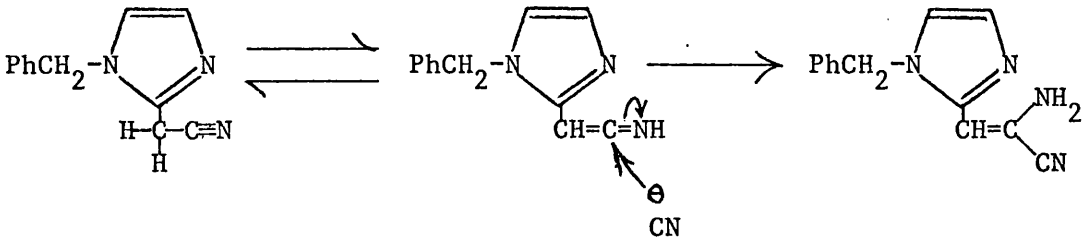
investigation of its infra-red spectrum; apart from this and an elemental analysis, no other data was given.

The related β-aminoacrylontriles, which are commonly represented as their enaminonitrile tautomers (II. 50), are the well known products of the Thorpe condensation reaction. The Thorpe products are usually obtained from the metal salts of nitriles.



(II. 50)

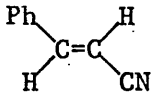
It is probable that our α-aminoacrylonitrile (II. 47) is formed by attack of the cyanide ion on the ketenimine tautomer (II. 51) of the nitrile (II. 4b). Ketenimines react readily with nucleophilic agents, and it is known that electron attracting groups attached to



(II. 4b) (II. 51) (II. 47)

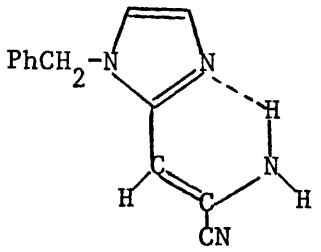
acetonitrilies favour the ketenimine structure. The product is a rare example of a stable primary enamine.

The spectral data indicate that the compound exists in the trans-form. The ultra-violet spectrum (λ_{max} 1322 mμ, log ε 4.25) is similar to that of trans-cinnamonitrile (II. 52), which has λ_{max} 273,



(II. 52)

and log ε 4.7,[72] whereas the extinction co-efficient of the cis-isomer is very much less than this. In fact our compound has log ε 4.25. The infra-red spectrum also shows absorptions corresponding to hydrogen bonding at 3488 and 3260 cm^{-1}. Hence the available evidence suggests that the conformation (II. 47a) predominates.

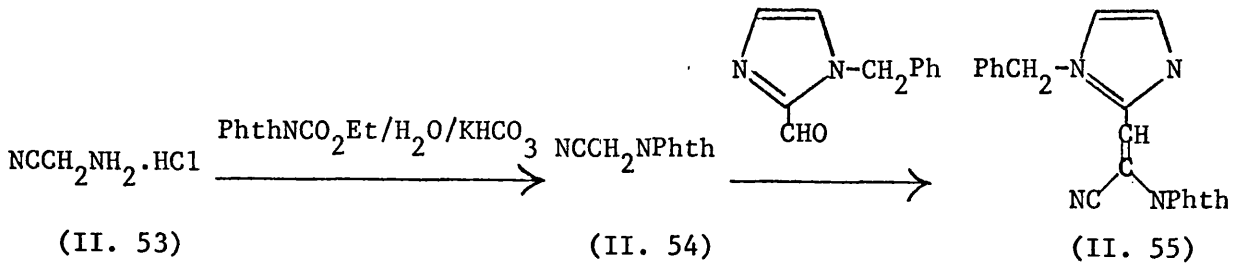


(II. 47a)

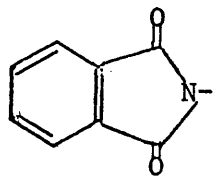
If our proposed mechanism is correct the compound (II. 47) should also be formed when the hydrochloride of the nitrile (II. 4b) reacts with sodium cyanide in dimethylformamide. We have shown that this occurs and the α-aminoacrylonitrile (II. 47) is again formed in approximately 10% yield. In order to substantiate our theories it would be of great interest to trap the intermediate ketenimine (II. 51) with ethanol or acetic acid, but this has yet to be done.

Kornfeld and his colleagues failed to detect this unusual product, which is surprising since similar conditions to ours were employed.[15] It will be noted that only modest yields of this material are formed under our conditions. This may be due to loss of hydrogen cyanide from the reaction mixture under the conditions employed (usually 80-90°). Reaction of the nitrile (II. 4b) with hydrogen cyanide under closed conditions might give rise to increased yields.

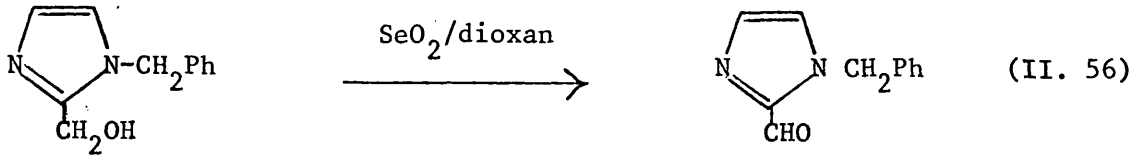
In an attempt to synthesise the aminoacrylonitrile (II. 47) unambiguously, the following sequence was investigated. The reaction of Nefkens' reagent with aminoacetonitrile (II. 53) under the usual conditions[73] gave the phthaloyl derivative (II. 54). The aldehyde (II. 57) had been prepared by the oxidation of 1-benzyl-2-hydroxymethyl-



(II. 53) (II. 54) (II. 55)

N.B. PhthN- = 

imidazole with selenium dioxide in dioxan as described by Iversen and Lund.[55] The aldehyde (II. 56) has not yet been condensed with



(II. 56)

phthalimidoacetonitrile. This reaction, which is a typical Michael addition, should proceed under the influence of a basic catalyst to give compound (II. 55). Either the phthalimide group of compound (II. 55) could be removed, or (II. 55) could be prepared from the aminoacrylonitrile (II. 47) to provide confirmation of the structure of II. 47. However, the reaction of Nefkens' reagent under the usual conditions with the aminonitrile (II. 47) did not furnish the required product. Currently a thermal condensation between (II. 47) and phthalic anhydride is under investigation and may yield the required compound (II. 55).

The discovery that this novel class of compounds may be obtained by the addition of hydrogen cyanide to a nitrile (albeit a potential

ketenimine) could have wide application. It would appear that the only requirement for reactions of this type to proceed is a cyanomethyl group attached to a suitable electron withdrawing moiety.

If this reaction had not been discovered towards the end of the present work, efforts would have been made to extend its range and to elucidate the chemistry of these novel structures.

EXPERIMENTAL SECTION

General Details

Melting points were taken using the "open capillary" method and are corrected.

Dry solvents were obtained using procedures described in ref. 67.

Picrate salts were converted into their corresponding hydrochlorides or free bases by the following method: the picrate (0.05 mole) was rubbed to a fine powder and shaken in a separating funnel with nitrobenzene (150 ml.) and cold 6N hydrochloric acid (100 ml.) until all the solid had dissolved. After separation of the nitrobenzene layer, the aqueous solution was extracted with portions of chloroform (75 ml.) until colourless washings were obtained. The aqueous solution was clarified with charcoal and evaporated under vacuum. The hydrochlorides were obtained from the residue. The free base was obtained from the aqueous solution of the hydrochloride by basification with an excess of sodium carbonate. The resulting mixture was extracted with portions of chloroform (50 ml.) and the dried (Na_2SO_4) extract was evaporated to give the free base.

Elemental analyses were determined on an F&M 185 instrument and were carried out by Mr. M.J. Graham and his staff.

All pure compounds were subjected to a thin layer chromatographic examination in acidic, neutral and basic solvent systems. A single mobile component was observed.

1-Substituted imidazoles

1-Benzylimidazole (II. 1a)

This was prepared by the method of Roe,[54] using the modification of Iversen and Lund;[55] m.p. 69-71°; 59% yield (lit.[54] m.p. 71-71.5°).

1-Methylimidazole (II. 1b)

This was prepared by the method of Roe;[54] $b.p._{16}$ 85-88°; 66% yield (lit.[54] $b.p._{18}$ 97°).

Hydroxymethylation of 1-substituted imidazoles

1-Benzyl-2-hydroxymethylimidazole hydrochloride (II. 2a)

This was prepared by the method of Jones,[9] m.p. 167°; 67% yield (lit.[9] m.p. 159-160°). The free base was obtained by the method of Iversen and Lund,[55] m.p. 95-97°; 80% yield (lit.[55] m.p. 94-95°).

1-Methyl-2-hydroxymethylimidazole (II. 2b)

This was prepared by the method of Iversen and Lund.[55] It was not found possible to isolate this compound as described, and the alcohol was obtained as its picrate salt. This material was converted into the hydrochloride salt, by the usual nitrobenzene/6N hydrochloric acid method, from which the free base was obtained, m.p. 115-117°; 56% yield (lit.[55] m.p. 116°).

1-Substituted-2-chloromethylimidazoles

1-Benzyl-2-chloromethylimidazole hydrochloride (II. 3a)

This was prepared by the method of Jones,[9] m.p. 185-187°; 91% yield (lit.[9] m.p. 181-182°).

1-Methyl-2-chloromethylimidazole hydrochloride (II. 3b)

This was prepared by the method of Jocelyn;[16] m.p. 175-177°; 79% yield (lit.[16] m.p. 168°).

Displacement reactions with cyanide ion as nucleophile

Jones' synthesis of isohistamine

1-Benzyl-2-cyanomethylimidazole (II. 4a) and 1-benzyl-5-cyano-2-methylimidazole (II. 6a). (cf. ref. 9)

1-Benzyl-2-chloromethylimidazole hydrochloride (27.75g.; 0.114 mole) in ethanol (200 ml.) was added over 1 hour to a stirred mixture of potassium cyanide (67.5g; 1.04 mole) in water (75 ml.), at below 5°. The mixture was stirred at room temperature for 16 hr. then filtered and the solid was washed with ethanol (2 x 150 ml.). The total filtrate was evaporated under vacuum to approximately 60 ml. and extracted with chloroform (3 x 250 ml.). The chloroform solution was washed with water (2 x 100 ml.) and 10% aqueous sodium chloride (150 ml.), dried ($CaSO_4$) and evaporated under vacuum to yield a brown oil which rapidly crystallised. This was shown to be a 2:3 mixture of the normal (II. 4a) and rearranged (II. 6a) products respectively. (See n.m.r spectra; p. 92). To this crude product in hot ethanol (110 ml.)

was added picric acid (27 g.) in boiling ethanol (100 ml.). A brown oil separated which readily crystallised. The mixture was slowly cooled to 70° and 1-benzyl-5-cyano-2-methylimidazole picrate was collected. This material was washed by suspension in warm ethanol and air dried to yield 13.71 g. (28%), m.p. 167-169°. Recrystallisation of a 1.5 g. sample of this material from ethanol afforded 1-benzyl-5-cyano-2-methylimidazole picrate (1.07 g.), m.p. 167-169°.

(Found: C, 50.65; H, 3.24; N, 19.90. $C_{12}H_{11}N_3.C_6H_3N_3O_7$ requires C, 50.72; H, 3.33; N, 19.71%)

The free base was obtained by the usual method. Recrystallisation of the crude material from benzene afforded 1-benzyl-5-cyano-2-methyl-imidazole, m.p. 123-124°.

(Found: C, 72.93; H, 5.76; N, 21.17. $C_{12}H_{11}N_3$ requires C, 73.06; H, 5.62; N, 21.32%)

The hydrochloride, obtained by treatment of the base with hydrogen chloride in isopropanol, was recrystallised from ethanol/ether to yield 1-benzyl-5-cyano-2-methylimidazole hydrochloride, m.p. 177-178.5°.

(Found: C, 61.68; H, 5.33; N, 18.09; Cl, 15.26. $C_{12}H_{11}N_3.HCl$ requires C, 61.66; H, 5.15; N, 17.99; Cl, 15.17%)

The picrate mother liquors were evaporated under vacuum and the residue was converted into its hydrochloride using the usual nitrobenzene/6N hydrochloric acid method. The aqueous hydrochloride was basified with an excess of sodium bicarbonate and extracted with chloroform (4 x 200 ml.) to yield a solid (5.8 g.) which was recrystallised three times from benzene to give 1-benzyl-2-cyano-methylimidazole (2.9 g; 13%), m.p. 101-103°.

(Found: C, 73.35; H, 5.65; N, 21.03. $C_{12}H_{11}N_3$ requires C, 73.06; H, 5.62; N, 21.32%)

The hydrochloride, obtained in the usual way, was recrystallised from ethanol/ether, m.p. 188-189.5° (decomp.).

(Found: C, 61.85; H, 5.15; N, 17.82; Cl, 15.36. $C_{12}H_{11}N_3.HCl$ requires C, 61.66; H, 5.15; N, 17.99; Cl, 15.17%)

The picrate, prepared from the free base, was recrystallised from ethanol, m.p. 131-133°.

(Found: C, 50.97; H, 3.36; N, 19.76. $C_{12}H_{11}N_3.C_6H_3N_3O_7$ requires C, 50.72; H, 3.33; N, 19.71%)

1-Benzyl-5-aminomethyl-2-methylimidazole (II. 7a) (cf. ref. 9)

1-Benzyl-5-cyano-2-methylimidazole (1.78 g.; 0.009 mole) was placed in the thimble of a Soxhlet extractor above a boiling mixture of lithium aluminium hydride (0.8 g.; 0.21 mole) in dry ether (100 ml.).

When all the nitrile had been dissolved (3.5 hr.), excess of lithium aluminium hydride and the complexed product were decomposed by the addition of water (2 ml.), followed by 40% aqueous sodium hydroxide (10 ml.). The granular solid was extracted with ether (3 x 50 ml.) and the ethereal solution was extracted with 2N hydrochloric acid (10 ml.). Basification of the acid extract with sodium hydroxide gave a crystalline solid (1.51 g.; 81%), m.p. 61-63°, which was recrystallised from ether/petroleum ether (b.p. 60-80°) to give 1-benzyl-5-aminomethyl-2-methylimidazole dihydrate m.p. 61.5-63.5°.

(Found: C, 60.94; H, 8.14; N, 17.46. $C_{12}H_{15}N_3.2H_2O$ requires C, 60.74; H, 8.07; N, 17.71%)

The dihydrochloride was prepared from the above by treatment with ethanolic hydrogen chloride and recrystallised from ethanol/ether, m.p. 226-228°.

(Found: C, 52.54; H, 6.14; N, 15.41; Cl, 25.63. $C_{12}H_{15}N_3.2HCl$ requires C, 52.55; H, 6.25; N, 15.34; Cl, 25.85%)

The dipicrate prepared from tbe base was recrystallised from ethanol/water, m.p. 189-191° (decomp.)

(Found: C, 43.74; H, 3.10; N, 19.03. $C_{12}H_{15}N_3.2C_6H_3N_3O_7$ requires C, 43.70; H, 3.16; N, 19.12%)

4(5)-Aminomethyl-2-methylimidazole (II. 8) (cf. ref. 9)

1-Benzyl-5-aminomethyl-2-methylimidazole (5.8 g.; 0.029 mole) in liquid ammonia (65 ml.) was treated with small pieces of sodium

metal (1.36 g.; 0.059 g. atom). After 0.5 hr., ammonium chloride was added and the ammonia was allowed to evaporate. Aqueous sodium carbonate was added and the solution was evaporated. The residue was extracted with ethanol (3 x 50 ml.) and the extracts were evaporated to yield an oil. Treatment with aqueous picric acid afforded a crude dipicrate (7.6 g.), m.p. 200-202°, which was converted into the dihydrochloride by the usual nitrobenzene/6N hydrochloric acid method. Recrystallisation from methanol/ether gave 4(5)-aminomethyl-2-methyl-imidazole dihydrochloride (2.3 g.; 44%), m.p. 229.5-231° (decomp.).

(Found: C, 32.66; H, 5.96; N. 22.89; Cl, 38.43. $C_5H_9N_3.2HCl$ requires c, 32.60; H, 5.98; N, 22.84; Cl, 38.54%)

The dipicrate, prepared from the above, was recrystallised from water m.p. 213-214° (decomp.).

(Found: C, 35.87; H, 2.44; N, 22.19. $C_5H_9N_3.2C_6H_3N_3O_7$ requires C, 35.87; H 2.66; N, 22. 13%)

1-Benzyl-2-(2-aminoethyl)imidazole, i.e. 1-benzylisohistamine (II. 5a) (cf. refs. 9 and 15)

Diborane, generated from 1M sodium borohydride in dry diglyme (250 ml.) and boron trifluoride etherate (63.5 ml.; 0.5 mole) was passed into 1-benzyl-2-cyanomethylimidazole (4.9 g.; 0.025 mole) in dry tetrahydrofuran (200 ml.) and the solution was then heated under reflux for 10 hr. The boron complex was decomposed by heating under reflux for 3 hr. with 6N hydrochloric acid and the solution was then evaporated. The residue, in water (100 ml.), was made strongly

basic with 40% aqueous sodium hydroxide and extracted with ether (5 x 200 ml.) to yield a liquid (4.74 g.). This was converted into its dipicrate under aqueous conditions. On cooling the hot picrate solution, successive quantities of an oil separated which were removed by filtration until crystals separated from the filtrate. These were recrystallised from aqueous ethanol to give 1-benzylisohistamine dipicrate (10.2 g.; 62%), m.p. 191-193°.

(Found: C, 43.47; H, 3.20; N, 18.87. $C_{12}H_{15}N_3.2C_6H_3N_3O_7$ requires C, 43.71; H, 3.21; N, 19.12%)

The dihydrochloride, obtained from the above picrate by the nitrobenzene/6N hydrochloric acid method could not be characterised owing to its very hygroscopic nature. The free base, used in subsequent operations, was obtained by passing a methanolic solution of the dihydrochloride through a basic ion exchange column (Amberlite IRA 401).

1-Benzyl-2-(2-benzyamidoethyl)imidazole (II. 10) [cf. compound (III. 15), p. 127]

Benzyl chloride (0.7 g.; 0.005 mole) was added dropwise to a shaken mixture of 1-benzylisohistamine (1.0 g.; 0.005 mole) in 0.5N sodium hydroxide (10 ml.). After 0.5 hr., the mixture was extracted with chloroform (3 x 30 ml.) to yield an oil (1.64 g.) which was dissolved in ethyl acetate and treated with petroleum ether (b.p. 60-80°). A small quantity of brown oil separated and was removed by filtration. Evaporation of the filtrate afforded a solid which was recrystallised from ethyl acetate/petroleum ether to give 1-benzyl-2-(2-benzamidoethyl) imidazole, (0.72 g.; 47%), m.p. 120-122°.

(Found: C, 74.46; H, 6.20; N, 13.62. $C_{19}H_{19}N_3O$ requires C, 74.73; H, 6.27; N, 13.76%)

Jocelyn's synthesis of 1-methylisohistamine

1-Methyl-2-cyanomethylimidazole (II. 4b) and

1,2-dimethyl-5-cyanoimidazole (II. 6b) mixed picrates (cf. ref. 16)

1-Methyl-2-chloromethylimidazole hydrochloride (6.1 g.; 0.036 mole) in ethanol (30 ml.) was added over 0.5 hr. to a stirred solution of potassium cyanide (20.2 g.; 0.31 mole) in water (20 ml.) at -10^{o}. The mixture was allowed to warm to room temperature over 1 hr. and then filtered. 20% Aqueous sodium carbonate was added to the filtrate and the solution was evaporated. Extraction of the residue with ethyl acetate yielded a dark viscous liquid which was dissolved in ethanol and treated with an excess of hot aqueous picric acid to give a solid. Recrystallisation from water gave a mixture of 1-methyl-2-cyanomethylimidazole picrate and 1,2-dimethyl-5-cyano-imidazole picrate in approximately 2:1 ratio (See n.m.r spectra; p. 95) (6.5 g.; 51%) m.p. 165-167^{o}.

(Found: C, 41.04; H, 2.78; N, 24.06. $C_6H_7N_3.C_6H_3N_3O_7$ requires C, 41.13; H, 2.86; N, 24.00%)

1-Methyl-2-cyanomethylimidazole (II. 4b) and 1,2-dimethyl-5-cyanoimidazole (II. 6b) (cf. ref. 16)

The mixture of 1-methyl-2-cyanomethylimidazole and 1,2-dimethyl-5-cyanoimidazole picrates was converted into the hydrochlorides via the

usual nitrobenzene/6N hydrochloric acid method. The aqueous hydrochloride was treated with an excess of sodium carbonate and evaporated to dryness. Extraction of the residue with chloroform (5 x 25 ml.) yielded a brown solid (0.74 g.) which was dissolved in benzene and placed on an alumina column, (50 g.; pH6 alumina; Brockmann activity IV). Elution with benzene separated the bases. The first product eluted was 1,2-dimethyl-5-cyanoimidazole. This material was sublimed at 60° under 0.03 mm.Hg. to yield a hygroscopic solid, (0.21 g.) m.p. 54-57°.

(Found: C, 59.23; H, 5.61; N, 34.84. $C_6H_7N_3$ requires C, 59.47; H, 5.82; N, 34.70%)

1,2-Dimethyl-5-cyanoimidazole picrate was prepared by the usual method and recrystallised from water, m.p. 211-212°.

(Found: C, 41.23; H, 2.86; N, 24.00. $C_6H_7N_3.C_6H_3O_7$ requires C, 41.13; H, 2.86; N, 24.00%)

The second fraction eluted, which was obtained as an oil, was converted into its hydrochloride by treatment with hydrogen chloride in isopropanol and recrystallised from ethanol/ether to give 1-methyl-2-cyanomethyl-imidazole hydrochloride, (0.24 g.), m.p. 236-238° (decomp.).

(Found: C, 45.66; H, 5.03; N, 26.89; Cl, 22.49. $C_6H_7N_3.HCl$ requires C, 45.72; H, 5.12; N, 26.67; Cl, 22.50%)

1-Methyl-2-cyanomethylimidazole picrate was recrystallised from aqueous ethanol, m.p. 179-180° (decomp.).

(Found: C, 40.87; H, 2.89; N, 23.72. $C_6H_7N_3.C_6H_3N_3O_7$ requires C, 41.13; H, 2.86; N, 24.00%)

Phase diagram of 1-methyl-2-cyanomethylimidazole (II. 4b) picrate and 1,2-dimethyl-5-cyanoimidazole (II. 6b) picrate

Mixtures containing known proportions of the isomeric nitriles (II. 4b) and (II. 6b) as picrates were prepared in a ball-mill and their melting points were determined.

MOLE % (II. 4b).Picr.	Mole % (II. 6b).Picr.	m.p.
100	0	178-180°
90	10	172-174
80	20	167-169
70	30	166-168
60	40	166-168
50	50	167-169
40	60	168-170
30	70	171-173
25	75	182-184
20	80	194-196
15	85	196-198
10	90	201-203
0	100	212-214

A graph of composition against melting point (See Figure II. 1 p.31) indicated that a compound with an incongruent melting point was formed with a composition approximately 20% (II. 4b)/80% (II. 6b). A eutectic was also observed at approximately 60% (II. 4b)/40% (II. 6b).

