STUDIES IN VINYL ISONITRILE AND THIOPHENIUM YLID CHEMISTRY

A Thesis in fulfillment of the
requirements for the degree of
Doctor of Philosophy
of the
University of Stirling

by

Timothy Bowles

February 1989

Chemistry Department
University of Stirling

ACKNOWLEDGEMENTS

I would like to thank Dr AEA Porter for his advice and assistance throughout this work. Profound thanks are also due to Dr H Maskill for his advice and encouragement during the latter stages of my research, particularly with the kinetics.

Thanks also to Gerry Castle for permitting me to examine, and occasionally to remove, the treasures lurking in the darkest recesses of his domain, to Greta Berry for elemental analyses, and to Don Dance for prompt and efficient mass spectral analyses.

I am also grateful to other members of staff, technical and academic, and to the postgrads, too numerous to mention here, for loans of chemicals, equipment and expertise.

I would like to thank the University of Stirling for a postgraduate studentship.

Last, but by no means least, I must extend my profound thanks to Nancy, for giving me a home to go to, and in particular to Marion, without whom none of this would have been worthwhile, let alone possible. Thanks, everybody.

ABSTRACT

A method for the reductive formylation of ketoximes was sought. Anhydrous titanium (III) chloride was ineffective, but reaction of cyclohexanone oxime with anhydrous titanium (III) acetate and acetic-formic anhydride in N,N-dimethylformamide solution gave 1-(N-formylamino)cyclohexene (12) in 90% yield. Difficulties in reproducing this reaction were ultimately overcome, and a further 8 ene-formamides were prepared by this method.

Dehydration of these formamides with phosgene and volatile amines gave azeotropic mixtures of isonitriles and amines. Replacement of the volatile amines with DABCO gave vinyl isonitriles in moderate yield. 8 examples were prepared.

A strategy for the synthesis of xanthocillin X was formulated. Condensation of p-hydroxybenzaldehyde with nitromethane followed by borohydride reduction and acetylation gave p-acetoxyphenylnitroethane (49). Reaction of this with phenyl isocyanate gave the furoxan (47), which was hydrogenated to the oxime (44). This material was inert to the reductive formylation procedure.

Reaction of cyclohexane-1,3-dione with ammonia followed by formylation and dehydration gave 1-isocyano-3-hydroxycyclohexa-1,3-diene (67).

The rearrangement of thiophenium ylids to thiophene-2-malonates was investigated. 2H-thiopyrans were identified as intermediates in this reaction. The kinetics of the rearrangements were studied. The rearrangement of thiophenium ylids to 2H-thiopyrans was discovered to

ABSTRACT (cont.)

have first-order kinetics with no long-lived intermediates. The rearrangement of 2H-thiopyrans to thiophene-2-malonates was a two-step process with an unknown long-lived intermediate being formed. A possible mechanistic pathway was proposed.

CONTENTS

SOME APPROACHES TOWARDS THE SYNTHESIS OF VINYL ISONITRILES

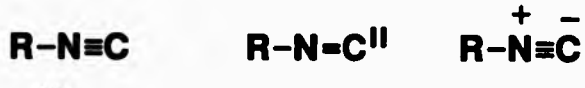
CONTENTS (cont.)

SOME INVESTIGATIONS INTO THE REARRANGEMENT OF THIOPHENIUM YLIDS

History

Although the isonitrile group was first identified well over a century ago, by Gautier[1] and almost simultaneously by Hoffman[2], isonitriles remained little-studied curiosities until relatively recently. Only in the last three decades have efficient and widely-applicable methods of synthesis become available, allowing extensive studies of this interesting and synthetically-useful class of compounds.

Initial interest in isonitriles was raised by the question of whether carbon could exist in divalent form. The original structure (1) proposed by Gautier and Hoffmann was rapidly superseded by that of Nef[3], who first proposed that the isonitrile carbon was divalent in nature (2) to account for the fact that it underwent α-addition. However, Langmuir disputed this structure, as it did not conform to his octet theory of valence[4], and proposed instead the triple-bonded dipolar structure (3), the most widely-accepted structure in recent times.



(1) (2) (3)

Further evidence for this structure was soon forthcoming. Measurement of the parachors of methyl[5] and ethyl[6] isonitriles suggested a triple-bonded structure, and dipole moment measurements[6] indicated that the C-N-C bonds were colinear. The nitrogen atom was observed to have a positive charge with respect to carbon, the reverse of the case in nitriles.This triple-bonded linear structure has also been confirmed by Raman spectral studies[7], and by comparison of bond lengths in methyl isonitrile and acetonitrile by electron diffraction[8]. To account for the above data,

and the observed chemistry of isonitriles, the structure is most conveniently described as a resonance hybrid of (2) and (3).

The nomenclature of these compounds has been inconsistent over the years, the terms isonitrile and isocyanide being the most commonly-used, although they are frequently referred to as carbylamines in the older literature. In this account, the term isonitrile will be used throughout, this term being currently in favour with the Chemical Abstracts Service. In the naming of individual compounds, the prefix isocyano- is universally used.

Physical and Spectral Characteristics

The lower isonitriles are all in general volatile, colourless liquids, with boiling points typically some 20° lower than those of the isomeric nitriles[9]. They have an odour which has been described variously as "pungent","vile", "horrible" and "characteristically disagreeable", and this property has found application in a chemical test for primary amines. The smell is sufficiently powerful to allow the detection of isonitriles in trace amounts.

In the infra-red, the isonitrile group shows a characteristic ν_{N-C} stretching vibration, of high intensity, in the region 2110-2150 cm^{-1}. This stretching frequency is typically ca. 100 cm^{-1} lower than the corresponding nitrile stretching vibration, implying a somewhat weaker N-C bond in the isonitrile. The dipolar structure (3) implies that the isonitrile bond should be somewhat stronger than that of the nitrile, but as yet no explanation has been suggested for this apparent anomaly.

Electron diffraction studies[8] show that the C-N triple bond in methyl isonitrile (117 pm) is marginally longer than that in acetonitrile (116 pm).

In the ^{13}C n.m.r. spectra of a variety of isonitriles[11] in non hydrogen-bonding solvents, the isonitrile carbon resonance typically appears in the range 154-158 ppm, increasing substitution at the α-carbon causing an upfield shift. In unsaturated (vinyl and aromatic) isonitriles, the isonitrile carbon resonance appears in the range 164-170 ppm. The chemical shifts reported for isonitriles in fact more resemble that for free cyanide ion (168.5 ppm for KCN in water) than those for nitriles (112-126 ppm)[12]. Coupling constants between the isonitrile carbon and nitrogen ($^1J_{N-C}$) lie in the range 3.7-5.8 Hz, with increasing substitution at the α-carbon causing a decrease. The coupling constants ($^1J_{N-C}$ between the α-carbon and nitrogen are in the range 5-7 Hz in aliphatic isonitriles, and 11.5-13.5 Hz in unsaturated examples.

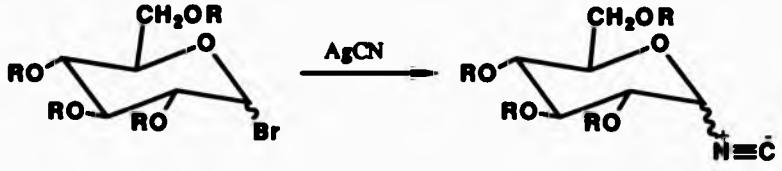
Preparation of Isonitriles

The reaction of free cyanide ion with alkyl halides proceeds predominantly *via* alkylation at carbon to produce nitriles, with isonitriles being formed only in trace amounts. If the cyanide ion is complexed to a heavy metal, however, alkylation occurs preferentially at nitrogen. Indeed, isonitriles were first prepared by Gautier[1] by alkylation of silver cyanide with alkyl iodides, the isonitriles being liberated from the complex by potassium cyanide.

$$R\text{-}I \xrightarrow{AgCN} [(RNC)AgI] \xrightarrow{KCN} R\text{-}\overset{+}{N}\equiv\overset{-}{C}$$

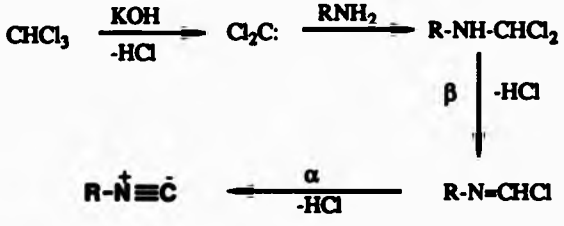
Mercuric cyanide HgCN is also effective in most cases.

This method of preparation has been superseded by the more widely-applicable and higher-yielding methods described below, although it has proved a clean and effective method for the preparation of some monosaccharide isonitriles[13].



Almost contemporaneous with Gautier's work was the discovery by Hoffman[2] that reaction of primary amines with chloroform in strongly basic conditions yielded isonitriles - the so-called Hoffman carbylamine reaction. This reaction was interpreted by Nef[3] as involving the addition of dichlorocarbene to the amine, followed by sequential β- and α-eliminations of HCl (scheme 1)

SCHEME 1



The rather drastic conditions required for this reaction have limited its

usefulness, application generally being restricted to a test for primary amines.

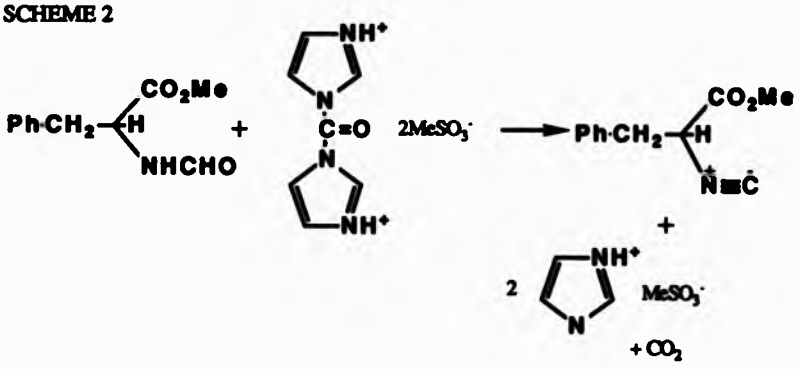
Until 1957, these two methods were the only ones available for the synthesis of isonitriles. The suggestion that these compounds might be prepared by dehydration of the formamides derived from primary amines was first made by Gautier[1], but his attempts to carry this out were not successful. However, in 1957 Hagedorn[73] and subsequently Corey[14] demonstrated that such a dehydration could be effected, using p-toluenesulphonyl chloride and pyridine, to give isonitriles in moderate to good yields.

A variety of reagents have since been used to effect this transformation, most notably phosgene/triethylamine[15], p-toluenesulphonyl chloride/quinoline[73] and phosphoroyl chloride/potassium t-butoxide[16] or pyridine[17]. Of these methods, the phosgene method is frequently preferred, as it is clean, rapid and high-yielding, and the isonitriles formed are usually stable to an excess of the reagent. However, phosgene has the disadvantages of volatility and extreme toxicity, requiring extreme care in routine laboratory work. A safer alternative is diphosgene (trichloromethyl chloroformate) which has been reported as being considerable easier and safer to handle than phosgene, with the added advantage of affording higher yields of isonitriles[18,19].

A recent report[20] has shown that phosphoroyl chloride, when used with diisopropylamine, provides significantly higher yields than when triethylamine is used. In many cases, the yields were comparable with or superior to those obtained using phosgene.

None of the above methods is applicable to the synthesis of base-sensitive isonitriles. Ugi and co-workers, in the course of synthesising chiral α-isocyanoesters, found that these could be prepared by the use of oxomethylenebis(3H⁺-imidazolium) bis(methanesulphonate) (4) as the dehydrating agent[21] (scheme 2).

SCHEME 2



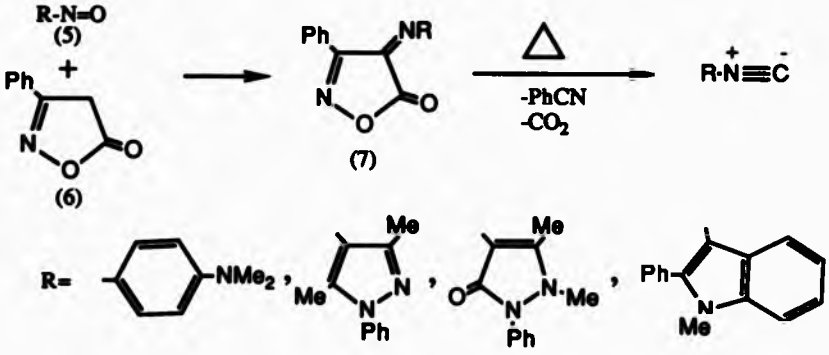
A variety of isonitriles, base-sensitive or otherwise, were prepared using this reagent.

Monosubstituted formamides have also been induced to undergo dehydration by reaction with triphenylphosphine, carbon tetrachloride and triethylamine[22].

Isonitriles have also been prepared by reduction of isothiocyanates with chlorosilane and triethylamine in moderate to good yield[23]. Carbamates are also reduced to isonitriles under these conditions, although in poorer yield.

The preparation of unusual heteroaryl and otherwise inaccessible aryl isonitriles from nitroso compounds has been reported by Wollweber and co-workers[24]. The nitroso compound (5) is condensed with 3-phenylisoxazol-5(4H)-one (6) to give the iminoisoxazolone (7), which decomposes at its melting point with the loss of benzonitrile and carbon dioxide to give the isonitrile (scheme 3).

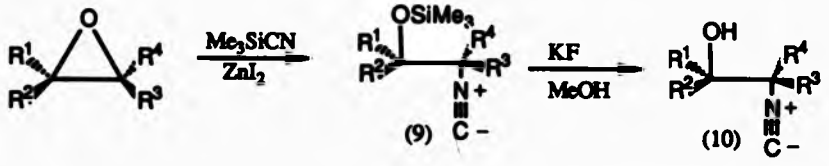
SCHEME 3



Yields in excess of 70% from the nitroso compound have been reported.

An efficient and stereospecific preparation of β-hydroxyisonitriles from epoxides has been reported[25]. The addition of trimethylsilyl cyanide to the epoxide yields the trimethylsilyl ether (9) which is cleaved quantitatively by potassium fluoride in methanol to afford the β-hydroxy-isonitrile (10).

SCHEME 4



Aromatic isonitriles have also been prepared by reaction of N-sulphinylimines with dichlorocarbene in excellent yields[26].

Reactions of Isonitriles

Rearrangement to nitriles

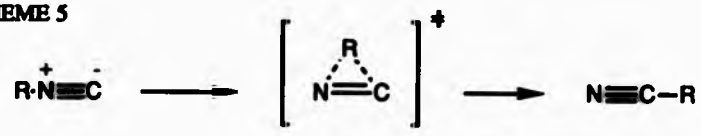
The rearrangement of isonitriles to nitriles at high temperature was first observed by Weith in 1873[28]. This rearrangement has been studied in some detail, as it is a classic example of an uncatalysed first-order unimolecular reaction.

A detailed study of the rearrangement of a number of isonitriles by Casanova *et al*[29] established a number of important points concerning this reaction. Heating of (+)-s-butylisonitrile at 200° in a sealed tube resulted in complete conversion to (+)-2-methylbutyronitrile, with complete retention of absolute configuration. Furthermore, on heating cyclobutylisonitrile under similar conditions, complete conversion to cyclobutanecarbonitrile was observed, with no rearrangement of the carbon skeleton.

It was also observed that, in the rearrangement of p-substituted aryl isonitriles, the nature of the p-substituent had little or no effect on the rate of rearrangement, and little or no solvent effect was observed.

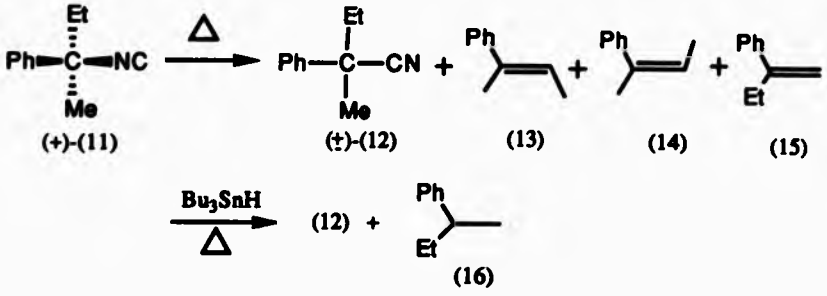
These data serve to indicate that the substrate remains closely associated throughout the rearrangement, with little or no charge separation, and that bond breaking and bond forming occur simultaneously (scheme 5).

SCHEME 5

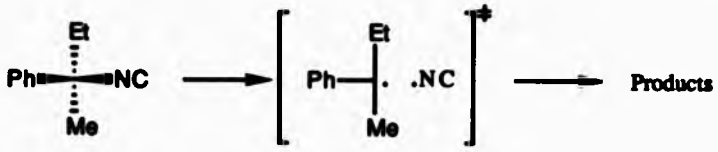


However, these results are in direct contrast to those obtained by Yamada et al[30]. Heating of (+)-(11), either as a neat liquid or in diphenyl ether solution, resulted in the formation of completely or partially racemised product (12), together with significant quantities of elimination products (13-15) (scheme 6).

SCHEME 6

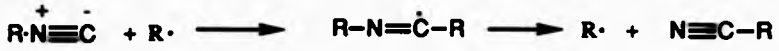


When the thermolysis was conducted in the presence of tributyltin hydride as a radical scavenger, s-butylbenzene was formed in addition to the racemic rearrangement product. This suggests that the rearrangement takes place by initial homolytic C-N fission to produce a radical pair.

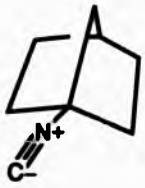


In general, the rearrangement of isonitriles in solution occurs with varying degrees of retention and racemisation in the migrating group, the degree of racemisation depending on both structure and concentration. This has been attributed[31] to competing reaction mechanisms, one *via* the cyclic transition state (scheme 5), with a free radical mechanism competing at higher concentrations (scheme 7).

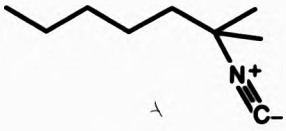
SCHEME 7



The same authors[32] conducted a detailed study of the rearrangement of a variety of aryl, alkyl and bridgehead isonitriles in solution, in the presence of a free-radical inhibitor to eliminate the competing radical mechanism. The remarkable feature of the results of this study was that the rate of rearrangement of 1-bicyclo[2.2.1]heptylisonitrile (18) was almost identical to that of t-octylisonitrile (19), indicating the complete absence of a bridgehead effect.

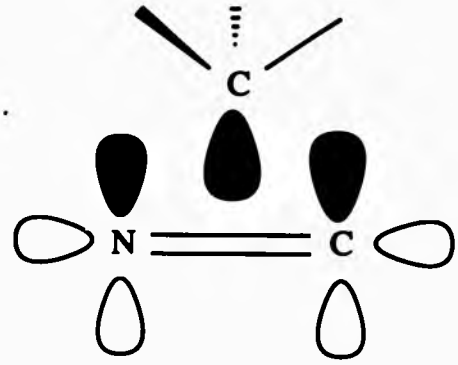


(18)



(19)

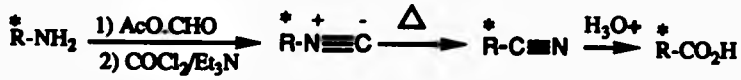
The absence of a marked structure-activity relationship in this rearrangement indicates that it is a typical sigmatropic 1,2-rearrangement *via* a non-polarised hypervalent 3-centre transition state (20).



(20)

The same authors[33] have demonstrated that, if the rearrangement is conducted by flash pyrolysis in the gas phase, the radical pathway is eliminated, and nitriles can be formed in excellent yields with complete retention of absolute configuration. This synthetically useful rearrangement presents an effective method for the conversion of optically-active primary amines to carboxylic acids with retention of stereochemistry (scheme 8).

SCHEME 8



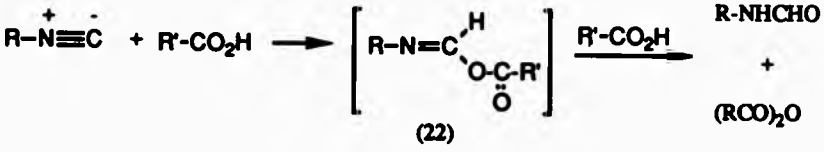
α-Addition reactions

Isonitrile chemistry is characterised by the conversion of the formally divalent isonitrile carbon to a more stable tetravalent state. Indeed, the ability of isonitriles to undergo α-addition of, for example, halogens to form isonitrile dihalides (21) was the principal argument put forward by Nef[3] for the divalency of the isonitrile carbon.

(21)

Anhydrous hydrogen halides also add to isonitriles to form imidoyl halides. With carboxylic acids, the intermediate acylimidate (22) reacts with a further molecule of the acid to form the formamide and acid anhydride (scheme 9).

SCHEME 9



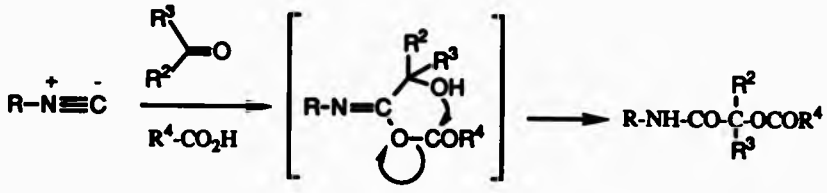
(22)

If R' is p-nitrophenyl, the acylimidate is isolable, as is the case with picric and p-toluenesulphonic acids[34].

Isonitriles react only slowly with water, but in the presence of acid catalysts rapid α-addition of water occurs to form the formamides.

An acylimidate intermediate is involved in the three-component condensation of an isonitrile, a carbonyl compound and a carboxylic acid (Passerini reaction) (scheme 10)[35].

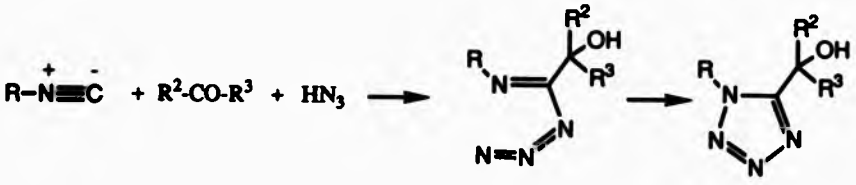
SCHEME 10



This reaction has been widely used for the preparation of depsipeptides.

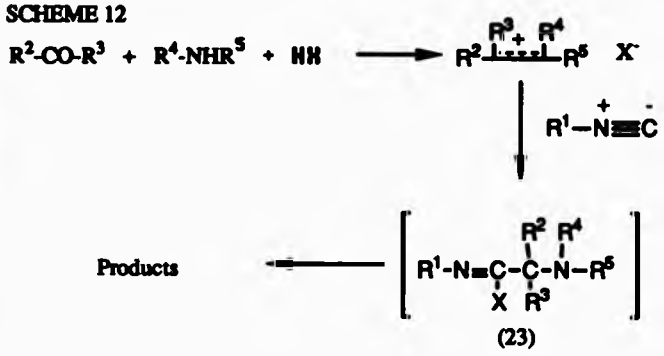
A closely related reaction in which the carboxylic acid is replaced by hydrazoic acid has been used for the synthesis of tetrazoles (scheme 11).

SCHEME 11



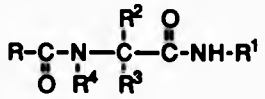
A class of reaction which bears a close resemblance to the above is the 4-component condensation or Ugi reaction[35]. This is a reaction between an isonitrile, a carbonyl compound, an amine and an acid to form the α-adduct (23), which then undergoes spontaneous secondary reactions, the nature of which depends to a large extent on the nature of the acid (scheme 12).

SCHEME 12



(23)

If HX is a carboxylic acid (RCO_2H) and the amine is primary (R^4 = H), intramolecular acyl transfer occurs to form an α-amino acid derivative (24).



(24)

This reaction has been adapted to provide an efficient, highly stereospecific approach to the preparation of peptides, with the advantage of providing a one-pot synthesis of two new peptide bonds.

This type of reaction has also been applied to the synthesis of a wide range of antibiotics[36].

Reactions with Nucleophiles

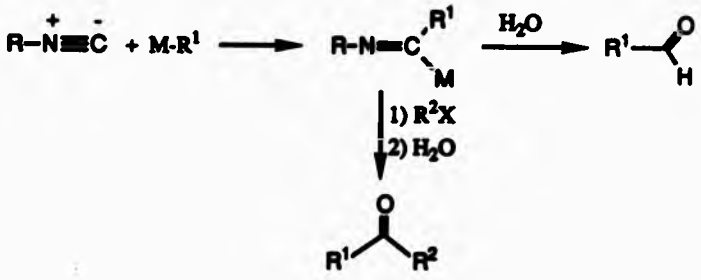
The representation of the isonitrile group as (3), in which the carbon atom carries a negative charge, indicates that this carbon will be resistant to nucleophilic attack. That this is the case is illustrated

by their stability to alkaline hydrolysis. As stated above, however, isonitriles are subject to acid-catalysed nucleophilic attack, as illustrated by their rapid hydrolysis in acidic solution. Isonitriles react similarly with arylamine hydrochlorides to form formamidines (scheme 13).

SCHEME 13

The isonitrile group is subject to attack by powerful nucleophiles such as organolithium or Grignard reagents, with the net result of α-addition of the organometallic reagent to form metallo-aldimines[37] (scheme 14).