1-Methyl-2-(2-aminoethyl)imidazole (II. 5b) (cf. ref. 16, and Section III, p. 128)

1-Methyl-2-cyanomethylimidazole hydrochloride (0.5 g.; 0.0032 mole) in methanol (15 ml.) was treated with small pieces of sodium metal (0.073 g.; 0.0032 g. atom) and the solution was evaporated. The residue was extracted with methanol (3 x 15 ml.) and filtered. The filtrate, with liquid ammonia (10 ml.), was hydrogenated in an autoclave at 100° under 100 atmospheres of hydrogen with Raney nickel as catalyst. The reaction mixture was filtered, evaporated and partitioned between 2N hydrochloric acid (20 ml.) and chloroform. Basification of the aqueous layer with 40% aqueous sodium hydroxide and extraction with ether (3 x 30 ml.) yielded an oil (0.3 g.) which was treated with hot aqueous picric acid. The crude product was recrystallised from ethanol/water to give 1-methyl-2-(2-aminoethyl)imidazole dipicrate (0.13 g.; 7%), m.p. 213-215°, (decomp.).

This material was found to be identical with an authentic sample, (p. 128), and a mixed melting point showed no depression.

1-Methyl-2-(2-ethylaminoethyl) imidazole (II. 11) and
di-[2-(1-methylimidazol-2-yl)ethyl]amine (II. 12)

1-Methyl-2-cyanomethylimidazole (1.64 g.; 0.0135 mole) in ethanolic ammonia (100 ml.) was hydrogenated at 140° under 100 atmospheres of hydrogen for 4.5 hr. in an autoclave, using Raney nickel (0.5 g.) as catalyst. Evaporation of the filtered reaction mixture gave an oil (2 g.), which was treated with an excess of hot aqueous picric acid. When the resulting solid was fractionally recrystallised from nitromethane/n-propanol two distinct fractions separated, m.p. 208-209° (decomp.) and 187-193°. The higher melting fraction was recrystallised from water to give di-[2-(1-methylimidazol-2-yl)ethyl]amine tripicrate, (60 mg.; 0.5%), m.p. 215-217° (decomp.).

(Found: C, 38.82; H, 3.03; N, 21.05. $C_{12}H_{13}N_5.3C_6H_3N_3O_7$ requires C, 39.14; H, 3.07; N, 21.30%)

Recrystallisation of the lower melting fraction from water afforded 1-methyl-2-(2-ethylaminoethyl)imidazole dipicrate, (80 mg.; 1%), m.p. 197-198°.

(Found: C, 39.24; H, 3.44; N, 20.54. $C_8H_{15}N_3.2C_6H_3N_3O_7$ requires C, 39.29; H, 3.46; N, 20.62%)

1,2-Dimethyl-5-aminomethylimidazole (II. 7b) (cf. ref. 16)

1,2-Dimethyl-5-cyanoimidazole (2.0 g.; 0.016 mole) in dry ether (250 ml.) was added over 0.5 hr. to lithium aluminium hydride

(2.0 g.; 0.053 mole) in dry ether (400 ml.) heated under reflux. After 1.5 hr. water (2 ml.), 15% aqueous sodium hydroxide (2 ml.) and water (6 ml.) were successively added. The mixture was filtered and the granular solid was extracted with dichloromethane to yield an oil which was treated with hydrogen chloride in isopropanol and evaporated. The residue, after recrystallisation from methanol/ether yielded 1,2-dimethyl-5-aminomethylimidazole dihydrochloride, (1.96 g.; 60%), m.p. 268-270° (decomp.).

(Found: C, 36.72; H, 6.56; N, 21.28; Cl, 35.64. $C_6H_{11}N_3.2HCl$ requires C, 36.47; H, 6.61; N, 21.22; Cl, 35.69%)

The dipicrate monohydrate was prepared in the usual way and purified by recrystallisation from water, m.p. 219-220° (decomp.).

(Found: C, 36.13; H, 3.06; N, 21.03. $C_6H_{11}N_3.2C_6H_3N_3O_7.H_2O$ requires C, 35.93; H, 3.18; N, 20.95%)

2-Methylimidazole (II. 15) (cf. ref. 15)

Small pieces of sodium metal (approximately 1 g.) were added to 1-benzyl-2-cyanomethylimidazole (2.2 g., 0.011 mole) in liquid ammonia until a blue colour persisted. Ammonium chloride (2.2 g.) was added and the ammonia was allowed to evaporate. Extraction of the residue with ethanol afforded an oil which was treated with ethanolic picric acid. Recrystallisation of the resulting solid material from ethanol gave pure 2-methylimidazole picrate (0.4 g., 12%) m.p. 204-206°.

(Found: C, 38.88; H, 2.78; N, 22.33. $C_4H_6N_2.C_6H_3N_3O_7$ requires C, 38.59; H, 2.91; N, 22.50%)

This material was identical to an authentic sample of 2-methylimidazole picrate, m.p. 205-207° and a mixed melting point showed no depression.

Displacement reactions with other nucleophiles

1-Benzyl-2-imidazolealanine (II. 16)

This was prepared by the method of Jones, who described the hemihydrate, 216-217° (decomp.).[9] Our material, 33% yield, m.p. 219-220° (decomp.), appeared to be the monohydrate.

(Found: C, 59.16; H, 6.67; N, 16.00. $C_{13}H_{15}N_3O_2.H_2O$ requires C, 59.20; H, 6.47; N, 16.02%)

2-Imidazolealanine (II. 17)

This was prepared by the method of Jones,[9] m.p. 253-255° (decomp.), 60% yield [lit.[9] m.p. 254-255° (decomp.)].

1-Benzyl-2-(2-ethoxycarbonylethyl-2-methylimidazole (II. 18) and 1-benzyl-5-ethoxycarbonylmethyl-2-methylimidazole (II. 19) (cf. ref. 9)

1-Benzyl-2-chloromethylimidazole hydrochloride (36.5 g.; 0.15 mole) in ethanol was added to a suspension of sodio-diethylmalonate, prepared by adding sodium metal (10.3 g.; 0.45 g. atom) to diethylmalonate (48.1 g.; 0.3 mole) in ethanol (190 ml.). The mixture was stored for

2 hr. at room temperature and then evaporated under vacuum to remove most of the alcohol. The residue was dissolved in ice-cold 2N hydrochloric acid and extracted with ethyl acetate (4 x 150 ml.) to remove unchanged malonic ester. The aqueous layer was neutralised with an excess of sodium carbonate and extracted with ether (3 x 150 ml.). The ether solution was evaporated to yield a liquid (52.4 g.), which was shown to comprise a 19:1 mixture of the normal and rearranged products respectively. (See Discussion, p.42). The crude material was heated with conc. hydrochloric acid (100 ml.) on a steam bath for 17 hr. and the acid obtained was esterified by heating under reflux for 18 hr. with 5% ethanolic hydrogen chloride. This material was distilled under vacuum to give 1-benzyl-2-(2-ethoxycarbonylethyl)imidazole (25 g. 65%). b.p. 169° (0.2 mm.).

(Found: C, 69.51; H, 7.08; N, 10.96. $C_{15}H_{18}N_2O_2$ requires C, 69.74; H, 7.02; N, 10.85%)

None of the rearranged material (II. 19) was isolated.

Compounds related to isohistamine

3-(1-Benzylimidazol-2-yl)propionamide (II. 20)

1-Benzyl-2-(2-ethoxycarbonylethyl)imidazole (10.32 g.; 0.04 mole), methanol (15 ml.) and liquid ammonia (15 ml.) were charged into a cooled autoclave, which was then heated at 130° for 30 hr. The reaction mixture was evaporated under vacuum to yield a green solid (9.3 g.) which was placed on a short alumina column (pH 9.5, Brockmann activity I). The amide was eluted from the column with ethanol and the eluate was evaporated. Recrystallisation of the residue

from ethyl acetate/petroleum ether (b.p. 60-80°) gave 3-(1-benzylimidazol-2-yl)propionamide, (7.9 g.; 86%), m.p. 133-135°.

(Found: C, 68.07; H, 6.73; N, 18.36. $C_{13}H_{15}N_3O$ requires C, 68.10; H, 6.59; N, 18.33%)

1-Benzyl-2-(3-aminopropyl)imidazole (II. 21)

Diborane, generated from a 1M diglyme solution of sodium borohydride (300 ml.; 0.3 mole) and boron trifluorate etherate (65 g.; 0.46 mole), was passed into 3-(1-benzylimidazol-2-yl)propionamide (5.89 g.; 0.26 mole) in dry tetrahydrofuran (250 ml.) and the solution was heated under reflux for 17 hr. The boron complex was decomposed by heating for 2 hr. with an excess of conc. hydrochloric acid and the solution was evaporated. The residue was dissolved in water (40 ml.), basified with 40% aqueous sodium hydroxide, and extracted with chloroform (6 x 50 ml.). The dried (Na_2SO_4) chloroform solution was evaporated and the residue was treated with picric acid in nitromethane. The crude material obtained was recrystallised from nitromethane to give 1-benzyl-2-(3-aminopropyl)imidazole dipicrate, (11.6 g.; 67%), m.p. 165-167°.

(Found: C, 44.82; H, 3.50; N, 18.69. $C_{13}H_{13}N_3.2C_6H_3N_3O_7$ requires C, 44.58; H, 3.44; N, 18.72%)

The amide was also reduced in 44% yield with lithium aluminium hydride.

The dipicrate was converted into its dihydrochloride by the usual method, but it was not characterised owing to its hygroscopic nature. The dihydrochloride was converted into its free base using a basic ion-exchange column (Amberlite IRA 401). This material was used in the preparation of compound (II. 46d), (see p. 86).

2-(3-Aminopropyl)imidazole (II. 22)

Small pieces of sodium metal (1.0 g.; 0.043 g. atom) were added to 1-benzyl-2-(3-aminopropyl)imidazole dihydrochloride (2.85 g.; 0.01 mole) in liquid ammonia (100 ml.). Ammonium chloride (1.65 g.) was added and the ammonia was allowed to evaporate. Aqueous sodium carbonate was added and the solution was evaporated under vacuum. Extraction of the residue with hot ethanol (2 x 60 ml.) gave an oil (1.39 g.) which was treated with hot aqueous picric acid. On cooling, a solid separated which was recrystallised from water to give 2-(3-aminopropyl)imidazole dipicrate, (4.5 g.; 78%), m.p. 207-209° (decomp.).

(Found: C, 37.39; H, 2.61; N, 21.75. $C_6H_{11}N_3.2C_6H_3N_3O_7$ requires C, 37.06; H, 2.94; N, 21.61%)

The hydrochloride, obtained by the usual method was hygroscopic and all handling operations were carried out under an inert atmosphere in a "Dry Box". Three recrystallisations from isopropanol/ethanol/ether afforded 2-(3-aminopropyl)imidazole dihydrochloride, m.p. 148-150°.

(Found: C, 36.59; H, 6.59; N, 20.94; Cl, 35.62. $C_6H_{11}N_3.2HCl$ requires C, 36.38; H, 6.61; N, 21.21; Cl, 35.80%)

1-Benzyl-2-(3-hydroxypropyl)imidazole (II. 23)

1-Benzyl-2-(2-ethoxycarbonylethyl)imidazole (5.2g.; 0.02 mole) in dry ether (150 ml.) was added dropwise to lithium aluminium hydride (1.0 g.; 0.025 mole) in dry ether (100 ml.). The mixture was heated under reflux for 2 hr., then water (1 ml.), 15% aqueous sodium hydroxide (1 ml.) and water (3 ml.) were successively added. The mixture was filtered and the granular precipitate was washed with hot ethanol (3 x 100 ml.). Evaporation of the combined filtrate gave an oil which was partitioned between 2N hydrochloric acid and chloroform. The aqueous layer was basified with an excess of potassium carbonate and extracted with chloroform (3 x 60 ml.). Evaporation of the dried (Na_2SO_4) chloroform solution gave 1-benzyl-2-(3-hydroxypropyl)imidazole (4.64 g.; 100%) as a liquid, which was used without purification in the subsequent experiment.

1-Benzyl-2-(3-chloropropyl)imidazole (II. 24)

1-Benzyl-2-(3-hydroxypropyl)imidazole (4.4 g.; 0.019 mole) in benzene (40 ml.) was added dropwise to thionyl chloride (20 ml.) heated under reflux. Water (0.5 ml.) was then added to the refluxing solution and after 0.5 hr. the mixture was evaporated to give a solid. Recrystallisation from ethanol/ether gave 1-benzyl-2-(3-chloropropyl)imidazole hydrochloride, (3.99 g.; 78%), m.p. 163.165°.

(Found: C, 57.85; H, 6.16; N, 10.35; Cl, 26.12. $C_{13}H_{15}N_2Cl.HCl$ requires C, 57.57; H, 5.95; N, 10.33; Cl, 26.15%)

1-Benzyl-2-(3-cyanopropyl)imidazole (II. 25)

1-Benzyl-2-(3-chloropropyl)imidazole hydrochloride (2.71 g.; 0.01 mole) was added over 15 min. to a stirred suspension of sodium cyanide (4.9 g.; 0.1 mole) in dimethyl sulphoxide (50 ml.) at 45°. After 3 hr. the mixture was diluted with dichloromethane (75 ml.) and extracted with water (4 x 50 ml.). Evaporation of the organic extract gave an oil which was treated with aqueous picric acid. The solid obtained was successively recrystallised from water and ethanol to give 1-benzyl-2-(3-cyanopropyl)imidazole picrate, (2.6 g.; 56%), m.p. 100-102°.

(Found: C, 52.95; H, 4.18; N, 18.51. $C_{14}H_{15}N_3.C_6H_3N_3O_7$ requires C, 52.86; H, 3.99; N, 18.50%)

The product was subsequently isolated as its hydrochloride salt in 76% yield, and recrystallised from isopropanol/ether, m.p. 159-161°.

(Found: C, 64.07; H, 6.23; N, 16.07; Cl, 13.77. $C_{14}H_{15}N_3.HCl$ requires C, 64.24; H, 6.16; N, 16.05; Cl, 13.55%)

1-Benzyl-2-(4-aminobutyl)imidazole (II. 26)

1-Benzyl-2-(3-cyanopropyl)imidazole hydrochloride (2.62 g.; 0.01 mole) in methanol was converted into its free base using Amberlite IRA 401 ion-exchange resin in the hydroxide form. The free base in anhydrous methanolic ammonia (65 ml.) was hydrogenated at 130° under 140

atmospheres of hydrogen for 4 hr., using Raney nickel (1 g.) as catalyst. Evaporation of the filtered mixture yielded an oil which was treated with hot ethanolic picric acid. Recrystallisation of the resulting solid from isopropanol gave 1-benzyl-2-(4-aminobutyl)imidazole dipicrate (5.43 g.; 78%), m.p. 167-169°.

(Found: C, 45.66; H, 3.75; N, 18.29. $C_{14}H_{19}N_3.2C_6H_3N_3O_7$ requires C, 45.42; H, 3.66; N, 18.34%)

The dipicrate was converted into its dihydrochloride in the usual way, but owing to its hygroscopic nature this material was not characterised.

2-(4-Aminobutyl)imidazole (II. 27)

The dihydrochloride, obtained from 1-benzyl-2-(4-aminobutyl)imidazole dipicrate (15.0 g.; 0.022 mole), in liquid ammonia (200 ml.) was treated with small pieces of sodium metal until a blue colour persisted. Ammonium chloride was added and the ammonia was allowed to evaporate. Aqueous sodium carbonate was added to the residue which was then evaporated and extracted with ethanol to yield an oil (3.1 g.). Treatment of this material with hot ethanolic picric acid afforded a solid which was recrystallised from aqueous ethanol to give 2-(4-aminobutyl)-imidazole dipicrate, (8.3 g.; 64%), m.p. 194-195° (decomp.).

(Found: C, 38.47; H, 3.32; N, 21.39. $C_7H_{13}N_3.2C_6H_3N_3O_7$ requires C, 38.20; H, 3.21; N, 21.10%)

The dihydrochloride, obtained in the usual way, was hygroscopic and all handling operations were carried out under an inert atmosphere in a "Dry Box". Recrystallisation from isopropanol/ethanol/ether afforded the required material, m.p. 229-231°.

(Found: C, 39.88; H, 7.25; N, 19.52; Cl, 33.09. $C_7H_{13}N_3.2HCl$ requires C, 39.63; H, 7.13; N, 19.81; Cl, 33.43%)

Isothioureas

2-Hydroxymethylimidazole (II. 28)

This was prepared by the method of Iversen and Lund[55], m.p. 112-114°, 90% yield (lit.[55] m.p. 114-115°).

The hydrochloride, prepared by the usual method was recrystallised from ethanol/ether, m.p. 115-116°.

(Found: C, 35.96; H, 5.37; N, 20.97; Cl, 26.22. $C_4H_6N_2O.HCl$ requires C, 35.70; H, 5.25; N, 20.82; Cl, 26.35%)

2-Chloromethylimidazole (II. 29)

2-Hydroxymethylimidazole hydrochloride (14.87 g., 0.113 mole) was added portionwise to purified thionyl chloride (25 ml.) in dry ether (25 ml.). The mixture was heated under reflux for 0.5 hr., and then evaporated under vacuum. Recrystallisation of the residue from isopropanol/ether gave 2-chloromethylimidazole hydrochloride (14.7 g.; 87%) m.p. 153-155°.

(Found: C, 31.62; H, 3.93; N, 18.33; Cl, 46.27%. $C_4H_5N_2Cl.HCl$ requires C, 31.40; H, 3.95; N, 18.31; Cl, 46.34%)

1-Methyl-2-(2-chloroethyl)imidazole (II. 33)

1-Methyl-2-(2-hydroxyethyl)imidazole (5.6 g.; 0.35 mole), [compound (IV. 7), p.142], and thionyl chloride (5 ml.) were heated under reflux for 0.5 hr. Cyclohexane (15 ml.) was added, the mixture was evaporated and the residue was recrystallised from ethanol/ether to yield 1-methyl-2-(2-chloroethyl)imidazole hydrochloride, (3.8 g.; 61%), m.p. 163-165°.

(Found: C, 40.07; H, 5.83; N, 15.59; Cl, 39.12. $C_6H_9N_2Cl.HCl$ requires C, 39.80; H, 5.57; N, 15.47; Cl, 39.16%)

1-Benzyl-2-ethoxycarbonylmethylimidazole (II. 35)

1-Benzyl-2-cyanomethylimidazole (15.4 g.; 0.078 mole) was heated under reflux for 18 hr. with 2N sodium hydroxide (70 ml.). The solution was acidified with 12N hydrochloric acid and evaporated under vacuum. The residue was extracted with ethanol and the extract was evaporated to give an oil which was heated under reflux for 3 days with 5% hydrogen chloride in ethanol (300 ml.) and then evaporated under vacuum. The residue was partitioned between saturated aqueous sodium carbonate and chloroform. The chloroform solution yielded an oil which was distilled under vacuum to give 1-benzyl-2-ethoxycarbonylmethylimidazole, (13.8 g.; 73%), b.p. 176-180° (0.3 mm.).

(Found: C, 68.67; H, 7.04; N, 11.74. $C_{14}H_{16}N_2O_2$ requires C, 68.83; H, 6.60: N, 11.47%)

1-Benzyl-2-(2-hydroxyethyl)imidazole (II. 36)

1-Benzyl-2-ethoxycarbonylmethylimidazole (1.2 g., 0.005 mole) in dry ether (50 ml.) was added dropwise to lithium aluminium hydride (1 g., 0.026 mole) in ether (100 ml.), heated under reflux. After 2 hr., water (1 ml.), 15% aqueous sodium hydroxide (1 ml.) and water (3 ml.) were successively added. The mixture was filtered and the granular solid was washed with hot methanol (3 x 50 ml.). Evaporation of the combined filtrate gave an oil which was partitioned between 2N hydrochloric acid and chloroform. The aqueous layer was neutralised with potassium carbonate and extracted with chloroform (4 x 50 ml.). The dried (Na_2SO_4) chloroform solution was evaporated and the solid obtained was recrystallised from benzene/petroleum ether (b.p. 60-80°) to give 1-benzyl-2-(2-hydroxyethyl)imidazole, (0.6 g.; 59%), m.p. 82-84°.

(Found: C, 71.55; H, 7.08; N, 14.14. $C_{12}H_{14}N_2O$ requires C, 71.26; H, 6.98; N, 13.85%)

2-(2-Hydroxyethyl)imidazole (II. 39)

Sodium metal (approximately 2 g.) was added to a suspension of 1-benzyl-2-(2-hydroxyethyl)imidazole (6.1 g., 0.03 mole) in liquid ammonia (100 ml.) until a blue colour persisted. Ammonium chloride (2.5 g.) was added and the ammonia was allowed to evaporate. The residue was extracted with ethanol (3 x 50 ml.) and the extracts were evaporated to give an oil, from which a hydrochloride could not be

satisfactorily obtained. Hence the material was converted into its picrate salt, which was recrystallised from ethanol/water to give 2-(2-hydroxyethyl)imidazole picrate, (4.6 g.; 41%), m.p. 148-149°.

This material was found to be identical with an authentic sample of 2-(2-hydroxyethyl)imidazole picrate [(IV. 11), p. 163] and a mixed melting point showed no depression.

The picrate, in water, was converted into its free base by passage through a basic ion-exchange column (Amberlite IRA 401). The base was eluted from the column with water and the eluate evaporated under vacuum to give a solid (1.4 g.) which was used without further purification.

Preparation of isothioureas

Most of the isothioureas described were obtained by the following method:

The chloroalkylimidazole, as its hydrochloride salt (0.01 mole), was heated under reflux for 1 hr. with thiourea (0.76 g.; 0.01 mole) in ethanol (20 ml.). The isothiourea,as its dihydrochloride salt, separated from the cooled solution and was recrystallised.

S-(1-Benzylimidazol-2-yl)methylisothiourea dihydrochloride (II. 30) was recrystallised from ethanol/ether, (73%), m.p. 195-196° (decomp.).

(Found: C, 45.37; H, 5.02; N, 17.66; Cl, 22.40; S, 9.95. $C_{12}H_{14}N_4S.2HCl$ requires C, 45.14; H, 5.05; N, 17.55; Cl, 22.21 S, 10.04%)

S-(Imidazol-2-yl)methylisothiourea dihydrochloride (II. 31) was recrystallised from methanol/ether, (72%), m.p. 222.5-223.5 (decomp.).

(Found: C, 26.40; H, 4.23; H, 24.51; Cl. 30.79; S, 14.09. $C_5H_8N_4S.2HCl$ requires C, 26.21; H, 4.40; N, 24.45; Cl, 30.95; S, 13.99%)

S-2-(1-Methylimidazol-2-yl)ethylisothiourea dihydrochloride monohydrate (II. 34)

The ethanolic reaction mixture was evaporated under vacuum to give an oil which crystallised after several days' exposure to the atmosphere. Recrystallisation from methanol/ether gave the title compound (0.5 g.; 19%) m.p. 173-174°.

(Found: C, 30.80; H, 5.60; N, 20.55; Cl, 25.48. $C_7H_{12}N_4S.2HCl.H_2O$ requires C, 30.55; H, 5.86; N, 20.36; Cl, 25.77%)

S-3-(1-Benzylimidazol-2-yl)propylisothiourea dihydrochloride monohydrate (II. 41)

This was prepared from 1-benzyl-2-(3-chloropropyl)imidazole hydrochloride (2.7 g.) with a reaction time of 18 hr. Ethanolic hydrogen chloride was added to the reaction mixture and the solution was evaporated under vacuum to give an oil which crystallised upon trituration with methanol. Recrystallisation from ethanol/ether gave the title compound, (2.4 g.; 65%), m.p. 121-123°.

(Found: C, 46.16; H, 6.24; N, 15.14; Cl, 19.68; S, 8.62. $C_{14}H_{18}N_4S.2HCl.H_2O$ requires C, 46.03; H, 6.07; N, 15.34; Cl, 19.41; S, 8.78%)

S-2-(Imidazol-2-yl)ethylisothiourea (II. 40)

2-(2-Hydroxyethyl)imidazole (1.4 g.; 0.0125 mole), thiourea (0.95 g.; 0.0125 mole) and 48% aqueous hydrobromic acid (8.6 ml.) were heated under reflux for 23 hr. The reaction mixture was diluted with water, clarified with charcoal, and evaporated under vacuum to yield a solid. Recrystallisation from isopropanol/ethanol/ether gave S-2-(imidazol-2-yl)ethylisothiourea dihydrobromide, (1.9 g.; 40%), m.p. 199-200°.

(Found: C, 21.81; H, 3.60; N, 16.64; Br, 48.40; S, 9.79 $C_6H_{10}N_4S.2HBr$ requires C, 21.70; H, 3.64; N, 16.87; Br, 48.13; S, 9.66%)

Guanidines

Preparation of guanidines

The amine dihydrochloride (1 mole) was converted into its free base using a basic ion-exchange resin (Amberlite IRA 401). An aqueous solution of the base was heated under reflux for several hours with an equimolar quantity of S-methylisothiuronium sulphate. The reaction mixture was filtered, acidified with 2N sulphuric acid until just acid to Congo Red indicator, and evaporated under vacuum. Recrystallisation from ethanol/water gave the required guanidine.

2-(2-Guanidinoethyl)imidazole sulphate (II. 46a)

This was prepared from 2-(2-aminoethyl)imidazole dihydrochloride (3.7 g., 0.02 mole) with a reaction time of 3 hr. (3.5 g.; 70%), m.p. 256-258° (decomp.).

(Found: C, 28.81; H, 5.26; N, 27.69; S, 12.79. $C_6H_{11}N_5.H_2SO_4$ requires C, 28.66; H, 5.21; N, 27.87; S, 12.76%)

1-Methyl-2-(2-guanidinoethyl)imidazole sulphate (II. 46b)

This was prepared from 1-methyl-2-(2-aminoethyl)imidazole dihydrochloride hemihydrate (4.14 g., 0.02 mole) with a reaction time of 6 hr. (4.9 g.; 93%) m.p. 271-273° (decomp.).

(Found: C, 31.41; H, 5.75; N, 26.16; S, 11.83. $C_7H_{13}N_5.H_2SO_4$ requires C, 31.69; H, 5.70; N, 26.40; S, 12.09%)

2-(3-Guanidinopropyl)imidazole sulphate monohydrate (II. 46c)

This was prepared from 2-(3-aminopropyl)imidazole dihydrochloride (0.9 g., 0.0045 mole) with a reaction time of 18 hr., (0.74 g., 62%), m.p. 260-262° (decomp.).

(Found: C, 29.71; H, 6.24; N, 24.60; S, 11.15. $C_7H_{13}N_5.H_2SO_4.H_2O$ requires C, 29.68; H, 6.05; N, 24.72; S, 11.32%)

1-Benzyl-2-(3-guanidinopropyl)imidazole sulphate (II. 46d)

This was prepared from 1-benzyl-2-(3-aminopropyl)imidazole (1.1 g., 0.005 mole) with a reaction time of 5 hr. (1.2 g., 67%), m.p. 292-294° (decomp.).

(Found: C, 47.61; H, 6.07; N, 19.60; S, 9.12. $C_{14}H_{19}N_5.H_2SO_4$ requires C, 47.31; H, 5.95; N, 19.71; S, 9.02%)

2-(4-Guanidinobutyl)imidazole (II. 46e)

This was prepared from 2-(4-aminobutyl)imidazole dihydrochloride (1.1 g.; 0.0056 mole) with a reaction time of 60 hr. The sulphate salt could not be purified by recrystallisation. Hence an aqueous solution of this material was treated with an excess of hot aqueous picric acid. The solid which separated was recrystallised from nitromethane saturated with water to give 2-(4-guanidinobutyl)-imidazole dipicrate, (1.4 g.; 35%), m.p. 227-228°.

(Found: C, 37.57; H, 3.18; N, 23.86. $C_8H_{15}N_5.2C_6H_3N_3O_7$ requires C, 37.56; H, 3.31; N, 24.10%)

The dihydrochloride, prepared from the above by the usual nitrobenzene/6N hydrochloric acid method, was recrystallised from isopropanol/ether, (0.37 g.; 78%), m.p. 189-191°.

(Found: C, 38.09; H, 6.70; N, 27.27; Cl, 28.12. $C_8H_{15}N_5.2HCl$ requires C, 37.80; H, 6.74; N, 27.56; Cl, 27.90%)

1-Benzyl-2-(4-guanidinobutyl)imidazole sulphate (II. 46f)

This was prepared from 1-benzyl-2-(4-aminobutyl)imidazole dihydrochloride (1 g.; 0.003 mole) with a reaction time of 18 hr., (0.6 g.; 46%), m.p. 264-266° (decomp.).

(Found: C, 48.83; H, 6.52; N, 18.87; S, 8.66. $C_{15}H_{21}N_5.H_2SO_4$ requires C, 48.76; H, 6.27; N, 18.96; S, 8.68%)

Synthesis of α-aminoacrylonitriles

1-Benzyl-2-cyanomethylimidazole (II. 4a) and 1-amino-2-(1-benzylimidazol-2-yl)acrylonitrile (II. 47) ((cf. ref. 15)

1-Benzyl-2-chloromethylimidazole hydrochloride (40 g.; 0.163 mole) was added to dry, powdered sodium cyanide (40 g.; 0.815 mole) in dry dimethyl sulphoxide (320 ml.) over 5 min. The temperature was kept below 45° during the addition, and then maintained at 40° for 1 hr. The reaction mixture was diluted with dichloromethane (1 l.) and the resulting solution washed with water (4 x 800 ml.). The organic layer was dried (Na_2SO_4) and evaporated to give a brown solid (30.3 g.). This material was continuously extracted for 3 hr. in a Soxhlet extractor with petroleum-ether (b.p. 60-80°). The extract was clarified with charcoal and evaporated under vacuum to give a solid, (3.3 g.), which was recrystallised from petroleum ether to give 1-amino-2-(1-benzylimidazol-2-yl)acrylonitrile, (2.6 g.; 7%), m.p. 75-77°.

(Found: C, 69.60; H, 5.43; N, 25.23. $C_{12}H_{13}N_4$ requires C, 69.62; H, 5.39; N, 24.98%)

The petroleum-ether insoluble material was continuously extracted with benzene for 2 hr. and the extract was placed on an alumina column (pH6, Brockmann activity III) and eluted with benzene. The eluate was evaporated, and the residue was recrystallised from benzene/petroleum-ether (b.p. 60-80°) to give 1-benzyl-2-cyanomethylimidazole, (23.4 g.; 73%), m.p. 101-103 (cf. II 4a, p. 60).

When the reaction was carried out in dry dimethyl formamide at 130°, the products were extracted into dichloromethane in the usual way and the material obtained was placed on an alumina column (pH6, Brockmann activity III) and eluted with benzene. The first fraction comprised 1-amino-2-(1-benzylimidazol-2-yl)acrylonitrile (9%), followed by 1-benzyl-2-cyanomethylimidazole (40%).

1-Amino-2-(1-benzylimidazol-2-yl)acrylonitrile (II. 47)

1-Benzyl-2-cyanomethylimidazole hydrochloride (1.2 g.; 0.005 mole) was added portionwise over 0.5 hr. to sodium cyanide (1.25 g.; 0.025 mole) in dry dimethyl formamide (100 ml.) at 80°. The mixture was heated to 130° for 7 hr., then extracted into dichloromethane in the usual way to give a brown oil (1.1 g.). This material was subjected to "Dry Column Chromatography"[71] using a nylon tube (24 x 1 inch) packed with "Dry Column" grade alumina. The column was developed with ether, and the two mobile components were located by irradiating the column with ultra-violet light. The appropriate length was cut from the column and extracted with chloroform. The chloroform solution was evaporated, and the residue was recrystallised from petroleum-ether (b.p. 60-80°) to give 1-amino-2-(1-benzylimidazol-2-yl)acrylonitrile, (100 mg.; 9%), m.p. 76-77°.

Phthalimidoacetonitrile (II. 54) (cf. ref. 75)

N-Ethoxycarbonylphthalimide (12.5 g., 0.057 mole) was added portionwise to a vigorously stirred solution of aminoacetonitrile hydrochloride (4.6 g., 0.05 mole) and potassium hydrogen carbonate (5.1 g.) in water (150 ml.). After 1 hr., the solid which separated was collected, washed with water and recrystallised from aqueous ethanol to give phthalimidoacetonitrile, (3.2 g.; 34%), m.p. 124-126° (lit.[75] m.p. 124-5°.

1-Benzylimidazole-2-carboxaldehyde (II. 56)

This was prepared by the method of Iversen and Lund,[55] using selenium dioxide as oxidising agent, b.p. 119-123° (0.09 mm.); 74% yield (lit.[55] b.p. 110° (0.1 mm.))

SPECTRA

Instrumentation

Infra-red spectra (i.r.) were recorded on a Beckman I.R.9 or Unicam S.P. 200 spectrometer and were taken on Nujol mulls, unless otherwise stated. Spectra are quoted in wave numbers (ν), i.e. cm^{-1}.

^1H nuclear magnetic reconance spectra (n.m.r.) were recorded on a Varian A.60A spectrometer. A computer of average transients (C.A.T.) was available and the instrument possessed facilities for spin-decoupling experiments. Samples were run in the solvents stated and the following abbreviation applies: DMSO-d_6 = $(CD_3)_2SO$. Chemical shifts are given in τ values, or in the case of multiplets in cycles per second (c/s), relative to an internal standard of tetramethyl silane or sodium 2,2-dimethyl-2-silapentane-5-sulphate. Coupling constants (J values) are given in cycles per second. The multiplicity of the peak is given and the following abbreviations apply:
s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet.
The relative intensity and assignment of the signal is included.

Mass spectra were determined on an A.E.I. M.S. 902 instrument operating at low resolution. In each case the mass peak is given first, followed by those of structural significance. An asterisk denotes a metastable peak.

Ultra-violet spectra (u.v.) were recorded on a beckman D.K.2 spectrometer in the solvent stated. Wave-lengths are given in millimicrons (mμ).

1-Benzylimidazole (II. 1a)

$\nu_{max.}$: 3108, 1603, 1510, 630 (imidazole); 3015, 1588, 1450, 1460, 735, 720 (aromatic).

τ; ($CDCl_3$): 2.49, 450-425 c/s, 3.87 (m; 8; 2-H, -Ph, 4-H, 5-H); 4.92 (s; 2; -$\underline{CH_2}$-).

1-Methylimidazole (II. 1b)

$\nu_{max.}$: (capillary film): 1518, 670, 610 (imidazole).

τ; ($CDCl_3$): 2.60 (broad s; 1; 2-H); 2.91 (t; 1; 5-H); 3.12 (t, 1, 4-H); 6.31 (s; 3; -$\underline{CH_3}$).

1-Benzyl-2-hydroxymethylimidazole (II. 2a)

(II. 2a). HCl $\nu_{max.}$: 3400 (OH); 1583, 1520, 720 (aromatic); 680 (imidazole).

τ; ($CDCl_3$): centred 473 c/s, 3.16, 3.54 (m; 8; -Ph, 4-H, 5-H, -$\underline{OH}$): 4.77 (s; 2; -$\underline{CH_2}$Ph); 5.38 (s; 2; -$\underline{CH_2}$O).

1-Methyl-2-hydroxymethylimidazole (II. 2b)

$\nu_{max.}$: 3106, 1498, 1145, 747 (imidazole); 2920 (OH).

τ; ($CDCl_3$): 3.14 (2 x d; 2; 4-H, 5-H); 3.40 (s; 1; -$\underline{OH}$); 5.47 (s; 2; -$\underline{CH_2}$O); 6.30 (s; 3; -$\underline{CH_3}$).

1-Benzyl-2-chloromethylimidazole hydrochloride (II. 3a)

$\nu_{max.}$: 3122, 630 (imidazole); 3095, 1590, 1495, 780, 780, 708 (aromatic).

τ; (D_2O): 2.22, 2.31 (2 x d; 2; 4-H, 5-H); 4.34 (s; 2; $-\underline{CH_2}Ph$); 4.74 (s; 2; $-\underline{CH_2}Cl$).

1-Methyl-2-chloromethylimidazole hydrochloride (II. 3b)

$\nu_{max.}$: 3102, 1595, 1530, 785, 670, 630 (imidazole).

τ; (D_2O): 2.43, 2.46 (2 x d; 2; 4-H, 5-H); 4.92 (s; 2; $-\underline{CH_2}Cl$); 6.01 (s; 3; $-\underline{CH_3}$).

1-Benzyl-2-cyanomethylimidazole (II. 4a) and 1-benzyl-5-cyano-2-methyl-imidazole (II. 6a) mixture

i.r.:owing to its complexity and poor resolution, little information was obtained from the spectrum. Two nitrile peaks were observed.

τ; ($CDCl_3$): 2.41 (s; 4-H); 455-430 c/s (m, -Ph); 2.94, 3.03 (2 x d; 4-H, 5-H); 4.80 (s; $-\underline{CH_2}Ph$); 6.29 (s; $-\underline{CH_2}CN$); 7.63 (s; $-\underline{CH_3}$).

The ratio of the areas under the signals at 4.80 and 6.29 indicated the mixture comprised approximately 40% (II. 4a) and 60% (II. 6a).

1-Benzyl-2-cyanomethylimidazole hydrochloride (II. 4a)

$\nu_{max.}$: 3095 (aromatic); 1595, 650, 630 (imidazole); 2250 (C≡N).

τ; (DMSO-d_6): 2.17, 2.24 (2 x d; J = 2.0; 2; 4-H, 5-H); 4.42 (broad s; 2; -$\underline{CH_2}$Ph); 5.10 (s; 2; -$\underline{CH_2}$CN).

When the spectrum was determined in deuterium oxide the signal attributable to -$\underline{CH_2}$CN was not observed, indicating rapid proton/deuteron exchange in this solvent.

1-Benzyl-5-cyano-2-methylimidazole (II. 6a)

$\nu_{max.}$: 3020, 1600, 1455, 730, 705 (aromatic); 642 (imidazole); 2220 (C≡N).

(II. 6a). HCl τ; (D_2O): 1.63 (s; 1; 4-H); 4.38 (s; 2; -$\underline{CH_2}$Ph); 7.15 (s; 3; -$\underline{CH_3}$).

1-Benzyl-5-aminomethyl-2-methylimidazole dihydrochloride (II. 7a)

$\nu_{max.}$: 3110-2300 (NH's); 1545, 722, 695 (aromatic); 1613, 620, 615 (imidazole).

τ; (D_2O): 2.22 (t,; 1; 4-H); 4.39 (s; 2; -$\underline{CH_2}$Ph); 5.62 (d; 2; -$\underline{CH_2}NH_2$); 7.26 (s; 3; -$\underline{CH_3}$).

4(5)-Aminomethyl-2-methylimidazole dihydrochloride (II. 8)

$\nu_{max.}$: 3200-2400, 880 (NH's); 1640, 807, 725, 653, 607 (imidazole).

τ; (D_2O): 2.42 (broad s; 1; 4-H); 5.60 (d; 2; $-CH_2-$); 7.31 (s; 3; $-\underline{CH}_3$).

1-Benzyl-2-(2-aminoethyl)imidazole dipicrate (II. 5a)

$\nu_{max.}$: 670 (imidazole). Strong picrate absorptions prevent further assignments.

τ; (DMSO-d_6): 2.28 (broad s; 2; 4-H, 5-H); 4.53 (s; 2; $-\underline{CH}_2Ph$); centred 198 c/s (m; 4; $-\underline{CH}_2\underline{CH}_2-$).

1-Benzyl-2-(2-benzamidoethyl)imidazole (II. 10)

$\nu_{max.}$ 3270 (NH); 3105, 1600, 1575, 1520 (aromatic); 1650, 1540 (C=O); 3050, 725, 697 (imidazole).

τ; ($CDCl_3$): 480-410 c/s (m; 13; N-H, 4-H, 5-H, 2 x -Ph); 4.97 (s; 2; $-\underline{CH}_2Ph$); 6.15 (q; 2; $-\underline{CH}_2NH-$); 7.13 (t; 4; $-\underline{CH}_2\underline{CH}_2-$).

1-Methyl-2-cyanomethylimidazole (II. 4b) and 1,2-Dimethyl-5-cyanoimidazole (II. 6b) picrate mixture

i.r.: strong picrate absorption prevents assignment of the various signals.

τ; (DMSO-d_6): 1.55 (s; 4-H); 2.22, 2.30 (2 x d; 4-H, 5-H); 5.30 (s; -$\underline{CH_2}$CN); 6.08 (s; N-$\underline{CH_3}$); 7.36 (s, C-$\underline{CH_3}$).

The ratio of the areas under the signals at 1.55 and 2.22, 2.30 indicated the mixture comprised approximately 70% (II. 4b) and 30% (II. 6b).

1-Methyl-2-cyanomethylimidazole (II. 4b)

(II. 4b). HCl $\nu_{max.}$: 2620 (NH); 2260 (C≡N): 1610, 1534, 765 (imidazole).

(II. 4b). Picr. τ; (DMSO-d_6): 2.24, 2.31 (2 x d; J = 2.0; 2; 4-H, 5-H); 5.31 (s; 2; -$\underline{CH_2}$-); 6.08 (s; 3; -$\underline{CH_3}$).

When the spectrum of the base was determined in deuterochloroform a similar spectrum was obtained. However, shaking the deuterochloroform solution with deuterium oxide removed the signal attributable to -$\underline{CH_2}$-, indicating exchange i.e. -CD_2-.

1,2-Dimethyl-5-cyanoimidazole (II. 6b)

$\nu_{max.}$: 2230 (C≡N); 1536, 855, 675, 640 (imidazole).
(II. 6b). Picr.; (DMSO-d_6): 1.53 (s; 1; 4-H); 6.17 (s; 3; N-$\underline{CH_3}$) 7.35 (s; 3; C-$\underline{CH_3}$).

λmax. (EtOH): 233; $\varepsilon_{max.}$: 13,200

1-Methyl-2-(2-ethylaminoethyl)imidazole dipicrate (II. 11)

i.r.: strong picrate absorption prevents assignment of structure.

τ; (DMSO-d_6): centred 451 c/s (broad s; 2; 4-H, 5-H); 6.92 (q; 2; N-$\underline{CH_2}CH_3$); centred 201 c/s (broad m; 4; -$\underline{CH_2CH_2}$-); 6.15 (s; 3; N-$\underline{CH_3}$).

Di-[2-(1-methylimidazol-2-yl)ethyl]amine tripicrate (II. 12)

i.r.: strong picrate absorption prevents assignment of structure.

τ; (DMSO-d_6): centred 462 c/s (q; 2; 4-H, 5-H); 6.13 (s; 3; N-$\underline{CH_3}$); centred 405 c/s (m; 4; -$\underline{CH_2CH_2}$-).

1,2-Dimethyl-5-aminomethylimidazole dihydrochloride (II. 7b)

$\nu_{max.}$: 3090, 840 (aromatic); 2700, 2005 1780 (NH_2); 1590, 655 (imidazole).

τ; (D_2O): 2.40 (t; 1; 4-H); 5.55 (d; 2; -$\underline{CH_2}$-); 6.17 (s; 3; N-$\underline{CH_3}$); 7.31 (s; 3; C-$\underline{CH_3}$).

2-Methylimidazole picrate (II. 15)

i.r.: strong picrate absorptions prevent assignment of structure.

τ ; (DMSO-d_6): 2.49 (s; 2; 4-H, 5-H); 7.42 (s; 3; -$\underline{CH_3}$).

1-Benzyl-2-imidazolealanine hydrate (II. 16)

$\nu_{max.}$: 3390, 3250 (H_2O); 2120, 1550 (NH_3) 1610 (CO_2 and NH_3); 1500, 1490, 747 (aromatic).

τ; (CF_3CO_2H): 460-435 c/s (m; 7; -Ph, 4-H, 5-H), 4.46 (s; 2; -$\underline{CH_2}$Ph); 5.17 (t; 1; -$CH_2\underline{CH}$-); 5.92 (d; 2; -$\underline{CH_2}$CH<).

2-Imidazolealamine (II. 17)

$\nu_{max.}$: 2120 (NH_3); 1585 (CO_2); 737 (aromatic).

τ; (CF_3CO_2H): 2.50 (s; 2; 4-H, 5-H); 4.99 (t; 1; -$CH_2\underline{CH}$<); 5.91 (d; 2; -$\underline{CH_2}$CH<).

1-Benzyl-2-2-ethoxycarbonylethyl)imidazole (II. 18) and 1-benzyl-5-ethoxycarbonylmethyl-2-methylimidazole (II. 19) mixture

τ; ($CDCl_3$): 3.06, 3.20 (d; 4-H, 5-H): 4.92 (s; -$\underline{CH_2}$Ph); 5.90 (q; -OCH_2CH_3); 180-155 c/s (broad s; -$\underline{CH_2}\underline{CH_2}$-); 8.83 (t; -$CH_2\underline{CH_3}$) i.e. normal product (II. 18).

3.27 (d; 4-H); 4.97 (s; -$\underline{CH_2}$Ph); 6.40 (s; -$\underline{CH_2}CO_2$-); 8.03 (s; C-$\underline{CH_3}$) i.e. rearranged product (II. 19).

From the ratio of the signals at 180-155 c/s and 8.03 it was concluded that the product comprised mainly the normal product (II. 18) with approximately 5% rearranged material.

3-(1-Benzylimidazol-2-yl)propionamide (II. 20)

$\nu_{max.}$: 3320, 3165 (NH_2); 1683 (C=O); 1583, 1525, 1500, 750, 698 (aromatic); 670, 616 (imidazole).

τ; ($CDCl_3$): 445-400 c/s (m; 8; -Ph, 4-H, 5-H, -NH); 4.92 (s; 2; $-\underline{CH_2}Ph$); 7.20 (q; 4; $-\underline{CH_2}\underline{CH_2}-$).

1-Benzyl-2-(3-aminopropyl)imidazole dipicrate (II. 21)

i.r: Strong picrate absorption prevents assignment of absorptions..

τ; ($DMSO-d_6$): 2.31 (s; 2; 4-H, 5-H); 2.60 (broad s; 5; -Ph); 4.54 (s; 2; $-\underline{CH_2}Ph$); 6.90 (m; 4; $-\underline{CH_2}CH_2\underline{CH_2}-$); 8.00 (m; 2; $-CH_2\underline{CH_2}CH_2-$).

2-(3-Aminopropyl)imidazole dipicrate (II. 22)

$\nu_{max.}$: 619 (imidazole). Strong picrate absorptions prevent further assignments.

τ; ($DMSO-d_6$): 2.41 (s; 2; 4-H, 5-H); centred 176 c/s (m; 4; $-\underline{CH_2}CH_2\underline{CH_2}-$); centred 127 c/s (m; 2; $-CH_2\underline{CH_2}CH_2-$).

1-Benzyl-2-(3-hydroxypropyl)imidazole (II. 23)

τ; ($CDCl_3$): 440-400 c/s (m; 7; -Ph, 4-H, 5-H); 4.68 (s; 1; -OH); 4.99 (s; 2; $-\underline{CH_2}Ph$); 6.37 (6; 2; $-\underline{CH_2}O$); 7.27 (6; 2; $-\underline{CH_2}CH_2CH_2O-$); 8.06 (q; 2; $-CH_2\underline{CH_2}CH_2-$).

1-Benzyl-2-(3-chloropropyl)imidazole hydrochloride (II. 24)

$\nu_{max.}$: 3120, 640 (imidazole); 1600, 1520, 690 (aromatic).

τ; (D_2O): centred 452 c/s (m; 7; -Ph, 4-H, 5-H); 4.51 (s; 2; $-\underline{CH_2}Ph$); 6.24 (t; 2; $-\underline{CH_2}Cl$); 6.66 (m; 2; $-\underline{CH_2}CH_2CH_2Cl-$); 7.72 (m; 2; $-CH_2CH_2CH_2-$).