SCHEME 14

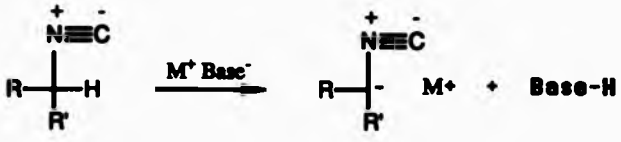


These intermediates can be hydrolysed to aldehydes, or sequentially alkylated and hydrolysed to form ketones.

If the isonitrile contains α-hydrogens, reaction with anionic reagents occurs *via* α-deprotonation rather than addition to form the α-metallated

isonitrile (scheme 15).

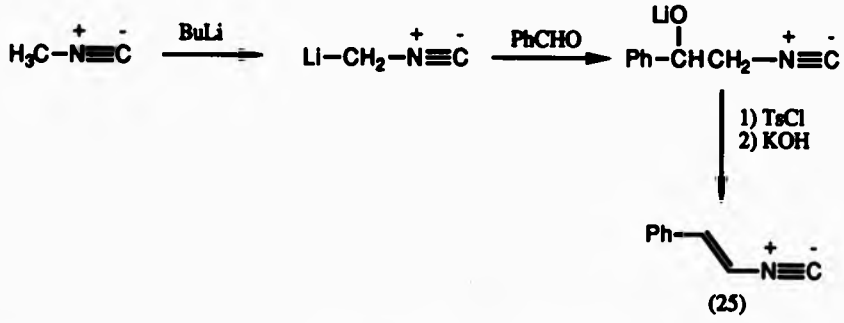
SCHEME 15



The bifunctional nature of these compounds, with a nucleophilic carbanionic centre and an electrophilic isonitrile group, makes them extremely versatile synthetic intermediates, particularly in the preparation of heterocyclic compounds. The use of α-metallated isonitriles has been extensively reviewed[38,39,40] and only more recent applications will be considered here.

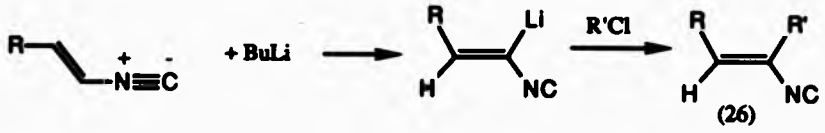
The use of α-metallated isonitriles as nucleophiles in the synthesis of otherwise difficultly-accessible vinyl isonitriles was developed by Schollkopf and co-workers[41]. A good example of this is the preparation of β-styrylisonitrile (25). Abstraction of a proton from methyl isonitrile generates the nucleophilic anion, which adds to benzaldehyde. Tosylation and elimination generates (E)-β-styrylisonitrile in overall 56% yield (scheme 16).

SCHEME 16



The vinyl isonitriles formed in this manner can be alkylated by conversion to the vinyllithium compounds (26), which react with suitable electrophiles (scheme 17)[41].

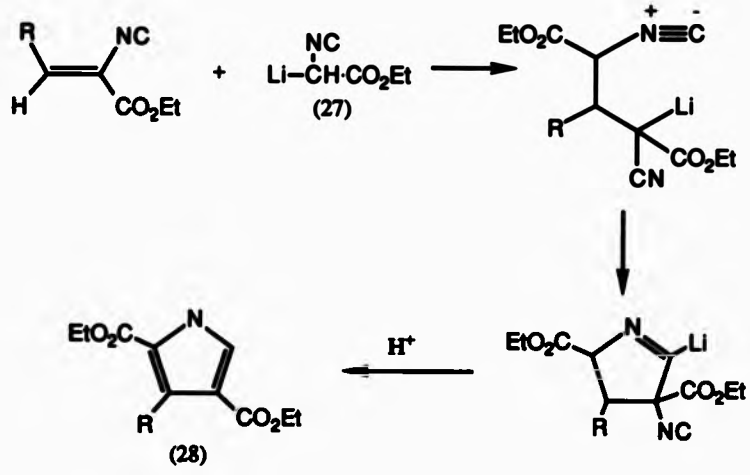
SCHEME 17



R= Me, Me_3Si, CO_2Et, COPh etc.

The isocyanoacrylates (26, R'= CO_2Et) formed above are subject to further nucleophilic attack by carbanions[42]. Michael addition of the anion of isocyanoacetic ester (27) to this results in a convenient synthesis of pyrroles (28) (scheme 18).

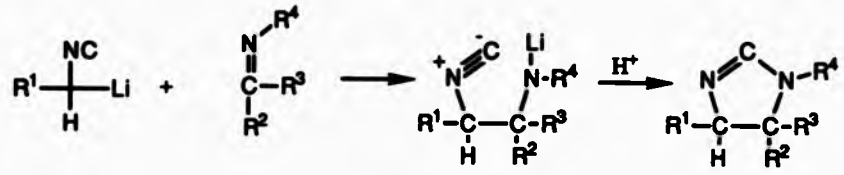
SCHEME 18



Isocyanoacrylates also undergo addition of Grignard reagents and malonic ester carbanions.

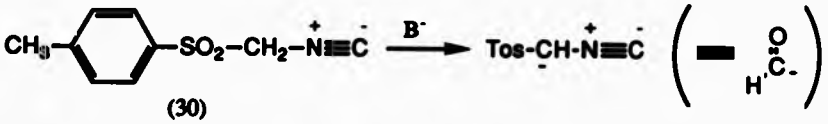
α-Metallated isonitriles also react with imines to afford an efficient synthesis of imidazolines (29) (scheme 19)[43].

SCHEME 19



(29)

Perhaps the most widely-used isonitrile in this type of reaction is tosylmethylisonitrile (TOSMIC) (30).

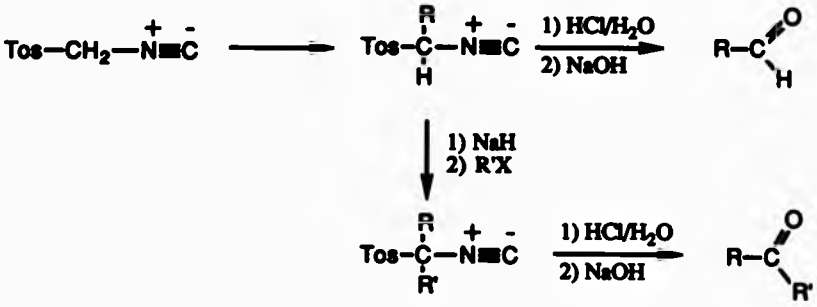


(30)

TOSMIC is in essence a masked formaldehyde, and the two electron-withdrawing groups greatly stabilise the anion formed by proton abstraction. An *umpolung* of carbonyl reactivity is thus achieved, forming what is essentially an acyl anion equivalent.

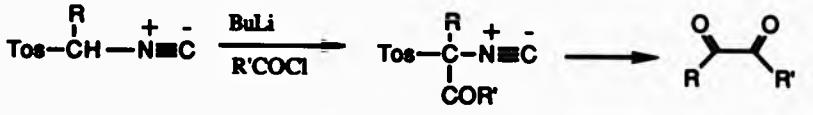
TOSMIC is thus readily alkylated to form carbonyl compounds in good yield (scheme 20)[44].

SCHEME 20



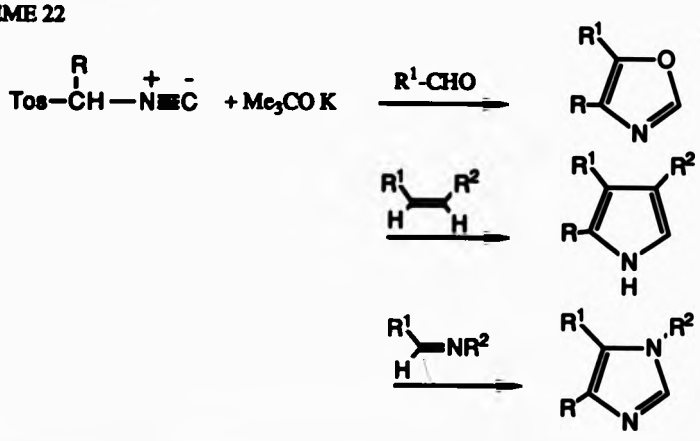
Similarly, anions derived from substituted TOSMIC can be acylated in good yield by acid chlorides to form 1,2-dicarbonyl compounds (scheme 21)[45].

SCHEME 21



The ease of elimination of the tosyl group from the initial adduct of TOSMIC with double bonds makes this reagent particularly useful for the synthesis of heterocycles such as isoxazoles, pyrroles and imidazoles (scheme 22)[46].

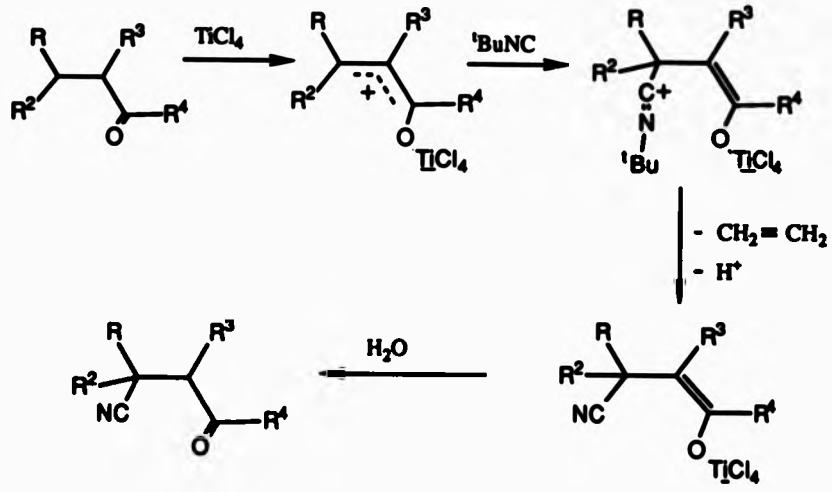
SCHEME 22



Nucleophilic reactions of isonitriles.

The negative charge on the isonitrile carbon relative to nitrogen implies that this carbon should act as a nucleophile. Isonitriles in general are, however, only weak nucleophiles, and will only attack suitably activated electrophilic centres. For example, activation of α,β-unsaturated ketones by a Lewis acid such as $TiCl_4$ renders them liable to nucleophilic attack by t-butylisonitrile (scheme 23)[47].

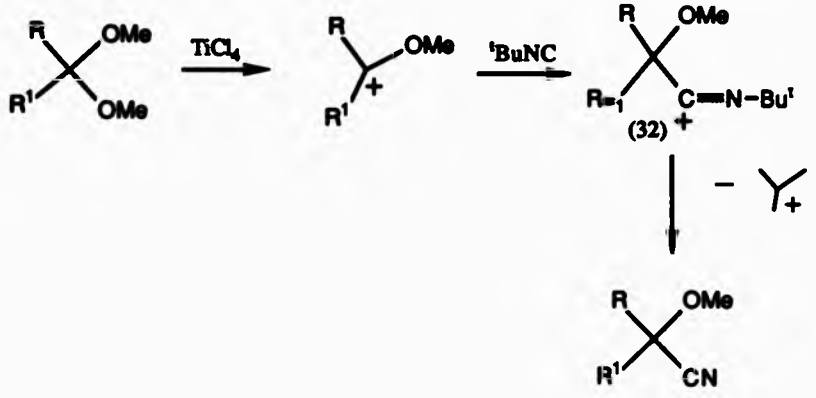
SCHEME 23



This reaction, a net addition of HCN across the double bond, yields β-cyanoketones in high yield.

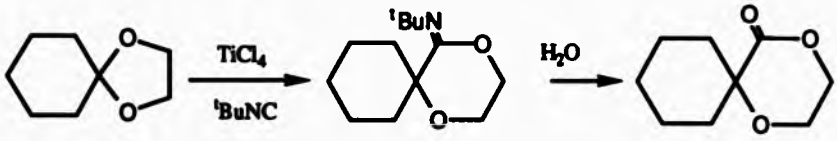
Under similar conditions, t-butylisonitrile reacts with acetals to effect the net substitution of one alkoxy group by cyanide (scheme 24)[48].

SCHEME 24



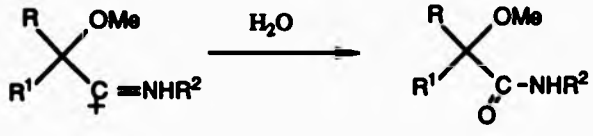
This reaction has been used to good effect in the preparation of spirolactones from ethylene acetals (scheme 25).

SCHEME 25



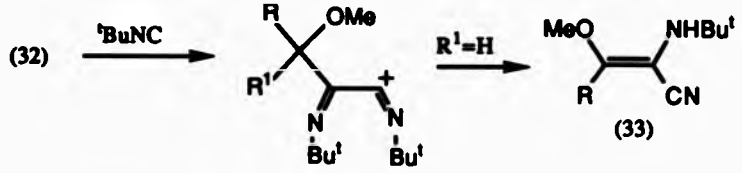
If the isonitrile used is primary or secondary, the imidoyl intermediate is hydrolysed to form the α-alkoxycarboxamide (scheme 26).

SCHEME 26



The positively-charged carbon in (32) is highly electrophilic, and Pelissier et al [49] have reported the nucleophilic addition of a second molecule of isonitrile to this intermediate, to form novel β-alkoxy-cyanoenamines (33) (scheme 27).

SCHEME 27

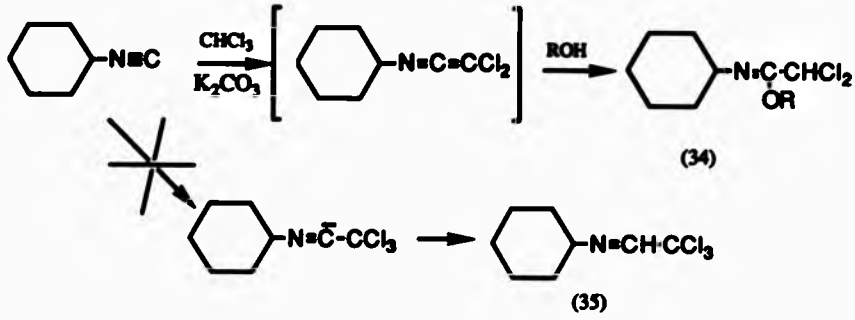


Carbene Additions

By virtue of their formally divalent nature, isonitriles readily undergo addition to other compounds of divalent carbon, namely carbenes.

Although α-addition of an electrophilic species XY to an isonitrile can be considered as insertion of the isonitrile carbon into the X-Y bond, the first conclusive evidence of an isonitrile behaving as a carbene was provided by the reaction of isonitriles with dichlorocarbene. Halleux[50] observed that cyclohexylisonitrile reacted with chloroform in the presence of anhydrous potassium carbonate to form N-cyclohexyldichloro-imidate (34) (scheme 28).

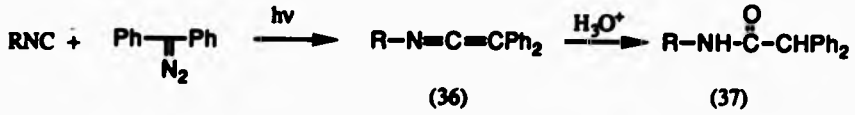
SCHEME 28



The observation that no trichloroethylidenecyclohexylamine (35) was formed demonstrates that trichloromethyl carbanion is not involved in the reaction.

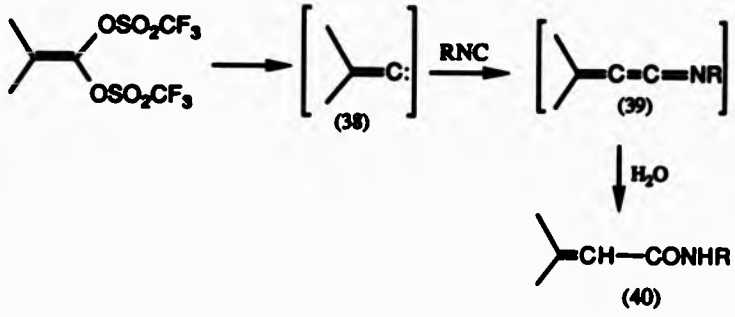
Isonitriles add in similar fashion to carbenes derived from diazoalkanes[51-53]. For example, photolysis of diphenyldiazomethane in the presence of isonitriles yields keteneimines (36) which are then hydrolysed to amides (37) (scheme 29)[51,52].

SCHEME 29



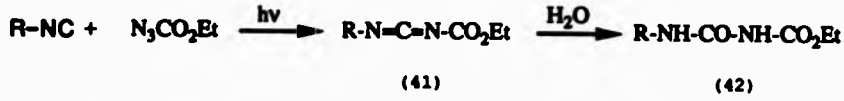
Isonitriles react in analogous fashion with alkylidenecarbenes (38) to form N-substituted acrylamides (40) *via* the unusual alkadienylidene-amines (39) (scheme 30)[54].

SCHEME 30



In a similar way, isonitriles add to nitrenes to form carbodiimides (41), which undergo hydrolysis to ureas (42) (scheme 31)[55].

SCHEME 31



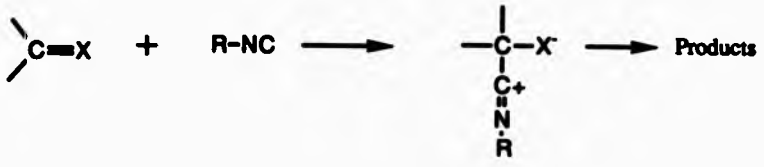
Cycloaddition Reactions

Isonitriles, again by virtue of their carbenoid nature, are capable of undergoing cycloaddition reactions with most unsaturated systems to form three-, four- and five-membered rings. These reactions are of enormous synthetic potential, despite the often bewildering array of products observed with superficially similar substrates.

The reactions of isonitriles with unsaturated systems occur in a stepwise manner, with initial formation of a zwitterionic intermediate (43). The

subsequent fate of this intermediate is dependent on the nature of both the unsaturated compound and the isonitrile (scheme 32).

SCHEME 32

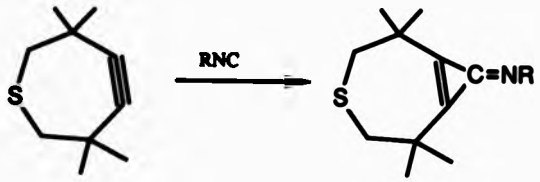


(43)

3-Membered Rings

Direct [1+2] cycloadditions of isonitriles to olefins to form cyclopropanes has not been reported. Reaction between electron-rich alkynes and isonitriles does, however, occur to form cyclopropeneimines. For example, the strained cyclic alkyne 3,3,6,6-tetramethyl-1-thia-4-cycloheptyne (44) reacts slowly with a variety of isonitriles to form the adducts (45) (scheme 33)[56].

SCHEME 33



(44) (45)

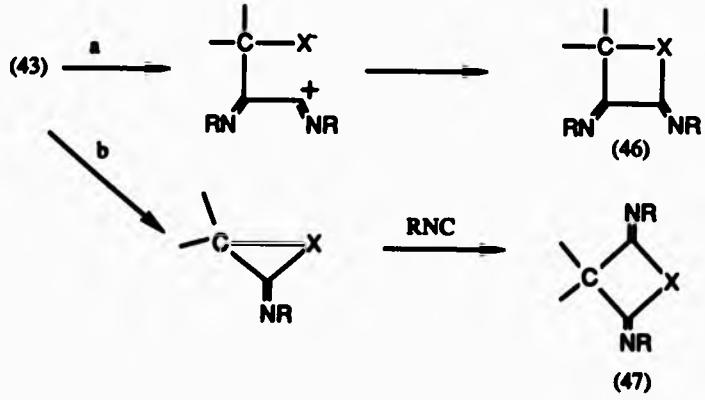
4-Membered Rings

A plethora of four-membered ring compounds have been prepared by cycloaddition reactions of isonitriles. This subject has recently been extensively reviewed[57], and only a broad outline will be given here.

[1+1+2] Cycloadditions

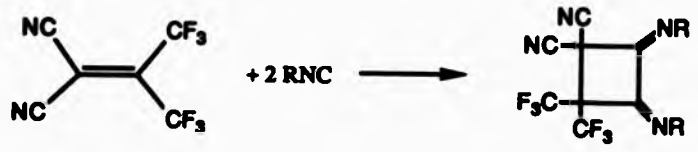
The intermediate (43) formed by initial attack of one isonitrile on a double bond is subject to attack by a further molecule of isonitrile to the electrophilic carbon (path a), or by cyclisation and insertion into the C-X bond (path b) (scheme 34).

SCHEME 34



Path a is by far the most common. When X is carbon, reaction occurs only when the olefin is heavily substituted with electron-withdrawing groups, eg (scheme 35).

SCHEME 35



The equivalent reaction with acetylenes is unknown. Aryl-substituted acetylenes will, however, react with transition-metal complexed aryl isonitriles to form 3,4-bis(arylamino)cyclobutenes (48) (scheme 36).

SCHEME 36

Alkyl isonitriles undergo [1+1+2] cycloaddition with symmetrically-substituted allenes to produce exomethylenecyclobutanes. Keteneimines are, in general, inert, as demonstrated by the many keteneimine syntheses from isonitriles.

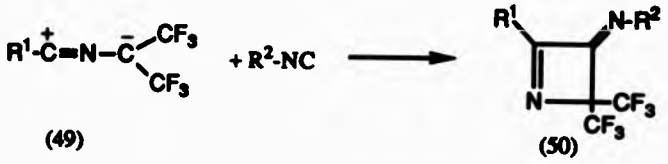
Under Lewis- or peroxy-acid catalysis, a number of isonitriles react with carbonyl compounds to form 2,3-bis(alkylamino)oxetanes (46,X=O), frequently in excellent yield. Similarly, azetidines (46,X= N-Ph-NO_2-p) have been formed by reaction of isonitriles with the condensation products of carbonyl compounds with p-nitroaniline.

[1+3] Cycloadditions

Isonitriles react with a number of 1,3-dipoles by [1+3] cycloaddition.

For example, nitrile ylids (eg 49) add isonitrile to form 3-iminoazetines (50) (scheme 37).

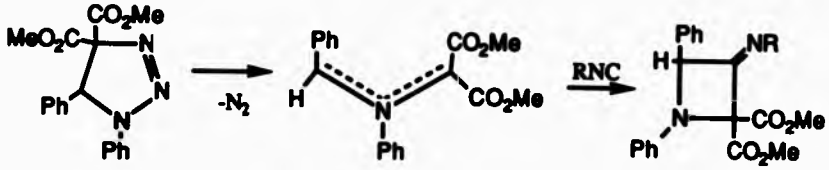
SCHEME 37



(49) (50)

Azomethine ylids (51), generated by thermolysis of triazolines or aziridines, cyclise with isonitriles to form similar adducts (scheme 38).

SCHEME 38



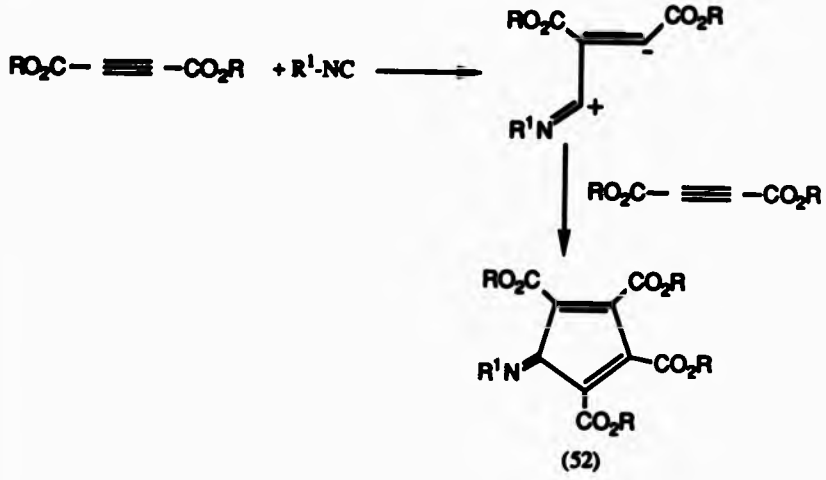
(51)

5-Membered Rings

[1+2+2] Cycloadditions

Alkynes bearing electron-withdrawing groups react at the nucleophilic centre of the initial adduct (43) to form iminocyclopentenes (52)[58] (scheme 39).

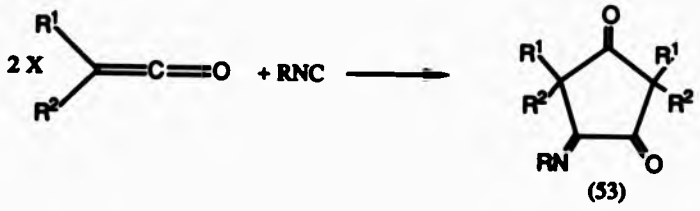
SCHEME 39



(52)

Ketenes react in exactly analogous manner, with cycloaddition across the carbon-carbon double bond to form 1-imino-3,4-cyclopentanediones (53) (scheme 40).

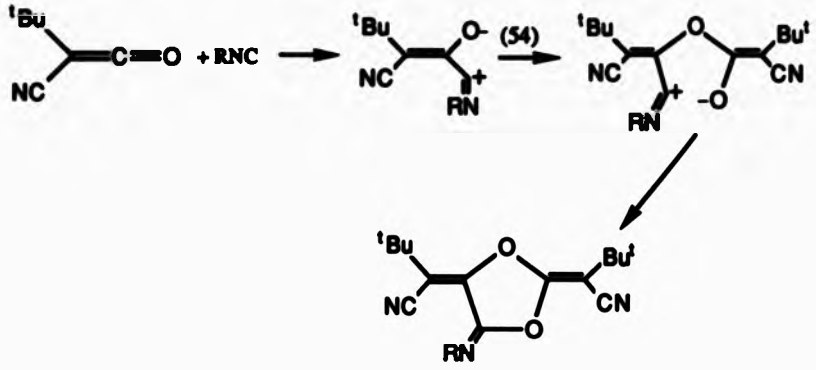
SCHEME 40



(53)

However, in the case of t-butylcyanoketene (54), addition occurs across the carbon-oxygen double bond (scheme 41).