1-Benzyl-2-(3-cyanopropyl)imidazole hydrochloride (II. 25)

$\nu_{max.}$: 2240 (C N); 3120, 1525 (imidazole); 3070, 720, 690 (aromatic).

τ; (D_2O): centred 449 c/s (m; 7; -Ph, 4-H, 5-H); 4.52 (s; 2; $-\underline{CH_2}Ph$); 6.80 (t; 2; $-\underline{CH_2}CH_2CH_2CN$); 7.40 (t; 2; $-\underline{CH_2}CN$); 8.00 (m; 2; $-CH_2\underline{CH_2}CH_2-$).

1-Benzyl-2-(4-aminobutyl)imidazole dipicrate (II. 26)

i.r.: strong picrate absorptions prevent assignment.

τ; (DMSO-d_6): 2.28, 2.59, 475-430 c/s (m; 10; 4-H, 5-H -Ph, $-\underline{NH}$, $-\underline{NH_2}$); 4.53 (s; 2; $-\underline{CH_2}Ph$); 195-155 c/s (m; 4; $-\underline{CH_2}CH_2CH_2\underline{CH_2}-$); 8.90 (m; 4; $-CH_2\underline{CH_2}\underline{CH_2}CH_2-$).

2-(4-aminobutyl)imidazole dihydrochloride (II. 27)

$\nu_{max.}$: 3300-2600 (NH_3); 1620, 1505, 1490, 1125, 760 (imidazole).

τ; (D_2O): 2.61 (s; 2; 4-H, 5-H); 6.89 (m; 4; -$\underline{CH_2}CH_2CH_2\underline{CH_2}$-); 8.15 (m; 4; -$CH_2\underline{CH_2}\underline{CH_2}CH_2$-).

2-Hydroxymethylimidazole hydrochloride (II. 28)

$\nu_{max.}$: 335, 1655 (OH); 3300-2400, 1620 (NH) 3145, 1575, 773, 623 (imidazole).

2-Choromethylimidazole hydrochloride (II. 29)

$\nu_{max.}$: 3130, 640 (imidazole); 1615, 1435, 1310, 795, 728 (aromatic);

τ; (D_2O): 2.49 (s; 2; 4-H, 5-H); 5.00 (s; 2; -$\underline{CH_2}$-).

1-Methyl-2-(2-chloroethyl)imidazole hydrochloride (II. 33)

$\nu_{max.}$: 3100-2200 (NH); 3150, 770, 668, 620 (imidazole); 1600, 1530 (aromatic).

τ; (D_2O): 2.58 (s; 2; 4-H, 5-H); 245-205 c/s (m; 7; -$\underline{CH_3}$, -$\underline{CH_2}\underline{CH_2}$-).

1-Benzyl-2-ethoxycarbonylmethylimidazole (II. 35)

$\nu_{max.}$: (capillary film): 3150, 690 (imidazole); 1730 (C=O); 1615, 1525 (aromatic).

τ; ($CDCl_3$): 450-425 c/s, 2.95, 3.05 (m; 7; -Ph, 4-H, 5-H); 4.83 (s; 2; -$\underline{CH_2}$Ph); 5.85 (q; 2; $CO_2\underline{CH_2}CH_3$); 6.24 (s; 2; -$\underline{CH_2}$-); 8.79 (t; 3; $-CH_2\underline{CH_3}$).

1-Benzyl-2-(2-hydroxyethyl)imidazole (II. 36)

$\nu_{max.}$: 3150, 1280 (OH); 3120, 698 (imidazole); 732 (aromatic).

τ; ($CDCl_3$): 450-425 c/s, 2.97, 3.10 (m; 7; -Ph, 4-H, 5-H); 4.88 (s; 2; -$\underline{CH_2}$Ph); 5.52 (s; 1; -$\underline{OH}$); 5.99 (t; 2; $-CH_2\underline{CH_2}O-$); 7.18 (t; 2; -$\underline{CH_2}CH_2O-$).

2-(2-Hydroxyethyl)imidazole (II. 39)

$\nu_{max.}$: 3100 (OH), 1430, 1320 (aromatic); 775 (imidazole).

S-(1-Benzylimidazol-2-yl)methylisothiourea dihydrochloride (II. 30)

$\nu_{max.}$: 3350-2400 (NH_2); 3135, 622 (imidazole); 1650 (thiourea), 1600, 1520, 1495, 750, 716, 697 (aromatic).

τ: (D_2O): 460-435 c/s (m; 5; -Ph); 2.39 (s; 2; 4-H, 5-H), 4.44 (s; 2; $\underline{CH_2}$Ph); 5.13 (s; 2; -$\underline{CH_2}$-S).

S-Imidazol-2-ylmethylisothiourea dihydrochloride (II. 31)

$\nu_{max.}$ 3150, 3130, 1610, 665 (aromatic); 1620 (thiourea).

τ; (D_2O): 2.47 (s; 4-H; 5-H); 5.13 (s;-CH_2S). Overlap of signal due to the presence of HDO in solvent D_2O prevents integration.

S-2-(1-Methylimidazol-2-yl)ethylisothiourea dihydrochloride monohydrate (II. 34)

$\nu_{max.}$: 1660 (thiourea); 1600, 1535 (aromatic).

τ; (D_2O): 2.60 (s; 2; 4-H, 5-H); 6.13 (s; 3;-N$\underline{CH_3}$) 6.42 (t; 4; -$\underline{CH_2}CH_2$-).

S-3-(1-Benzylimidazol-2-yl)propylisothiourea dihydrochloride monohydrate (II. 41)

$\nu_{max.}$: 1645 (thiourea); 1520 (imidazole); 725, 702 (aromatic).

τ; (D_2O): 460-435 c/s, 2.40 (m; 7; -Ph, 4-H, 5-H) 4.47 (s; 2; -$\underline{CH_2}$Ph); 6.75 (t; 4; -$\underline{CH_2}CH_2\underline{CH_2}$-); 7.95 (m; 2; -$CH_2\underline{CH_2}CH_2$-).

S-2-(Imidazol-2-yl)ethylisothiourea dihydrobromide (II. 40)

$\nu_{max.}$:3350-300, 2800-2000, 690 (NH_2); 1650 (thiourea).

τ; (D_2O): 7.52 (s; 2; 4-H, 5-H); 3.62 (m; 4; -$\underline{CH_2}CH_2$-).

2-(2-Guanidinoethyl)imidazole sulphate (II. 46a)

$\nu_{max.}$: 1690 (guanidine); 1630,620 (NH_2) 1510, 776, 756 (imidazole); 1100 (SO_4).

τ; (D_2O): 2.69 (s; 2; 4-H, 5-H); centred 217 c/s (m; 4; $-\underline{CH_2}\underline{CH_2}-$).

1-Methyl-2-(2-guanidinoethyl)imidazole sulphate (II. 46b)

$\nu_{max.}$: 1690 (guanidine); 1620 (NH_2); 1530 (imidazole).

τ; (D_2O): 2.61 (s; 2; 4-H, 5-H); 6.15 (s; 3; $-\underline{CH_3}$); 6.30 (m; 2; $-\underline{CH_2}CH_2N-$); 6.68 (m; 2; $-CH_2\underline{CH_2}N-$).

2-(3-Guanidinopropyl)imidazole sulphate monohydrate (II. 46c)

$\nu_{max.}$: 1695 (guanidine); 1640, 620 (NH_2); 1110 (SO_4); 720 (imidazole).

τ; (D_2O); 2.62 (s; 2; 4-H, 5-H); 6.18, 6.87 (m; 4; $-\underline{CH_2}CH_2\underline{CH_2}-$); 7.90 (m; 2; $-CH_2\underline{CH_2}CH_2-$).

1-Benzyl-2-(3-guanidinopropyl)imidazole sulphate (II. 46d)

$\nu_{max.}$: 1680 (guanidine); 1520 (imidazole); 1100 (SO_4); 724, 696 (aromatic).

τ; (D_2O/DMSO-d_6/CF_3CO_2H): 2.48 (s; 4-H; 5-H); centred 448 c/s (m; -Ph); 4.57 (s; -$\underline{CH_2}$Ph); centred 190 c/s (m; -$\underline{CH_2}CH_2\underline{CH_2}$-); centred 115 c/s (m; -$CH_2\underline{CH_2}CH_2$-).

Owing to the relative insolubility of this material the above three component solvent system was necessary for the n.m.r. determination.

2-(4-Guanidinobutyl)imidazole dipicrate (II. 46e)

$\nu_{max.}$: 3400-3200, 1655 (NH_2); 1675 (guanidine).

τ; (DMSO-d_6): 460-400 c/s, 2.47 (m; 7; -Ph, 4-H, 5-H); 7.00 (m; 4; -$\underline{CH_2}CH_2CH_2\underline{CH_2}$-); 8.40 (m; 4; -$CH_2\underline{CH_2}\underline{CH_2}CH_2$-).

1-Benzyl-2-(4-guanidinobutyl)imidazole sulphate (II. 46f)

$\nu_{max.}$: 3600-2600, 750-500 (NH_2); 1660 (guanidine); 1545, 620 (imidazole); 1100 (SO_4); 760, 710 (aromatic).

; (D_2O): 460-435 c/s (m; 7; -Ph, 4-H, 5-H); 4.54 (s; 2; -$\underline{CH_2}$Ph); 200-175 c/s (m; 4; -$\underline{CH_2}CH_2CH_2\underline{CH_2}$-); 100-85 c/s (m; 4; -$CH_2\underline{CH_2}\underline{CH_2}CH_2$-).

1-Amino-2-(1-benzylimidazol-2-yl)acrylonitrile (II. 47)

$\nu_{max.}$: 3488, 3260 (NH_2); 2231 (conjugated nitrile).

τ; ($CDCl_3$): 450-415 c/s, 3.13, 2.95 (m; 7; -Ph, 4-H, 5-H); 3.90 (broad s; 2; -$\underline{NH_2}$); 4.40 (s; 1; =$\underline{CH}$-); 4.93 (s; 2; -$\underline{CH_2}$Ph).

m/e 224, 208, 207, 197, 193.2*, 191.2*, 173.7*, 108, 106, 92, 91, 82, 65, 53, 46.45*.

$\lambda_{max.}$; (EtOH): 322 mμ; $\varepsilon_{max.}$: 17,600.

Phthalimidoacetonitrile (II. 54)

$\nu_{max.}$: 2300 (C≡N); 1720 (C=O); 740, 720 (aromatic).

1-Benzylimidazole-2-carboxaldehyde (II. 56)

$\nu_{max.}$; (capillary film): 3120, 1605, 1505 (imidazole); 1690 (C=O); 3050, 1585, 1460, 720 (aromatic).

SECTION III

FORMATION OF THE IMIDAZOLE RING BY CYCLISATION REACTIONS

DISCUSSION

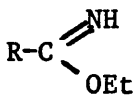
The compounds discussed in this section were prepared by the reaction between aminoacetals or aminoketals and iminoethers.

Synthesis of iminoethers

The classical Pinner synthesis [75,76] afforded a convenient method of obtaining iminoethers. This reaction utilizes the addition of an alcohol to a nitrile catalysed by hydrogen chloride. In our example ethanol was used exclusively and it was noted that the nitriles employed differed markedly in their reactivity. Reaction times from a few hours up to several weeks were required and the yields were also quite variable.

Initially the iminoether free bases were used in the cyclisation reactions, but it was subsequently found that the iminoether could be used as the hydrochloride. From the synthetic viewpoint this offered several advantages. The conversion of the hydrochloride into its free base involves an extra stage in the synthesis, only fair yields are generally obtained and the product is very labile.

The following iminoethers were prepared:



a, R = $-CH_2CN$

b, R = $-CH_2CO_2Et$

c, R = $-CH_2CH_2NHCOPh$

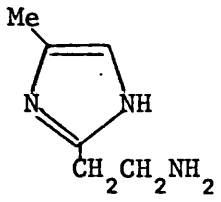
Synthesis of aminoacetals and aminoketals

The aminoacetals used in this work were either commercially available or could be prepared using literature methods;[77] the following were used.

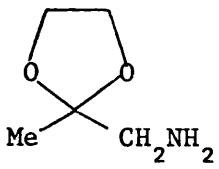
$(EtO)_2CHCH_2NH\text{-}R$

a, R = -H
b, R = -Me
c, R = $-CH_2Ph$

Previous attempts to obtain aminoacetone hydrochloride in our laboratories had been unsatisfactory. This compound was required in the synthesis of 4(5)-methylisohistamine (III.1) using the method of Ellinger and Goldberg.[43] In view of our success with aminoacetals,

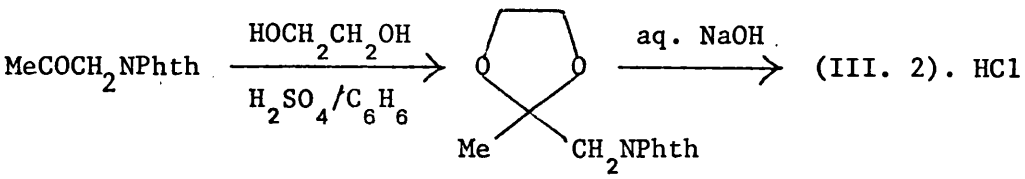


(III. 1)

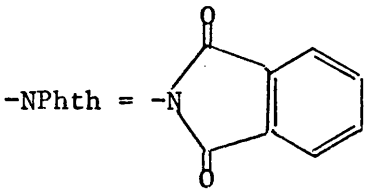


(III. 2)

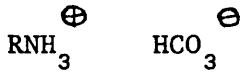
we decided to protect aminoacetone as its ketal 2-Aminomethyl-2-methyl-1,3-dioxolane (III.2) was used, since it had been prepared as its hydrochloride by the route shown.[78]

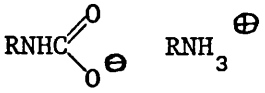


(III. 3)

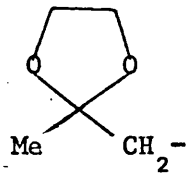


We were able to improve the yields significantly in the above sequence of reactions. In addition we established conditions for the hydrolysis of the phthalimido compound (III.3) with aqueous potasium hydroxide, which enabled us to isolate the ketal (III.2) as the free base. This was a high boiling liquid which rapidly formed the carbonate (III.4) or carbamate (III.5) in air.



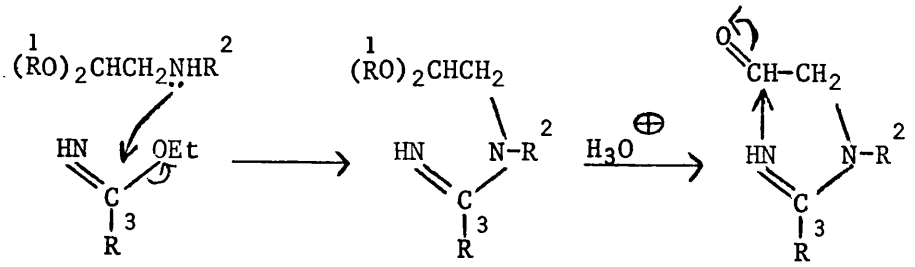


(III. 4) R = (III. 5)

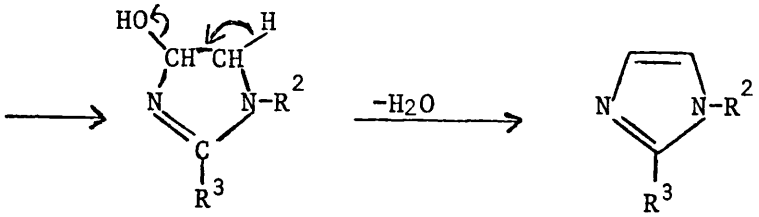


Cyclisation Reactions

The condensation between aminoacetals or aminoketals and iminoethers to form the imidazole ring is a two stage process. Attack of the amine function on the imine carbon leads to the substituted amidine (III.6) with elimination of ethoxide. Treatment of this amidinoacetal with acid liberates the free carbonyl group which reacts with the imine group to give the hydroxyimidazoline (III.7). Aromatisation with loss of water affords the imidazole (III.8).



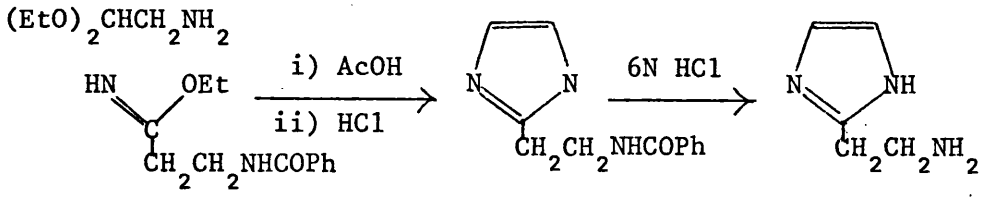
(III.6)



(III.7) (III.8)

Amidine formation has been carried out using both glacial acetic acid and ethanol. Cyclisation of the amidinoacetal was generally effected in dilute hydrochloric acid. In our hands the yields from these reactions never exceeded 50% and it is possible that the factors which lead to these relatively low yields are the interaction of the iminoethers with solvent alcohol to form the orthoesters, or the condensation of the iminoethers and acetals (or ketals) with elimination of ammonia and production of the N-substituted iminoethers which are known[43] to cyclise to the 2-substituted oxazoles.

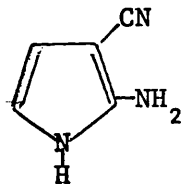
The original isohistamine (III.9) synthesis, carried out in our laboratories by Mr. J.M. Loynes,[8] involved reaction between ethyl β-benzamidopropionimidate and aminoacetaldehyde diethylacetal in glacial acetic acid, followed by treatment with 1N hydrochloric acid. Removal of the benzoyl protecting group was effected by heating under reflux with 6N hydrochloric acid. Isohistamine (III.9) was isolated as its dihydrochloride in 40% yield.



(III. 9)

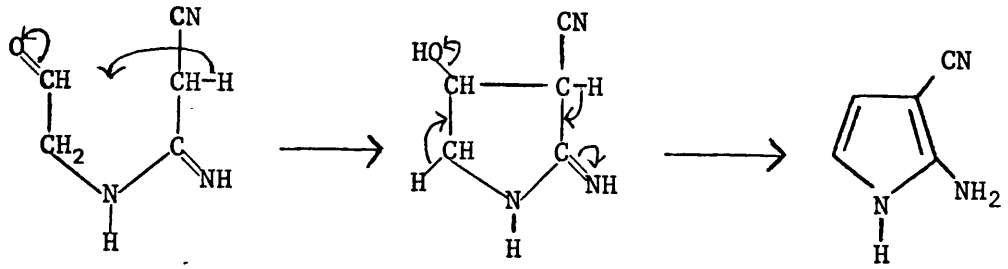
Although other 1- and 4(5)-substituted isohistamines were prepared by modifying this procedure (see below) we will outline our experiences with this method.

The reaction between ethyl cyanoacetimidate and aminoacetaldehyde diethylacetal using the above conditions did not give the desired 2-cyanomethylimidazole, but instead gave rise to a very low yield (approximately 1%) of a compound whose i.r. and n.m.r. spectra were consistent with its formulation as 2-amino-3-cyanopyrrole (III.10). Insufficient of this material was available for complete characterisation.



(III. 10)

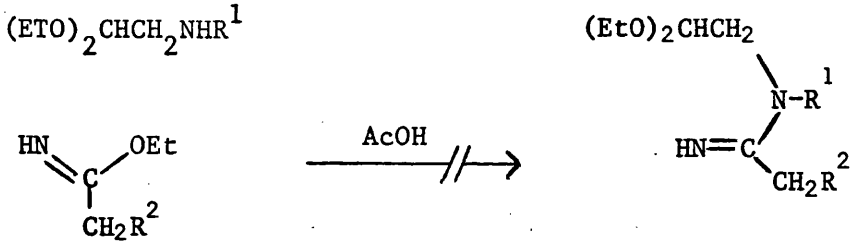
However, if this structure is correct, the pyrrole (III.10) is most likely to have arisen from the amidinoacetal by attack of the carbon adjacent to the nitrile group on the carbonyl, due to the acidity of the methylene protons.



(III.10)

A low yield (approximately 2%) of 3-benzamidopropionamide was isolated from the reaction between benzylaminoacetaldebyde diethylacetal and ethyl β-benzamidopropionimidate under the above conditions. This material is likely to have been present as an impurity in the iminoether and could have been formed on conversion of the iminoether hydrochloride into its free base.

Various attempts were made to isolate the intermediate amidinoacetals from the reaction between the iminoethers as hydrochlorides and the aminoacetals in methanol, following A Lawson,[46] who isolated some related amidines as their picrolonate salts. None of the required compounds was isolated from the following reactions (a), (b) and (c).



a, $R^1 = -H, R^2 = -CH_2NHCOPh$

b, $R^1 = -CH_2Ph$, $R^2 = -CN$

c, $R^1 = -CH_2Ph$, $R^2 = -CH_2NHCOPh$

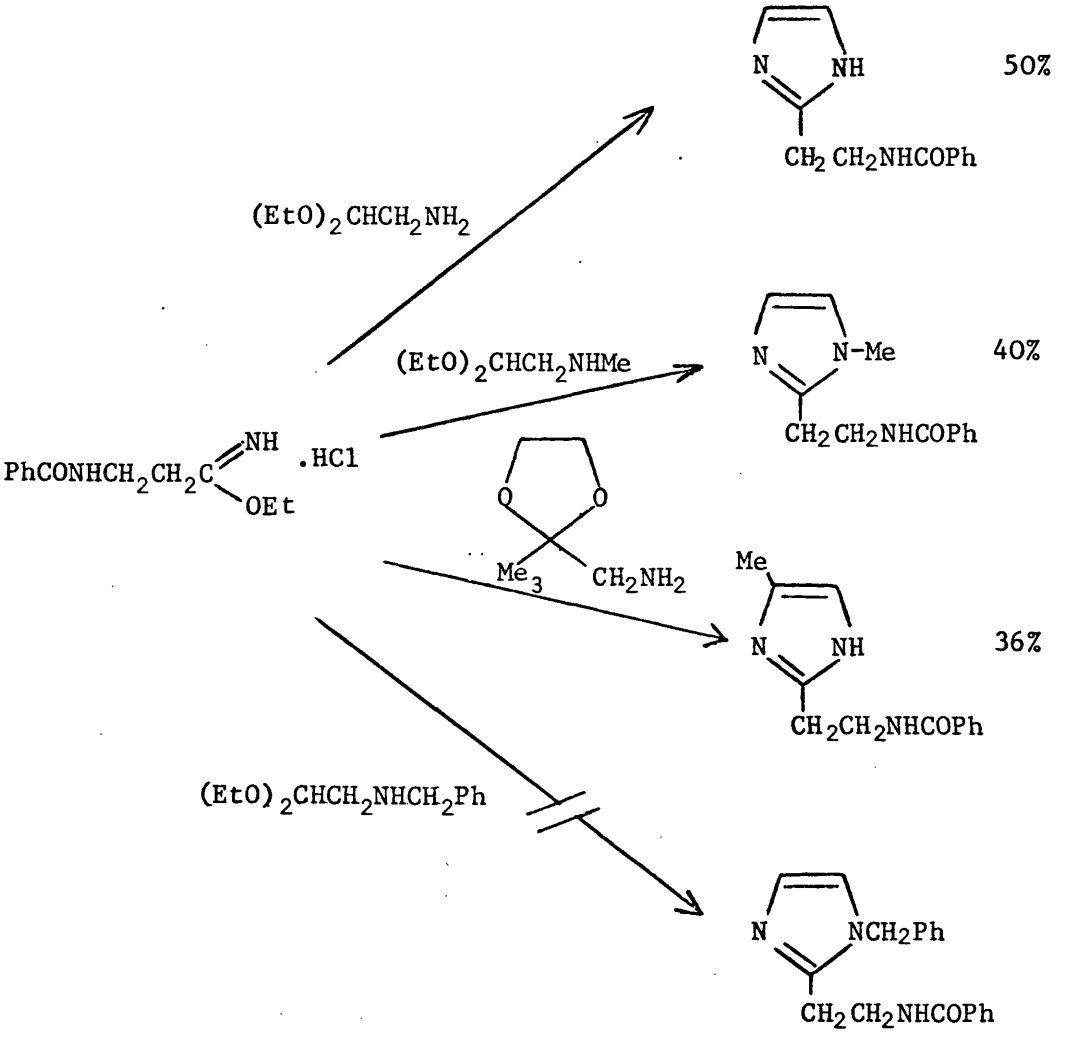
In case (c), β-benzamidopropionamidine was isolated and characterised in 23% yield. We believe that this material arose from the self-condensation of the iminoether to form a substituted amidine. These compounds are known to condense with liberation of ammonia, which would account for the formation of this material.