SCHEME 41

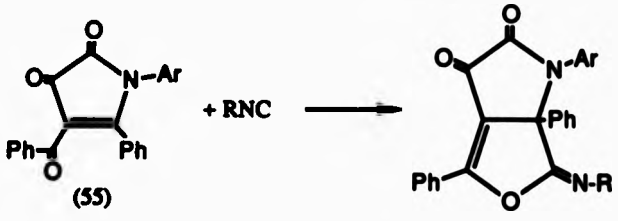


The most likely explanation for this anomalous cycloaddition is that steric congestion by the bulky t-butyl group prevents "normal" addition.

[1+4] Cycloaddition

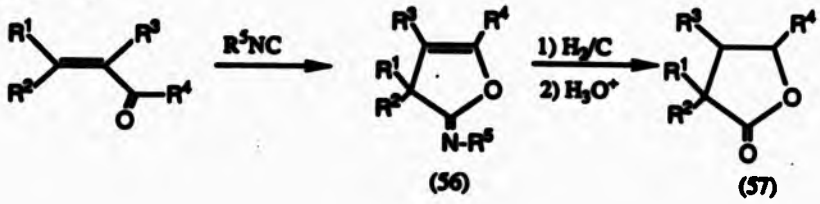
Activated α,β-unsaturated carbonyl compounds, such as (55) react with isonitriles by 1,4-addition (scheme 42)[61,62].

SCHEME 42



It was subsequently observed[62] that a wide variety of enones, provided they can adopt a cisoid conformation, will react in the same way to form iminolactones (56) in good yield (scheme 43).

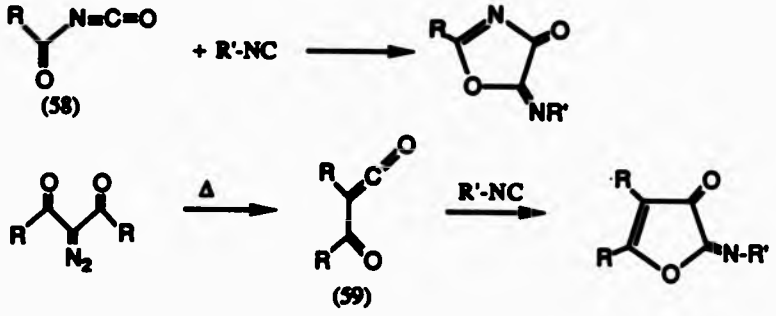
SCHEME 43



Hydrogenation and hydrolysis of these products affords an efficient route to γ-lactones (57).

Similar 1,4-additions occur with acyl isocyanates (58)[64] and acyl ketenes (59)[56] (scheme 44).

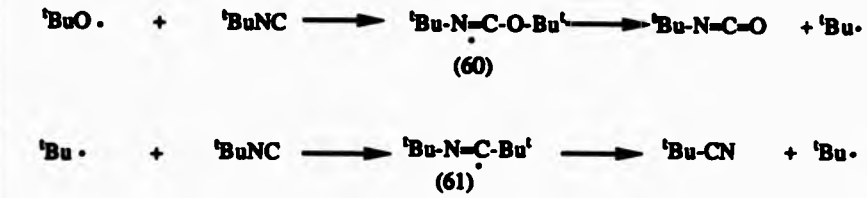
SCHEME 44



Radical Reactions of Isonitriles

Thermolysis of di-t-butylperoxide in the presence of t-butylisonitrile leads to the formation of both t-butylisocyanate and pivalonitrile[66], presumably via the intermediate imidoyl radicals (60) and (61) (scheme 45).

SCHEME 45

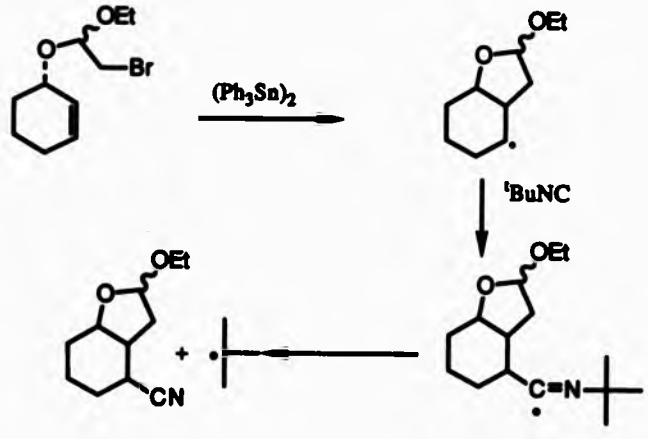


(cf scheme 8)

The fact that the isonitrile-nitrile rearrangement is radical in nature in this case is demonstrated by the introduction of benzoyl peroxide, in which instance benzonitrile is formed[67]. That the intermediate is an imidoyl radical in each case has been shown by e.s.r. spectroscopy[68].

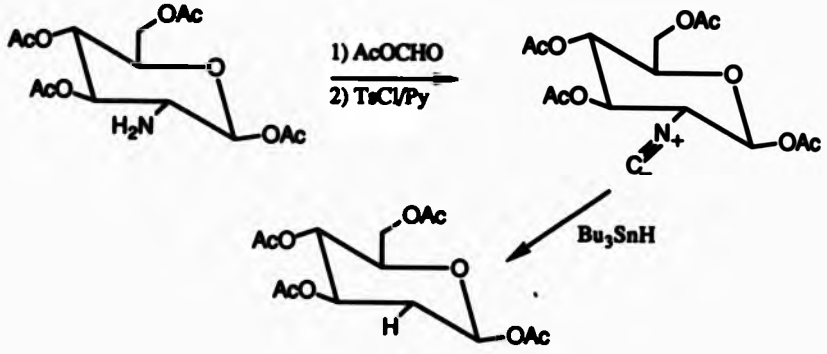
The facility with which isonitriles undergo addition of free radicals has been exploited in the synthesis of cyclic nitriles (scheme 46)[69].

SCHEME 46



Isonitriles undergo radical reduction to hydrides with tri-n-butyl-stannane[70]. This reaction has been applied to the deamination of amino-glycosides, in high yield and under mild conditions[70,71] (scheme 47).

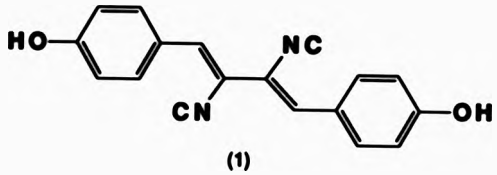
SCHEME 47



PART TWO

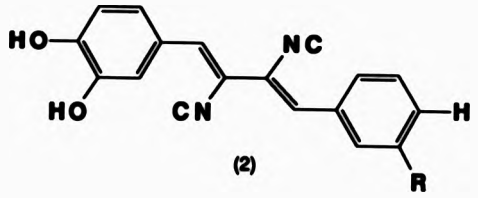
NATURALLY-OCCURRING ISONITRILES

The isonitrile group is rare in naturally-occurring compounds, and until the discovery of xanthocillin X (1), no examples of this unusual class were known. Xanthocillin X, a metabolite of *Penicillium Notatum* Westling, was observed to have antibiotic properties by Rothe[72] in 1950. It was not until 1957 however that the structure was shown to be (1), as a result of work by Hagedorn and Tonjes[73].



(1)

For more than a decade, this compound remained the sole example of a naturally-occuring isontrile. In 1972, however, two more closely-related isonitrile metabolites of the same organism were isolated and identified as xanthocillins Y_1 (2, R=H) and Y_2 (2, R=OH)[74].

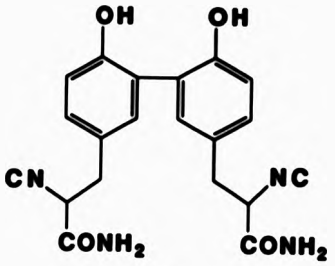


(2)

It was not until the following year that another source of naturally-occurring isonitriles was discovered. In this case the source was a marine sponge. The sponges (phylum *Porifera*) have since proved a rich source of isonitriles.

Terrestrial sources of isonitriles have proved few and far between. With

the exception of the xanthocillins, only two isonitriles have been isolated from bacterial cultures. These are the isomeric hazimycins I (R,R) and II (R,S) (3)[75].



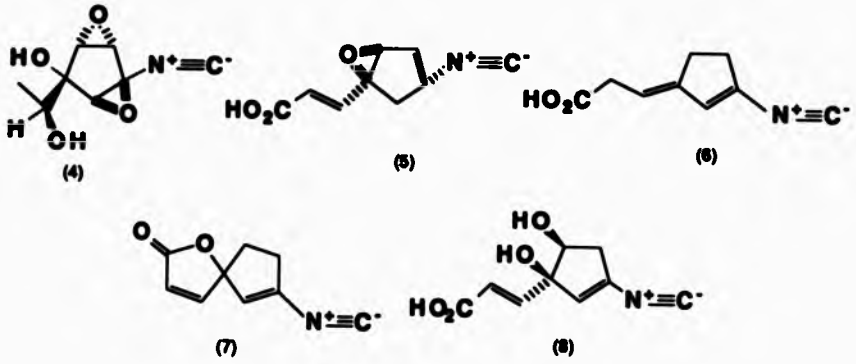
(3)

The hazimycins are metabolites of the bacterium *Micromonospora echinospora*, and in common with the xanthocillins exhibit broad-spectrum antibacterial and antifungal activity.

Only one other terrestrial organism has been shown to biosynthesise compounds containing the isonitrile group, the fungus *Trichoderma hamatum*. Interestingly, this fungus has been reported[76] as an important component of the microflora in pastures where poor ruminant growth is a problem, in particular the condition known colloquially as ovine "ill thrift". A possible cause of this problem is the ingestion of a compound or compounds toxic to the rumenal microflora, and the *Trichoderma* isonitriles are prime suspects.

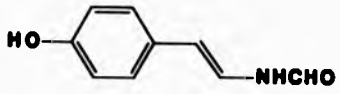
The first active metabolite to be isolated and identified from this fungus was trichoviridine (4)[77,78]. Subsequently, four more isonitrile metabolites (5-8) were isolated[79,80]. All have a number of structural

features in common. They are all 1-isocyanocyclopentene derivatives, and as such are, with the exception of the xanthocillins, the only known naturally-occurring vinyl isonitriles. These four vinyl isonitriles also contain a C_3-subunit at position 3 on the cyclopentene ring, and are certainly of common biosynthetic origin.



All the *Trichoderma* isonitriles have considerable antibiotic properties.

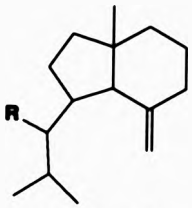
These few compounds (1-8) constitute the complete list of naturally-occurring isonitriles yet isolated from terrestrial sources. However, mention should be made of the naturally-occurring formamide tuberin (9), isolated from cultures of the bacterium *Streptomyces amakusaensis*[81]. Although not an isonitrile, it is formally derived from one, and it is possible that it is indeed derived from an isonitrile in nature. Tuberin is weakly active against mycobacteria, but has no other antibiotic activity.



(9)

All other naturally-occurring isonitriles have been isolated from marine sources, specifically from marine sponges (phylum *Porifera*). These primitive multicellular organisms have proved a rich source of unusual compounds with pharmacological potential, and this is the case with isonitriles.

In 1973, Fattorusso *et al*[82] isolated from the sponge *Axinella cannabina* a sesquiterpene with a strong infra-red absorption at 2130 cm^{-1}, characteristic of an isonitrile group. Further analysis by spectroscopic and chemical means enabled this compound, axisonitrile I, to be assigned the structure (10). Also isolated from this sponge was the closely related axisothiocyanate I (11), and subsequently the formamide axamide I (12)[83].

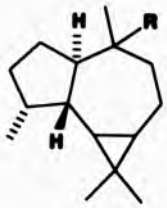


(10 R = -NC)

(11 R = -NCS)

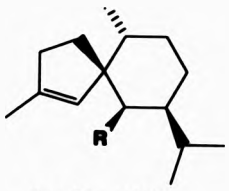
(12 R = -NHCHO)

The following year a second isonitrile component of *A. cannabina* was reported[84]. This compound, axisonitrile II (13) is based on the aromadendrane skeleton, although the stereochemistry at C_{10} has not been determined. As in the previous case, the related axisothiocyanate II (14) and axamide II (15) were also isolated[83].



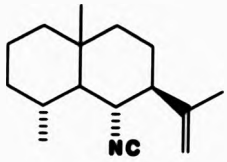
(13 R = -NC)
(14 R = -NCS)
(15 R = -NHCHO)

Subsequently, a third trio of sesquiterpenoids were obtained from this sponge[85] which have been assigned the structures (16-18) and named, in accordance with the previous examples, axisonitrile III etc.



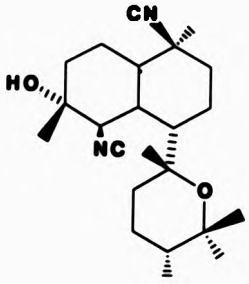
(16 R = -NC)
(17 R = -NCS)
(18 R = -NHCHO)

Another sponge of the same order, *Acanthella acuta*, has yielded a variety of isonitriles. Initial extraction of the fresh sponge yielded three principal fractions with strong absorbances at 2140 cm^{-1} in the infra-red. The major fraction was shown by spectroscopic and chemical means to be the sesquiterpenoid isonitrile acanthellin I (19)[89]. This compound was observed to have antibacterial activity.



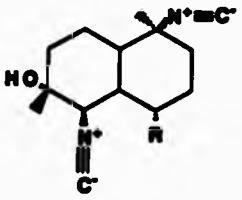
(19)

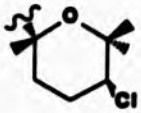
A second metabolite of this sponge was isolated and identified as the unusual highly functionalised diterpenoid isonitrile kalihinol A (20)[87].

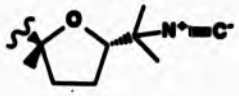


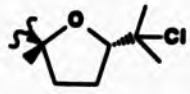
(20)

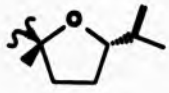
This compound, in common with the other isonitriles, exhibits *in vitro* antibacterial activity, and this prompted the isolation of a further four similarly highly functionalised diterpenoid kalihinols (21-24), including the unique triisonitrile kalihinol F (22). The molecular structure of (22), as determined by X-ray crystallography, is such that all three isonitrile groups are located on the same face of the molecule. The relationship between (24) (isoprenyl), (23) (chloroisoprenyl) and (22) (isocyanoisopropyl) may indicate a biosynthetic sequence[87], although this has still to be investigated. (21-24) show similar biological activity to (20).



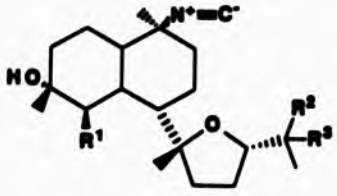
(21) R= 

(22) R= 

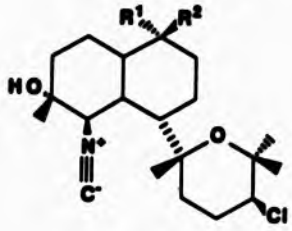
(23) R= 

(24) R= 

A further five kalihinols have recently been isolated from *Acanthella* (25-29)[87a].



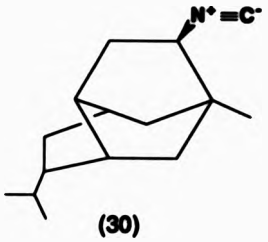
	R^1	R^2	R^3
(25)	Cl	Me	NC
(26)	NC	Me	NCS



	R^1	R^2
(27)	NCS	Me
(28)	=CH_2	
(29)	NC	Me

The nudibranch, or sea-slug, *Phyllidia varicosa* Lamark 1801 secretes mucus containing a substance characterised by its powerful and unpleasant

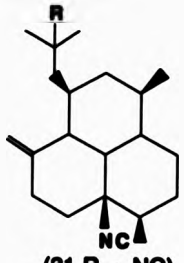
odour and its toxicity to fish and crustaceans[88]. The active ingredient was identified as a tricyclic sesquiterpenoid isonitrile, 9-isocyano-pupukeanane (30)[89].



(30)

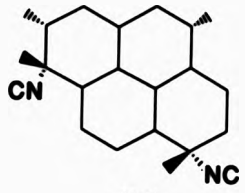
The unusual source of this isonitrile was explained when *P. varicosa* was observed feeding on a sponge, *Hymeniacidon* sp. Extraction of this sponge led to the isolation of (30), identical in all respects to that isolated from the mollusc. Although this relationship has obvious advantages to the mollusc, the benefits to the sponge are less clear.

A further two isonitriles, both diterpenoids, have been obtained from this sponge[90]. These two related compounds (31) and (32) display *in vitro* activity against a variety of bacteria.



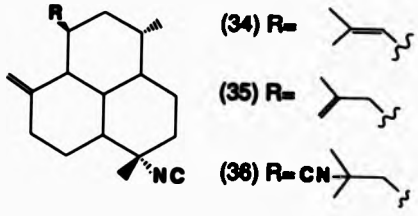
(31 R = -NC)
(32 R = -NHCHO)

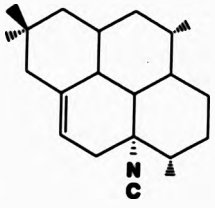
(31) and (32) bear a close structural resemblance to the tetracyclic diisonitrile diisocyanoadociane (33) isolated from an unrelated sponge of the genus *Amphimedon* (ex *Adocia*)[91].



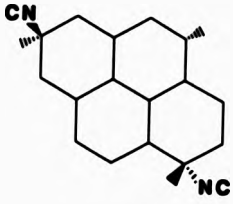
(33)

This sponge has proved a rich source of terpenoid isonitriles, a further six examples having been identified (34-39)[92]. The presence of (36) exemplifies the close similarity between these and the *Hymeniacidon* isonitriles.

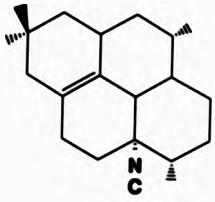




(37)



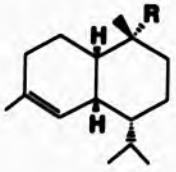
(38)



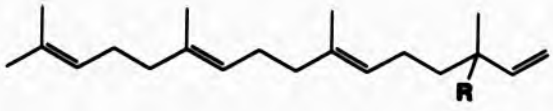
(39)

Compound (33) and the unseparated mixture containing (34-39) exhibited marked *in vitro* antibacterial activity, but *in vivo* were characterised only by their toxicity to the host.

The coexistence of the isonitrile, isothiocyanate and formamide observed in *Axinella* has also been noted in *Halichondria* sp.[93] The first isonitrile isolated from this sponge was the bicyclic sesquiterpenoid (40). This sponge was also found to biosynthesise a diterpenoid isonitrile (43), which is unique in that it is the sole known example of a naturally occurring acyclic isonitrile.



(40, R = -NC)
(41, R = -NCS)
(42, R = -NHCHO)

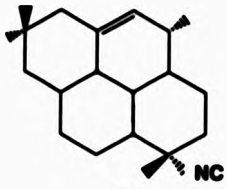


(43, R = -NC)
(44, R = -NCS)
(45, R = -NHCHO)

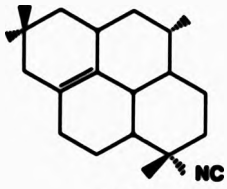
Both of these isonitrile/isothiocyanate/formamide triads were also accompanied by the unfunctionalised hydrocarbons. The sponge extract, and by implication the isonitrile metabolites, once again show antibacterial activity.

More recently[94] this sponge has yielded four more terpenoid isonitriles, three of which were previously unreported (46-48). (46) and (47) are unique among the diterpenoid isonitriles in that they have *cis*-fused ring junctions. The fourth isonitrile had identical spectroscopic properties

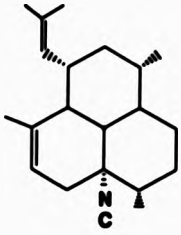
to that assigned structure (39) isolated from *Amphimedon*. However, in this case crystals were obtained and crystallographic analysis showed the structure to be (49).



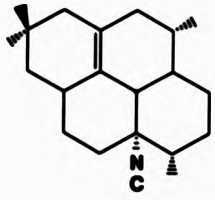
(46)



(47)

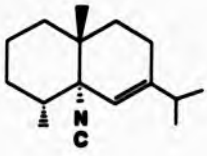


(48)



(49)

The most recently isolated isonitrile of natural origin is stylotelline (50)[95], discovered in extracts of a sponge, *Stylotella* sp., closely related to *Hymeniacidon*.



(50)

The isonitriles listed above are the only examples reported in the literature to date (1988). It has been reported, however, that an (unidentified) isonitrile (or isonitriles) contributes to the disagreeable odour of foetid tremolite skarn, or more aptly stinktstone, found near Posio, Finland[96].

The fact that all the naturally occurring isonitriles which have been screened show at least some degree of biological activity indicates that this interesting class of compounds has great pharmacological potential.

Biosynthetic Origin of Isonitriles

The interesting and puzzling question of the biosynthetic origin of the isonitrile group has received little attention, perhaps due in part to the relative scarcity of these compounds.

From the coexistence of the related formamides with a number of these isonitriles[83,85,90,93] it has been implied that these formamides are the biosynthetic precursors of the isonitriles. However, injection of labelled axamide I (12) into *A. cannabina* did not yield any labelled axisonitrile I (10) after 5 days[97].

Similar labelling experiments with *Hymeniacidon* sp.[98] also suggested that the isonitriles were not derived from formamides. This research also indicated that formate ion was not incorporated into the isonitrile group. It was, however, unequivocally demonstrated that the isonitrile group was the biosynthetic precursor of both formamide and isothiocyanate, in this species at least.

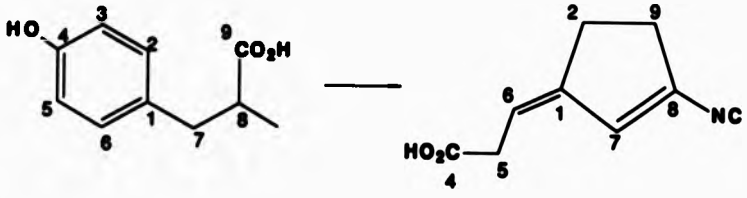
However, the question of the origin of the isonitrile carbon remained. Labelling studies in an *Amphimedon* sponge have shown that the isonitrile groups in diisocyanoadociane (33) originate from cyanide ion[99]. Incubation of the sponge with Na ^{14}CN showed incorporation of ^{14}C equally into both isonitrile groups. Under the same conditions, no [2-^{14}C]-

acetate was incorporated.

These results are in contrast to those obtained by Herbert and co-workers, studying the biosynthesis of xanthocillin monomethyl ether[100]. In this compound it was observed that although ^{14}CN was well incorporated, only the O-methyl group was labelled. However, [^{15}N]-tyrosine was incorporated into the molecule, a result in agreement with earlier work on the biosynthesis of xanthocillin X (1)[101]. In this study, it was observed that only one of the isonitrile nitrogen atoms was derived directly from tyrosine. This confirmed that the molecule is not derived directly from coupling of two C_6-C_2-N units derived from tyrosine. It was also observed that the presence of p-hydroxyphenyl-pyruvic acid significantly increased the rate of incorporation of [^{15}N]-tyrosine, indicating that the keto-acid was also involved.

Incorporation studies by Baldwin and co-workers[102] have shown that the carbon skeleton of metabolites of *Trichoderma* (in particular (6)) is also derived from tyrosine. Even more surprisingly, perhaps, the cyclopentene ring is derived from the tyrosine side-chain (scheme 1).

SCHEME 1



However, the fundamental question of the origin of the isonitrile carbon has yet to be answered. It is not unlikely that this carbon will prove to originate in the tetrahydrofolic acid pathway.

REFERENCES

1. A Gautier, Ann. Chem., 1867, 142, 289; *ibid*, 1868, 146, 119; *ibid*, 1869, 149, 29, 155; *ibid*, 1869, 151, 239.
2. A W Hoffmann, Compt. Rend., 1867, 65, 484; Ann. Chem., 1867, 144, 114; *ibid*, 1868, 146, 107.
3. I U Nef, Ann. Chem., 1895, 287, 265.
4. I Langmuir, J. Amer. Chem. Soc., 1919, 41, 1543.
5. H. Lindemann and L Wiegrebe, Chem. Ber., 1930, 63, 1650.
6. D L Hammick, R C A New, N V Sidgwick and L E Sutton, J. Chem. Soc., 1930, 1876.
7. A Dadieu, Chem. Ber., 1931, 64B, 358.
8. L O Brockway, J. Amer. Chem. Soc., 1936, 58, 2516.
9. N V Sidgwick, "The Organic Chemistry of Nitrogen" 3rd ed., p 460, Clarendon Press, Oxford, 1966.
10. I Ugi and R Meyr, Chem. Ber., 1960, 93, 239.
11. R W Stephany, M J R De Bie and W Drenth, Org. Magn. Reson., 1974, 6, 45.
12. G C Levy and G L Nelson, "Carbon-13 Nuclear Magnetic Resonance for Chemists." p 129, John Wiley and Sons Inc., New York, 1972.
13. P Boullanger, D Marmet and G Descotes, Tetrahedron, 1979, 35, 163.
14. W R Hertler and E J Corey, J. Org. Chem., 1958, 23, 1221.
15. I Ugi, U Fetzer, U Eholzer, H Knupfer and K Offermann, Angew. Chem. Int. Ed., 1965, 4, 472.
16. H W Johnson and H Krutzsch, J. Org. Chem., 1967, 32, 1939.
17. I. Ugi and R Meyr, Chem. Ber., 1960, 93, 239.
18. G Skorna and I Ugi, Angew. Chem. Int. Ed., 1977, 16, 259.
19. E Efrati, I Feinstein, L Wacherle and A Goldman, J. Org. Chem., 1980, 45, 4059.