Unsuccessful attempts were also made to prepare other 1-substituted isohistamines, namely 1-methyl- and 1-benzyl-2-(2-aminoethyl)imidazole under the same conditions as those employed in the original successful isohistamine synthesis. Using the appropriate N-substituted aminoacetals, the reactants did not condense under the influence of heat or in the presence of a catalytic amount of p-toluenesulphonic acid.

As has been indicated, our original isohistamine synthesis was highly specific and did not form the basis for a general method of obtaining 2-substituted imidazoles. Ultimately by the choice of suitably mild reaction conditions we were to achieve a facile, general synthetic route to to isohistamines.

In a typical experiment ethyl β-benzamidopropionimidate hydrochloride was treated with the aminoacetal in hot ethanol. The intermediate amidine was not isolated, but was treated with very dilute hydrochloric acid at pH2. This procedure resulted in the formation of fewer by-products and higher overall yields were obtained.

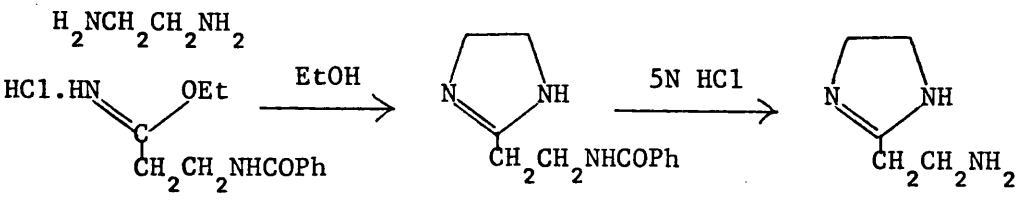
The following reactions were carried out:



Under no circumstances were we able to obtain 1-benzylisohistamine by cyclisation methods and it was concluded that steric effects associated with the relatively large benzyl group hindered this reaction.

We had proposed to extend this reaction to the synthesis of 4(5)-benzylisohistamine. A five stage synthesis of 2-aminomethyl-2-benzyl-1,3-dioxolane from phenylacetyl chloride was envisaged, which would then be condensed with ethyl β-benzamidopropionimidate. However, other considerations prevented this. We have no reason to suppose this general method could not be used to prepare a range of suitable 1- and 4(5)-substituted isohistamines and related compounds.

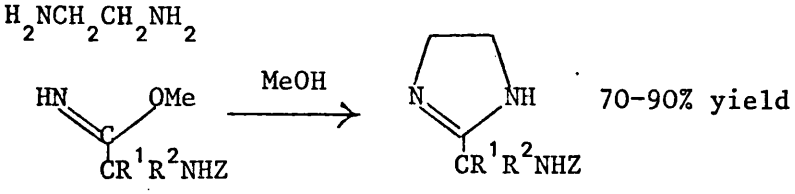
4(5)-Dihydroisohistamine (III.12) was also synthesised by the method of Jilek and Protiva.[79] Essentially this synthesis is less complex than that of isohistamine since a 1,3-diamine replaces the aminoacetal



(III. 11) (III. 12)

and the complete reaction can be carried out in ethanol. The benzoyl derivative (III.11) was obtained as the free base; we were unable to isolate this material as the pure picrate, as claimed by Jilek and Protiva. Hydrolysis of the amide (III.11) with 5N hydrochloric acid afforded the dihydroisohistamine (III.12) as its dihydrochloride together with a small quantity of ethylene diamine. Attempts to remove ethylene diamine under high vacuum resulted in decomposition and the modified isolation procedure, described in the experimental section, was employed.

Generally the synthesis of 2-substituted imidazolines can be accomplished with greater ease than that of the related 2-substituted imidazoles. Of direct relevance to the present work is the finding that iminoethers, as bases, react with ethylene diamine to form



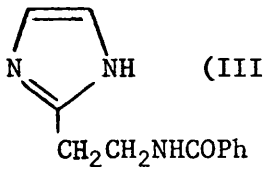
Z = p-tolyl or benzyloxycarbonyl

R^1,R^2 = -H, -Me, -Et or -Ph

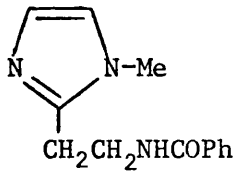
2-substituted imidazolines in high yield.[80] It has recently been demonstrated that imidazolines can be conveniently dehydrogenated to imidazoles with both selenium[81] and manganese dioxides.[82] Hence the synthesis of suitable 2-substituted imidazolines, followed by dehydrogenation could offer a potentially useful synthetic route to isohistamines.

N-Alkylation of 2-(2-benzamidoethyl)imidazole

As an alternative to cyclisation reactions involving N-substituted aminoacetals, the direct alkylation of 2-(2-benzamidoethyl) imidazole (III.13) was investigated for the purpose of preparing 1-substituted isohistamines.



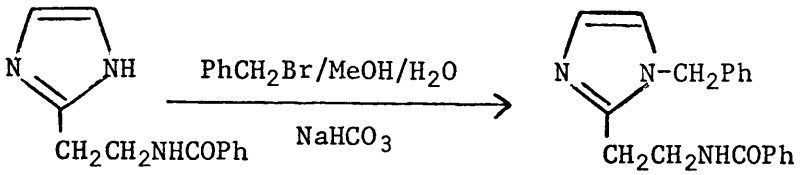
(III.13)



(III.14)

It was found that 1-methyl-2-(2-benzamidoethyl)imidazole (III.14) could be conveniently obtained by the action of dimethyl sulphate on the benzoyl compound (III.13) in aqueous methanol using sodium bicarbonate to neutralise the acid liberated in this reaction. This route, although satisfactory, gave a lower overall yield than the cyclisation procedure and only 30% conversion was attained.

Attempts were made to prepare 1-benzyl-2-(2-benzamidoethyl)imidazole (III.15) by the action of benzyl bromide on the benzoyl compound (III.13) under the same conditions as those employed for the methylation reaction. However, mixtures resulted which were not amenable to separation. When the reaction was carried out in acetone and the products partitioned between chloroform and dilute hydrochloric acid during the work up, the acid layer was found to contain only a trace of starting material. The chloroform layer yielded a compound whose elemental analysis was consistent with the 1,3-dibenzyl quaternary bromide strucutre (III.16a), but it was insoluble in water and generally its physical properties were inconsistent with those of a true quaternary salt. Treatment of a solution in aqueous ethanol with silver nitrate resulted in only slow precipitation of silver bromide.

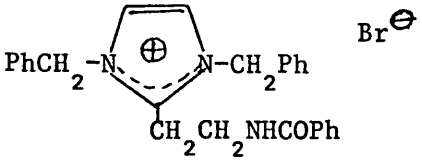


(III.13) (III.15)

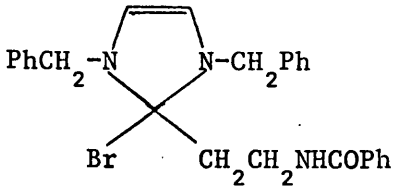
If this material was the quaternary salt (III. 16a) the bromide would have been expected to undergo complete exchange for chloride during the work up.

A possible alternative structure which was in agreement with its properties was the completely covalent compound (III. 16b).
The mass spectrum of the material did not enable us to decide whether the compound was the quaternary salt (III.16a) or the covalent compound (III.16b). On the evidence available we favour the covalent structure (III. 16b).

A sample of this compound (III.16b) was heated under high vacuum (0.04 mm. Hg) at 190^{o} for several hours. A volatile product was collected and a gas-liquid chromatographic examination of this material confirmed its identity as benzyl bromide. A thin-layer chromatographic examination of the residue in four different solvent systems supported its formulation as the benzyl compound (III.15) by comparison with an authentic sample of this material, prepared by an unambiguous method (see Section II, p.[28]).



(III. 16a)



(III. 16b)

Hydrolysis of the benzoyl protecting group

In all cases hydrolysis of the 2-(2-benzamidoethyl)imidazoles was accomplished without difficulty by heating under reflux for several hours with 5N hydrochloric acid. The amines were characterised as their dihydrochlorides and dipicrates.

EXPERIMENTAL SECTION

General Details

As described in Section II, p. 58.

Iminoethers

Ethyl cyanoiminoacetate

This was prepared by the method of McElvain and Schroeder;[77] m.p. 78-81°; 59% yield (lit.[77] m.p. 71-71.5°).

Ethyl β-benzamidopropionimidate

This was prepared by the method of Ainsworth;[83] m.p. 71-72°; 66% yield. (lit.[83] m.p. 72-74°).

Aminoacetals and aminoketals

Benzylaminoacetaldehyde diethylacetal

This was prepared by the method of Jones and his coworkers;[84] b.p. 110-113° (0.25 mm.); 58% yield [lit.[84] b.p. 153-155° (14 mm.)]

Phthalimidoacetone

This was prepared by the method of Ellinger and Goldberg;[43] m.p. 113-115°; 73% yield (lit.[43] m.p. 118-120°).

2-Methyl-2-phthalimidomethyl-1,3-dioxolane (III. 3)

This was prepared by the method of Stetter and Zoller;[78] m.p. 92-93°; 82% yield (lit.[78] m.p. 92-93°).

2-Aminomethyl-2-methyl-1,3-dioxolane (III. 2) (cf. ref. 78)

2-Methyl-2-phthalimidomethyl-1,3-dioxolane (82.6g.; 0.37 mole) was heated under reflux for 20 hr. with 25% aqueous sodium hydroxide (966 ml.). The reaction mixture was continuously extracted with ether for 20 hr. and the dried (K_2CO_3) extract was evaporated. The residue was distilled under high vacuum to give 2-aminomethyl-2-methyl-1,3-dioxolane, (27.5 g.; 64%), b.p. 51-51.5° (11 mm.).

(Found: C, 51.28; H, 9.72; N, 11.80. $C_5H_{11}NO_2$ requires C, 51.26; H, 9.46; N, 11.96%)

Cyclisation reactions

Attempted preparation of 2-cyanomethylimidazole

Ethyl cyanoacetimidate (2.24g.; 0.02 mole) and aminoacetaldehyde diethylacetal (2.06 g.; 0.02 mole) in glacial acetic acid (1.20 g.; 0.04 mole) were heated on a steam bath for 3 hr. 1N Hydrochloric acid (40 ml.) was added to the yellow solution and heating was continued for 45 min. When the evaporated solution was basified with an excess of saturated aqueous sodium carbonate a solid separated. The mixture was continuously extracted with chloroform. Evaporation of the chloroform solution gave a solid (190 mg.) which was dissolved in ethanol and converted into its picrate. Recrystallisation from ethanol gave a material whose n.m.r. and i.r. spectra were consistent with its formulation as 3-amino-2-cyanopyrrole dipicrate (III. 1), (100 mg.; 1.5%), m.p. 253-255° (decomp.).

Attempted preparations of 1-benzyl-2-(2-benzamidoethyl)imidazole

(a) Ethyl β-benzamidopropionimidate (4.40 g.; 0.02 mole) and benzylaminoacetaldehyde diethylacetal (4.46 g.; 0.02 mole) in glacial acetic acid (1.20 g.; 0.04 mole) were heated on a steam bath for 3 hr. 1N Hydrochloric acid (40 ml.) was added and the mixture was heated for a further 30 min., and washed with chloroform. After adjustment to pH 5 with 40% aqueous sodium hydroxide the solution was extracted with chloroform and ether to remove water-insoluble material. The solution was then basified to pH 11 and the product was extracted into chloroform. Recrystallisation from methyl ethyl ketone gave 3-benzamidopropionamide, (110 mg.; 1.8%), m.p. 169-171°.

(Found: C, 62.43; H, 6.31; N, 14.75. $C_{10}H_{12}N_2O$ requires C, 62.43; H, 6.28; N, 14.58%)

Subsequently:

(b) Benzylaminoacetaldehyde diethylacetal (11.16 g.; 0.05 mole) and ethyl β-benzamidopropionimidate hydrochloride (13.0 g.; 0.051 mole) in absolute ethanol (100 ml.) were heated under reflux for 17 hr. The solution was evaporated to remove ethanol and diluted with water (100 ml.). The resulting solution was adjusted to pH 2 with hydrochloric acid and extracted with chloroform. The aqueous layer was heated under reflux for 1 hr., clarified, extracted with chloroform and evaporated under vacuum to yield an oil which solidified upon trituration with ethanol/ether. This material was

recrystallised three times from ethanol/ether to give a product identified as 2-benzamidopropionamidine hydrochloride, (2.91 g.; 23%) m.p. 178-180°.

(Found: C, 52.60; H, 6.13; N, 18.49; Cl, 15.62. $C_{10}H_{13}N_3O$. HCl requires C, 52.75; H, 6.20; N, 18.46; Cl, 15.57%)

2-(2-Benzamidoethyl)imidazole (III. 13)

(a) Aminoacetaldehyde diethylacetal (26.64 g.; 0.2 mole) and ethyl β-benzamidopropionimidate (44.03 g.; 0.2 mole) in glacial acetic acid (24.0 g.; 0.4 mole) were heated on a steam bath for 3 hr. 1N Hydrochloric acid (400 ml.; 0.4 mole) was added and heating was continued for a further 45 min. The solution was evaporated under vacuum to approximately 200 ml. and extracted with ether (2 x 100 ml.). The aqueous layer was basified with solid sodium carbonate when a solid separated which was collected and recrystallised twice from acetonitrile to yield 2-(2-benzamidoethyl)-imidazole, (20.5 g.; 48%), m.p. 216-218°.

(Found: C, 66.95; H, 6.10; N, 19.73. $C_{12}H_{13}N_3O$ requires C, 66.95; H, 6.09; N, 19.52%)

(b) Ethyl-β-benzamidopropionimidate hydrochloride (52 g.; 0.227 mole) and aminoacetaldehyde diethylacetal (26.8 g.; 0.201 mole) were heated under reflux in absolute ethanol (400 ml.) for 4 hr. and the solution was evaporated. The residue was dissolved in water (250 ml.), acidified to pH 2 with hydrochloric acid and heated

under reflux for 2 hr. The mixture was extracted with chloroform (3 x 200 ml.) and the aqueous layer was basified to pH 9 with sodium carbonate. A solid separated which was collected and recrystallised from ethanol/acetonitrile to give 2-(2-benzamidoethyl)imidazole, (21.5 g.; 50%), m.p. 217-218°.

1-Methyl-2-(2-benzamidoethyl)imidazole (III. 14) (cf. p. 126)

Ethyl β-benzamidopropionimidate hydrochloride (13.0 g.; 0.051 mole) and methylaminoacetaldehyde diethyl acetal (7.36 g.; 0.05 mole) were heated under reflux in absolute ethanol (100 ml.) for 4 hr. The solution was evaporated and the residue was dissolved in water (100 ml.), acidified to pH 2 with hydrochloric acid, then heated under reflux for 1.5 hr. The reaction mixture was filtered, basified with an excess of sodium carbonate and extracted with chloroform (4 x 100 ml.). The dried (Na_2SO_4) extract was evaporated and the residue was recrystallised twice from ethyl acetate/petroleum ether (b.p. 60-80°) to give 1-methyl-2-(2-benzamidoethyl)imidazole, (4.64 g.; 40%), m.p. 104-106°.

(Found: C, 68.17; H, 6.50; N, 18.25. $C_{13}H_{15}N_3O$ requires C, 68.10, H, 6.58; N, 18.33%).

4(5)-Methyl-2-(2-benzamidoethyl)imidazole (III. 1)

Ethyl β-benzamidopropionimidate hydrochloride (13.0 g.; 0.051 mole) and 2-aminomethyl-2-methyl-1,3-dioxolane (5.86 g.; 0.05 mole) were heated under reflux in absolute ethanol for 5 hr. The solution was evaporated and the residue was dissolved in water (100 ml.). After

acidifying this solution to pH 2 with hydrochloric acid, it was washed with chloroform, and heated under reflux for 2.5 hr. The filtered reaction mixture was extracted with chloroform, basified with an excess of sodium carbonate, and evaporated to dryness. The product was extracted from the residue with ethanol, and an oil was obtained which crystallised upon trituration with water. Recrystallisation from water/acetone/ether gave 4(5)-methyl-2-(2-benzamidoethyl)imidazole, (4.14 g.; 36%), m.p. 207-208° (decomp.).

(Found: C, 67.92; H, 6.58; N, 18.57. $C_{13}H_{15}N_3O$ requires C, 68.10; H, 6.58; N, 18.33%).

2-(2-Benzamidoethyl)-4,5-dihydroimidazole (III. 11)

Ethylene diamine (10.0 g.; 0.166 mole) and ethyl β-benzamidopropionimidate hydrochloride (43.0 g.; 0.167 mole) were dissolved in absolute ethanol (250 ml.). An exothermic reaction took place. After 1 hr., the stirred solution was heated under reflux for 6 hr., diluted with water (250 ml.), treated with an excess of sodium carbonate and evaporated under vacuum. Extraction of the residue with ethanol yielded a yellow solid which was recrystallised four times from acetonitrile to give 2-(2-benzamidoethyl)-4,5-dihydroimidazole (5.5 g.; 15.3%) m.p. 171-173°.

(Found: C, 66.24; H, 6.86; N, 19.51. $C_{12}H_{15}N_3O$ requires C, 66.34; H, 6.96; N, 19.34%).

Alkylation of 2-(2-benzamidoethyl)imidazole.

1-Methyl-2-(2-benzamidoethyl)imidazole (III. 14) (cf. p. 124)

Dimethyl sulphate (5.04 g.; 0.04 mole) in ethanol (50 ml.) was added over 30 min. to 2-(2-benzamidoethyl)imidazole (8.6 g.; 0.04 mole) and sodium bicarbonate (7.2 g.; 0.088 mole) in methanol (200 ml.) and water (25 ml.), heated under reflux. After 1 hr. a further portion of dimethyl sulphate (5.04 g.) in methanol (50 ml.) was added. After heating under reflux for a further 1 hr. the mixture was evaporated and water (100 ml.) was added to the residue. Starting material was removed by filtration and the product was extracted into chloroform (5 x 100 ml.). Evaporation of this solution gave a yellow oil which solidified upon trituration with petroleum ether (b.p. 60-80°). Recrystallisation from ethyl acetate/ petroleum ether (b.p. 60-80°) gave 1-methyl-2-(2-benzamidoethyl)-imidazole, (2.76 g.; 30%), m.p. 102.5-104.5°.

(Found: C, 68.32; H, 6.61; N, 18.42. $C_{13}N_{15}N_3O$ requires C, 68.10; H, 6.58; N, 18.33%)

This material was found to be identical with a sample prepared by a cyclisation procedure and a mixed melting point showed no depression.

1,3-Dibenzyl-2-(2-benzamidoethyl)-2-bromoimidazoline (III. 16b)

2-(2-Benzamido)ethylimidazole (10.76 g.; 0.05 mole) and benzyl bromide (17.1 g.; 0,1 mole) in acetone (3 l.) were heated under reflux for 64 hr. Acetone was evaporated under vacuum and the

residue, dissolved in 2N hydrochloric acid (100 ml.), was extracted with chloroform (5 x 200 ml.). The extracts yielded an oil (18.2 g.) which solidified upon trituration with ethyl acetate. Eight recrystallisations from ethanol/ethyl acetate/petroleum ether (b.p. 60-80°) gave 1,3-dibenzyl-2-(2-benzamidoethyl)-2-bromoimidazoline, (4.0 g.; 17%) m.p. 181-182°.

(Found: C, 65.26; H, 5.56; N, 8.89; Br, 16.95. $C_{26}H_{26}N_3BrO$ requires C, 65.55; H, 5.50; N, 8.82; Br, 16.77%)

1-Benzyl-2-(2-benzamidoethyl)imidazole (III. 15) [cf. Compound (II. 10) p. 65]

1,3-Dibenzyl-2-(2-benzamidoethyl)-2-bromoimidazoline (100 mg.; 0.002 mole) was heated at 190° under 0.04 mm. Hg. for 14 hr. in a sublimation apparatus. A viscous liquid collected in the upper part of the apparatus. This material was subjected to a thin-layer chromatographic examination. Comparison with an authentic sample of the required compound (II. 10) confirmed its identity as 1-benzyl-2-(2-benzamidoethyl)imidazole.

A volatile liquid was also obtained which was identified as benzyl bromide using gas-liquid chromotographic techniques.

Hydrolysis of the benzoyl protecting group

The benzamidoethylimidazole (0.04 mole) was heated under reflux for 16-18 hr. with 5N hydrochloric acid (100 ml.). Benzoic acid separated from the solution on cooling and was removed by filtration.

The filtrate was then extracted with ether (2 x 100 ml.) and the clarified aqueous layer was evaporated under vacuum to give the crude product as its dihydrochloride.

2-(2-Aminoethyl)imidazole dihydrochloride (Isohistamine dihydrochloride) (III. 9) was recrystallised from ethanol/ether, (95% yield), m.p. 262-263° (decomp.).

(Found: C, 32.83; H, 5.99; N, 22.51; Cl, 38.39. $C_5H_9N_3$. 2HCl requires C, 32.63; H, 6.02; N, 22.82; Cl, 38.52%)

The dipicrate prepared in the usual way was recrystallised from water, m.p. 217-218° (decomp.).

(Found: C, 35.73; H, 2.49; N, 21.87. $C_5H_9N_3$. $2C_6H_3N_3O_7$ requires C, 35.87; H, 2.66; N, 22.13%).

1-Methylisohistamine dihydrochloride hemihydrate was recrystallised from isopropanol/ethanol, (55% yield), m.p. 193-195° (decomp.).

(Found: C, 34.77; H, 7.00; N, 20.55; Cl, 34.11. $C_6H_{11}N_3$. 2HCl. $\frac{1}{2}$ H_2O requires C, 34.79; H, 6.81; N, 20.29; Cl, 34.24%)

The dipicrate, prepared in the usual way was recrystallised from water, m.p. 214-215° (decomp.).

(Found: C, 37.04; H, 3.09; N, 21.34. $C_6H_{11}N_3$. $2C_6H_3N_3O_7$ requires C, 37.06; H, 2.94; N, 21.61%)

4(5)-Methylisohistamine dihydrochloride (III. 1) was recrystallised from methanol/ethanol/ether, (25% yield), m.p. 261-262° (decomp.).

(Found: C, 36.69; H, 6.48; N, 21.17; Cl, 35.54. $C_6H_{11}N_3 \cdot 2HCl$ requires C, 36.38; H, 6.61; N, 21.21; Cl, 35.80%)

The dipicrate prepared in the usual way was recrystallised from aqueous ethanol, m.p. 222-223° (decomp.).