20. R. Obrecht, R Herman and I Ugi, Synthesis, 1985, 400.

21. G Giesemann, E Von Hinrichs and I Ugi, J. Chem. Res. (S), 1982, 79.

22. R Appel, R Kleinstuck and K D Ziehn, Angew. Chem., 1971, 83, 143.

23. J E Baldwin, J C Bottaro, P D Riordan and A E Derome, J. Chem. Soc., Chem. Commun., 1982, 942.

24. C Wentrup, U Stutz and H-J Wollweber, Angew. Chem. Int. Ed., 1978, 17, 688.

25. P G Gassman and T L Guggenheim, Org. Synth., 1986, 64, 39.

26. G Domschke, R Beckert and R Meyer, Synthesis, 1977, 275.

27. W P Fehlhammer, K Bartel, R Weinberger and U Plaia, Chem. Ber., 1985, 118, 2220.

28. W Weith, Chem. Ber., 1873, 6, 210.

29. J Casanova,Jr, N D Werner and R E Schuster, J. Org. Chem., 1966, 31, 3473.

30. S Yamada, M Shibasaki and S Terashima, J. Chem. Soc., Chem. Commun., 1971, 1008.

31. M Meir and C Ruchardt, Tetrahedron Lett., 1983, 24, 4671.

32. M Meir, B Mueller and C Ruchardt, J. Org. Chem., 1987, 52, 648.

33. M Meir and C Ruchardt, Tetrahedron Lett., 1984, 25, 3441.

34. J Gloede, J. Prakt. Chem., 1982, 324, 667.

35. P Hoffman, D Marquarding, H Kliimann and I Ugi in "The Chemistry of the Cyano Group.",ed. Z. Rappaport, Interscience, New York, 1970.

36. I Ugi, Angew. Chem. Int. Ed., 1982, 21, 810.

37. G E Miznik, W H Morrison III and H M Walborsky, J. Org. Chem., 1974, 39, 600.

38. D Hoppe, Angew. Chem. Int. Ed., 1974, 13, 789.

39. U Schoellkopf, Pure Appl. Chem., 1979, 51, 1347.

40. U Schoellkopf, Angew. Chem. Int. Ed., 1977, 16, 339.

41. U Schoellkopf, D Stafforst and R Jentsch, Liebigs Ann. Chem., 1977, 1167.

42. U Schoellkopf and R Meyr, Liebigs Ann. Chem., 1977, 1174.

43. R Meyer, U Schoellkopf and P Boehm, Liebigs Ann. Chem., 1977, 1183.

44. O Possel and A M Van Leusen, Tetrahedron Lett., 1977, 4229.

45. D Van Leusen and A M Van Leusen, Tetrahedron Lett., 1977, 4233.

46. O Possel and A M Van Leusen, Heterocycles, 1977, 7, 77.

47. Y Ito, H Kato, H Imai and T Saegusa, J. Amer. Chem. Soc., 1982, 104, 6449.

48. Y Ito, H Imai, K Segoe and T Saegusa, Chem. Lett., 1984, 937.

49. H Pelissier, A Meou and G Gil, Tetrahedron Lett., 1986, 27, 2979.

50. A Halleux, Angew. Chem. Int. Ed., 1964, 3, 752.

51. J Boyer and W Beverung, J. Chem. Soc., Chem. Commun., 1978, 1057.

52. J A Green and L A Singer, Tetrahedron Lett., 1969, 1377.

53. E Ciganek, J. Org. Chem., 1970, 35, 862.

54. P J Stang and J A Bjork, J. Chem. Soc., Chem. Commun., 1978, 1057.

55. E Kozlowska-Gramsz and G Descotes, Tetrahedron Lett., 1982, 23, 1585.

56. A Krebs and H Kimling, Angew. Chem. Int. Ed., 1971, 10, 409.

57. D Moderhack, Synthesis, 1985, 1083.

58. E Winterfeldt, Angew. Chem. Int. Ed., 1966, 5, 741.

59. I Ugi and K Rosendahl, Chem. Ber., 1961, 94, 2233.

60. H W Moore and C-C Yu, J. Org. Chem., 1981, 46, 4935.

61. G Kollanz, W Ott, E Ziegler, K Peters, H G Von Schnering and H Quast, Liebigs Ann. Chem., 1980, 1801.

62. G Kollanz, W Ott, E Ziegler, E-M Peters, K Peters, H G Von Schnering, V Formacek and H Quast, Liebigs Ann. Chem., 1984, 1137.

63. Y Ito, H Kato and T Saegusa, J. Org. Chem., 1982, 47, 741.

64. R Meidlein, Chem. Ber., 1964, 97, 3476.

65. L Capuano and T Tammer, Chem. Ber., 1981, 114, 456.

66. L A Singer and S S Kim, Tetrahedron Lett., 1974, 861.

67. S S Kim, Tetrahedron Lett., 1977, 2741.

68. P M Blum and B P Roberts, J. Chem. Soc., Perkin Trans II, 1978, 1313.

69. G Stork and P M Sher, J. Amer. Chem. Soc., 1983, 105, 6765.

70. D H R Barton, G Bringmann, G Lamotte, R S Hay-Motherwell and W B Motherwell, Tetrahedron Lett., 1979, 2291.

71. Z J Witzak, Tetrahedron Lett., 1986, 27, 155.

72. W Rothe, Pharmazie, 1950, 5, 190.

73. I Hagedorn and H Tonjes, Pharmazie, 1957, 12, 567.

74. H Achenbach, H Strittmatter and W Kohl, Chem. Ber., 1972, 105, 3061.

75. J A Waitz, J A Marquez, M G Patel and A C Horan, J. Antibiotics, 1983, 36, 1101.

76. D Brewer, A Taylor and M M Hoehn, J. Agric. Soc. (Camb.), 1972, 78, 257.

77. M Nobuhara, H Tazima, K Shudo, A Atai, T Akamoto and Y Itaka, Chem. Pharm. Bull., 1976, 24, 823.

78. W D Ollis, M Ray, W O Gottfriedson, N Rastrup-Anderson, S Vangedahl and T J King, Tetrahedron, 1980, 36, 515.

79. D Brewer, E J Gabe, A W Hanson, A Taylor, J W Keeping, W Thaller and B C Das, J. Chem. Soc., Chem. Commun., U1979, 1061.

80. J E Baldwin, R M Adlington, J Chondrogianni, M S Edenborough, J W Keeping and C B Ziegler, J. Chem. Soc., Chem. Commun., 1985, 816.

81. K Okuma, K Anzai and S Suzuki, J. Antibiotics (Japan) Ser. A, 1962, 15, 115.

82. F Cafiera, E Fattorusso, S Magno, C Santacroce and D Sica, Tetrahedron, 1973, 29, 4259.

83. E Fattorusso, S Magno, L Mayol, C Santacroce and D Sica, Tetrahedron, 1975, 31, 269.

84. E Fattorusso, S Magno, C Santacroce and D Sica, Tetrahedron, 1974, 30, 3911.

85. B Di Blasio, E Fattorusso, S Magno, L Mayol, C Pedone, C Santacroce and D Sica, Tetrahedron, 1976, 32, 473.

86. L Minale, R Riccio and D Sodano, Tetrahedron, 1974, 30, 1341.

87. A Patra, C W J Chang, P J Scheuer, G D Van Duyne, G K Matsumoto and J Clardy, J. Amer. Chem. Soc., 1987, 109, 6119.

88. R E Johannes, Veliger, 1963, 5, 104.

89. B J Burreson, P J Scheuer, J Finer and J Clardy, J. Amer. Chem. Soc., 1975, 97, 4763.

90. S J Wratten, D J Faulkner, K Hirotsu and J Clardy, Tetrahedron Lett., 1978, 19, 4345.

91. J T Barker, R J Wells, W E Oberhansli and G B Hawes, J. Amer. Chem. Soc., 1976, 98, 4010.

92. R Kazlauskas, P J Murphy, R J Wells and J F Blount, Tetrahedron Lett., 1980, 21, 315.

93. B J Burreson, C Christopherson and P J Scheuer, Tetrahedron, 1975, 31, 2015.

94. T F Molinski, D J Faulkner, G D Van Dutne and J Clardy, J. Org. Chem., 1987, 52, 3334.

95. M Pais, C Fontaine, D Laurent, S La Barre and E Giuttet, Tetrahedron Lett., 1987, 28, 1409.

96. R Piispanen and P Laehdesmaeki, Geol. Foehran. Stockholm Foerh., 1985, 107, 161.

97. A Iengo, C Santacroce and G Sodano, Experientia, 1979, 35, 10.

98. M R Hagadore and P J Scheuer, J. Amer. Chem. Soc., 1984, 106, 2447.

99. M J Garson, J. Chem. Soc., Chem. Commun., 1986, 35.

100. K M Cable, R B Herbert and J Mann, Tetrahedron Lett., 1987, 28, 3159.

101. H Achenbach and F Koenig, Chem. Ber., 1972, 105, 784.

102. J E Baldwin, A E Derome, L D Field, P T Gallagher, A E Taha, V Thaller, D Brewer and A Taylor, J. Chem. Soc., Chem. Commun., 1981, 1227.

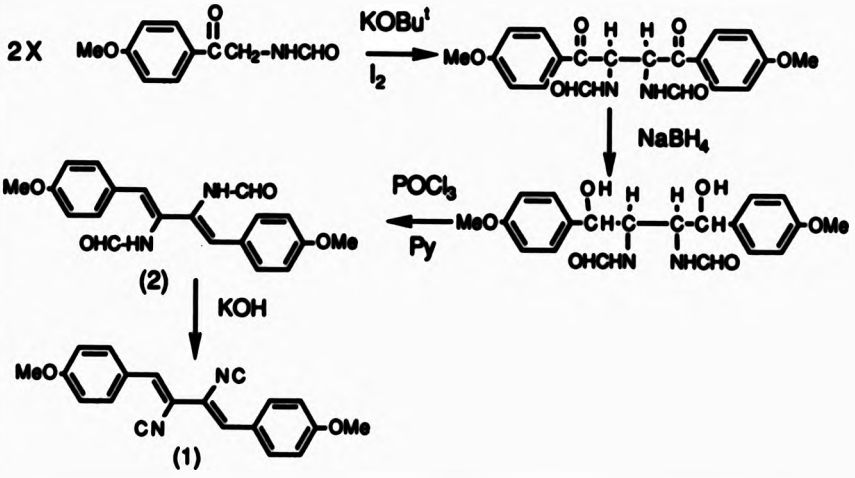
PART THREE

SOME APPROACHES TOWARDS THE SYNTHESIS OF VINYL ISONITRILES

As described in part two, all the naturally occurring vinyl isonitriles thus far discovered exhibit some degree of antibiotic activity. In the light of this, and in particular given the apparent relationship between the antibiotic activity of the *Trichoderma* metabolites and a relatively serious veterinary condition, considerable interest might be expected in the synthesis of these unusual compounds. Surprisingly, comparatively few attempts have been made towards this end. It was apparent therefore that the development of a general strategy for the synthesis of vinyl isonitriles would go some way towards rectifying this deficiency in the chemical literature.

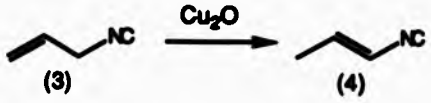
The synthesis of xanthocillin dimethyl ether (1) was achieved by Hagedorn and Eholzer soon after its discovery[1]. This synthesis (scheme 1), although elegant, is extremely inefficient. The final step, involving two sequential double elimination reactions, proceeds in very poor yield (ca. 6%). This is almost certainly due to competing side-reactions in the final dehydration of the dihydroxydiisonitrile (2).

SCHEME 1



This approach is therefore far from ideal, and is unlikely to be suitable as a general strategy for the synthesis of other vinyl isonitriles. The ideal synthesis would be clean, efficient, should use readily available starting materials and reagents and must be applicable to the synthesis of a wide range of examples. Few, if any, of the methods so far published meet these criteria. The procedure of Schoellkopf and Schroeder, for example (part one, schemes 16 and 17) although useful in a number of cases, is not suitable for the synthesis of vinyl isonitriles in which the vinyl group bears 1,2-dialkyl substitution. This description fits all the naturally occurring examples.

The isomerisation of allyl isonitrile (3) to 1-propenyl isonitrile (4) catalysed by copper (I) oxide has been reported[2].

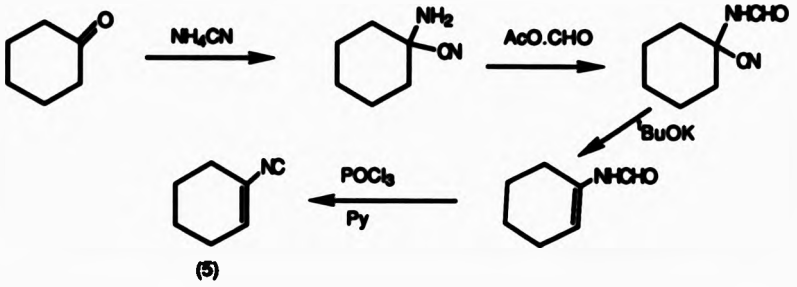


(3) (4)

The applicability of this isomerisation to substituted allylic isonitriles has not been investigated. In any case, this approach would result merely in replacing the problem of synthesising vinyl isonitriles with one of preparing the allylic isomer, which is unlikely to be any easier.

The synthesis of 1-cyclohexenyl isonitrile (5) (scheme 2) by Ugi and Rosendahl[3] is attractive in that it meets most of the criteria laid down above. The low overall yield of only some 30% from cyclohexanone may, however, limit its usefulness.

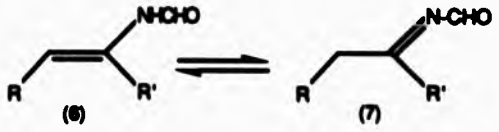
SCHEME 2



(5)

As few methods were available for the synthesis of vinyl isonitriles, and none appeared immediately suitable for the synthesis of xanthocillin in particular, it was deemed necessary to attempt to devise a new strategy.

As described in part one, isonitriles are in general most efficiently prepared by dehydration of the corresponding formamides. In order to perfect a general synthesis of vinyl isonitriles, it therefore follows that a reliable method of generating the precursor unsaturated formamides (6) was required.

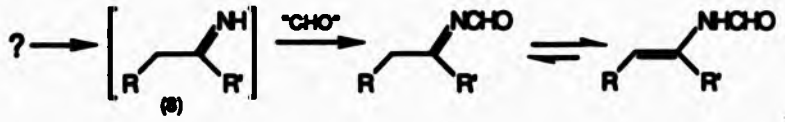


(6) (7)

As the formamide (6) is theoretically in equilibrium with the tautomeric N-formylimine (7), a possible route to (6) might lie in generating the imine (8) under conditions in which formylation can occur (scheme 3). This formylation must take place *in situ* immediately the imine has been formed, because of the instability of N-unsubstituted imines,

particularly to acid-catalysed hydrolysis.

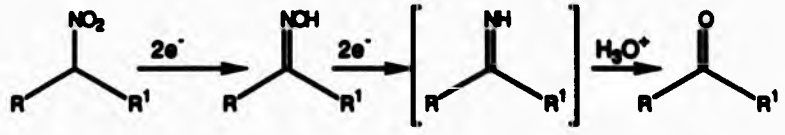
SCHEME 3



A method by which the imine might be generated from readily available starting materials was therefore required.

Secondary nitro compounds (9) are converted to ketones by titanium trichloride in aqueous acidic solution[4]. It is thought that this reaction proceeds by sequential reduction of the nitro compound to the oxime (10) and thence to the imine, which under the reaction conditions is rapidly hydrolysed to the ketone (scheme 4).

SCHEME 4



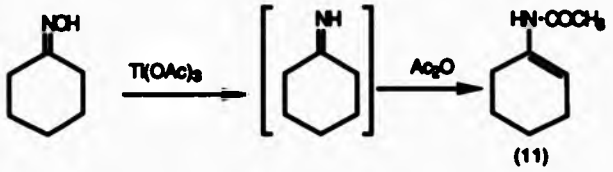
The possible intermediacy of the oxime (10) suggests that these compounds, generally readily available from the corresponding ketones, might prove suitable starting materials for this reaction. If this proved to be the case it would be useful, if somewhat unusual, in that reduction of oximes with traditional reducing agents usually proceeds to give hydroxylamines (B_2H_6) or the primary amine ($LiAlH_4$).

Timms and Wildsmith demonstrated that oximes are indeed converted to ketones by titanium trichloride in aqueous HCl/dioxane solution[5]. Once again, the implication is that the initial product is the imine, which cannot survive the strongly acidic conditions. Because of this, trapping of the imine is clearly impossible, and all that is achieved is the regeneration of the ketone from which the oxime was originally derived. If the Ti^{3+} ion is to prove a satisfactory reducing agent for the preparation of ene-formamides (6), the reaction must be carried out in the absence of acid. As titanium (III) is not stable in neutral or basic aqueous solution, a method whereby this species could be employed in anhydrous conditions was sought.

Titanium trichloride is available in powder form, and this seemed the logical reagent to attempt the reduction of oximes. Accordingly, a solution of cyclohexanone oxime in dry DMF was cooled in ice, and acetic-formic anhydride and a catalytic quantity of imidazole added. Under an inert atmosphere, anhydrous titanium trichloride was slowly added. The reaction mixture darkened immediately, and once all the starting material had been consumed and the solvent removed, the reaction was worked up to leave a thick black resin. No identifiable products were isolated, and as anhydrous titanium trichloride is pyrophoric and hazardous to use, this approach was not pursued further.

The use of anhydrous titanium (III) acetate for the reductive acetylation of cyclohexanone oxime has been reported by Barton *et al*[6]. The reasoning behind this was essentially identical to that outlined above. The oxime was reduced to the imine, which was trapped in this case by an acylating agent, acetic anhydride (scheme 5).

SCHEME 5

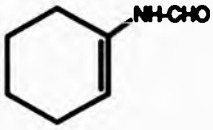


(11)

This reaction proceeded precisely as anticipated, and the ene-acetamide (11) was isolated in good yield. As the only difference between this and that required for the preparation of the ene-formamide was the nature of the acylating agent, it was confidently expected that this reaction could be adapted as required.

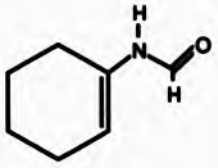
The titanium triacetate used in this reaction was prepared by the addition of an aqueous solution of titanium trichloride to a saturated solution of sodium acetate. The triacetate was formed as a precipitate, which was collected and dried[6]. As an elderly bottle of titanium trichloride solution (15% w/v $TiCl_3$ in 10% HCl, containing 55g/l $ZnCl_2$)[7] was immediately to hand, this was used to prepare the triacetate as described.

When this triacetate was added to a cooled solution of cyclohexanone oxime and formic-acetic anhydride in DMF, containing a catalytic quantity of imidazole, a deep green solution was obtained. On warming to room temperature, this solution developed a deep blue colour, which faded over a period of a few hours. The solvent was removed, and the residue neutralised with an aqueous sodium carbonate solution. Extraction into ethyl acetate and evaporation of solvent led to the isolation of a white crystalline solid, which spectroscopic evidence revealed to be the desired ene-formamide (12).

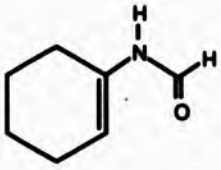


(12)

The ^1H n.m.r. spectrum of this compound showed two broad signals in the vinyl region, at δ5.2 and 5.9, with integral ratio of approximately 3:1. This indicated the presence of two rotamers, (12A) and (12B), due to restricted rotation about the amide bond.



(12A)



(12B)

The reductive formylation of cyclohexanone oxime was repeated several times to ensure reproducibility, and in each case the formamide (12) was isolated in yields in excess of 90%. At this point the original supply of titanium trichloride was exhausted, and fresh stocks were obtained. In this case the solution was purer than the original, containing no zinc chloride, with a concentration of $TiCl_3$ of 30% w/v[8]. Using this solution, titanium triacetate was prepared as before, and the reductive formylation procedure carried out using cyclohexanone oxime as substrate, exactly as before. However, when this reaction was worked up, a mixture of products was obtained. When this was resolved into its components, it was observed that the formamide (12) had been formed in less than 20% yield. The remainder of the product mixture was predominantly the

unreacted oxime, with traces of cyclohexanone. It was assumed that this failure was no more than a temporary aberration, and the reaction was repeated, adhering rigidly to the procedure applied with success on previous occasions. However, once again the yield of (12) was poor.

The only apparent difference between the two procedures was the presence of the zinc chloride in the titanium trichloride used in the former. The inference was, therefore, that the zinc was in some way necessary for the reaction to proceed, perhaps by acting as a Lewis acid catalyst. The obvious remedy was therefore to add zinc chloride to the solution. Accordingly, sufficient zinc chloride was added to make the mole ratio between zinc and titanium similar to that in the original solution - approximately 1:1. This zinc-doped solution was then used exactly as before. However, this had no discernible effect, giving poor yields of (12) and large amounts of unreacted oxime.

The only other obvious difference between the two solutions, apart from age, was the concentration of titanium trichloride - 15% in the original, and 30% in the latter. Although it was not immediately obvious how this could affect the final result, the intention was to attempt to duplicate the original solution, and the 30% zinc-doped solution was accordingly diluted with 10% HCl to give a final solution 15% w/v in titanium trichloride. Despite this, however, the reductive formylation procedure still failed to give satisfactory results. Attention was consequently turned to more subtle potential differences between the two solutions.

It was thought possible that the original solution may have contained some metal contaminant other than zinc which in some way catalysed the

reductive formylation reaction. As the original solution was long gone, this was impossible to determine experimentally, and it was necessary to conduct a series of experiments in which the titanium trichloride solution was doped with a small amount of the candidate metal.

The most immediately obvious candidate was iron, which could have come into contact with the solution during manufacture or storage, and which is a common constituent of titanium ores. A small amount of iron metal was added to the solution, which was stirred until all the metal had dissolved. This solution was then used exactly as before, but as in previous attempts the results were unsatisfactory. This procedure was then repeated using a variety of likely and less likely metals, namely arsenic, chromium, cobalt, copper and nickel. On each occasion no discernible improvement in the performance of the reaction was recorded.

At this stage, the decision was made to go right back to the beginning. A supply of the original 15% w/v solution of titanium trichloride, containing zinc chloride[7] was obtained. From this, the triacetate was prepared, and this was used exactly as before to attempt the reductive formylation of cyclohexanone oxime. It was with considerable surprise that the reaction was worked up to reveal the now-familiar mixture of ene-formamide (12), unreacted oxime and cyclohexanone.

At this point, having occupied a considerable amount of time and resources, the project had provided little encouragement and was almost abandoned. However, it was felt that, as the reductive formylation had been successful in the past, conditions must exist under which it would

give reproducible results. It had already been observed that, under conditions in which the reductive formylation was unsuccessful, the analogous acetylation reaction procedure conceived by Barton gave consistently good results. The formylation reaction must therefore be uniquely sensitive to some factor in the experimental conditions. The problem lay in finding and controlling that factor. Accordingly, over a period of several months, a systematic study was carried out in which all identifiable factors were considered. The substrate used in all cases was cyclohexanone oxime, chosen for its ready availability and absence of stereochemical or regiochemical complications.

In order to make this study as systematic as possible, the problem had to be clearly defined. The known facts were:

1. The reductive formylation reaction initially gave excellent results, with essentially pure product before recrystallisation.
2. In subsequent experiments, a considerable proportion of the oxime was recovered, and some cyclohexanone was also isolated. This cyclohexanone can only have been formed by hydrolysis of the intermediate imine or the final product.
3. The equivalent reductive acetylation reaction was consistently successful.

If the original conditions could not be reproduced exactly, it would be satisfactory to find alternative, reproducible conditions under which consistent results could be obtained.

1. Acylating Agent

The only difference between the conditions for the reductive formylation and the equivalent acetylation reaction was the nature of the acylating agent - acetic-formic anhydride in the former and acetic anhydride in the latter. This was therefore an obvious candidate for investigation.

Acetic-formic anhydride was prepared by warming a 2:1 v/v mixture of acetic anhydride and formic acid in a procedure described by Fieser and Fieser[9]. The ^{1}H n.m.r. spectrum of the anhydride prepared by this method revealed that it was something of a cocktail, with considerable contamination by acetic acid, formic acid and acetic anhydride. As described above, the intermediate imine in the reductive formylation reaction is highly susceptible to acid-catalysed hydrolysis, and this is also the case with the product ene-formamide. The presence of large quantities of acidic components in the reaction mixture is therefore likely to have a profound bearing on the course of the reaction, and it was thought prudent to attempt to eliminate contamination by these compounds.

Acetic-formic anhydride can be prepared by an alternative method, involving the reaction of acetyl chloride with sodium formate[10]. The ^{1}H n.m.r. spectrum of the anhydride prepared by this method revealed that it was free of the contaminants noted above. However, using this material for the reductive formylation reaction as before led to identical results, with large amounts of unreacted oxime recovered. As the latter method of preparation of the anhydride was time-consuming and led to no improvement in the efficiency of the reaction, the former procedure,

which had given successful results initially, was used in subsequent experiments.

An alternative formylating agent, triethyl orthoformate,was tried in place of the anhydride. However, no reaction was observed over a long period at room temperature. At the elevated temperatures usually required for formylation with this reagent, rapid decomposition of the titanium triacetate occurred and the oxime was recovered unchanged.

2. Acyl Transfer Catalyst

In all the previous experiments, imidazole had been used in the reaction mixture in the capacity of an acyl transfer catalyst. When the reaction was carried out in the absence of this catalyst, no reaction occurred. Imidazole decomposes slowly on standing, and the possibility that this was the source of the problem could not be ignored, despite the proven efficacy of this material in the acetylation reaction. To eliminate this possibility, the imidazole was purified by recrystallisation, and the purity confirmed by ^{1}H n.m.r. and t.l.c. However, when the reaction was attempted using this material, the results were indistinguishable from those obtained previously.

The reaction was attempted using an alternative acyl transfer catalyst, 4-(N',N'-dimethylamino)pyridine (DMAP). In this case the results were identical to those obtained with imidazole.

3. Solvent

The solvent used throughout in the previous experiments was DMF, for the simple reason that this was the solvent used for the reductive acetylation by Barton. However, solvating ability apart, this solvent is less than ideal. DMF is notoriously hygroscopic, and traces of water in the solvent are likely to catalyse the decomposition of acetic-formic anhydride to carbon monoxide and acetic acid. The acid formed, in the presence of water, will inevitably lead to some hydrolysis as mentioned above. DMF is also liable to decomposition on standing, and because of its relative involatility is difficult to remove at the end of the reaction. Given these factors, it was apparent that the use of an alternative solvent might be advantageous. The ideal solvent would be cheap, easily purified, less hygroscopic and preferably more volatile than DMF, and sufficiently polar to dissolve all the components of the reaction mixture. A solvent which looked as if it might meet these criteria was acetonitrile, which is reputedly an excellent solvent for electron-transfer reactions[11]. The reductive formylation reaction was therefore attempted using this solvent in place of DMF, maintaining all other factors as before. Although on this occasion the work-up was facilitated by the volatility of the solvent, in all other respects the results were indistinguishable from those obtained using DMF, and so the latter solvent was used in subsequent experiments. To avoid all possibility of contamination by water, the solvent was distilled from calcium hydride immediately before use.

4. Preparation of Titanium Triacetate.

Titanium (III) acetate was originally prepared by addition of the

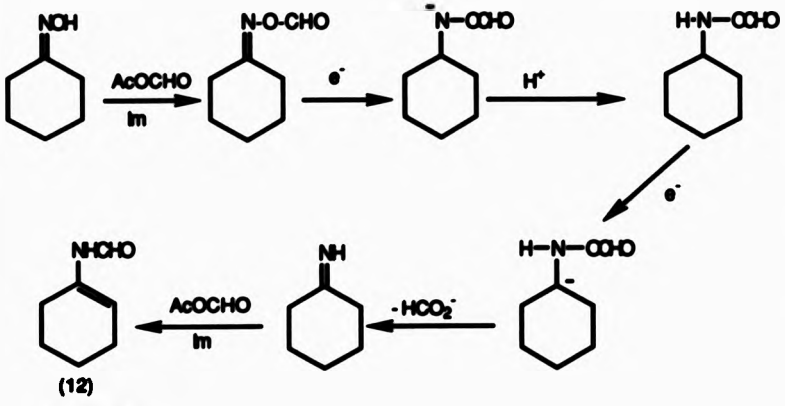
titanium (III) chloride solution to a saturated solution of sodium acetate. The precipitated triacetate was collected by filtration, washed once with ice-cold water to remove any sodium acetate, and dried under vacuum for several days. However, due to the clay-like nature of the precipitate, it was possible that this procedure might not be sufficient to drive off all traces of water, and a more efficient drying procedure was developed. After washing with ice-cold water, a large volume of acetone was added to the precipitate, and the cake broken up until finely divided. The acetone was removed and the procedure repeated. The precipitate was then washed in the same way with ether to remove the acetone and any remaining traces of water. Drying under vacuum for 24 hours left a green, finely divided powder. When the vacuum was released and air introduced into the vessel, a startling difference between this material and that prepared previously was immediately obvious. Within seconds the powder became extremely hot and copious amounts of acetic acid vapour were produced. Within the space of a few minutes, all that remained was a grey-white cake of titanium dioxide. This at least indicated that the material was somewhat more reactive than before.

This decomposition did not take place when the vacuum was released under an inert atmosphere, and the material could then be handled with relative ease, provided that all transfers were performed rapidly. Unfortunately, when the reductive formylation was attempted using this material, no improvement in either yield or reliability was observed. Despite this, this drying procedure was subsequently adopted as standard practice, as it was believed that this produced more consistently dry triacetate.

5. Excess of Titanium (III) Acetate.

The reductive formylation reaction proceeds, in all likelihood, via two sequential one-electron reductions, as shown in scheme 6.

SCHEME 6



Im = Imidazole

From this mechanism it is apparent that two equivalents of titanium (III) are required to effect the reduction of one equivalent of oxime. In all previous trials, 3g of triacetate were used for 0.5g oxime, corresponding to an excess of approximately 1.5-fold. In an attempt to force the reaction, the procedure was tried using a 2-fold excess of the titanium reagent. On work-up of this reaction, the ene-formamide (12) was isolated in excellent yield, with no unreacted oxime recovered. This success implied that the source of the problem had at last been identified, and to confirm this the procedure was repeated. To great surprise and no little disappointment, all attempts to repeat this result

were unsuccessful, implying that this had been no more than a fluke. This was somewhat puzzling, as the conditions were as far as could be determined identical in each case.

A fact that should be noted here, although its significance did not become clear until later, is that at this time the titanium trichloride solution could not be obtained in bulk quantities from the supplier. The reagent was instead supplied in small batches of 250 ml each.

6. Purification of Oxime.

Cyclohexanone oxime, prepared by standard oximation techniques, was initially purified by recrystallisation from petroleum ether, and this material showed acceptable melting point and n.m.r. data. However, the oxime retained an acrid odour, and was observed to undergo discolouration over a period of a few days. As multiple recrystallisation would be time-consuming, an alternative and more effective method of purification was preferred. The oxime could easily be sublimed to give extremely pure, brilliant white crystals, which could be stored for prolonged periods without discolouration. However, no improvement in yield or consistency of the reaction was observed.

7. Work-up Procedure.

Once the reaction was complete, i.e. all the titanium triacetate had been consumed, the reaction was worked up by removal of the solvent and the majority of the excess anhydride under reduced pressure. The residue was then neutralised by addition of a large excess of sodium carbonate solution, and the product extracted from the resulting suspension. The

residue remaining after removal of the solvent was extremely viscous, and it was possible that the mixing of this with the carbonate solution was not sufficiently rapid or efficient. This would give rise to localised regions of acidity in the solution, causing hydrolysis of the product. This would at least account for the presence of cyclohexanone in the product mixture.

To try and eliminate this possibility of hydrolysis, the work-up procedure was modified. The reaction mixture was slowly added to a well-stirred sodium carbonate solution at such a rate as to ensure that the pH, monitored potentiometrically, never went below 7. These precautions indeed eliminated the production of cyclohexanone, but otherwise no improvement in the yield of (12) was achieved.

8. Temperature

In previous experiments, after initial mixing of the reagents at 0°, the reaction mixture was allowed to warm to room temperature, and this temperature was maintained until the reaction was complete. In order to ensure that all possible variables had been thoroughly investigated, the effect of variation of temperature was studied.

At temperatures at or below 0°, no reaction was observed, and the green colour persisted indefinitely. When the temperature was allowed to rise, the characteristic colour change from green to blue took place only when the temperature reached 10-15°. As the temperature was raised, the rate of the reaction, as indicated by the time taken for the blue colour to

disappear, increased substantially. At 80°, the reaction time was approximately 15 minutes, compared with about 2 hours at room temperature. Above this temperature rapid decomposition of the titanium triacetate occurred. In all the temperature trials carried out, however, no improvement in the yield of formamide was observed, and indeed the yield decreased with increasing temperature.

9. Presence of Radicals.

The initial experiments, in which the successful reductive formylation of cyclohexanone had been achieved, were carried out in a well-lit laboratory in summer. It was thought remotely possible that the high light intensities might induce free radical formation, and that this might in some way facilitate the reaction. To test this somewhat unlikely hypothesis, the reaction was carried out in the presence of AIBN as a radical initiator. However, less than surprisingly, no effect was observed on the course or result of the reaction.

10. Source of Titanium Trichloride Solution.

It was now apparent that at this stage only one possible variable remained to be investigated, namely the quality of the titanium trichloride solution. Several batches had been received from the supplier, and it was possible that some subtle variation in the manufacture or storage of this reagent might account for the inconsistencies in the reductive formylation reaction. As this was a factor which could not be controlled in the laboratory, and incidentally because of increasing difficulties in obtaining the material, the problem

was circumvented by the preparation of the reagent under known and reproducible conditions.

The high concentration of zinc chloride in the commercially-produced solution indicated that the material was prepared by the reduction of titanium tetrachloride by zinc metal in hydrochloric acid solution. This method was therefore adopted. A solution of titanium tetrachloride in aqueous HCl was treated with one equivalent of zinc metal to produce a solution as close as possible in constitution to the commercial product. Thus was prepared a solution 15% w/v $TiCl_3$ in 9% HCl, containing approximately 55 g/l zinc chloride.

This solution was then used to prepare titanium triacetate as before, and the reductive formylation was carried out as before. The reaction was monitored by t.l.c., and after the final colour change had occurred, t.l.c. showed a large iodine-negative spot corresponding to the ene-formamide. The reaction was worked up, and the ene-formamide was isolated in excellent yield.

To eliminate the possibility that this was another fluke, the reaction was repeated several times, and under these conditions proved entirely reproducible, with isolated yields of (12) consistently in excess of 90%.

Although the source or nature of the inconsistency in the commercial titanium trichloride solution had not been identified, therefore, this problem has been overcome to provide a rapid, clean and efficient synthesis of (12). This reaction is potentially useful, and subsequent

experiments were conducted to determine the scope and limitations of this reaction when applied to other substrates.

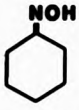
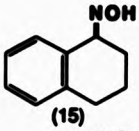
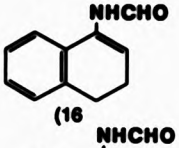
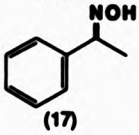
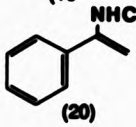
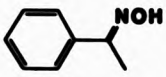
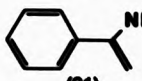
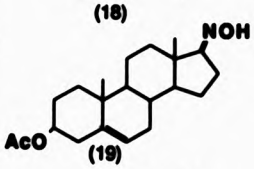
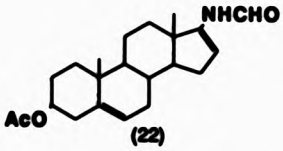
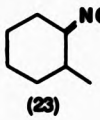
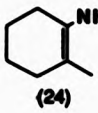
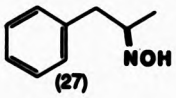
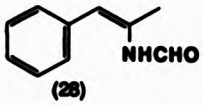
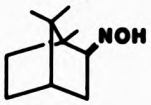
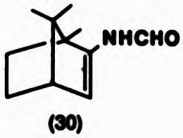
When the reductive formylation procedure was applied to cyclopentanone oxime (13), the reaction was somewhat more rapid at room temperature than was the case with cyclohexanone oxime. The reaction went to completion in the space of about 30 minutes, and the ene-formamide (14) was isolated in somewhat poorer yield. However, when the reaction temperature was maintained below about 10° the rate was moderated, and (14) was isolated in excellent yield.

In the case of α-tetralone oxime, the reaction was slow at room temperature, the blue colour persisting for several days. The reaction was worked up at this stage, and the yield of ene-formamide was poor. However, on raising the temperature to 80°, the rate of reaction was substantially increased. The reaction was complete within 3 hours, and the product (16) was isolated in yields once again in excess of 90%.

In much the same manner, the oximes of acetophenone (17), p-methoxyacetophenone (18) and dehydroisoandrosterone (19) were converted to the ene-formamides (20-22), varying the reaction temperature and time to obtain optimum yields of products. These results are summarised in Table 1.

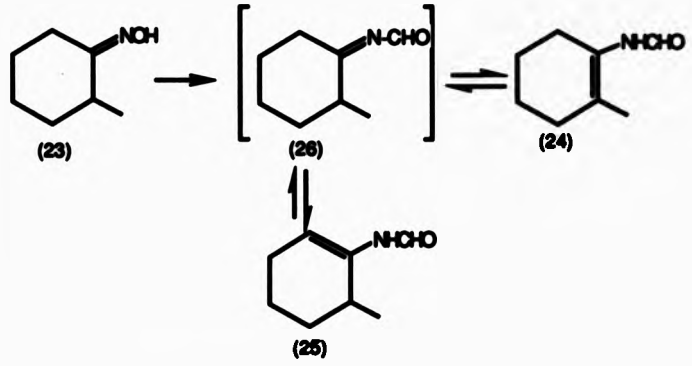
The reductive formylation of 2-methylcyclohexanone oxime (23) can in principle give rise to two possible products. If the reaction is controlled by thermodynamics, the product will be the thermodynamically

Table 1: Reductive Formylation of Oximes to Ene-Formamides

Oxime	Temperature (°C)	Time (hr)	Formamide	Yield (%)
	20	4	 (12)	97
 (13)	10	3	 (14)	96
 (15)	80	3	 (16	93
 (17)	50	4	 (20)	73
 (18)	65	8	 (21)	71
 (19)	20	18	 (22)	91
 (23)	60	6	 (24)	77
 (27)	20	5	 (28)	43
 (29)	20	16	 (30)	52

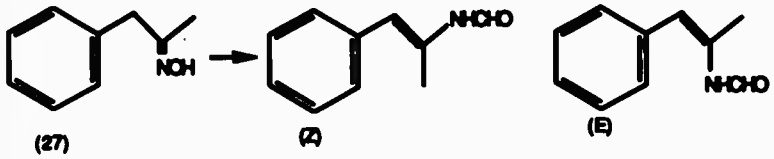
more stable (24), with a tetra-substituted double bond. If, however, the reaction is dominated by kinetic control the product will be (25). If the proposed mechanism (scheme 6) is correct, the initial product will be the N-formylimine (26), and the tautomerism between this and (24) and (25) will be thermodynamically controlled. This would give rise to (24) as the sole product, and this is indeed the case (scheme 7). In this case the yield was lower than in previous examples, as insufficient time was available to optimise the reaction conditions.

SCHEME 7



A similar argument applies in the case of (27), and once again only the thermodyanamic product (28) was isolated. The exact stereochemistry, i.e. whether it is the (E) or (Z) isomer, has yet to be determined. That only one isomer is present is indicated by t.l.c. and ^{1}H n.m.r., and the presence of two widely-separated vinyl proton signals suggest that it has the (Z)-stereochemistry. In this isomer, the vinyl proton and formyl group are in close proximity, and rotation about the amide bond is likely

to have a more profound effect on the chemical shift of the vinyl proton than would be the case with the (E)-isomer.



(27) (Z) (E)

(28)

The reductive formylation of (+)-camphoroxime (29) was less straightforward than the above examples. In repeated experiments, the t.l.c. of the reaction mixture indicated that two products were formed. These products were separated on a silica column, and the faster-running of the two was identified as the anticipated ene-formamide (30). The other product, comprising approximately 50% of the product mixture was a viscous yellow oil which has yet to be identified. It is not unlikely that this will prove to be the product of some rearrangement of the carbon skeleton, for which bicyclic systems of this nature are notorious.

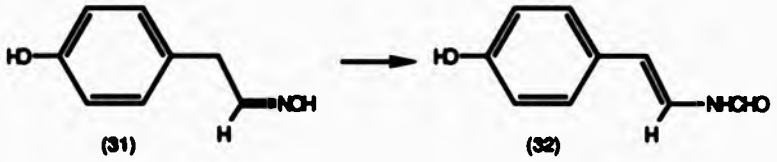
As was the case with the cyclohexenyl system (12), the ^{1}H n.m.r. spectra of the ene-formamides bearing vinyl protons (i.e. (14), (16), (28), (30) and (22)) showed two resonances for this vinyl proton. Once again, this can be attributed to rotational isomerism arising from restricted rotation about the amide bond. The energy barrier to rotation about this bond has not yet been determined, as insufficient time was available to carry out the variable temperature n.m.r. studies required.

The proton spectra of the ene-formamides (20) and (21) derived from the

oximes of acetophenone and p-methoxyacetophenone were somewhat more complicated in that three vinyl proton signals were recorded. Two of these signals can be attributed to the proton *cis* to the amide group, due to the restricted rotation mentioned above. The proton *trans* to the amide group is obviously sufficiently remote as to be unaffected by the stereochemistry of the amide group.

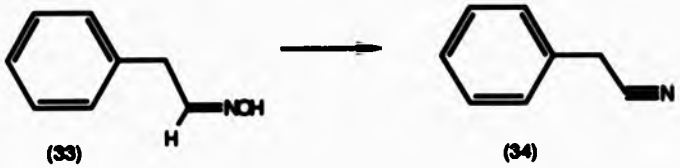
[redacted]

The *Streptomyces* metabolite tuberin (32) can formally be derived from p-hydroxyphenylacetaldoxime (31) *via* the reductive formylation methodology developed above.



This reaction, if successful, would be highly attractive in providing a one-step synthesis of an interesting natural product. Tuberin is a tuberculostat, and the (E)-isomer is an efficient inhibitor of blood platelet aggregation, making this compound of some pharmacological interest. To test the feasibility of this reaction, phenylacetaldoxime (33) was subjected to the reduction under the usual conditions. In this case, however, the usual blue colour did not develop, the colour changing directly from green to orange. The reaction was worked up in the usual manner, and a clear oil was isolated as the only product. This product

was identified by spetroscopic means as phenylacetonitrile (34), and this was confirmed by t.l.c. against an authentic sample. This result was not altogether unexpected in view of the fact that aldoximes are known to undergo relatively facile dehydration to give nitriles.



(33) (34)

Dehydration of Formamides to Isonitriles.

An efficient and widely applicable synthesis of ene-formamides having finally been developed, it was necessary to determine the optimum conditions for the conversion of these compounds to the desired vinyl isonitriles. A variety of reagents have been used in the past to effect this type of transformation, as described in part one. No problems were initially envisaged in determining the most effective reagents for the desired reaction, and a number of trials were conducted, using 1-N-formylcyclohexene (12) as substrate.

The most attractive dehydrating agent for this reaction was phosgene. Dehydration of formamides with this reagent is usually rapid and efficient, and the product isonitriles are in general reasonably tolerant of an excess of the reagent. Although phosgene is extremely toxic, it can be used without hazard in solution, provided that stringent safety precautions are observed.

The first choice of base to use in conjunction with phosgene is generally triethylamine, as this is cheap and generally easy to remove at the end of the reaction. Accordingly, this combination of reagents was the first used to attempt the preparation of 1-isocyanocyclohexene (35). A solution of (12) in dichloromethane containing an excess of triethylamine was cooled in ice and a two-fold excess of phosgene in dichloromethane was slowly introduced. The reaction was monitored by t.l.c., and once all the starting material had been consumed, the reaction was worked up. Distillation of the residue gave a clear oil with the characteristically repellent odour of an isonitrile. The presence of the isonitrile was confirmed by the presence of a strong stretching vibration at 2100 cm^{-1} in the infra-red, due to the isonitrile triple bond. However, the ^{1}H n.m.r. spectrum of this liquid revealed that it was a mixture of the isonitrile (35) and triethylamine, in proportions of approximately 1:1. These compounds proved inseparable by further distillation, suggesting that an azeotropic mixture had been formed. Attempts to remove the triethylamine by conventional chemical means, i.e. by washing with dilute aqueous acid, merely resulted in the destruction of the isonitrile, presumably by acid-catalysed hydrolysis to the ketone. To attempt to overcome this setback, an alternative base was sought.

When the reaction was repeated, but this time using pyridine as base, the presence of isonitrile was again confirmed in the distillate by infra-red spectroscopy. However, as was the case with triethylamine, an inseparable mixture of isonitrile and amine was formed. However, it was hoped that the use of a less volatile base might overcome the problem.

For the preparation of the highly volatile methyl isonitrile, Schuster et al[12] used p-toluenesulphonyl chloride in quinoline. The reaction was carried out at elevated temperature, and the isonitrile distilled off as it formed. It was hoped that this approach could be adapted for the preparation of (35). A mixture of tosyl chloride and quinoline was heated to 75° under reduced pressure, and a solution of (12) in quinoline was slowly added. The product was collected in a cold-trap as it distilled. Once again, the isonitrile was present in the distillate, but as in previous attempts, ^{1}H n.m.r. revealed that the product was a mixture of isonitrile and amine, this time in approximately 2:1 ratio.

It was by now apparent that the use of an amine base might not be practicable. A possible alternative approach was to use a non-amine base, and the dehydration was therefore attempted using a combination of phosphoroyl chloride and potassium t-butoxide. However, in this instance the familiar fragrance of isonitrile was absent from the product, and the absence of the characteristic isonitrile stretching vibration in the infra-red confirmed that no reaction had occurred. This was somewhat surprising, in that this combination of reagents has been used to effect precisely this transformation[3], albeit in poor yield. This failure was in all likelihood due to the elderly nature of the potassium t-butoxide used. However, this procedure was not pursued as an alternative strategy was showing signs of success.

The problem of co-distillation of the amine base with the product might be avoided by the use of an amine which is solid, or at least extremely involatile. A suitable high-melting amine was sought, and poly(4-vinyl-

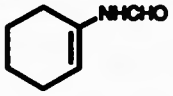
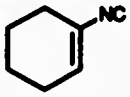
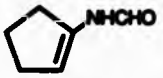
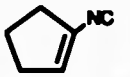
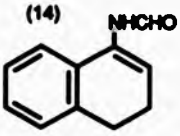
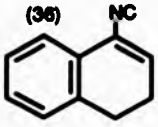
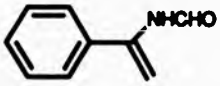
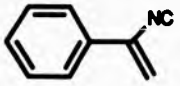
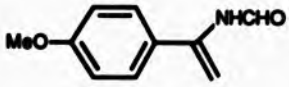
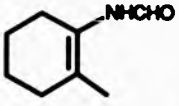
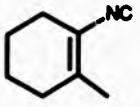
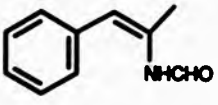
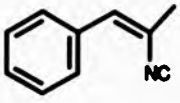
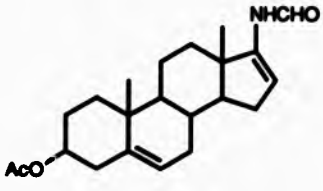
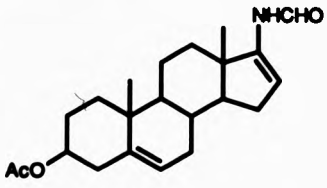
pyridine) was thought to be a promising candidate. However, this polymeric amine proved insoluble in all suitable solvents, and attempts to use the base in suspension did not meet with success.

A possible alternative base to test this strategy was diazabicyclo-[2.2.2]octane (DABCO), a readily available solid amine with a melting point of 160°, which is soluble in a variety of organic solvents. This base was therefore used in conjunction with phosgene to attempt the dehydration of (12), using a similar procedure to that tried with triethylamine. In this case the distillate was a colourless oil which darkened rapidly in contact with air. Analysis of this product by infra-red and ^{1}H n.m.r. spectroscopy confirmed that it was the isonitrile (35), free from contamination with amine. Accurate elemental analysis of this compound was not possible due to its instability, overpowering odour and the fact that it is a liquid, for which accurate facilities were not available. That this product is indeed (35) was however confirmed by mass spectroscopy.

This dehydration procedure was subsequently applied to the synthesis of the vinyl isonitriles (36-41) (Table 2). In all cases the reaction was smooth and efficient, giving products which gave satisfactory spectral data. Although yields were in general only moderate (with the exception of (28)), these reactions were only performed once, and it is likely that these yields can be improved substantially by optimisation of the reaction conditions.

The steroidal isonitrile (42) was prepared by standard techniques, using

Table 2: Preparation of Vinyl Isonitriles

Formamide	Isonitrile	Yield (%)
 (12)	 (35)	68
 (14)	 (36)	40
 (16)	 (37)	41
 (20)	 (38)	65
 (21)	 (39)	52
 (24)	 (40)	56
 (28)	 (41)	92
 (22)	 (42)	83

phosphoroyl chloride and pyridine. (42) is a highly involatile solid, and consequently the problems of co-distillation with the amine did not arise.