(Found: C, 37.23; H, 2.86; N, 21.42. $C_6H_{13}N_3 \cdot 2C_6H_3N_3O_7$ requires C, 37.06; H, 2.94; N, 21.61%)

2-(2-Aminoethyl)-4,5-dihydroimidazole (III. 12)

Unsuccessful attempts were made to purify the crude dihydrochloride. Hence, it was converted into the base by passing a methanolic solution of the material through a column containing basic ion-exchange resin (Amberlite IRA 401). The base was converted into its dipicrate by the usual method. Recrystallisation from water gave 2-(2-aminoethyl)-4,5-dihydroimidazole dipicrate, (64% yield) m.p. 191-193°. (lit.[79] m.p. 193-195°).

(Found: C, 35.87; H, 3.12; N, 21.84. $C_5H_{11}N_3 \cdot 2C_6H_3N_3O_7$ requires C, 35.73; H, 3.00; N, 22.06%).

The dipicrate was converted into its dihydrochloride by the usual nitrobenzene/6N hydrochloric acid method, and was recrystallised from methanol/ethanol/ether, containing a few drops of ethanolic hydrogen chloride, m.p. 212-214° (lit.[79] m.p. 219-221°).

(Found: C, 32.50; H, 6.94; N, 22.44; Cl, 38.13. $C_5H_{11}N_3$. 2HCl requires C, 32.27; H, 7.04; N, 22.58; Cl, 38.11%)

SPECTRA

Instrumentation

As described in Section II. (p. 90).

2-Aminomethyl-2-methyl-1,3-dioxolane (III. 2)

$\nu_{max.}$: (Capillary film): 3395, 3320, 1603, 845 (NH_2); 1450, 1375 ($-CH_2CH_3$); 1220, 1405 (ether)

τ; ($CDCl_3$): 6.03 (s; 4; $-\underline{CH_2}\underline{CH_2}-$); 7.28 (s; 2; $-\underline{CH_2}N$); 8.70, 8.80 (2 x s; 5; $-\underline{CH_3}$, $-\underline{NH_2}$).

3-Amino-2-cyanopyrrole dipicrate (III. 10)

$\nu_{max.}$: 3350, 1645 (NH_3); 3250, 1595 (pyrrole); 2220 ($C\equiv N$);

τ; (DMSO-d_6): 1.6 (s; $-\underline{NH_2}$); 2.86, 3.14 (2 x d; 4-H, 5-H).

Other minor signals are also present, suggesting impurities.

3-Benzamidopropionamide

$\nu_{max.}$: 3240, 1660, 1555 (amide); 1610, 720 (aromatic).

τ; (DMSO-d_6): 1.6 (broad t; -$\underline{NH_2}$); 485-430 c/s (m; -Ph); 3.2 (broad s; -$\underline{NH_2}$); 6.52 (q; -$\underline{CH_2}$N-); 7.64 (t; -$\underline{CH_2}$CO-).

2-Benzamidopropionamidine hydrochloride

$\nu_{max.}$: 3260, 1640, 1555 (amide); 3050, 1705 (amidine); 1601 (aromatic).

τ; (DMSO-d_6): 0.73, 1.10 (2 x s; 4; 2 x -$\underline{NH}$, $\underline{NH_2}$); 490-435 c/s (m; 5; -Ph); centred 6.36 (m; 2; -NH$\underline{CH_2}CH_2$-); 7.20 (t; 2; NHCH$_2\underline{CH_2}$-).

2-(2-Benzamidoethyl)imidazole (III. 13)

$\nu_{max.}$: 3100, 1660, 1540 (amide); 756 (aromatic).

; (DMSO-d_6): 1.40 (s; 1; -$CH_2\underline{NH}$CO-); 480-440 c/s (m; 5; -Ph); 6.36 (q; 2; -$CH_2\underline{CH_2}$NH-); 7.07 (t; 2; -$\underline{CH_2}CH_2$NH-).

4(5)-Methyl-2-(2-benzamidoethyl)imidazole (III. 1)

$\nu_{max.}$: 3300, 1640, 1556 (amide); 1603, 1580 (aromatic); 642 (imidazole).

τ; (DMSO-d_6): centred 460 c/s (m; 5; -Ph); 3.42 (broad s; 1; 4(5)-H); 6.40 (q; 2; -$CH_2\underline{CH_2}$NH-); 7.20 (t; 2; -$\underline{CH_2}CH_2$NH-); 7.90 (d; 3; -$\underline{CH_3}$).

2-(2-Benzamidoethyl)-4,5-dihydroimidazole (III. 11)

$\nu_{max.}$: 3170, 1635, 1540 (amide); 716, 696 (aromatic).

τ; (DMSO-d_6): 1.42 (s; 1; $-CH_2\underline{NH}CO-$); 480-440 c/s (m; 5; -Ph); 223-198 c/s (m; 6; 4,5-$\underline{CH_2}\underline{CH_2}$-, $-CH_2\underline{CH_2}NH-$); 7.60 (t; 2; $-\underline{CH_2}CH_2NH-$).

1-Methyl-2-(2-benzamidoethyl)imidazole (III. 14)

$\nu_{max.}$: 3240, 1660, 1650 (amide), 705 (aromatic).

τ; ($CDCl_3$): centred 480 c/s (m; 5; -Ph); 3.02, 3.14 (q, J=1.4; 2; 4-H, 5-H); 6.10 (q; 2; $-CH_2\underline{CH_2}NH-$); 6.40 (s; 5; $-\underline{CH_3}$, $-\underline{CH_2}Ph$); 7.05 (t; 2; $-\underline{CH_2}CH_2NH-$).

1,3-Dibenzyl-2-(2-benzamidoethyl)-2-bromoimidazoline (III. 16)

$\nu_{max.}$: 3240, 1655, 1530 (amide); 1600, 728 (aromatic).

τ; ($CDCl_3$): 0.78 (s; 1; $-CH_2\underline{NH}CO-$); 1.94 (m; 2; 2 x ortho -H of NHCOPh); 445-435 c/s (m; -3; 2 x -Ph, meta and pora -H of NHCOPh); 4.47 (s; 4; 2.x $-\underline{CH_2}Ph$); 340-310 c/s m; 4; $-\underline{CH_2}\underline{CH_2}NH-$).

The 4- and 5- protons have a shift of 427 c/s to low field of tetramethylsilane which is 20-25 c/s to higher field than expected for the aromatic compound. This may be due to a vinylic structure and could suggest that the compound has the covalent structure (III. 16b) rather than the ionic (III. 16a).

Isohistamine dihydrochloride (III. 9)

$\nu_{max.}$: 3170-2650 (NH_3); 1620, 765 (aromatic); 1525, 660 (imidazole)

τ; (D_2O): 2.50 (s; 2; 4-H, 5-H); 6.47 (s; 4; $-\underline{CH_2}\underline{CH_2}-$).

1-Methylisohistamine dihydrochloride

$\nu_{max.}$: 3120-2620 (NH_3); 1525, (imidazole); 772 (aromatic)

τ; (D_2O); 2.52 (s; 2; 4-H, 5-H); 6.08 (s; 3; $-\underline{CH_3}$); 6.48 (s; 4; $-\underline{CH_2}\underline{CH_2}-$).

4(5)-Methylisohistamine dihydrochloride

$\nu_{max.}$: 3100-2670 (NH_3); 1640, 798 (aromatic); 1530, 630 (imidazole).

τ; (D_2O): 2.85 (q, J=1.0; 1; 4(5)-H); centred 208 c/s (m; 4; $-\underline{CH_2}\underline{CH_2}-$); 7.67 (d, J=1.0; 3; $-\underline{CH_3}$).

2-(2-Aminoethyl)-4,5-dihydroimidazole dihydrochloride

$\nu_{max.}$: 3200-2600, (NH_3); 1530 (imidazole); 750 (aromatic).

τ; (D_2O): 6.05 (s; 4; ring -$\underline{CH_2}\underline{CH_2}$-); centred 192 c/s (m; 4; side-chain -$\underline{CH_2}\underline{CH_2}$-).

SECTION IV

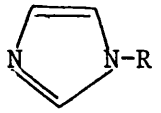
METALATION OF IMIDAZOLES WITH ORGANOLITHIUM COMPOUNDS

DISCUSSION

Since the synthesis of isohistamine and its analogues using a cyanide replacement reaction was complicated by the formation of abnormal products, other routes to 2-substituted imidazoles were investigated. Among these were reactions involving the metalation of imidazoles with organolithium compounds which are now discussed.

1-Substituted imidazoles

Metalation experiments were carried out with the following 1-substituted imidazoles (IV. 1 a-d).

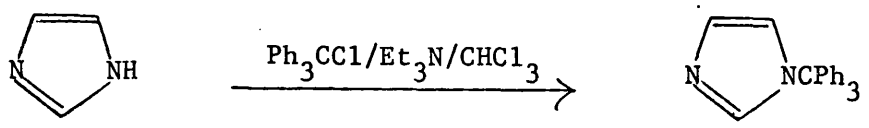


(IV. 1)

a, R = $-CH_2Ph$; b, R = -Me; c, R = $-SiMe_3$; d, R = $-CPh_3$.

Protection of the 1-position of the imidazole ring was necessary to prevent metalation occurring at this position. Of the above compounds (IV. 1a) and (IV. 1b) were obtained by literature procedures.[9,55] The trimethylsilyl derivative (IV. 1c) was commercially available. The trityl derivative (IV. 1d) is reported to have been prepared by the reaction of the silver salt of imidazole with triphenylmethylchloride.[85] Such a procedure is expensive and an alternative synthesis was sought.

Histamine has been selectively "tritylated" at the ring nitrogen.[86] By analogy with this method 1-triphenylmethylimidazole (IV. 1d) was prepared by the reaction of imidazole with triphenylmethylchloride and triethylamine in chloroform and its melting point agreed with the literature figure.



(IV. d)

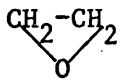
Metalating Reagents

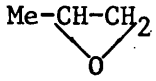
Originally n-butyl lithium was used in the metalation studies as an ethereal solution. This reagent was obtained by the method of Jones and Gilman.[87] Subsequently use was made of a commercially available solution of the material in n-hexane. Several metalations were also carried out using sodium methylsulphinylmethide ("dimsyl sodium"), and sodium hydride in dimethylformamide.

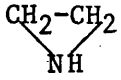
Electrophiles

All the electrophiles used in this work were commercially available and included the following compounds:

D_2O Me_2SO_4

CO_2 

$ClCH_2CN$ 

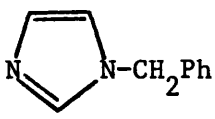
$BrCH_2CO_2Et$ 

Metalation Procedures

Most of the reactions discussed were carried out in diethylether; in addition, n-hexane was present when the n-butyl lithium was added in this solvent. Tetrahydrofuran has also been used, and the role played by solvent in these reactions will be discussed later. The metalations, which were usually carried out at temperatures between -40 and -60°, are most conveniently discussed with reference to the electrophiles used.

Reactions involving halogen containing electrophiles

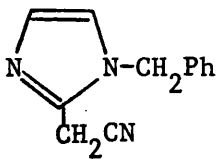
Due to the initial difficulty in obtaining 1-benzyl-2-cyanomethylimidazole (IV. 2) from 1-benzyl-2-chloromethylimidazole, attempts were made to prepare this nitrile (IV. 2) by treatment of



(IV. 1a)

i) n-BuLi/Et_2O

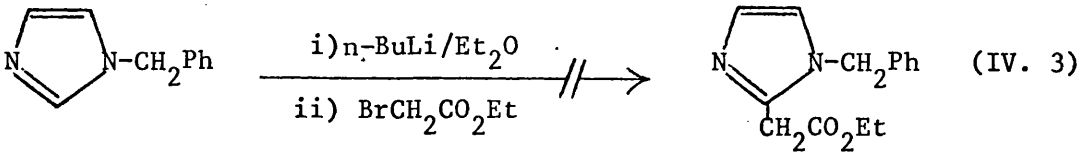
ii) $ClCH_2CN$



(IV. 2)

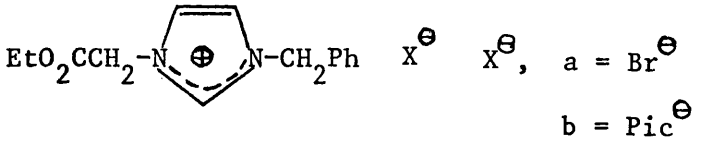
the lithio derivative of 1-benzylimidazole (IV. 1a) with chloracetonitrile. This reaction afforded a resinous mixture of unidentifiable products. Work by ourselves and other investigators has shown that the use of halogen containing electrophiles often failed to yield the required products.

By analogy with the successful reaction of ethyl chloroformate with lithiated imidazoles,[53] the following reaction was attempted with ethyl bromoacetate. Once again a resinous product was obtained from which a very low yield (approx. 1%) of material was isolated



(IV. 3)

as its picrate salt. Elemental analysis and the n.m.r spectrum of this material were consistent with its formulation, not as the 2-substituted ester (IV. 3), but as the quaternary picrate (IV. 4b).

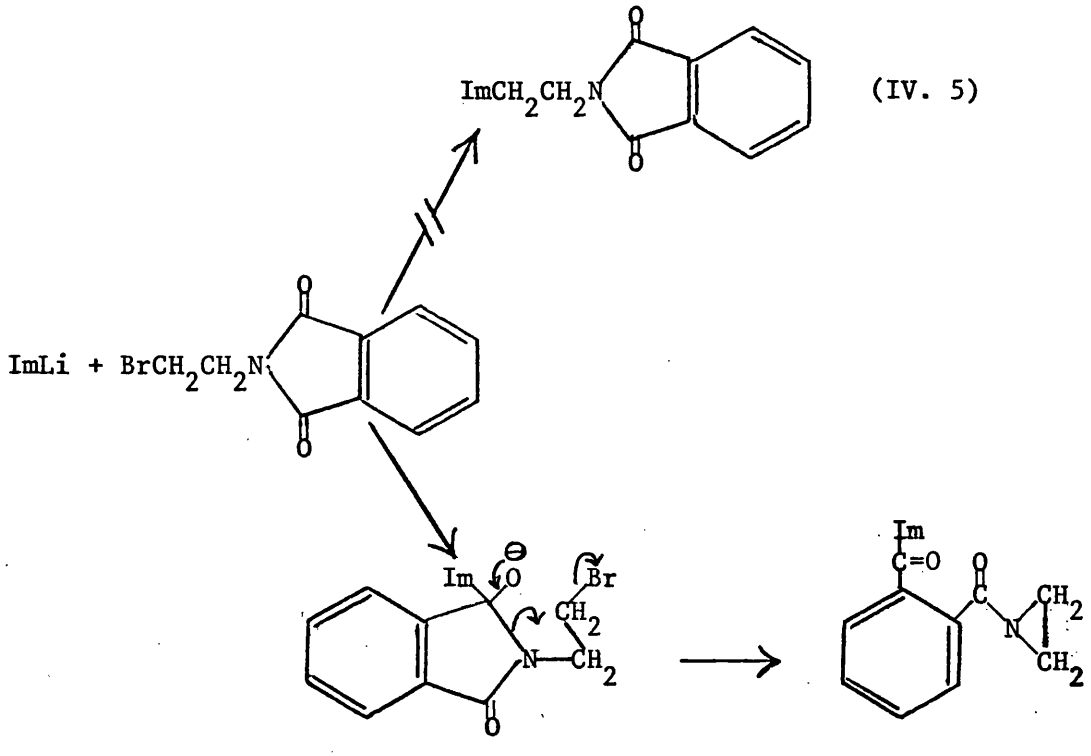


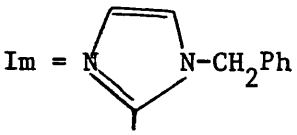
(IV. 4)

An authentic sample of this material was obtained by reacting ethyl bromoacetate and 1-benzylimidazole in ether to give the bromide (IV. 4a), conversion of which into the picrate (IV. 4b) afforded a product identical with that isolated from the metalation reaction.

The failure of chloracetonitrile and ethyl bromoacetate to react smoothly with the lithio derivative of 1-benzylimidazole may be ascribed to one or more competing reactions occurring. Attack of the nucleophile could occur at the cyano or the ester group and not at the methylene carbon atom. The nucleophile could take up a proton from the electrophile or from the expected product since the methylene protons in the nitrile (IV. 2) are acidic and then the neutral base can, as we have shown, suffer quaternisation.

It is of interest that Kornfeld and his coworkers reacted bromoethylphthalimide with the lithio derivative of 1-benzylimidazole



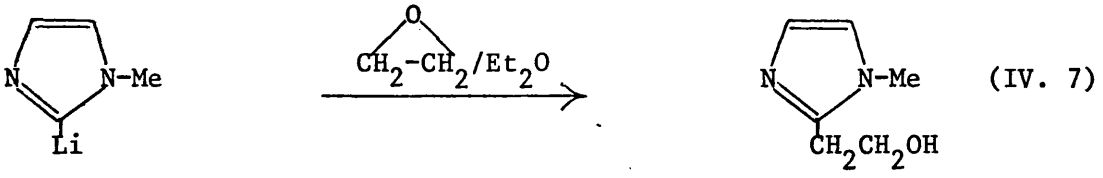
Im = 

in ether.[15] Bromoethylphthalmide reacted at the carbonyl group, rather than at the side chain, to form the aziridine amide (IV. 6), and not the expected phthalimidoethyl compound (IV. 5).

Reactions involving ethylene oxide

In view of our findings and those mentioned above, the use of halogen containing electrophiles was discontinued in favour of reactants likely to cause fewer complications. Up to this point we had not been able to introduce a two-carbon side chain containing a simple functional group into the 2-position of the imidazole ring using metalation techniques. It was decided that by analogy with other heterocyclic systems[56] the use of ethylene oxide could offer a potentially attractive route to isohistamine derivatives.

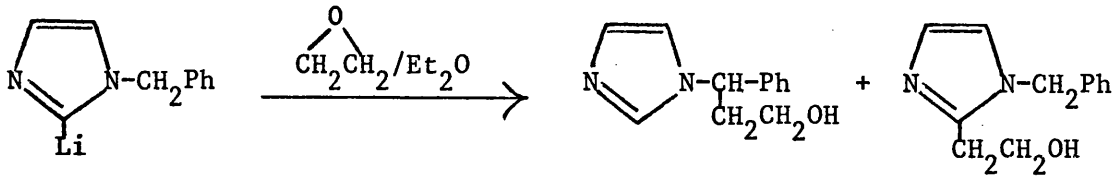
The lithio derivative of 1-methylimidazole was reacted with ethylene oxide in ether. The required hydroxyethyl compound (IV. 7),



(IV. 7)

which had previously been prepared by a cyclisation procedure,[50] was obtained in 44% yield as a high boiling liquid.

When a similar reaction was carried out using 1-benzylimidazole, the crude product was distilled under high vacuum and a high boiling liquid was obtained, whose composition corresponded to the hydroxyethyl compound (IV. 9). The n.m.r spectrum in deuterochloroform, however, clearly showed that the compound was not (IV. 9), but (IV. 8),



(IV. 8) (IV. 9)

(Table IV.1). Subsequently it was demonstrated that a mixture of the hydroxyethyl compounds (IV. 8) and (IV. 9) was formed. The n.m.r signals were reasonably well separated in deuterochloroform and could be used for estimating the ratio of products obtained.

n.m.r. of crude product from reaction between ethylene oxide and lithio derivative of 1-benzylimidazole

Chemical Shift (τ)	Multiplicity	Assignment
2.49	broad s	2-H
2.74	broad m	-Ph
Centred 3.05	m	4&5-H
4.50	t	$-\underset{\underset{\text{Ph}}{\vert}}{\overset{\overset{\text{CH}_2}{\vert}}{\text{CH}}}-$
4.75	s	$-\underline{\text{OH}}$
4.95	s	$-\underline{\text{CH}_2}\text{Ph}$
Centred 6.18	q	$-\text{CH}_2\underline{\text{CH}_2}\text{OH}$
" 6.48	m	$\text{CHCH}_2\underline{\text{CH}_2}\text{OH}$
" 7.22	m	$-\underline{\text{CH}_2}\text{CH}_2\text{OH}$
" 7.73	m	$\text{CH}\underline{\text{CH}_2}\text{CH}_2\text{OH}$

Table IV. 1

From the assignments and ratios of peak integrals, (Table IV. 1), it was estimated that when the reactants were used in equimolar quantities, the hydroxyethyl compounds (IV. 8) and (IV. 9) were present in 75% and 25% yields respectively. We were unable to separate the reaction mixture and relied on n.m.r. evidence for confirmation of structure.

In an effort to gain an insight into this rare example of participation of the benzyl protecting group in a metalation reaction, the effect of varying the proportion of the reactants was investigated and the the results are tabulated below (Table IV. 2). The total product

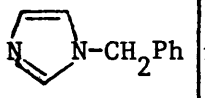
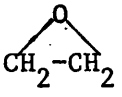
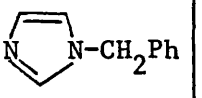
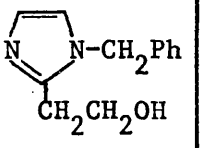
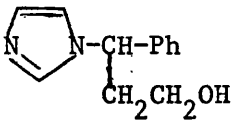
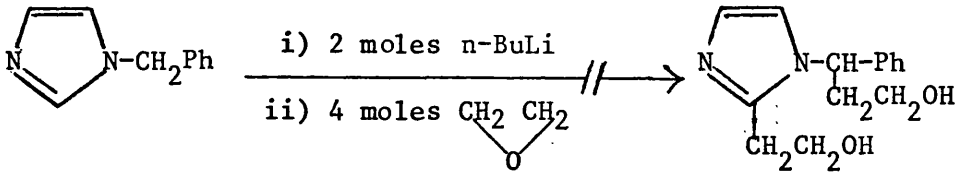
Moles of Reactant			Approximate Ratio of products Estimated by n.m.r		
	n-BuLi				
1	0.8	0.9	1	-	3
1	1.05	1.3	-	1	3
1	2	4	-	1	9

Table IV. 2

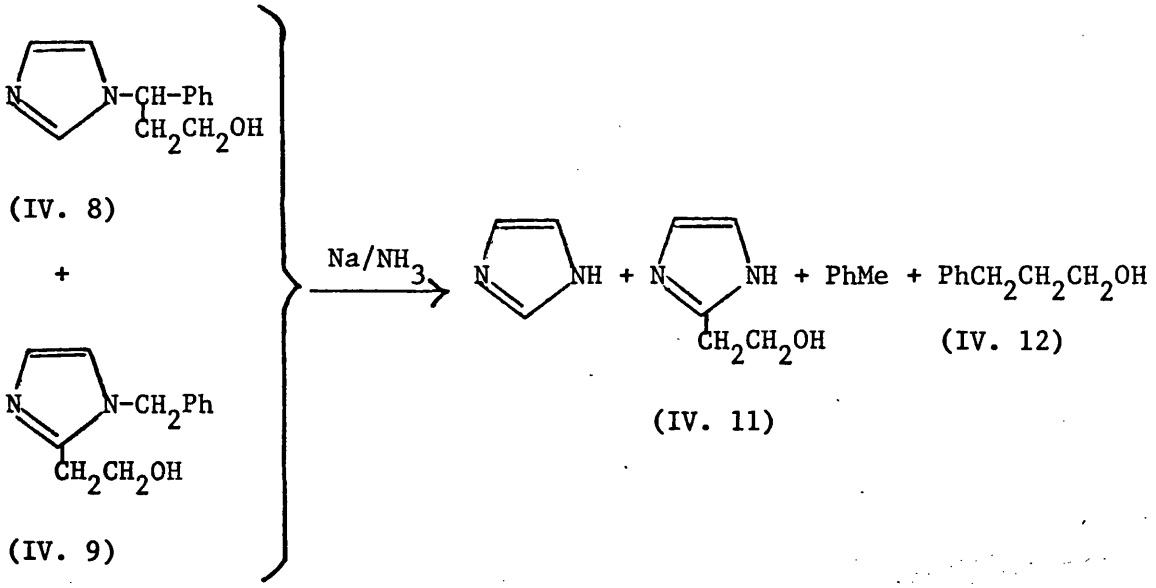
from the reaction was examined but no definite trend could be discerned from these results. In particular, the attempt to prepare the bis-hydroxyethylated compound (IV.10) by treating 1-benzylimidazole with two moles of n-butyl lithium and a corresponding excess of



(IV. 10)

ethylene oxide was not successful. If this method had succeeded, cleavage of the N-(phenylpropanol) protecting group with sodium in liquid ammonia could have presented an alternative route to 2-(2-hydroxyethyl)imidazole (IV. 11).