The ^{13}C n.m.r. spectra of these isonitriles merit some attention. The isonitrile carbons showed very weak resonances in the region 160-165 ppm. These carbon atoms are some distance removed from the nearest protons, and consequently have very long relaxation times. Saturation of these signals is therefore achieved very rapidly, causing very low amplitude signals. The resonances due to the isonitriles carbons of (37) and (40) were in fact too weak to be distinguished from the baseline noise. This was also the case with (41), and an attempt was made to develop this signal by delaying the excitation pulse, thereby allowing the nuclei to relax, and thus prevent saturation. A relaxation delay of 10 seconds allowed a very weak signal to be observed at 161.7 ppm.

In some cases, most notably in the case of 1-cyclopentenyl isonitrile (36), these signals could be resolved into triplets due to coupling to nitrogen. The coupling constants ($^1J_{N-C}$) were very small, and due to the low intensities of these signals could not be measured with any accuracy.

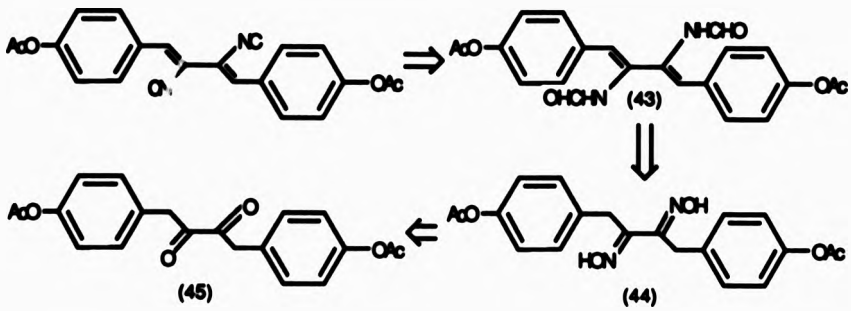
The ^{13}C resonances due to the vinyl carbon bearing the isonitrile group were stronger, due to their greater proximity to the nearest protons, but were still very weak. They appeared in the region 120-130 ppm, with coupling constants ($^1J_{N-C}$) of approximately 6 Hz. The fact that this is greater than the isonitrile carbon-nitrogen coupling is rather

surprising, given that the isonitrile carbon-nitrogen bond is likely to be considerably shorter than the vinyl carbon-nitrogen bond. Not unexpectedly, the introduction of a 10 second relaxation delay in the spectrum of (41) led to a greater enhancement of the signal due to this carbon than the isonitrile carbon.

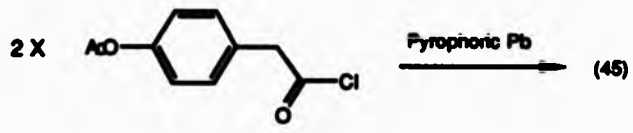
Approaches Towards the Synthesis of Xanthocillin

The synthesis of xanthocillin dimethyl ether (2) devised by Hagedorn and Eholzer (scheme 1) is extremely inefficient and consequently somewhat impractical. In view of the pharmacological potential of this and related compounds, a more effective synthesis was highly desirable, and it was hoped that the methods developed above might provide a means to this end. With the ultimate aim of preparing xanthocillin X itself, attempts were made to develop a synthesis of the acetoxy analogue of (2). It was likely that the acetyl group would be easier to remove. Subjecting this compound to retrosynthetic analysis, bearing in mind the reductive formylation/dehydration methodology, the ideal starting material is the α-diketone (45) (scheme 8).

SCHEME 8



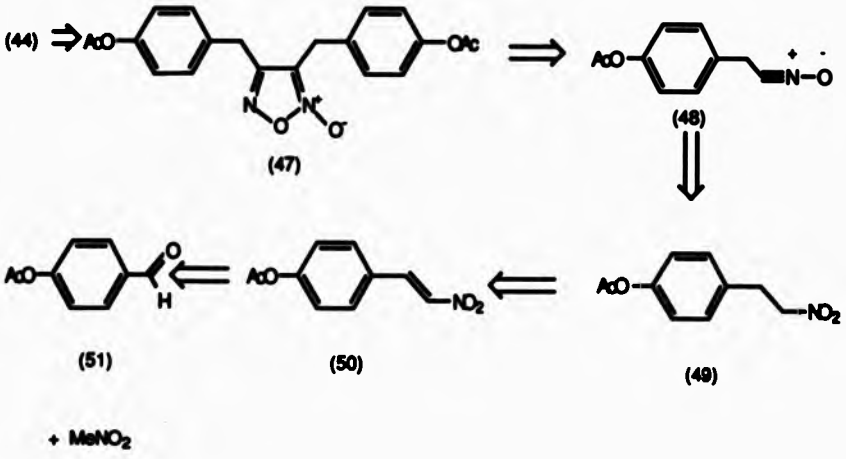
Unfortunately, the synthesis of (45) was likely to be problematical, as few reliable methods of preparing such compounds are available. One possible route is *via* a Wurtz-type coupling of two molecules of p-acetoxyphenylacetyl chloride (46)[13].



However, reactions of this type are rarely efficient, and an alternative and more attractive route to the dioxime (44) was sought.

α-Dioximes can be prepared by the reduction of furoxans[14]. In this case, then, the required furoxan would be (47), and a potential route to this compound lies in the dimerisation of the nitrile oxide (48) derived from p-acetoxyphenyl-2-nitroethane (49) (scheme 9).

SCHEME 9



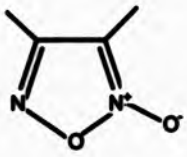
This approach was attractive in that it uses readily available starting materials to produce the final product in a relatively small number of potentially high-yielding steps.

The condensation of nitromethane with p-hydroxybenzaldehyde (51) in the presence of triethylamine yielded the p-hydroxy-β-nitrostyrene (50) in straightforward manner as anticipated, and this was successfully converted to (49) by reduction and acetylation. The conversion of this compound to the furoxan (47) was the next step in the procedure.

Primary nitro compounds react with dehydrating agents such as isocyanates with the loss of water to form nitrile oxides (eg (48)). These highly reactive compounds then undergo secondary reactions, most commonly dimerisation to form furoxans. It was hoped that this would be the case in this example.

Accordingly, phenyl isocyanate was added to a solution of the nitro compound (49) and triethylamine. Once the reaction was complete, the products were separated by chromatography. The major product was a viscous orange oil, which ^{1}H n.m.r. suggested was the desired furoxan (47). This oil was eventually induced to crystallise after prolonged storage in the refrigerator, and on recrystallisation gave the furoxan (47) as a white crystalline solid.

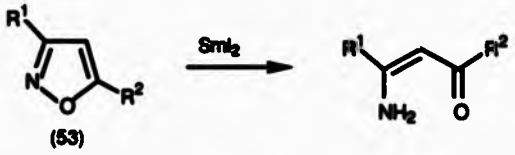
It was hoped that one reduction step might be eliminated by subjecting this compound directly to the reductive formylation procedure. This possibility was originally tested on 3,4-dimethylfuroxan (52) to conserve stocks of (47). However, (52) was completely inert under the usual conditions, and no reaction was observed at temperatures of up to 80°.



(52)

Despite this, it was hoped that (47) might be less resistant to the reductive formylation reagents, given the substantial increase in conjugation that would be gained in the course of the reaction. Unfortunately, this was not the case, and the furoxan (47), like (52), was completely unchanged by the reaction conditions.

At this point, an alternative strategy for accomplishing this transformation was formulated. Natale[15] has observed that the N-O bond of isoxazoles (53) undergoes reductive cleavage by samarium iodide.



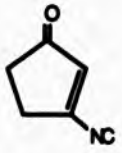
(53)

If this reagent were to have a similar effect on the N-O bonds of the furoxan, this would provide an alternative and perhaps more powerful reducing agent to titanium triacetate for the reductive formylation. This procedure was therefore carried out as before, with samarium iodide replacing the titanium reagent. However, no reduction was observed and only starting materials were recovered. As samarium diiodide is considerably less stable and easy to prepare than titanium triacetate, and no more effective, this approach was not pursued further.

As the furoxan (47) itself is resistant to the reductive formylation, the next step was to reduce this to the dioxime (44). This was achieved in essentially quantitative yield by catalytic hydrogenation over palladium on charcoal at atmospheric pressure. This compound was then subjected to the reductive formylation procedure as before. However, as was the case with the furoxans, no reduction was observed. In repeated attempts, the dioxime remained completely inert to the reaction conditions. If this general approach to the synthesis of xanthocillin is ultimately to succeed, therefore, an alternative reducing agent must be found. Unfortunately, insufficient time was available to carry out this work.

Approaches Towards the Synthesis of *Trichoderma* Isonitriles

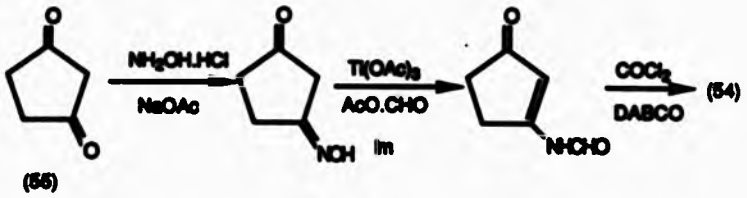
The isonitrile metabolites of *Trichoderma hamatum* (Part two,(5-8)) all contain a 1-cyclopentenyl isonitrile system with a substituent at the 3-position. In any attempts to prepare these compounds, a suitable precursor is likely to be (54).



(54)

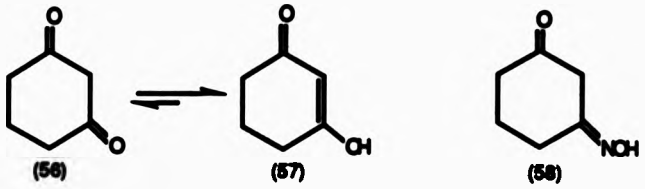
This can in principle be obtained, using the reductive formylation procedure, from cyclopentane-1,3-dione (55) (scheme 10).

SCHEME 10



(55)

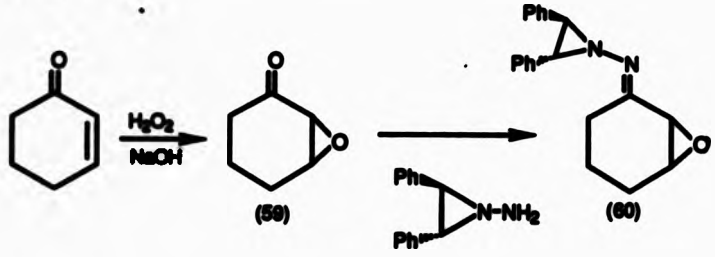
The first step in this sequence is the conversion of the diketone to the monoxime. As cyclopentane-1,3-dione is expensive, research was carried out using the 6-membered analogue, which is considerably cheaper, to avoid excessive expenditure of limited funds. It was expected that any results achieved could readily be applied to the 5-membered system later. However, no reference could be found to cyclohexane-1,3-dione monoxime in the literature, or indeed to any method of preparation of 1,3-diketone monoximes, although the monoximes of both 1,2- and 1,4-diketones are well known. The fact that 1,3-diketones exist entirely or predominantly in the mono-enol form (eg (57)) undoubtedly has some bearing on the matter.



(56) (57) (58)

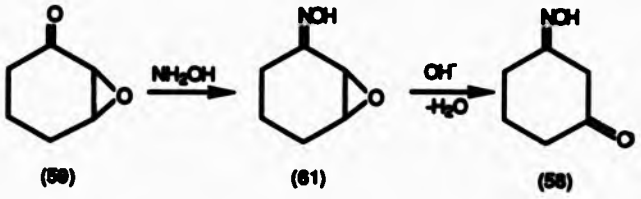
It was therefore clear that this approach was likely to fail at the first hurdle, and an alternative route to the monoxime (58) was required. Such an approach was suggested by work by Eschenmoser et al[16] in which the hydrazone (60) of α,β-epoxycyclohexanone (59) was prepared (scheme 11).

SCHEME 11

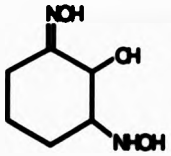


If (59) would react in analogous fashion with hydroxylamine, the oxime (61) would result. This might then be converted to the ketone monoxime (58), perhaps by ring-opening of the epoxide and dehydration (scheme 12).

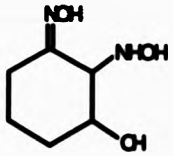
SCHEME 12



Reaction of the epoxyketone (59) with hydroxylamine resulted in the formation of a compound which mass spectral evidence suggested had incorporated two molecules of hydroxylamine, with the loss of one molecule of water. The structure of this compound was deduced from ^1H n.m.r. evidence to be either (62) or (63), derived from nucleophilic ring-opening of the epoxide by hydroxylamine. Which structure is correct has yet to be determined.



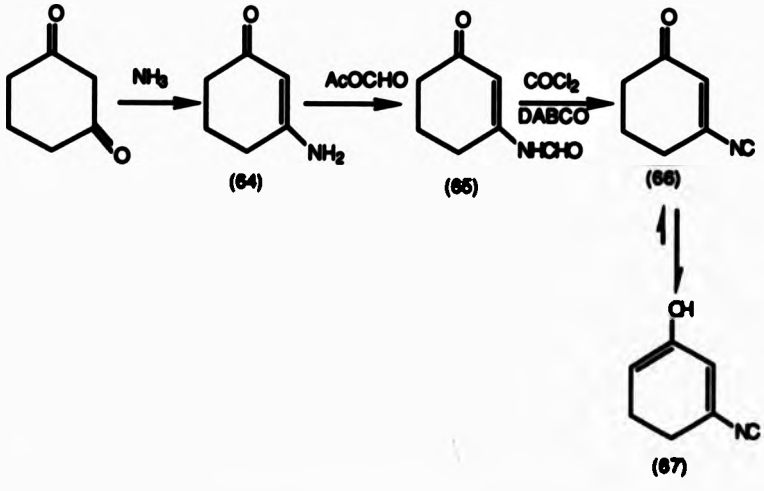
(62)



(63)

However, at this point this approach became redundant when it was discovered that 1-aminocyclohexane-3-one (64) is a known, stable compound formed by simple condensation of ammonia with cyclohexane-1,3-dione[17]. The preparation of this compound formed the basis of a straightforward synthesis of the isonitrile without recourse to the monoxime (58) or the reductive formylation procedure. The vinylogous amide (64) was formylated with acetic-formic anhydride, and the resultant ene-formamide (65) was dehydrated under the usual conditions to the isonitrile. Spectral evidence suggests that this compound exists in the enol form (67) (scheme 13).

SCHEME 13



(64) (65) (66) (67)

Confirmation that the final product in this sequence is indeed the isonitrile by accurate mass determination was not possible as no molecular ion was formed. For the reasons stated above, accurate elemental analysis was also impossible. However, ^{1}H and ^{13}C n.m.r. and infra-red spectroscopy, combined with the unmistakable odour and the provenance of this compound all serve to indicate that this is indeed (67).

Adaptation of this procedure to the 5-membered system should give (54) without trouble, and thereby provide a potential route to the *Trichoderma* isonitriles. The fact that (67), and in all likelihood (54), exists in the enol form may, however, cause problems in the alkylation of this compound at position 3, and preliminary experiments suggest that a simple Wittig-type reaction will not suffice.

PART FOUR

EXPERIMENTAL

EXPERIMENTAL

All solvents were purified by standard techniques before use.

^{1}H n.m.r. spectra were recorded on either a Perkin-Elmer R24 (60 MHz) or R32 (90MHz) n.m.r. spectrometer. Unless otherwise specified, spectra were run in deuterochloroform as solvent, with tetramethylsilane as internal standard. Chemical shifts are reported as ppm from TMS.

^{13}C n.m.r. spectra were recorded on a Bruker WP80 (80 MHz) n.m.r. spectrometer, in $CDCl_3$, and chemical shifts are reported as ppm from TMS.

Infra-red spectra were recorded on either a Shimadzu IR-435 or a Perkin-Elmer model 577 grating infra-red spectrometer.

Mass spectra were recorded using a JEOL D-100 mass spectrometer.

Melting points were determined using a Gallenkamp melting point apparatus, and are uncorrected.

Elemental analyses were obtained using a Carlo Erba Strumentazione Model 1106 elemental analyzer.

Attempted Reductive Formylation of Cyclohexanone Oxime with $TiCl_3$.

A solution of 0.5g cyclohexanone oxime in 10 ml dry DMF under an inert atmosphere was cooled in ice and 2.5 ml acetic-formic anhydride was slowly added. A crystal of imidazole was added, and the solution stirred for 1 hour at 0°. 2g (3 eq.) anhydrous titanium trichloride was then added, followed by a further 2.5 ml acetic-formic anhydride. The mixture darkened immediately on addition of the $TiCl_3$ to give a deep brown solution. The mixture was stirred under nitrogen and monitored by t.l.c. (EtOAc). After 1 hour, no starting material remained and the solvent was removed to leave a dark brown resin. To this was added 50 ml aqueous sodium carbonate solution, and the resulting suspension was extracted with ethyl acetate. The organic layer was separated, dried and the solvent removed to leave a dark brown gum which contained a complex mixture of products. No separation was attempted.

Titanium (XXX) Acetate

To 200 ml saturated sodium acetate solution was added 50 ml titanium trichloride solution (15% w/v $TiCl_3$ in 10% HCl, containing 55 g/l $ZnCl_2$)[7], and the mixture left to stand for 10 minutes. A thick green precipitate was formed, and this was collected by filtration. The precipitate was washed once with ice-cold water, dried by suction and then under vacuum for 3 days.

Yield ca. 12g.

Reductive Formylation of Cyclohexanone Oxime - Original Conditions.

A solution of 0.5g (4.2 mmol) cyclohexanone oxime in 5 ml dry DMF was cooled in ice under nitrogen, and 2.5 ml acetic-formic anhydride was added. A crystal of imidazole was added, and the solution stirred at 0° under nitrogen for 1 hour. 3g (13 mmol, 3 eq.) titanium (III) acetate was added, and the mixture stirred for 5 minutes, after which time a further 2.5 ml acetic-formic anhydride and crystal imidazole were added. The mixture was stirred under nitrogen while the cooling bath was allowed to warm up to room temperature, at which point the mixture developed a deep blue colour. After stirring for 2 hours at room temperature, this colour faded to a pale orange, and t.l.c. revealed a strong iodine-negative spot with rf 0.3.

The DMF and excess anhydride were removed on the rotary evaporator, and the residue neutralised with 0.5M sodium carbonate solution. The resulting milky suspension was filtered - an extremely slow process due to the almost colloidal nature of the suspension - and the cake of titania washed with ethyl acetate. The aqueous solution was extracted twice with ethyl acetate, and the organic fractions combined and dried ($MgSO_4$). Evaporation of the solvent left a pale cream solid which recrystallised from a small volume of ethyl acetate to give pure 1-N-formylaminocyclohexene.

Yield 0.5g (90.4%).

M. Pt. 58-59°.

^1H n.m.r. δ 1.6-1.8 (4H,m);2.0-2.3 (4H,m); 5.4 and 6.4 (1H, broad singlets); 8.2-8.5 (2H,m).

IR ($CHCl_3$) (cm^{-1}) 3900 (s); 2955; 1750; 1690.

$C_7H_{11}NO$ Requires m/e = 125.0841

Found m/e = 125.0841

Attempted Repeat of Above, using $Ti(OAc)_3$ derived from new $TiCl_3$.

Using an identical procedure to that described above, the reductive formylation of cyclohexanone oxime was attempted using titanium triacetate derived from 30% w/v $TiCl_3$. In this case the product was a pale yellow semi-crystalline material. T.l.c. (EtOAc) showed three spots. The material was loaded onto a short neutral alumina column and eluted with 10% ethyl acetate in petroleum ether. The first product eluted was cyclohexanone (0.08g, 18%), followed by (12) (0.11g, 19%) and finally cyclohexanone oxime (0.28g, 56%).

ATTEMPTED OPTIMISATION OF REACTION CONDITIONS.

In all the experiments listed below, the reductive formylation of cyclohexanone oxime was attempted, using $Ti(OAc)_3$ derived from 30% w/v $TiCl_3$ solution, using identical conditions and procedures as described above, with the exceptions stated.

Doping with Zinc.

To 100 ml 30% $TiCl_3$ solution was added 2.6g zinc chloride. The mixture

was stirred until all the zinc chloride had dissolved, and the resulting solution was used to prepare the triacetate as describe above. Use of this material for the reductive formylation procedure gave a mixture of (12) and cyclohexanone oxime. The mixture was loaded onto a neutral alumina column, and elution with 10% ethyl acetate in petroleum ether gave 0.32g cyclohexanone oxime and 0.13g (23.5%) (12).

Runs with Other Metals.

To 100 ml $TiCl_3$ solution was added approximately 50 mg of the appropriate metal (Fe, As, Cr, Co, Cu, Mn, Ni) and the solution stirred until the metal had dissolved. From this solution was prepared the triacetate, and the reductive formylation procedure attempted. In all cases a mixture as above was obtained. No separations were attempted.

Use of Triethyl Orthoformate as Acylating Agent.

A solution of 0.5g cyclohexanone oxime and 2.6g (4 eq.) triethyl orthoformate in 10 ml DMF was cooled to 0° under nitrogen and 3g $Ti(OAc)_3$ was added. The cooling bath was allowed to warm up to room temperature, and the mixture stirred for 2 hours, during which time the triacetate remained in suspension. Monitoring by t.l.c. revealed that no reaction had taken place, and the reaction vessel was immersed in an oil bath. A reflux condenser was fitted, and the mixture was heated slowly. No reaction was observed until the temperature of the bath reached 90°, at which point the colour rapidly changed from green to white. T.l.c. revealed that no reaction had occurred, and no attempt was made to isolate the product.

Amended Work-Up Procedure

The reductive formylation procedure was carried out as before up to the point at which the colour changed from blue to pale orange. To this mixture was slowly added saturated sodium bicarbonate solution with stirring, and the pH was monitored potentiometrically to ensure that it remained above 7. Once the neutralisation was complete a milky suspension was obtained. This was extracted twice with 50 ml portions of ethyl acetate. The organic fractions were combined, dried and evaporated to leave a mixture of products. Separation on an alumina column as before gave 0.14g (11) and 0.30g cyclohexanone oxime.

Acetic-Formic Anhydride

Method 1[9]

To 50 ml acetic anhydride cooled in ice was slowly added 25 ml formic acid. Once the addition was complete, the mixture was heated to 50° for 15 minutes, and then immediately cooled in ice.

^1H n.m.r. δ 2.0; 2.1; 2.25; 7.9; 9.05.

Method 2[10]

150g of finely ground sodium formate and 125 ml anhydrous ether were placed in a one-litre three-necked flask equipped with mechanical stirrer, dropping funnel and reflux condenser. 133 ml acetyl chloride was added over about 5 minutes, with the flask immersed in a water bath at 25°. The mixture was stirred at this temperature for 6 hours, after

which time the solid was removed by filtration. The solid was washed with 50 ml anhydrous ether, and the ether was removed by distillation at the water pump. The mixed anhydride was distilled (27-8°/10 mm Hg).

Yield 106g (65%).

^1H n.m.r ∂ 2.25(3H,s); 9.05 (1H,s).

IR (thin film) (cm^{-1}) 1765; 1790; 1050.

[illegible] (III) [illegible] Amended Procedure.

To 400 ml saturated sodium acetate solution was added 100 ml of titanium (III) chloride solution. The solution was left to stand with occasional stirring for 15 minutes, during which time a thick green paste formed. The paste was collected by filtration under vacuum until approximately 400 ml of liquid had been collected, and the solid was then washed with a small amount of ice-cold water. The solid was then washed thoroughly with acetone (2 X 300 ml) and then with ether (2 X 300 ml). The resulting pale green powder was then dried under vacuum for 24 hours before use, and was stored under vacuum at all times.

[illegible] (III) Chloride Solution

To 340 ml water was added 110 ml concentrated hydrochloric acid. This solution was cooled in ice and a slow stream of argon introduced. To the cold solution was slowly added 55 ml titanium tetrachloride over a period of 1 hour.

Once the addition was complete, 64g of granulated zinc was added in small portions while the cooling bath was allowed to warm up to room

temperature. The purple solution was stirred under argon until all the zinc had dissolved, to give a solution approximately 15% w/v in $TiCl_3$ in 9% HCl.

Cyclohexanone Oxime[18]

A solution of 10 g hydroxylamine hydrochloride and 16 g sodium acetate trihydrate in 40 ml water was heated to 40° and 10 g cyclohexanone was added. The mixture was stirred for a few minutes, until the oxime separated out as a white solid. The solid was collected and recrystallised from petroleum ether, and sublimed *in vacuo* (80°).

Yield 9.8g (85%).

M. Pt. 89-90° (Lit. 90°)[18]

Cyclopentanone Oxime

A solution of 30g hydroxylamine hydrochloride and 45g sodium acetate trihydrate in 120 ml water was heated to 40° and 25.5g cyclopentanone was added. Methanol was added until all the ketone had dissolved. The mixture was stirred for 1 hour, and the methanol was removed on the rotary evaporator. The precipitated oxime was collected from petroleum ether and sublimed *in vacuo* (60°).

Yield 23.6g (78.5%).

M. Pt. 56-57° (Lit. 56.5°)[18].

α-Tetralone Oxime

10g α-tetralone was added to a solution of 7g hydroxylamine hydrochloride

and 11g sodium acetate trihydrate in 40 ml water. Sufficient methanol was added to effect solution, and the solution was stirred for 1 hour. The methanol was removed on the rotary evaporator, and the precipitated oxime was collected and recrystallised from petroleum ether, followed by sublimation *in vacuo* (80°).

Yield 8.7g (79).

M. Pt. 103-104° (Lit. 103°)[18].

[redacted]

A solution of 20g hydroxylamine hydrochloride and 20g sodium acetate trihydrate in 100 ml water was heated to 60° and 20g acetophenone was added. The mixture was stirred and sufficient ethanol added to produce a homogeneous solution. The solution was left to cool to room temperature and then cooled in ice. The oxime precipitated out, and was collected by filtration. Cooling of the mother liquor resulted in a second crop, which was combined with the first. The oxime was recrystallised from petroleum ether and sublimed *in vacuo* (100°).

Yield 21g (93.4%).

M. Pt. 59-60° (Lit. 60°)[18].

2-Methylcyclohexanone Oxime

A solution of 10g hydroxylamine hydrochloride and 10g sodium acetate trihydrate in 40 ml water was warmed to 40° and 10g 2-methylcyclohexanone was added. The mixture was stirred at 40° and sufficient methanol was added to produce a homogeneous solution. The solution was stirred for 2

hours and the methanol removed on the rotary evaporator. The precipitated oxime was collected, recrystallised from petroleum ether and sublimed *in vacuo* (60°).

Yield 8.3g (73.2%).

M. Pt. 42-43° (Lit. 43°)[19].

p-Methoxyacetophenone oxime

A solution of 20g hydroxylamine hydrochloride and 20g sodium acetate trihydrate in 100 ml water was heated to 60° and 20g p-methoxyacetophenone was added. The mixture was stirred at this temperature and sufficient ethanol added to dissolve the ketone. The solution was left to cool to room temperature, and then cooled in ice. The precipitated oxime was collected by filtration and recrystallised from petroleum ether.

Yield 9.3g (42.3%).

M. Pt. 75-77° (Lit. 61-2° and 78-9°)[18].

Methyl Benzyl Ketoxime

A solution of 5g methyl benzyl ketone, 5g hydroxylamine hydrochloride and 5 ml pyridine in 50 ml ethanol was refluxed for 1 hour. The solution was cooled, and the ethanol removed on the rotary evaporator to a volume of approximately 10 ml. 10 ml water was added to the residue, which was then cooled in an ice/water bath. The precipitated oxime was collected, washed with ice-cold water and recrystallised from petroleum ether.

Yield 4.2g (75.5%).

M. Pt. 68° (Lit. 68°)[18].

Cyclohexene-3-one Oxime

A solution of 5g cyclohexene-3-one, 5g hydroxylamine hydrochloride and 5 ml pyridine in 50 ml ethanol was refluxed for 1 hour. The solution was cooled, and the volume reduced to approximately 10 ml on the rotary evaporator. Addition of 10 ml water to the residue caused precipitation of the oxime, which was collected, washed with ice-cold water and dried *in vacuo*.

Yield 3.5g (60.5%).

M. Pt. 88-89° (Lit. 89-90°)[18].

(d)-Camphoroxime

A solution of 10g (d)-camphor, 10g hydroxylamine hydrochloride and 10 ml pyridine in 100 ml ethanol was refluxed for 1 hour. The solution was cooled, and the volume reduced to approximately 30 ml on the rotary evaporator. 50 ml water was added to the residue, and the precipitated oxime was collected and washed with water. Recrystallisation from ethanol followed by sublimation *in vacuo* 100°) yielded the oxime.

Yield 8.4g (76.5%).

M. Pt. 118° (Lit. 118°)[19].

Phenylacetaldoxime

To a solution of 20g hydroxylamine hydrochloride in 80 ml water was added 80 ml 10% sodium hydroxide solution. 8g phenylacetaldehyde was added, and the solution stirred for 30 minutes. The precipitated oxime was

collected, and the mother liquor extracted with ethyl acetate. The ethyl acetate was dried and evaporated to leave a white solid, which was combined with the first crop and recrystallised from petroleum ether.

Yield 6.7g (74.4%).

M.Pt. 98-99° (Lit. 98.5°)[19].

[redacted]

0.5g dehydroisoandrosterone in 5 ml pyridine and 2.5 ml acetic anhydride was heated to 70-80° for 2 hours. The mixture was poured onto a large excess of ice-water, and the precipitated acetate was collected and dried.

Yield 0.49g (85.5%)

M. Pt. 170-171° (Lit. 171-172°)[19].

[redacted] Acetate Oxime[20]

To 0.49g dehydroisoandrosterone acetate in 10 ml pyridine was added 0.5g hydroxylamine hydrochloride, and the mixture was heated under reflux for 3 hours. The pyridine was removed under reduced pressure and the residue poured onto ice-water. The precipitated oxime was collected and dried.

Yield 0.5g (97.6%)

M. Pt. 181-182‡ (Lit. 182°)[20]

[redacted] (64)[17]

A solution of 10g cyclohexa-1,3-dione in 50 ml toluene was heated to

reflux and ammonia gas introduced with stirring, with a Dean and Stark trap fitted. The solution was stirred at reflux until no more water collected in the trap (ca. 2.5 hours), and cooled. The orange crystals which formed were collected and dissolved in hot chloroform. The hot solution was filtered, and on cooling the product crystallised and was collected by filtration.

Yield 6.0g (61%)

M. Pt. 134° (Lit. 134°)[17]

1-(N-Formylamino)cyclohexene (12)

To 0.5g (4.4 mmol) cyclohexanone oxime in 10 ml dry acetonitrile at 0° was slowly added 2.5 ml acetic-formic anhydride. A crystal of imidazole was added, and the solution stirred at 0° under a nitrogen atmosphere for 1 hour. 4g (17.8 mmol, 4 equivalents) of titanium (III) acetate was added, and after stirring for 5 minutes a further 2.5 ml acetic-formic anhydride and another crystal of imidazole were added. The mixture was stirred under nitrogen while the cooling bath was allowed to warm up to room temperature. The mixture developed a deep blue colour, which persisted for some 4 hours, after which time it began to fade. The solvent and excess anhydride were removed under reduced pressure, and to the residue was slowly added saturated sodium bicarbonate solution, ensuring that the solution remained alkaline, until the effervescence stopped. The resulting white suspension was extracted with ethyl acetate, and the organic layer dried and evaporated to leave a pale yellow oil which crystallised on standing. The product was recrystallised from a small volume of ethyl acetate.

Yield 0.54g (97.6%)

M. Pt. 58-59°

NMR ^1H ($CDCl_3$) δ 1.6-1.8 (4H,m); 2.0-2.3 (4H,m); 5.4 and 6.2 (1H, broad s); 8.2-8.5 (2H,m).

IR ($CHCl_3$) (cm^{-1}) 3900 (s); 2955; 1750; 1690.

$C_7H_{11}NO$ requires m/e = 125.0841

found m/e = 125.0846

1-(N-Formylamino)-cyclopentene (14)

To 0.5g (5 mmol) cyclopentanone oxime in 10 ml dry acetonitrile at 0° was added 2.5 ml acetic-formic anhydride and a crystal of imidazole. The mixture was stirred at 0° under nitrogen for 1 hour. 4g titanium (III) acetate was added, and after 5 minutes stirring, a further 2.5 ml acetic-formic anhydride and another crystal of imidazole were added. The mixture was stirred under nitrogen while the ice in the cooling bath was allowed to melt. Ensuring that the temperature of the cooling bath remained below 10°, the mixture was stirred for a further three hours, during which time the colour of the mixture changed to deep blue and finally to pale yellow. The solvent and excess anhydride were removed under reduced pressure, and to the residue was slowly added saturated sodium bicarbonate solution. The resulting milky suspension was extracted with ethyl acetate, and the organic layer dried and evaporated to leave a thick yellow oil, which crystallised on standing. The product was recrystallised from a small volume of ethyl acetate.

Yield 0.54g (96%)

M. Pt. 56-57°

NMR ^1H ($CDCl_3$) δ 1.3-1.5 (6H,m); 5.1 and 5.9 (1H, broad singlets); 8.1-8.4 (2H, m).

IR ($CHCl_3$) (cm^{-1}) 3400; 2900; 1690

C_6H_9NO requires m/e = 111.0684

found m/e = 111.0683

1-(N-Formylamino)-3,4-dihydronaphthalene (16)

To a solution of 0.5g α-tetralone oxime in 10 ml dry acetonitrile at 0° was added 2.5 ml acetic-formic anhydride and a crystal of imidazole. The solution was stirred at 0° under a nitrogen atmosphere for 1 hour. 4.2g titanium (III) acetate was then added, and after stirring for 5 minutes, a further 2.5 ml acetic-formic anhydride and another crystal of imidazole were added. The mixture was stirred under nitrogen until the bath had warmed up to room temperature, and the flask was then immersed in an oil bath at 80°. The mixture was stirred at this temperature under nitrogen for three hours, during which time it turned deep blue and finally orange. The mixture was cooled, and the solvent and excess anhydride removed at reduced pressure. To the residue was added saturated sodium bicarbonate until no more effervescence was observed. The resulting milky suspension was extracted with ethyl acetate, and the organic layer dried and evaporated. The resulting cream solid was recrystallised from ethyl acetate.

Yield 0.50g (93%)

M. Pt. 113-114°

NMR ^1H ($CDCl_3$) δ 2.3-2.6 (2H,m); 2.7-3.0 (2H,m); 5.85 and 6.65 (1H, broad triplets); 7.1-7.3 (4H,m); 8.3-8.5 (2H, bs).

IR (KBr) (cm^{-1}) 3090; 2815; 1670; 1300

$C_{11}H_{11}NO$ requires m/e = 173.0840

found m/e = 173.0838

1-(N-Formylamino)-1-Phenylethene (20)

To a solution of 0.5g acetophenone oxime in 10 ml dry acetonitrile at 0° under nitrogen was aded 2.5 ml acetic-formic anhydride and a crystal of imidazole. The solution was stirred at 0° for 1 hour, and 4g titanium (III) acetate was added. After stirring for 5 minutes, a further 2.5 ml acetic-formic anhydride and another crystal of imidazole were added, and the mixture was stirred until the cooling bath had warmed up to room temperature. The flask was then immersed in an oil bath heated to 50°, and the mixture was stirred at this temperature under nitrogen for 4 hours. During this time the mixture turned deep blue and then orange. The solvent and excess anhydride were removed at reduced pressure, and to the residue was slowly added saturated sodium bicarbonate solution until no more effervescence was observed. The milky suspension was extracted with ethyl acetate, and the organic fraction dried and evaporated. The resulting cream solid was recrystallised from a small volume of ethyl acetate.

Yield 0.40g (73%)

M. Pt. 74°

NMR ^1H ($CDCl_3$) δ 4.9 (1H,s); 5.1 and 5.9 (1H, broad singlets); 7.3 (5H,bs); 7.9-8.4 (2H,m)

IR ($CHCl_3$) (cm^{-1}) 3500; 1690; 1640

C_9H_9NO requires m/e = 147.0684

found m/e = 147.0684

1-(N-Formylamino)-1-2-methylcyclohexene (24)

2.5g 2-methylcyclohexanone oxime in 50 ml dry acetonitrile was cooled to 0° under a nitrogen atmosphere, and 10 ml acetic-formic anhydride and a crystal of imidazole were added. The solution was stirred for 1 hour, and 20g titanium (III) acetate was added. After stirring for 10 minutes, a further 10 ml acetic-formic anhydride and another crystal of imidazole were added. The mixture was stirred under nitrogen until the cooling bath had warmed up to room temperature, and was then immersed in an oil bath heated to 60°. The mixture was stirred at this temperature for 6 hours, during which time it turned deep blue and then yellow. The solvent and excess anhydride were removed under reduced pressure and to the residue was added saturated sodium bicarbonate solution until effervescence ceased. The resulting suspension was extracted with ethyl acetate, and the organic fraction was dried and evaporated to leave a yellow oil. This was distilled (90-100°/ca. 1mm Hg) to give a colourless oil, which solidified at low temperature.

Yield 2.1g (76.7%)

NMR ^1H ($CDCl_3$) δ 1.4-1.7 (7H,m); 1.9-2.3 (4H,m); 8.0-8.9 (2H,m)

IR (thin film) (cm^{-1}) 3250; 2950; 1670

$C_8H_{13}NO$ requires m/e = 139.0997

found m/e = 139.0986

1-(N-Formylamino)-1-(4'-methoxyphenyl)ethene (21)

1.5g p-methoxyphenylacetophenone oxime in 30 ml dry acetonitrile was cooled to 0° under nitrogen, and 7.5 ml acetic-formic anhydride and a

crystal of imidazole were added. The solution was stirred at 0° for 1 hour, and 12g titanium (III) acetate was added. The mixture was stirred for 10 minutes, and a further 7.5 ml anhydride and another crystal of imidazole were added. The mixture was stirred under nitrogen while the bath warmed up to room temperature, and the flask was then immersed in an oil bath heated to 65°. The mixture was stirred at this temperature for 8 hours, during which time the colour changed from green to deep blue, and finally to yellow. The solvent and excess anhydride were removed at reduced pressure, and to the residue was added saturated sodium bicarbonate solution until effervescence ceased. The resulting milky suspension was extracted with ethyl acetate, and the organic fraction dried and evaporated to leave a pale yellow oil which crystallised on standing. The product was recrystallised from ethyl acetate.

Yield 1.14g (71%)

M. Pt. 123°

NMR ^1H ($CDCl_3$) δ 3.85 (3H,s); 5.3 (1H,d); 5.9 (1H,d); 6.8-7.4 (4H, ABq); 9.1 (2H,s)

IR (KBr) (cm^{-1}) 3450; 3000; 1680

$C_{10}H_{11}NO_2$ requires m/e = 177.0790

found m/e = 177.0803

2-(N-Formylamino)-1-phenylpropene (28)

5.4g methyl benzyl ketoxime in 85 ml dry acetonitrile was coole to 0° under nitrogen, and 20 ml acetic-formic anhydride and a crystal of imidazole were added. The mixture was stirred for 1 hour, and 34g titanium (III) acetate was added in ca. 5g portions, allowing the

temperature to equilibrate between additions. The mixture was stirred at 0° under nitrogen for 10 minutes, and a further 20 ml anyhdride and another crystal of imidazole were added. The mixture was stirred while the bath was left to come up to room temperature. After 5 hours stirring, during which time the colour changed from green to blue and ultimately to white, the solvent and excess anhydride were removed at reduced pressure. To the residue was added saturated sodium carbonate solution, until the mixture was strongly alkaline. The milky suspension was extracted with ethyl acetate, and the organic fraction dried and evaporated to leave a white crystalline material, which was recrystallised from ethyl acetate.

Yield 2.5g (43%)

M. Pt. 143-144°

NMR ^1H (TFA) δ 2.1 (3H,s); 6.2 (1H,s); 7.1 (5H,s); 7.8-8.2 (2H,m)

IR ($CHCl_3$) (cm^{-1}) 3390; 1680; 1600

$C_{10}H_{11}NO$ requires m/e = 161.0841

found m/e = 161.0851

2-(N-Formylamino)-1,7,7-trimethylbicyclo[2.2.1]heptane (30)

A solution of 2g D-camphoroxime in 50 ml dry DMF was cooled to 0° under nitrogen and 10 ml acetic-formic anhydride was added slowly over 10 minutes. A crystal of imidazole was added and the solution stirred at 0° under nitrogen for 1 hour. 16g titanium (III) acetate was added, and the mixture stirred for 10 minutes at 0°, after which time a further 10 ml anhydride and crystal of imidazole were added. The mixture was stirred for 16 hours, the cooling bath being allowed to warm up to room

temperature. During this time the colour changed from green to deep blue. The solvent and excess anhydride were removed at reduced pressure, and the residue was made alkaline by the addition of saturated sodium bicarbonate solution. The solid titania was removed by filtration and washed with chloroform. The filtrate was extracted with chloroform, and the combined extracts dried and evaporated to give the formamide as a solid, which was recrystallised from ethanol.

Yield 0.47g (91%)

$[\alpha]_D^{20}$ = -6.86° (0.1M in $CHCl_3$)

M. Pt. 251-253° dec.

NMR ^1H ($CDCl_3$) δ 0.8-2.5 (31H,m); 5.3 (1H,s); 6.0 (1H.s); 8.2-8.6 (2H,m)

IR ($CHCl_3$) (cm^{-1}) 3400; 2840; 1690

ATTEMPTED PREPARATION OF 1-ISOCYANOCYCLOHEXENE (151)

1. With Triethylamine

A solution of 1g 1-(N-formylamoni)cyclohexene and 2 ml triethylamine in 20 ml dichloromethane was cooled in ice-water, and 16 ml (2 eq.) 10% phosgene solution in dichloromethane was slowly added. The mixture was stirred at 0° for 2 hours, and then filtered. The solvent was removed and the product flash-distilled, the distillate being collected in a cold-trap.

Yield 1.4g approximatley 1:1 isonitrile:triethylamine.

2. With pyridine

A solution of 1g (12) and 2 ml pyridine in 20 ml dichloromethane treated exactly as above gave 1.15g colourless oil, approximately 1.5:1 pyridine:isonitrile.

3. With quinoline

16g p-toluenesulphonyl chloride in 20 ml quinoline was placed in a 50 ml 2-necked round-bottomed flask fitted with dropping funnel and still-head connected directly to a 100 ml flask immersed in an acetone-cardice bath. The flask was immersed in an oil bath and evacuated, and heated to 80° with stirring. 3.5g (12) in 12 ml quinoline was added dropwise from the dropping funnel with stirring. As the addition progressed, a clear oil distilled over and was collected in the cooled receiver. Once the addition was complete, the condensate was collected and identified as containing isonitrile by smell.
Yield 1.55g, approximately 2:1 quinoline:isonitrile.

3. With Potassium t-Butoxide

0.34g potassium t-butoxide was dissolved in 20 ml t-butanol, and 3g (12) in 14 ml t-butanol was added. The solution was cooled to 0° and 2.5g phosphoroyl chloride was added over a period of 15 minutes. The mixture was stirred for 1 hour at 30-35°, and then poured ont an ice-cold solution of 1.36g sodium bicarbonate in 136 ml water. The solution was extracted with petroleum ether, and the organic fraction dried and

evaporated.

Yield 1.25g (12).

4. With Diazabicyclo-[2.2.2]-octane

A solution of 2.37g (12) and 6.4g DABCO in 20 ml dry dichloromethane was cooled in an ice-water bath and 20 ml of 10% phosgene solution in dichloromethane was added slowly over 20 minutes. The mixture was stirred at 0° for 2 hours and monitored by t.l.c. After this time, starting material was still present, so a further 3g DABCO and 10 ml phosgene solution were added. The mixture was stirred for a further 2 hours at 0°, and filtered. The filtrate was washed once with 50 ml saturated sodium chloride solution and dried ($MgSO_4$). The solvent was removed at reduced pressure, and the product flash-distilled at reduced pressure (30-35°/0.5mm), the product being trapped by immersion of the receiver in an acetone/cardice bath.

Yield 1.38g (68%)

NMR ^1H ($CDCl_3$) δ 1.2-1.7 (4H,m); 1.8-2.2 (4H,m); 5.8 (1H,s)

^{13}C ($CDCl_3$) ppm. 21t; 22t; 24t; 28.5t; 129d; 125t (weak); 160t (weak).

IR (thin film) (cm^{-1}) 2950; 2100; 1645

C_7H_9N requires m/e = 107.0735

found m/e = 107.0743

1-Isocyanocyclopentene (36)

2.5g 1-(N-formylamino)cyclopentene and 7.5g DABCO in 50 ml dry

dichloromethane was cooled in an ice bath, and 50 ml 10% phosgene solution in dichloromethane was added over 15 minutes. The mixture was stirred for 2 hours and monitored by t.l.c. Starting material was still present, so a further 25 ml phosgene solution was added to the cooled mixture. The mixture was stirred for a further 2 hours, filtered and washed rapidly with 50 ml saturated sodium carbonate solution. The organic fraction was dried, and the solvent removed by distillation at reduced pressure. The product was flash-distilled into a receiver cooled in acetone/cardice to produce a clear oil, which rapidly discoloured.

Yield 0.83g (40%)

B. Pt 28°/0.1mm

NMR ^{1}H ($CDCl_3$) δ 1.8-2.7 (6H,m); 5.9 (1H,bs)

^{13}C ($CDCl_3$) ppm. 22.0t; 30.7t; 33.9t; 126.8t (weak); 131.0d; 165.5t (weak).

IR (thin film) (cm^{-1}) 3000; 2250; 1640

C_9H_7N requires m/e = 93.0579

found m/e = 93.0582

<u>1-Isocyano-3,4-dihydronaphthalene (37)</u>

A solution of 1g 1-(N-formylamino)-3,4-dihydronaphthalene and 1.94g (3 eq.) DABCO in 10 ml dichloromethane was cooled in an ice bath, and 11.4 ml 10% phosgene solution in dichloromethane (2 eq.) was added slowly with stirring. The solution was stirred at room temperature overnight, filtered and washed with 50 ml saturated sodium carbonate solution. The organic layer was dried and the solvent removed by distillation at

reduced pressure. The product was flash-distilled (60°/0.1mm) to give a viscous, clear oil.

Yield 0.37g (41%)

NMR ^{1}H ($CDCl_3$) δ 2.2-2.45 (2H,t); 2.55-2.8 (2H,m); 6.0-6.3 (1H,bs); 7.0-7.3 (5H,m).

^{13}C ($CDCl_3$) ppm. 22.5; 26.5; 122.7; 127.7; 128.7; 129.1; 135.0; 160.5t (weak).

IR (thin film) (cm^{-1}) 2940; 2120; 1620.

$C_{11}H_9N$ requires m/e = 155.0735

found m/e = 155.0738

1-Isocyano-1-phenylethene (38)

A solution of 1.55g 1-(N-formylamino)-1-phenylethene and 3.5g DABCO in dichloromethane was cooled in an ice bath, and 21 ml 10% phosgene solution in dichloromethane was slowly added. The mixture was stirred at room temperature overnight, filtered and the solvent removed by distillation at reduced pressure. The product was flask-distilled at 0.1 mm in a Kugelrohr apparatus with the oven preheated to 80° to yield a clear oil.

Yield 0.88g (65%)

NMR ^{1}H ($CDCl_3$) δ 5.4-5.7 (2H,m); 7.2-7.6 (5H,m)

^{13}C ($CDCl_3$) ppm. 114.0; 125.0; 125.8; 126.4-127.0t (weak); 128.2; 128.4; 128.7; 129.8

IR (thin film) (cm^{-1}) 2210; 1631; 1310

C_9H_7N requires m/e = 129.0579

found m/e = 129.0587

1-Isocyano-2-methylcyclohexene (40)

A solution of 1g 1-(N-formylamino)-2-methylcyclohexene and 2.5g (3 eq.) DABCO in 10 ml dichloromethane was cooled in ice, and 15 ml 10% phosgene solution in dichloromethane was added slowly with stirring. The solution was stirred at room temperature overnight, and filtered. The solvent was removed by distillation under reduced pressure, and the product flash-distilled at 0.5 mm in a Kugelrohr apparatus with the oven preheated to 50° to yield a clear oil.

Yield 0.5g (56%)

NMR ^{1}H ($CDCl_3$) δ 1.4-1.7 (4H,m); 1.8 (3H,s); 1.9-2.3 (4H,m)

^{13}C ($CDCl_3$) ppm. 20.2; 22.5; 22.8; 29.6; 30.7; 120t (weak).

IR (thin film) (cm^{-1}) 2995; 2120; 1610; 1440

$C_8H_{11}N$ requires m/e = 121.0892

found m/e = 121.0897

1-Isocyano-1-(p-methoxyphenyl)ethene (39)

A solution of 0.45g 1-(N-formylamino)-1-(p-methoxyphenyl)ethene and 0.81g (3 eq.) DABCO in 10 ml dichloromethane was cooled in ice and 4.8 ml (2 eq.) 10% phosgene solution in dichloromethane was added slowly with stirring. The mixture was stirred at room temperature overnight, and filtered. The solvent was removed by distillation at reduced pressure, and the residue was loaded onto a 20g silica gel chromatography column and eluted with ethyl acetate. The fastest-running fraction was collected to yield 0.21g (52%) isonitrile.

NMR ^{1}H ($CDCl_3$) δ 3.75 (3H,s); 5.4-5.7 (2H,m); 6.75-7.5 (4H, ABq)

^{13}C ($CDCl_3$) ppm. 55.3q; 111.7d; 114.1d; 124.0s; 126.6; 130.5; 160.9; 162.3.

IR (thin film) (cm^{-1}) 2840; 2100; 1600; 1250

$C_{10}H_9NO$ requires m/e = 159.0684

found m/e = 159.0677

2-Isocyano-1-phenylpropene (41)

A solution of 1.2g 2-(N-formylamino)-1-phenylpropene and 2.5g (3 eq.) DABCO in 20 ml dichloromethane was cooled in ice and 15 ml 10% phosgene solution in dichloromethane (2 eq.) was added slowly with stirring. The mixture was stirred for 3 hours, then filtered. The solvent was removed by distillation at reduced pressure, and the product was flash-distilled (0.5 mm) in a Kugelrohr apparatus with the oven preheated to 120°.

Yield 0.98g (92%)

NMR ^{1}H ($CDCl_3$) δ 2.0 (3H,s); 5.1 and 6.1 (1H, pair of broad singlets); 7.0-7.4 (5H,m)

^{13}C ($CDCl_3$) (10s relaxation delay) ppm. 18.5; 122t (weak); 127.0; 127.7; 128.2; 128.5; 128.7; 129.7; 161.7 (weak).