Treatment of the mixture with sodium in liquid ammonia[59] afforded

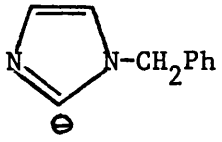


a mixture of products from which we were able to isolate the hydroxyethyl compound (IV. 11). The presence of imidazole and toluene was established by t.l.c. and g.l.c. methods respectively.

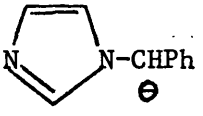
3-Phenylpropanol (IV. 12) was separated by preparative g.l.c. and identified from its n.m.r spectrum and by comparison of its i.r. spectrum with that of an authentic sample. Unfortunately the overall yield from this sequence was low (approximately 3%) and consequently other methods of preparing the hydroxyethyl compound (IV. 11) were sought.

The nature of the lithio derivative of 1-benzylimidazole is not known. It may be a covalent species, alternatively it may exist as an ion pair, either intimate or solvent separated. For the purpose of describing this reaction the unsolvated anion description will be used without implying that this species predominates or is even present.

A possible explanation for our results is that a mixture of anionic species (IV. 13) and (IV. 14) is produced by metalating 1-benzylimidazole with n-butyl lithium. The anionic species could be in equilibrium and the ratio of products obtained could depend on the solvent, reaction temperature, the nature of the electrophile



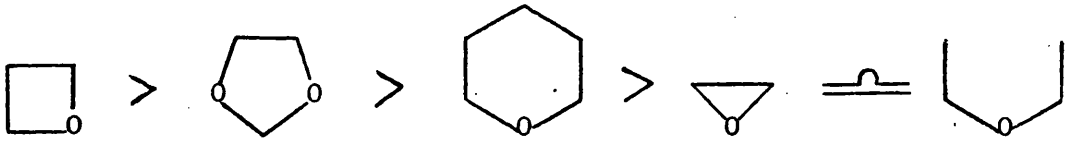
(IV. 13)



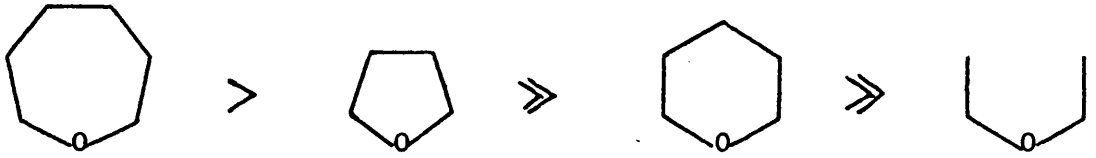
(IV. 14)

and its rate of reaction with the particular species present. It should be stressed that the ratio of products does not provide evidence for a particular ratio of anionic species and we cannot estimate this ratio.

It is likely that solvent effects are of paramount importance in determining the nature of the products from this reaction. It appears that ethylene oxide is an "anomalous" electrophile and in common with all ethers it can solvate cations.[88] The basicity of the solvent is a measure of the ease of cation solvation. The basicity of various cyclic ethers has been estimated from their heat of mixing with chloroform and by the shift of the MeO-D band in the i.r. spectrum of ether/deuteromethanol mixtures.[89] The ethers in decreasing order of basicity, as determined by these methods, are:



The pKa's of several cyclic ethers have been measured by extraction of an ether/iso-octane mixture with sulphuric acid.[90] The results are given in order of decreasing basicity:



pKa:

-2.02 -2.08 -2.79 -3.59

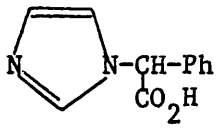
Ethylene oxide has a similar order of basicity to diethyl ether, consequently the epoxide is likely to be found in the solvation shell of the equilibrium mixture of the anionic species described, and thus alter the reactivity of the anions or their equilibrium.

This might explain the anomalous reaction product obtained with ethylene oxide.

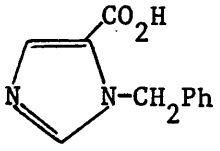
Initially all metalation reactions were carried out in ether/hexane mixtures. If the above reasoning is correct then the use of tetrahydrofuran as solvent, which is more basic and consequently a more powerful solvator than ethylene oxide, could reduce the tendency for unusual product formation in this reaction.

Reactions involving other electrophiles

The reported work on the metalation of imidazoles involved the use of electrophiles other than ethylene oxide. Shirley and Alley,[53] Roe[54], and Iversen and Lund,[55] have treated the lithio derivative of several 1-substituted imidazoles with various electrophiles and have not reported the formation of anomalous products, although it is unlikely that rigorous attempts were made to find such materials. The published work reports only the formation of 2-substituted products, but it is conceivable that some of the published structures are incorrect. In view of this it was decided to repeat the early work on the carbonation of the lithio derivative of 1-benzylimidazole.[53] Examination of the



(IV. 15)



(IV. 16)

material isolated from this reaction appears to exclude the possibility of formation of the acids (IV. 15) and (IV. 16). The n.m.r. spectrum of the product is given in (Table IV. 3).

a) In acid (D_2O/DCl at pH1)

Chemical Shift (τ)	Multiplicity	Integration	Assignment
2.20	s	2	4&5-H
2.57	s	5	-Ph
4.26	s	2	$-\underline{CH_2}Ph$

b) In alkali (D_2O/NaOD at pH11)

Chemical Shift (τ)	Multiplicity	Integration	Assignment
425-445 c/s	m	5	-Ph
Centred 2.96	q	2	4&5-H
4.47	s	2	$-\underline{CH_2}Ph$

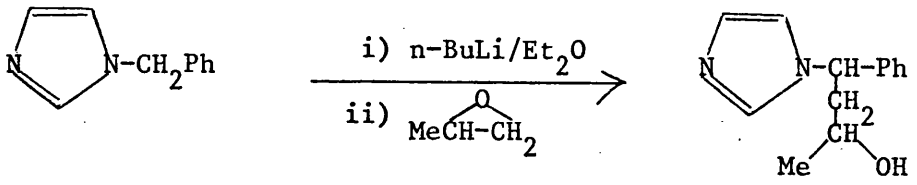
n.m.r. spectrum of 1-benzylimidazole-2-carboxylic acid

Table IV. 3

These spectra clearly illustrate the absence of a 2-proton. In dimethyl sulphoxide at 40° resonance from a 2-proton develops due to decarboxylation. This finding suggests that decarboxylation of these acids may be carried out advantageously under mild conditions in this solvent.

When the lithio derivative of 1-benzylimidazole, prepared from equimolar quantities of 1-benzylimidazole and n-butyl lithium, was treated with propylene oxide under the usual conditions, a mixture comprising

the benzyl substituted product (IV. 17) in 70% conversion and 1-benzylimidazole was formed.



(IV. 17)

This reaction was carried out in an attempt to shed some light on the formation of benzyl substituted products first observed with ethylene oxide. Since the isolated product is the secondary alcohol, it is unlikely that this material arises from a rearrangement of a 2-substituted imidazole. It has been established that propylene oxide reacts with the lithio derivatives of heterocycles with formation of the secondary alcohol,[52] (cf. compound IV. 17).

Chemical Shift (τ)	Multiplicity	Assignment
2.43	broad s	2-H
2.72	m	-Ph
3.00	m	4&5-H
4.43	q(A)	>CH-CH_2
4.82	s	-OH
4.93	s	-CH_2Ph
6.37	m(B)	CH_3-CH(CH_2)-OH
7.73	m(C)	>CH-CH_2-OH
8.80	d(D)	>CH-CH_3

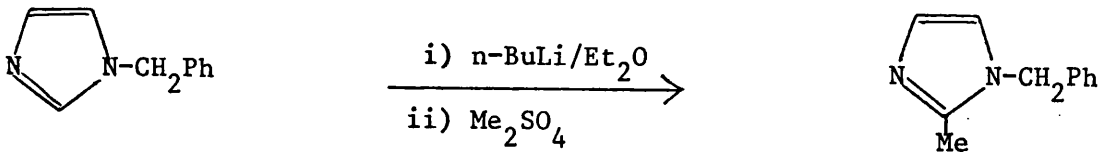
n.m.r. spectrum in deuterochloraform of the product from the reaction between the lithio derivative of 1-benzylimidazole and propylene oxide

Table IV. 4

The structure of this material was determined from the n.m.r spectrum of the total product (Table IV. 4). Spin decoupling experiments on the peaks (A), (B), (C) and (D) confirmed the assignments given to these signals. It was also clear that substitution had not occurred at the 2-position. Although the alcohol (IV. 17) has two asymmetric centres and can exist in the threo-and erythro-forms, the n.m.r. spectrum did not differentiate between these isomers.

When the alcohols (IV. 7), (IV. 8), (IV. 9) and (IV. 17) were shaken with deuterium oxide the peak assigned to the hydroxyl hydrogen in the n.m.r. spectrum disappeared.

These two examples of reaction at the benzyl methylene group have occurred when the anion is attacking an sp^3 carbon atom, whereas when an sp^2 carbon atom is involved, such as with carbon dioxide and aldehydes or ketones, substitution at the 2-position only has been observed. In order to see whether this might have significance, dimethyl sulphate was added to the lithio derivative of 1-benzylimidazole.

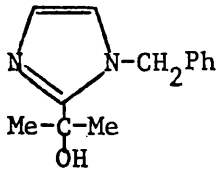


(IV. 18)

The n.m.r. spectrum of the total product showed it comprised almost exclusively the 2-substituted compound (IV. 18). Only trace quantities of other components were present. Owing to the small amounts involved

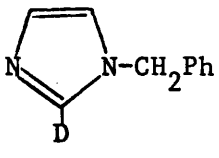
any assignment of structure would have been speculative, but, in addition to compound (IV. 18) the n.m.r spectrum did not rule out the presence of other methylated products. The above system was chosen because the products were likely to be amenable to separation by g.l.c. techniques. Unfortunately this was not found to be possible, because resolution of the components was not attained at low temperatures, and at high temperatures, even on a smectic column, decomposition of the material occurred which precluded isolation and identification of the components.

The reaction of acetone with lithio derivative of 1-benzylimidazole afforded only the 2-substituted product (IV. 19).

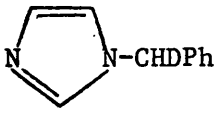


(IV. 19)

In a further experiment, the lithio derivative, prepared from equimolar quantities of 1-benzylimidazole and n-butyl lithium, was quenched with deuterium oxide. Integration of the n.m.r. spectrum of the product indicated that approximately 85% of the deuterium was incorporated at the 2-position (IV. 20) and only 15% at



(IV. 20



(IV. 21)

the benzyl methylene (IV. 21). In view of the inherent inaccuracy of this particular assay, the detection of deuteration at the benzyl methylene could probably be regarded as just significant.

The possibility that deuterium might exchange with protons during the above reaction or its work up was examined and found to be insignificant. Exchange studies were carried out on 1-benzylimidazole under acidic, basic and neutral conditions. Our results,determined using n.m.r techniques, are tabulated below (Table IV. 5) and the half lives of this exchange reaction are given. Even under basic conditions the

pH	Temp.	Solvent	1-Benzylimidazole Concentration	$t_{\frac{1}{2}}$ (hr.)
1	24°	30% DCl in D_2O	0.6M	∞ (a)
7	24	33% DMSO-d_6/67% D_2O	0.6M	84
14	41.5 (b)	50% DMSO-d_6/50% D_2O+NaOD	0.6M	11.6

Deuterium exchange studies on 1-benzylimidazole

Table IV. 5

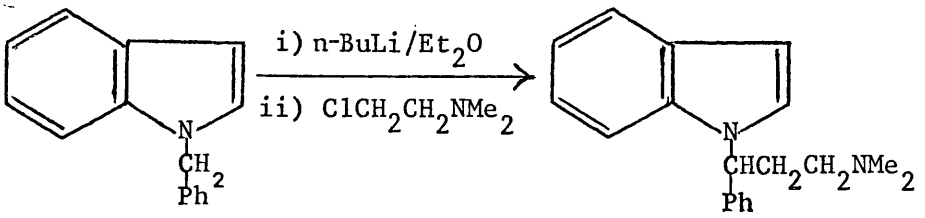
Notes

(a) No observable exchange after 65 hr.

(b) This temperature was necessary to effect solution of the 1-benzylimidazole.

2-proton of 1-benzylimidazole exchanges very slowly. No evidence was obtained for deuterium exchange at the benzyl methylene. Hence deuterium exchange is unlikely to have influenced our results which were in agreement with those of Harris and Randall who studied the rate of deuterium exchange in 1-methylimidazole, up to pH8 and found that the rate of exchange increased with increasing pH.[91]

The only other instance known to us of the addition of an electrophile at a benzyl protecting group during metalation procedures occurred in the indole series.



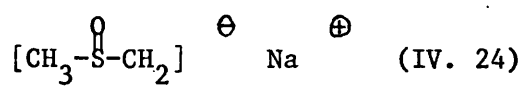
(IV. 22) (IV. 23)

Treatment of the lithio derivative of 1-benzylindole (IV. 22) with N.N-dimethylaminoethylchloride afforded the benzyl substituted product (IV. 23).[92] Ganellin and Ridley pointed out that under the conditions of their experiment, the acidity of the benzylic protons and the nucleophilicity of the derived carbanion combined to favour substitution at the benzylic position rather than at the 3-position.

Reactions involving other metalating reagents

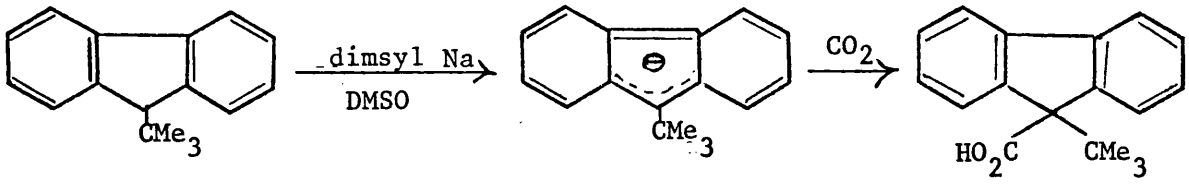
Since the use of n-butyl lithium resulted in the production of mixed products, several attempts were made to selectively remove the 2-proton from the imidazole ring. By analogy with the work of Uff and Kershaw,[93] who prepared the anions of Reissert compounds using sodium hydride in dimethylformamide, 1-benzylimidazole was treated with these reagents under similar conditions. No evidence for proton abstraction was obtained and it was concluded that this reagent was too weak a base to remove protons from 1-substituted imidazoles.

Recently sodium methylsulphinylmethide (dimsyl sodium) (IV. 24) has found application in metalation reactions.[94]



(IV. 24)

Dimsyl sodium is an extremely powerful base. Unlike other metalating agents it is not solvated and is thus not very demanding sterically. Compounds which are not readily metalated with more conventional reagents are susceptible to attack by this compound. A striking example of its efficacy is to be found in metalation experiments carried out on 9-teriary butylfluorene (IV. 25). This material cannot be metalated with n-butyl lithium. When dimsyl sodium is used abstraction of the 9-proton occurs and the aromatic anion produced can be carbonated to give the acid (IV. 26).[95]



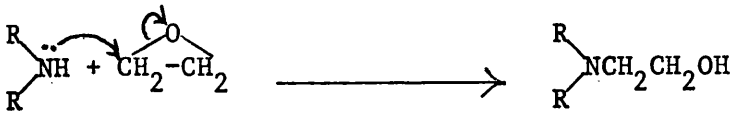
(IV. 25) (IV. 26)

Attempts were made to metalate 1-benzylimidazole with dimsyl sodium at room temperature. Carbonation did not furnish any acidic material and only starting material was isolated. We concluded that proton abstraction did not occur although a colour change was apparent. Dimethyl sulphoxide can act as an oxidising agent and it is conceivable that the difficulties we encountered could have arisen from this source.

As an alternative to the use of metalating reagents other than n-butyl lithium we considered using a different protecting group at the 1-position of the imidazole ring which would not react with ethylene oxide and was also readily removed. One group which appeared to meet these requirements was the triphenylmethyl (trityl). Attempts were made to metalate 1-tritylimidazole with n-butyl lithium in both ether and tetrahydrofuran and to hydroxyethylate and carbonate the reaction mixture. The required products were not obtained. Dimsyl sodium also failed to metalate 1-tritylimidazole and it was concluded that steric hindrance by the bulky protecting group rendered the 2-position of the imidazole ring inaccessible to attack, even by dimsyl sodium.

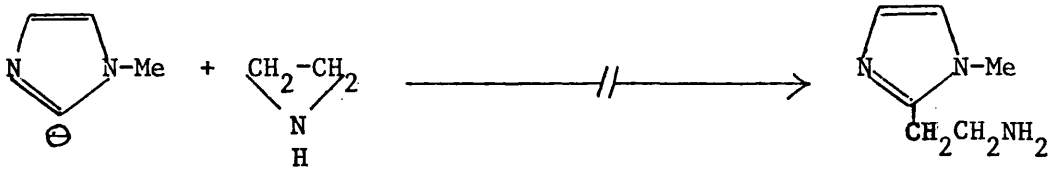
Unsuccessful attempts were also made to metalate 1-trimethylsilyl-imidazole under similar conditions to the above and it was again concluded that steric hindrance by the protecting group prevented metalation.

Ethylene oxide can react with suitable nucleophiles under relatively mild thermal conditions. A typical example of this is the direct hydroxyethylation of amines. Since 1-substituted imidazoles themselves are sufficiently nucleophilic to react with aliphatic and



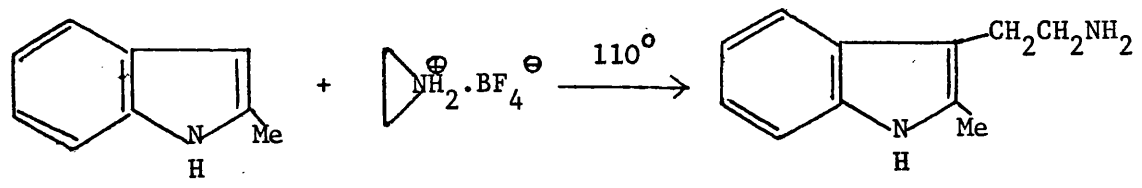
aromatic aldehydes to give 2-substituted carbinols,[54] attempts were made to condense ethylene oxide with 1-benzylimidazole under both thermal, and catalytic conditions, using trace quantities of p-toluenesulphonic acid. All these reactions were unsuccessful. 2-(2-hydroxyethyl)imidazole (IV. II) has now been obtained by other methods (Section II, p.47).

Perhaps the simplest of all routes to isohistamines would be the direct aminoethylation of suitable 1-substituted imidazoles with ethylene imine via metalation. The reaction between the lithio derivative of 1-methylimidazole and ethylene imine in ether gave rise to a mixture of products. The n.m.r spectrum of this material



gave no evidence for the formation of the required product.

A method for the direct introduction of the aminoethyl group into indoles, using aziridinium tetrafluoroborate, to give the tryptamine derivative (IV. 27) has been described,[96] and this would be another

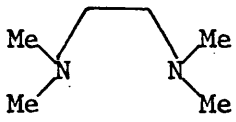


(IV. 27)

method worth investigation in the imidazole series.

Recently it has been shown that modification of n-butyl lithium by exchange of the alkyl group for a different anion can lead to the preferential metalation of selected positions of heterocyclic nuclei. A typical example of this has been the use of thienyl lithium to selectively metalate the methyl group of picolines.[97] It has been discovered that organolithium compounds form coordination complexes with amines. These complexes can exhibit a markedly different spectrum of reactivity from the uncoordinated material. From the synthetic standpoint the most interesting complexes are formed from triethylene-diamine (DABCO), (IV. 28) and tetramethylethylene diamine (TMEDA),

(IV. 28)



(IV. 29)

(IV. 29).[98,99] These complexes can metalate compounds not ordinarily or only poorly metalated by simple alkyl lithium derivatives.[100-102]

A study of the reactions of these and other metalating reagents with 1-substituted imidazoles could prove interesting and might offer more selection between the various reaction pathways.

EXPERIMENTAL SECTION

General Details

As described in Section II (p. 58).

1-Substituted imidazoles

1-Triphenylmethylimidazole (IV.1d) (Cf. ref. 86)

Imidazole (3.4 g.; 0.05 mole), triphenylmethylchloride (13.9 g.; 0.05 mole) and triethylamine (6 g.; 0.06 mole) in chloroform (75 ml.) were heated under reflux for 2.5 hr. The cooled reaction mixture was extracted with water (2 x 100 ml.). Evaporation of the dried (Na_2SO_4) chloroform solution gave a solid (15.4 g.) which was recrystallised from xylene to yield 1-triphenylmethylimidazole, (11.1 g.; 71%), m.p. 220-222° (lit.[86] m.p. 229-230°).

(Found: C, 84.79; H, 5.89; N, 9.33. $C_{22}H_{18}N_2$ requires C, 85.13. H, 5.84; N, 9.03%)

Metalating Reagents

n-Butyl lithium

An etheral solution of this material was prepared and standardised by the method of Jones and Gilman.[87]

Metalation Procedures

Reactions involving halogen containing electrophiles

Attempted preparation of 1-benzyl-2-ethoxycarbonylmethylimidazole (IV. 3)

1.4M n-Butyl lithium in ether (37.5 ml., 0.052 mole) was added to a stirred suspension of 1-benzylimidazole (7.9 g.; 0.05 mole) in dry ether (50 ml.), at -60^{o}, under dry nitrogen. After 3 hr. the solution was poured onto ethyl bromoacetate (16.7 g.; 0.1 mole) in dry ether (50 ml.) at -60^{o}. The mixture was allowed to warm to room temperature overnight, poured onto crushed ice (100 g.) and continuously extracted with ether for 13 hr. The evaporated extract was partitioned between chloroform and water. Evaporation of the dried (Na_2SO_4) chloroform solution gave an oil (2.6 g.) which was dissolved in ethanol and treated with hot ethanolic picric acid. On cooling the solution, the mother liquor was decanted from successive quantities of resinous material until crystals separated. Recrystallisation from ethanol gave pure 1-benzyl-3-ethoxycarbonylmethylimidazolium picrate, (IV. 4b), (0.1 g.), m.p. 143-145°, undepressed on admixture with the picrate described below.

(Found: C, 50.56; H, 3.99; N, 14.75. $C_{14}H_{17}N_2O_2 \cdot C_6H_2N_3O_7$ requires C, 50.72; H, 4.04; N, 14.79%)

1-Benzyl-3-ethoxycarbonylmethylimidazolium bromide (IV. 4a) and picrate (IV.

1-Benzylimidazole (1.6 g.; 0.001 mole) in ether (70 ml.) was treated with ethyl bromoacetrate (1.7 g., 0.001 mole). The solid obtained was recrystallised from ethanol/ethyl acetate/ether to give 1-benzyl-3-ethoxy-carbonylmethylimidazolium bromide, (3.2 g.; 98%), m.p. 115-117°.

(Found: C, 51.57; H, 5.12; N, 8.51; Br, 24.90. $C_{14}H_{17}N_2BrO_2$ requires C, 51.69; H, 5.27; N, 8.61; Br, 24.58%)

The picrate salt was prepared by treatment of an aqueous solution of the bromide (IV. 4a) with picric acid and was found to be identical to that described above.

Reactions involving ethylene oxide

General method for preparing and using imidazole lithium derivatives

n-Butyl lithium in hexane (0.105 mole) was added dropwise over 1 hr. to a stirred suspension of the 1-substituted imidazole (0.1 mole) in dry ether (200 ml.) at -60 to -70° under dry nitrogen. After 2 hr. the electrophile (0.105 mole) in dry ether (75 ml.) was added and the mixture was allowed to warm to room temperature overnight. Water (40 ml.) and conc. hydrochloric acid (25 ml.) were then added. The aqueous layer was extracted with chloroform (2x75 ml.) and basified with an excess of aqueous sodium carbonate. The product was extracted into chloroform and the dried (Na_2SO_4) chloroform solution was evaporated under vacuum to give the crude product.

1-Methyl-2-(2-hydroxyethyl)imidazole (IV.7) (Cf. ref. 50)

The crude product from the reaction between the lithio derivative of 1-methylimidazole and ethylene oxide was distilled under vacuum. The fraction boiling at 109-119° (0.15 mm) was collected and recrystallised from ethyl acetate/petroleum ether (b.p. 60-80°) to give 1-methyl-2-(2-hydroxyethyl)imidazole, (44%), m.p. 68-70° (lit[50] m.p. 68.5-69.5°).

(Found: C, 57.14; H, 8.09; N, 22.34. $C_6H_{10}N_2O$ requires C, 57.12; H, 7.99; N, 22.21%)

3-(Imidazol-1-yl)-3-phenylpropan-1-ol (IV. 8)

The crude product from the reaction between the lithio derivative of 1-benzylimidazole and ethylene oxide was distilled under vacuum. The fraction boiling at 130-180° (0.1 mm) was collected and recrystallised from ethyl acetate/petroleum ether (b.p. 60-80°) to give 3-(imidazol-1-yl)-3-phenylpropan-1-ol, (16%) m.p. 93-95°.

(Found: C, 70.95; H, 7.09; N, 14.15. $C_{12}H_{14}N_2O$ requires C, 71.26; H, 6.98; N, 13.85%)

Reaction between the lithio derivative of 1-benzylimidazole and ethylene oxide

Three reactions were carried out using different proportions of reactants as tabulated below

Moles of Reactant		
1-Benzylimidazole	n-Butyl lithium	Ethylene oxide
1	0.8	0.9
1	1.05	1.3
1	2	4

The crude products, obtained in the usual way, were examined using n.m.r. techniques (See Discussion, p.144).

2-(2-Hydroxyethyl)imidazole (IV.11) and 3-phenylpropan-1-ol (IV.12)

The crude product, (32 g.), from the reaction between the lithio derivative of 1-benzylimidazole (23.7 g.; 0.15 mole) and ethylene oxide (8.8 g., 0.2 mole) was suspended in liquid ammonia (300 ml.) and treated with sodium metal (approximately 12g.) until a blue colour persisted. Ammonia was allowed to evaporate and 26% aqueous ammonium chloride (100 ml.) was added. The solution was adjusted to pH2 with conc. hydrochloric acid and continuously extracted with chloroform for 18 hr. The dried (Na_2SO_4) chloroform solution was carefully distilled. The residue, comprising mainly toluene and 3-phenylpropan-1-ol was subjected to preparative gas-liquid chromatography, and both components were isolated.

The aqueous layer was basified with an excess of sodium carbonate and continuously extracted with chloroform for 64 hr. The dried (Na_2SO_4) chloroform solution was evaporated to give a solid (8.4 g.) which was extracted with ether. Evaporation of the ether extract gave a mixture comprising mainly imidazole (identified by thin-layer chromatography). The ether-insoluble material was converted into its picrate salt. Seven recrystallisations from ethanol gave 2-(2-hydroxyethyl)imidazole picrate, (1.3.; 3%), m.p. 149-151°.

(Found: C, 38.69; H, 2.95; N, 20.32. $C_5H_8N_2O$. $C_6H_3N_3O_7$ requires C, 38.72; H, 3.25; N, 20.52%)

This material was found to be identical with the hydroxyethyl compound (II.3b), (p.81) and a mixed melting point showed no depression.

Reactions involving other electrophiles

1-Benzylimidazole-2-carboxylic acid hydrate

This was prepared by the method of Shirley and Alley;[53] m.p. 101-102° (decomp); 78% yield [lit.[53] m.p. 103-104° (decomp)].

4-(Imidazol-1-yl)-4-phenylpropan-2-ol (IV.17)

The crude product was obtained from the reaction between the lithio derivative of 1-benzylimidazole and propylene oxide. The assignment of structure is discussed on p.150.

1-Benzyl-2-methylimidazole (IV.18) (Cf. ref. 104)

A 1 g. sample of the crude product from the reaction between the lithio derivative of 1-benzylimidazole and dimethyl sulphate was converted into its picrate. Recrystallisation from ethanol/water gave 1-benzyl-2-methylimidazole picrate, m.p. 151-152° (lit.[104] m.p. 153-154°).

(Found: C, 51-27; H, 3.96; N, 17.50. $C_{11}H_{12}N_2 \cdot C_6H_3N_3O_7$ requires C, 50.87; H, 3.77; N. 17.45%)

1-Benzylimidazol-2-ylisopropanol (IV.19)

The crude product was obtained from the reaction between the lithio derivative of 1-benzylimidazole and acetone. The assignment of structure is discussed on p. 152.

Deutero-1-benzylimidazole

The crude product was obtained from the reaction between the lithio derivative of 1-benzylimidazole and deuterium oxide. The assignment of structure is discussed on p. 152.

SPECTRA

Instrumentation

As described in Section II (p. 90).

1-Triphenylmethylimidazole (IV. 1d)

$\nu_{max.}$: 1595, 1490, 752, 704 (aromatic); 664, 641 (imidazole).

τ; (DMSO-d_6): 450-420 c/s (m; 2-H, 3 x -Ph); 3.17 (2 x d; 4-H, 5-H).

1-Benzyl-3-ethoxycarbonylmethylimidazolium picrate (IV. 4b)

$\nu_{max.}$: 1730 (C=O). Strong picrate absorption prevents further assignment.

τ; (DMSO-d_6): 0.48 (broad s; 1; 2-H); centred 2.16 (m; 2; 4-H, 5-H); 2.52 (s; 5; -Ph); 4.45 (s; 2; $-\underline{CH_2}Ph$); 4.71 (s; 2; $-N\underline{CH_2}CO-$); centred 5.75 (q; 2; $-O\underline{CH_2}CH_3$); 8.73 (t; 3; $-OCH_2\underline{CH_3}$).

Spin decoupling experiments confirmed the assignments given to the signals at 0.48 and 2.16τ.

1-Methyl-2-(2-hydroxyethyl)imidazole (IV. 7)

$\nu_{max.}$: 3300-2400, 780 (OH); 3115, 1630, 1475 (aromatic); 1080 (C-O); 3140, 1510, 629 (imidazole).

τ; ($CDCl_3$): centred 3.14 (2 x d; 2; 4-H, 5-H); 5.42 (s; 1; -OH); 6.0 (t; 2; $-CH_2\underline{CH_2}O-$); 6.30 (s; 3; $-\underline{CH_3}$); 7.18 (t; 2; $-\underline{CH_2}CH_2O$).

3-(Imidazol-1-yl)-3-phenylpropan-1-ol (IV.8)

$\nu_{max.}$: 3420-2500 (OH); 3130, 1510, 730, 645 (imidazole); 3040, 1625, 1590, 1485, 745, 709 (aromatic); 1055 (C-O)

τ; ($CDCl_3$): 2.47, 2.71, 3.04 (m; 8; 2-H, 4-H, 5-H, -Ph); 4.47 (t; 1; -CHPh); 5.30 (s; 1; -OH); 6.44 (m; 2; $-CH_2\underline{CH_2}O$); 7.62 (m; 2; $-CH\underline{CH_2}CH_2O-$).

2-(2-Hydroxyethyl)imidazole picrate (IV. 11)

$\nu_{max.}$: 3440, 1165 (OH); 3160, 3140 (imidazole); 1065 (C-O).

τ; (DMSO-d_6): 2.46 (s; 2; 4-H, 5-H); 6.20 (t; 2; $-CH_2\underline{CH_2}O-$); 6.95 (t; 2; $-\underline{CH_2}CH_2O-$).

1-Benzyl-2-methylimidazole picrate (IV. 18)

i.r: strong picrate absorption prevents assignment.

τ; (DMSO-d_6): 2.30 (d; 5-H); 2.38 (d; 4-H); 2.60 (s; -Ph); 4.55 (s; $-\underline{CH_2}Ph$).

SECTION V

PHARMACOLOGY

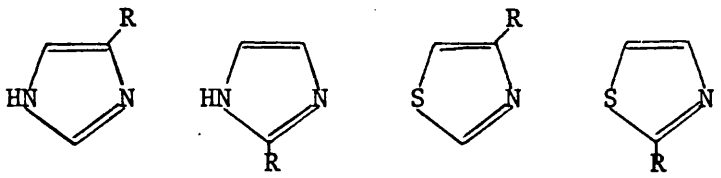
DISCUSSION

The purpose of the present work, which was part of a more intensive investigation in these laboratories, was to shed some light on the steric, electronic and physico-chemical properties which are important in determining the biological properties of histamine. The physiological effects produced by histamine have been discussed and the concept of the H_1 and H_2 receptors has been defined (Section I. p. 2-4).

Histamine is exceptionally sensitive to changes in its structure and the smallest change usually leads to a drastic decrease in activity. One method of evaluating the properties which confer such pronounced activity upon histamine is to assess the activity of various histamine analogues. It is therefore essential to be able to detect and measure the pharmacological activity of these histamine analogues, and in addition it is desirable to be able to specify the action of the compounds to be evaluated in more than one relevant test situation.

The compound to be evaluated could mimic the effect of histamine, i.e. exhibit agonist activity; or it could block the effect of histamine, i.e. exhibit antagonist activity. The H_1 activity of the compounds under test was measured on the isolated guinea pig ileum. The H_2 activity of the histamine analogues was determined on the gastric acid secretion of the rat and on the isolated guinea pig atrium. The methods used to assay these compounds have been described in detail.[104]

Specifically we were interested in developing a selective H_2 receptor antagonist; thus any evidence of selectivity in agonist activity, in a histamine analogue, might be of value in designing such an antagonist. The isomer of histamine which might be expected to bear the greatest similarity to histamine is the 2-substituted imidazole (isohistamine). As we have shown, the compound formulated as isohistamine by R.G. Jones[9] was, in fact, 4(5)-aminomethyl-2-methylimidazole and similarly P.C. Jocelyn's claim[16] to have prepared 1-methylisohistamine was incorrect. Rocha e Silva[12b] tried to rationalise the H_1 activities of the following imidazoles and thiazoles. Despite the fact that



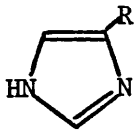
R = $-CH_2CH_2NH_2$

RELATIVE ACTIVITY ON SMOOTH MUSCLE (i.e. H_1)	100	0 (0.15 our result	2	30

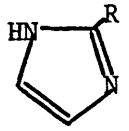
the data for isohistamine was determined using 4(5)-aminomethyl-2-methylimidazole, our figure for authentic isohistamine is only 0.15, so the enigma remains. Jocelyn[11] made a brave attempt to explain the inactivity of Jones' compound and he postulated that 1-methylisohistamine should possess high histamine-like activity. Subsequently he found that the compound which he formulated as 1-methylisohistamine was completely inactive. We now know that he had obtained 5-aminomethyl-1,2-dimethylimidazole, but authentic 1-methylisohistamine is equally inactive. The parent compound of these rearranged products, i.e. 4(5)-aminomethylimidazole, was

prepared by the method of Turner and his coworkers[105] and was found to exhibit no activity in any of the pharmacological assays. Isohistamine has been tested for H_2 receptor activity and was found to have 0.15% of the agonist activity of histamine. It is not an antagonist.

In the 4(5)-substituted imidazole series, certain isothioureas[106] and guanidines[107] of the type (V. 1), m=2, n=2 or 3, have been prepared which did exhibit selective H_2 receptor antagonism. Therefore we have prepared the isomeric compounds of the type (V. 2), where the side-chain is in the 2-position.



(V. 1)



(V. 2)

R = $-(CH_2)_m SC(=NH)NH_2$

= $-(CH_2)_n NHC(=NH)NH_2$

In order to determine whether the presumed affinity of the imidazole ring in the H_2 antagonists is stereochemically critical, the homologues (V. 2, m=3, n=4) have been synthesised. Furthermore it was thought possible that homologues of isohistamine, i.e. 2-(3-aminopropyl)imidazole and 2-(4-aminobutyl)imidazole might interact at either the H_1 or H_2 receptor more favourably than isohistamine itself. If this proved to be so, as evidenced by enhanced activity, then some very useful information about the topology of the receptors would have been obtained.

RESULTS

H_1 Receptor Activity

None of the compounds examined exhibited more than very weak agonist activity at the H_1 receptor. In 2+2 assays on the isolated guinea pig ileum isohistamine and 1-methylisohistamine were 0.15 (0.14 - 0.16)% and 0.11 (0.105 - 0.132)% of the activity of histamine; the values in parenthesis are the 95% confidence limits. 4(5)-Methylisohistamine, 4,5 -dihydroisohistamine, 2-(3-aminopropyl)imidazole, 2-(4-aminobutyl)-imidazole, isohistidine and its 1-benzyl analogue were all inactive.

H_2 Receptor Activity

Several compounds showed weak agonist activity, both on the isolated guinea pig atrium and on the rat stomach. These were isohistamine and its aminobutyl analogue, S-(1-benzylimidazol-2-yl)methylisothiourea, S-2-(imidazol-2-yl)ethylisothiourea, (V. 2, m = 2), S-3-(1-benzylimidazol-2-yl)propylisothiourea, and 2-(3-guanidinopropyl)imidazole (V. 2, n = 3). Some of the responses of these weak agonists were not dose-related.

The following compounds showed activity as H_2 antagonists: S-3-(1-benzylimidazol-2-yl)propylisothiourea, 2-(3-guanidinopropyl)- and 2-(4-guanidinobutyl)- imidazoles (V. 2, n = 3 and 4).

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Abstract

"Isohistamine", (2-(2-aminoethyl)imidazole), and Related Compounds

As part of a programme to prepare structural analogues of histamine for pharmacological examination, the positional isomer, 2-(2-aminoethyl)-imidazole, (isohistamine) was required.

The synthesis of this compound, published in 1949, involved the nucleophilic displacement of chlorine by cyanide ion in 1-benzyl-2-chloromethylimidazole. Repetition of this reaction has shown that a previously undetected rearrangement occurs and that a mixture of nitriles is obtained. The subsequent stages of the published synthesis led to 4(5)-aminomethyl-2-methylimidazole, and not isohistamine. This reformulation explains the anomalous properties of the compound previously thought to be isohistamine. A similar published synthesis of 2-(2-aminoethyl)-1-methylimidazole has been investigated and shown to be in error.

When the cyanide ion displacement reaction on 1-benzyl-2-chloromethyl-imidazole was carried out in dimethylformamide, the expected 2-cyano-methyl compound was obtained together with a novel type of stable primary enamine, 1-amino-2-(1-benzylimidazol-2-yl)acrylonitrile.

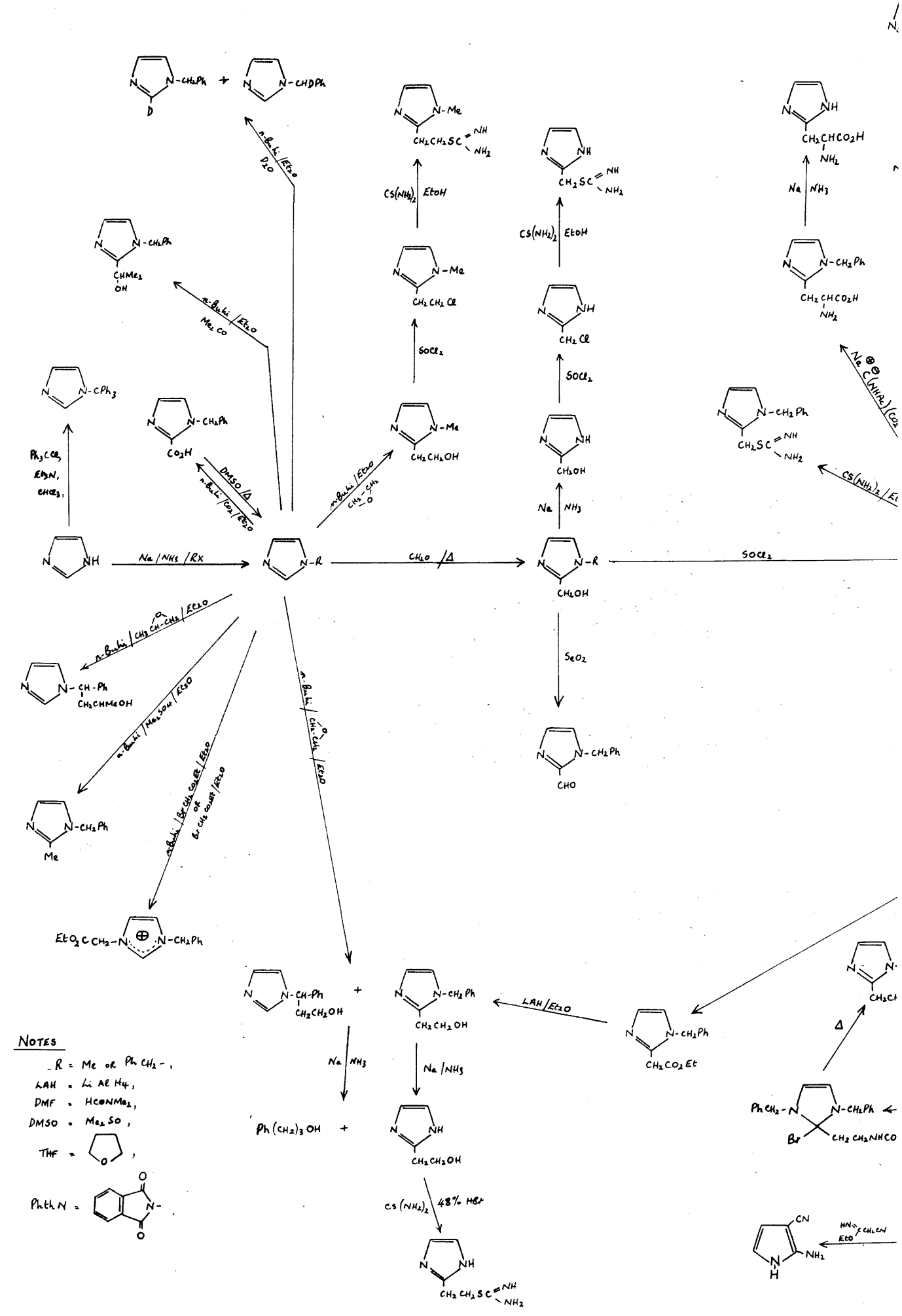
The homologues of isohistamine, 2-(3-aminopropyl)imidazole and 2-(4-aminobutyl)imidazole have been synthesised and the isothioureas and guanidines related to these amines have also been made for

pharmacological examination.

In order to provide alternative syntheses of the foregoing compounds, the preparation of 2-substituted imidazoles by cyclisation of the appropriate iminoethers has been investigated.

The metalation of 1-substituted imidazoles with organo-lithium compounds, as another route to 2-substituted imidazoles, is discussed, and the reaction of these lithio derivatives has been investigated. The anomalous behaviour of ethylene oxide, which reacts with the lithio derivative of 1-benzylimidazole at the benzylic methylene group has been studied.

The biological rationale for the synthesis of the compounds described in this work is briefly discussed.



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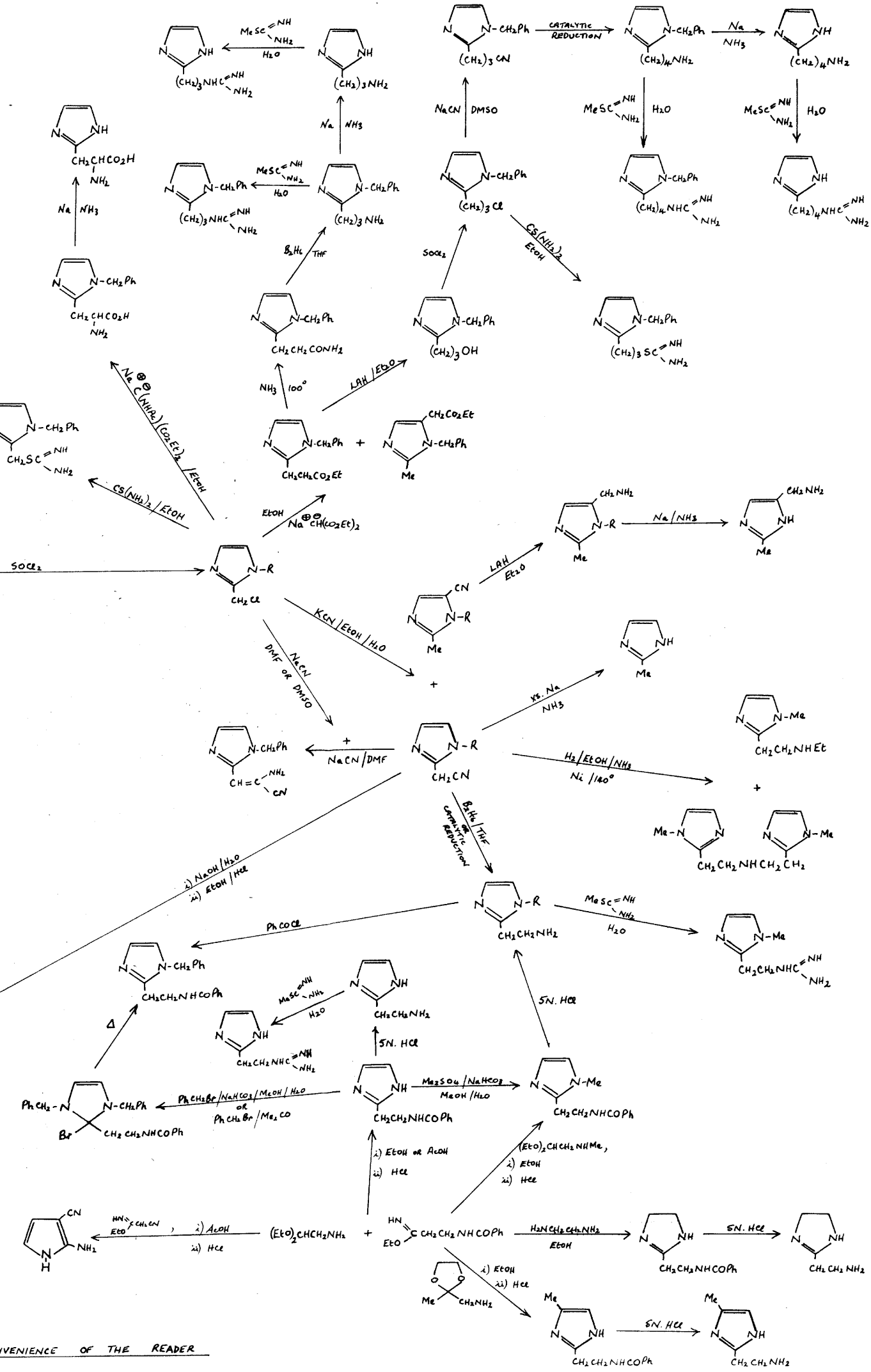

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