IR (thin film) (cm^{-1}) 3050; 2100; 1720; 1440

$C_{10}H_9NO$ requires m/e = 143.0735

found m/e = 143.0732

[illegible] (42)

A solution of the formamide (22) in 10 ml dry pyridine was stirred while 1 ml phosphoroyl achloride was slowly added. The mixture was stirred under reflux for 1 hour, then at room temperature for 1 hour. The solution was then cooled in an ice-water bath, and stirred 0° for a further 30 minutes. 100 ml water was then carefully added, and the precipitate collected. This precipitate was dried and recrystallised from methanol.

Yield 0.39g (83%)

M. Pt 187-188°

$[\alpha]_D^{20}$ = -6.86° (0.1M in $CHCl_3$)

[illegible] (50)

A solution of 6g p-hydroxybenzaldehyde and one drop of ethylamine in 20 ml nitromethane was heated with stirring at 90° for 7 hours. The solution was cooled in ice, and an orange precipitate was formed. This was collected and recrystallised from methanol.

Yield 4.87g (60%)

M. Pt. 168-169°

NMR ^1H ($CDCl_3$) δ 7.7 (4H, AA',BB' quartet); 8.1 (2H, AB quartet); 9.4 (1H,bs)

1-(p-Hydroxyphenyl)-2-nitroethane

To a solution of 0.84g sodium borohydride in 20 ml tetrahydrofuran and

20 ml isopropanol under an inert atmosphere was added 1.65g (50) in portions. Once the addition was complete, a solution of 7 ml glacial acetic acid in 100 ml water was added, and the mixture extracted with ether. The organic extracts were washed with saturated sodium bicarbonate solution and dried. Evaporation of the solvent gave the title compound as a dark orange oil.

Yield 1.53g (91.6%)

NMR ^1H (CD_3COCD_3) δ 3.17 (2H,t); 4.65 (2H,t); 7.0 (4H, AA',BB'q); 8.35 (1H,bs).

1-(p-Acetoxyphenyl)-2-nitroethane (48)

0.77g 1-(p-hydroxyphenyl)-2-nitroethane was dissolved in 10 ml dichloromethane and acetic anhydride and a catalytic quantity of pyridine were added. The mixture was stirred for 10 minutes, and the solvent removed under reduced pressure to leave an orange oil.

Yield 0.83g (86%)

NMR ^1H ($CDCl_3$) δ 2.73 (3H,s); 3.2 (2H,t); 4.5 (2H,t); 7.13 (4H, AA',BB'q).

3,4-Bis(4'-acetoxybenzyl)-1,2,5-oxadiazole-2-oxide (47)

A solution of 0.40g (49) in 3 ml dry ether was cooled under nitrogen to 0° and 0.46g phenyl isocyanate was added. 6 drops of triethylamine were added and the mixture stirred for 30 minutes. The mixture was filtered and the filtrate evaporated to dryness. The crude product was separated on a silica column eluted with 10% ethyl acetate in dichloromethane to

yield the product as a thick yellow oil which crystallised from ethanol.

Yield 0.14g (34.4%)

NMR ^1H ($CDCl_3$) δ 2.23 (6H,s); 3.57 (2H,s); 3,77 (2H,s); 6.71-7.22 (8H, 2 superimposed AA',BB' quartets).

IR ($CHCl_3$) (cm^{-1}) 3000; 2950; 1750; 1600; 1570; 1245; 1160.

$C_{20}H_{18}N_2O_6$ requires m/e = 382.1166

found m/e = 382.1190

1,4-Bis(p-acetoxyphenyl)-2,3-bis(oximino)ethane (44)

1g of the furoxan (47) was dissolved in 50 ml dry ethyl acetate, and the flask was flushed with nitrogen. A catalytic quantity (ca.50 mg) of palladium on charcoal was added, and the flask placed under a hydrogen atmosphere at a pressure of 1 atmosphere. The mixture was stirred at room temperature under hydrogen and monitored by t.l.c (60:40 CH_2Cl_2:EtOAc). After 24 hours, no starting material remained, and the mixture was filtered through Celite. The filtrate was evaporated to dryness to leave a white solid, which was recrystallised from isopropanol.

Yield 0.95g (95%)

M. Pt. 117°

NMR ^1H (CD_3COCD_3) δ 2.2 (6H,s); 3.55 (2H,s); 4.05 (2H,s); 6.75-7.0 (8H,m); 10.2-10.6 (2H,broad).

IR (KBr) (cm^{-1}) 3100; 1750; 1510; 1210.

$C_{20}H_{20}N_2O_6$ requires C = 62.49%; H = 5.24%; N = 7.29%

found C = 63.25%; H = 5.29%; N = 7.15%

Attempted reductive formylation of (44)

0.5g of the dioxime (44) in 15 ml acetonitrile was cooled in ice under an argon atmosphere, and 2.5 ml acetic-formic anhydride and a crystal of imidazole were added. The mixture was stirred for 1 hour at 0°, and 3.5g titanium (III) acetate were added. The mixture was stirred for 10 minutes, and a further 2.5 ml anhydride and another crystal of imidazole were added. The mixture was stirred under argon at room temperature overnight. After this time the mixture was still green, and no reaction had taken place. The flask was placed in an oil bath and heated to reflux. After 1 hour, the mixture had become deep red in colour, and t.l.c. showed that no starting material remained.

The mixture was cooled, and the solvent and excess anhydride were removed at reduced pressure. To the residue was added saturated sodium bicarbonate solution until the mixture was strongly alkaline. The milky suspension was extracted with ethyl acetate, and the organic extracts dried and evaporated. T.l.c. of the resultant yellow oil revealed it to be a mixture of a number of compounds, and no separation was attempted.

Samarium Diiodide

A 500 ml flask fitted with 250 ml dropping funnel and magnetic follower was baked in an oven for 2 hours, and flushed with argon as it cooled. 1g Samarium metal was placed in the flask. Into the dropping funnel was placed 1.7g 1,2-diiodoethane dissolved in 150 ml freshly-distilled THF. Approximately 25 ml of this solution was run into the flask, and the mixture warmed until it developed a pale green colour. The remainder of

the diiodoethane solution was run in slowly with stirring, and the resultant deep blue solution stirred under argon for 24 hours.

[illegible] formulation of (47) with [illegible]

A solution of 0.5g (47) and 2.5 ml acetic-formic anhydride in 5 ml DMF was cooled under argon to 0° and 65 ml of the samarium diiodide solution prepared above was added by syringe. The solution was stirred under argon for 2 hours while the temperature of the cooling bath rose to ambient. During this time the blue colour faded. 10 ml methanol was added, and the solvent removed on the rotary evaporator. To the residue was added 75 ml ammonium chloride solution, and the mixture was extracted with dichloromethane. The organic extracts were dried and evaporated to leave an orange oil which t.l.c. revealed was predominantly starting material. No separation was attempted.

2,3-Epoxycyclohexanone[16]

A solution of 15.5g 2-cyclohexenone in 160 ml methanol was cooled in an ice-water bath. 48 ml 30% aqueous hydrogen peroxide solution was then added, followed by 0.24 ml 20% aqueous sodium hydroxide solution. The mixture was stirred for 1 hour, then poured onto 240g ice and 320 ml saturated sodium chloride solution. The resulting mixture was extracted with dichloromethane, and the organic fraction dried. The dichloromethane was distilled off, and the product distilled through a 4" Vigreux column (86°/10 mm).

Yield 11.5g (66%)

NMR ^1H ($CDCl_3$) δ 1.8-2.6 (6H,m); 3.4 (1H,d); 3.8 (1H,m)

[redacted]

To 1.86g hydroxylamine hydrochloride (0.027 mol) in 20 ml methanol was added 0.62g sodium (0.027 mol) in 10 ml methanol. The sodium chloride precipitate was filtered and the solution added directly to 1g 2,3-epoxycyclohexanone. The mixture was stirred until no starting material remained (t.l.c., ether). The methanol was removed to leave a white solid, which was washed with carbon tetrachloride. The solid was recrystallised from water.

Yield 0.29g

M. Pt. 165-167° dec.

NMR ^1H (D_2O) δ 1.6-1.9 (4H,m); 2.5-2.7 (2H,m); 3.7 (1H,d); 4.2 (1H,m).

IR (KBr) (cm^{-1}) 3250; 2900; 1660; 1495; 1060

Mass spectrum M^+ = 160

3-(N-formylamino)-2-cyclohexenone (65)

A solution of 3g 3-amino-2-cyclohexenone in 20 ml acetonitrile was cooled in ice and 10 ml acetic-formic anhydride and a crystal of imidazole were added. The solution was stirred at 0° for 1 hour, and the solvent and excess anhydride evaporated to leave a white solid, which was recrystallised from acetonitrile.

Yield 3.1g (84%)

M. Pt. 161-163° dec.

NMR ^1H ($(CF_3CO)_2$) δ 1.6-2.0 (2H,m); 2.2-2.5 (4H.m); 6.4 (1H,s); 8.3 (1H,d); 8.9 (1H,bs)

IR ($CHCl_3$) (cm^{-1}) 3450; 3400; 2950; 1710; 1620; 1600.

$C_7H_9NO_2$ requires C = 60.42%; H = 6.52%; N = 10.07%

found C = 60.35%; H = 6.50%; N = 10.17%

1-Isocyano-3-hydroxycyclohexa-1,3-diene (67)

A solution of 1g (65) and 2.4g DABCO (3 eq.) in 25 ml dichloromethane was cooled to 0° and 14.2 ml (2 eq.) 10% phosgene in dichloromethane was added over 30 minutes. The mixture was stirred for 30 minutes, filtered and the solvent evaporated to a small volume. The mixture was loaded onto a short neutral alumina column and eluted with dichloromethane. The product was a clear oil which darkened rapidly.

Yield 0.43g (49%)

NMR ^1H ($CDCl_3$) δ 2.5 (4H,s); 5.9 (2H,s)

^{13}C ($CDCl_3$) (ppm.) 22.7; 29.4; 119.2; 122.6; 123.5; 135.8; 162.8 (weak triplet).

IR (thin film) (cm^{-1}) 3400b; 2995; 2100; 1640; 1350; 940.

Attempted Wittig Reaction of (67) With Carbomethoxymethylene-triphenylphosphine

A solution of 0.2g (67) and 0.6g carbomethoxymethylenetriphenylphosphine in 20ml dry toluene was stirred under nitrogen overnight. T.l.c. showed that no reaction had occured, so the mixture was heated to reflux for 2 hours, during which period the mixture darkened perceptibly. T.l.c. showed that a plethora of compounds was present in the reaction mixture, which showed no isonitrile absorbance in the infra-red. No separation was attempted.

REFERENCES

1. T Hagedorn and U Eholzer, Angew. Chem. Int. Ed., 1962, 1, 212.
2. T Saegusa, I Murase and Y Ito, Tetrahedron., 1971, 27, 3795.
3. I Ugi and F K Rosendahl, Liebigs Ann. Chem., 1963, Bd 666, 65.
4. J E McMurry and J Melton, J. Am. Chem. Soc., 1971, 93, 5309, J. Org. Chem., 1973, 38, 4367.
5. G H Timms and E Wildsmith, Tetrahedron Lett., 1971, 195.
6. R B Boar, J F McGhie, M Robinson, D H R Barton, D C Horwell and R V Stick, J. Chem. Soc. Perkin Trans. I, 1975, 1237.
7. BDH Product N°. 30447
8. BDH Product N°. 26205
9. L F Fieser and M Fieser, Reagents for Organic Synthesis", Vol.1, p4 John Wiley and Sons, Inc, New York, 1967.
10. Idem, *Ibid.* Vol.2, p10.
11. B G Cox, private communication.
12. R E Schuster, J E Scott and J Casanova, Jr, Org. Synth., Coll. Vol. V, 772.
13. L Meszaros, Tetrahedron Lett., 1967, 4951.
14. A R Katritzky and L M Lagoroski, "Chemistry of the Heterocyclic N-Oxides" p227 and refs. therein, Academic Press, London, 1971.
15. M R Natale, Tetrahedron Lett., 1982, 23, 5009.
16. D Felix, C Winter and A Eschenmoser, Org. Synth. 55, 52.
17. M A T Dubas-Schluyter, W N S Specharnp and H O Huisman, Rec. Trav. Chim. Pays-Bas, 1972, 91, 157.
18. A I Vogel, "A Textbook of Practical Organic Chemistry" 3rd Ed., Longmans, London, 1966.

19. "Dictionary of Organic Compounds", G Harris, Ed., Eyre and Spottiswoode, London, 1965.

20. R Anliker, M Muller, J Wohlfahrt and H Heusser, Helv. Chim. Acta, 1955, 38, 1404.

AND NOW...

SOME INVESTIGATIONS INTO THE REARRANGEMENT OF THIOPHENIUM YLIDS

INTRODUCTION

The thiophene molecule is typically described as a planar ring with sp^2-hybridised carbon and sulphur atoms. The framework of the ring is formed by σ-bonding between these orbitals. This arrangement leaves one electron in the p_z orbital of each carbon atom. These p_z orbitals are orthogonal to the plane of the ring, and are consequently able to overlap, forming a π-electron cloud above and below the ring. As there are six π-electrons, a stable closed shell - the classical "aromatic sextet" - is formed. Thiophene thus behaves as a typical π-excessive heterocycle, showing for example a preference for electrophilic substitution over addition. The aromatic stabilisation energy of thiophene has been calculated as 121 kJ mol^{-1}, compared with a value of 172 kJ mol^{-1} for benzene[1].

The remaining sp^2-hybrid orbital on sulphur contains a lone pair of electrons which is not involved in bonding. In principle, therefore, the sulphur atom is potentially a target for electrophilic attack. In practice, as observed above, this is not the case, with the preferred site of electrophilic attack being the 2-position of the thiophene ring, if available.

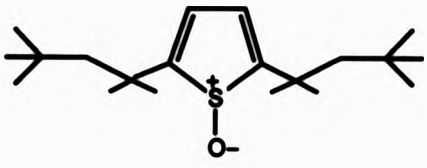
Powerful electrophiles will, however, attack sulphur, as has been shown by Brumlick and co-workers[2] who demonstrated that trimethyloxonium fluoroborate methylates thiophene at sulphur to form the S-methylthiophenium salt (1).

(1)

In S-alkylthiophenium salts, the geometry about sulphur is no longer planar, but pyramidal[3], implying sp^3-hybridisation of sulphur. This would be expected to cause a loss of aromatic stabilisation, as an electron pair in an sp^3-hybrid orbital will be less able to overlap with the p_z orbitals of adjacent carbon atoms. This is supported by MNDO calculations on the 1-methythiophenium ion[4], which suggest a greater degree of diene character. However, these conclusions are not borne out in practice, as S-alkylthiophenium salts do not in general behave as dienes in the Diels-Alder reaction. S-alkylthiophenium salts are, however, highly susceptible to nucleophilic attack at the methyl group, due to the nucleofugacity of the thiophene molecule.

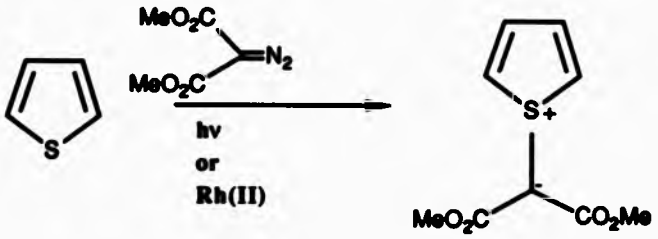
When the lone pair on sulphur is involved in bonding to oxygen, a much greater loss of aromatic stability is encountered. Thiophene-1-oxides are extremely unstable, undergoing spontaneous Diels-Alder dimerisation and in general behaving as anti-aromatic conjugated dienes. There is strong evidence that the sulphur atom in these compounds is sp^3-hybridised. In particular, in the dynamic proton n.m.r. spectra of (2), the methylene protons in the side-chains are diastereotopic, indicating pyramidal geometry about sulphur. The free energy barrier to inversion about sulphur was determined as 61.9 kJ mol^{-1} .[5] This compares with a value of 150 kJ mol^{-1} for diaryl sulphoxides. The considerable

lowering of this activation barrier in the thiophene derivative has been attributed to stabilisation of the planar, and therefore aromatic, transition state.



(2)

Reaction of thiophene with dimethyl diazomalonate under photolytic[6] or rhodium (II) catalysed[7] conditions results in the formation of the thiophenium ylid (3), which is a stable crystalline solid. Under rhodium catalysis, formation of (3) is virtually quantitative.

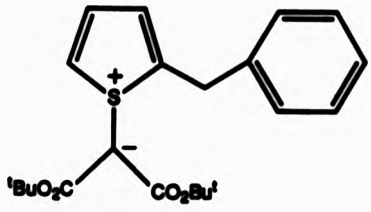


(3)

The structure of this compound has been established by X-ray crystallography[6]. The geometry about sulphur is unquestionably pyramidal, with the plane containing the two ester groups lying orthogonal to the plane of the thiophene ring. This pyramidal geometry

implies some degree of sp^3 hybridisation, and this compound might therefore be expected to show a similar degree of reactivity to that of the thiophenium salts and oxides. That this is not the case is amply demonstrated by the indefinite shelf life of thiophenium ylids in general. Unlike the salts and oxides, the thiophene ring in these ylids retains a considerable degree of aromatic character. The chemical shifts of the ring protons of thiophenium ylids are effectively identical to those of the parent thiophenes, suggesting that no loss of ring current occurs on bonding to sulphur. This implies that the lone pair on sulphur must still be fully involved in the delocalised π-system, which is unlikely if the sulphur atom is sp^3-hybridised. Some degree of d-orbital participation in the bonding is therefore likely.

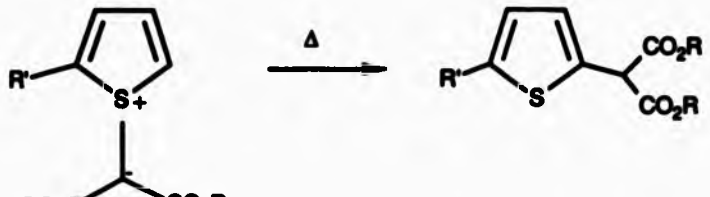
Dynamic proton n.m.r. studies[8] of (4), in which the benzylic protons are diastereotopic, indicate a free energy barrier to inversion about sulphur of 51.7 kJ mol^{-1} , which is somewhat lower than that observed for thiophene-1-oxides. As the ester groups in (4) are non-equivalent, analysis of the dynamic proton n.m.r. spectra of these protons provides a probe for rotation about the ylidic S-C bond. A combination of this and SCF-MNDO calculations provides an estimate of the rotational free energy barrier of 113 kJ mol^{-1}. This high rotational barrier has been attributed to pπ-dπ bonding between carbon and sulphur.



(4)

Thermolysis of thiophenium ylids in refluxing toluene solution results in quantitative conversion to thiophene-2-malonates (6)[9] (scheme 2).

Scheme 2

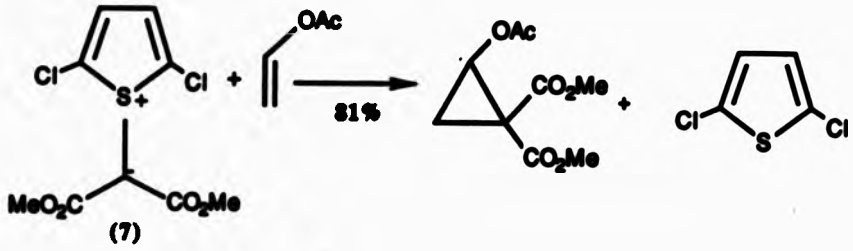


(5) (6)

This reaction is unquestionably unimolecular in nature. Thermolysis of (5, R=Me, R'=H) in 2-methylthiophene resulted in formation of (6, R=Me, R'=H) exclusively, with none of the 2,5-disubstituted product which would be expected if the rearrangement proceeded by initial decomposition of the ylid into thiophene and carbene. Further evidence that the reaction is intramolecular was furnished by thermolysis of (5, R=Me, R'=H) in the presence of a variety of olefins, which did not yield any of the cyclopropanated products which would be formed by reaction of the liberated carbene with the olefin.

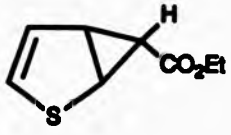
In contrast to this, it should be noted that if the ylid is substituted in positions 2 and 5 by halogen, the rearrangement cannot occur and decomposition into thiophene and carbene does indeed occur[10]. Thermolysis of the ylid (7) in the presence of a variety of olefins yields cyclopropanated products (eg scheme 3).

Scheme 3



(7)

Thiophenium ylids are only stable if the ylid carbon is flanked by two electron-withdrawing groups (eg ester, cyclopentadiene etc.). Reaction of thiophene with ethyl diazoacetate yields only the cyclopropanated product (8)[10].

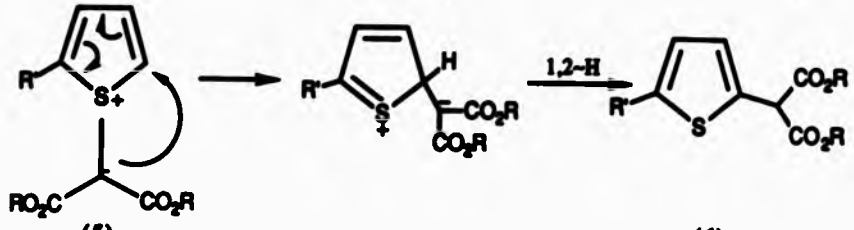


(8)

It is possible that this and similar reactions proceed by initial electrophilic attack on sulphur to form the ylid. The subsequent fate of this ylid will depend on its stability. To throw some light on the subject, a study of the rearrangement of carbonyl-stabilised thiophenium ylids was undertaken.

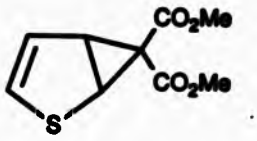
As described above, there is convincing evidence that the rearrangement of thiophenium bis(alkoxycarbonyl)methylides is intramolecular in nature. It was initially proposed[9] that the 2-(2'-thienyl)malonates (6) were formed by an intramolecular "walk" of the ylid carbon atom from sulphur to position 2 of the ring (scheme 4).

Scheme 4



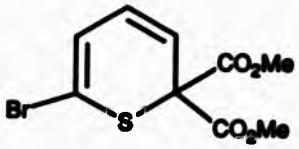
(5) (6)

As part of an investigation into the generality of this reaction, a crude kinetic study of the rearrangement of (5, R=Me, R'=H) was undertaken. It was observed that, on heating for short contact times (ca. 2 minutes) in refluxing xylene followed by rapid quenching, a yellow oil was formed. The proton n.m.r. spectrum of this product revealed that it was a mixture of the malonate (6, R=Me, R'=H) and another compound. The spectrum of this unknown product showed a number of vinylic proton signals between δ6 and 7, and it was initially thought that this compound might be the cyclopropanated species (9).



(9)

Purification of this compound by column chromatography did not yield any further information on its structure. However, a similar intermediate was observed in the rearrangement of the 2-bromo ylid (5, R=Me, R'=Br). In this case, the isolated mixture was a deep red oil, in which the proportion of the intermediate to the malonate was somewhat higher than in the previous case. Close examination of the ^{1}H and ^{13}C n.m.r. spectra of the purified compound suggested that the structure was in fact that of the (2H)-thiopyran (10).



(10)

Due to the unexpected nature of this intermediate, a crystalline derivative was desired to enable detailed analysis and preferably an X-ray crystal structure to be carried out, to confirm that this assignment was in fact correct. A number of methods of derivatisation of (10) were attempted.

(2H)-Thiopyrans such as (10) are conjugated dienes, held in the *cisoid* configuration, and as such would therefore be expected to undergo Diels-Alder cycloaddition with suitable dienophiles. However, (10) failed to react with either maleic anhydride or N-phenylmaleimide at room temperature. At elevated temperatures, only the thiophene-2-malonate (6, R=Me, R'=Br) was formed. It would appear, therefore, that the activation barrier to cycloaddition is somewhat higher that that for rearrangement.

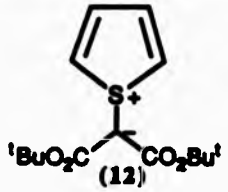
Further attempts at derivatisation were concerned with attempted cleavage of one or both ester groups, either by hydrolytic or reductive methods.

Initial attempts to saponify the ester groups with sodium hydroxide yielded only tars. Further attempts to liberate the free acid with trimethylsilyl iodide[12] and boron tribromide[13] met with a similar lack of success, no reaction being observed in either case. Aluminium trichloride induced polymerisation to a black tarry material which defied identification.

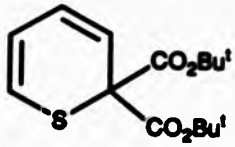
The thiopyran (10) also proved remarkably resistant to lithium aluminium hydride reduction, no reaction being observed on prolonged stirring with the reducing agent.

As all attempts to derivatise (10) had failed, an alternative approach was required. It was thought that, if the methyl esters were replaced with tertiary butyl esters, cleavage of the ester function would be greatly facilitated.

Accordingly, thiophene was reacted in the presence of rhodium (II) hexanoate with di-t-butyl diazomalonate to form the ylid (12). This was then heated for 2 minutes in refluxing xylene and quenched by rapidly cooling in ice. During this process, a solid material crystallised in the flask. Recrystallisation of this material yielded the thiopyran (13). The structure of (13) was confirmed by ^{1}H and ^{13}C n.m.r. spectroscopy.

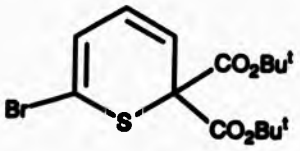


(12)

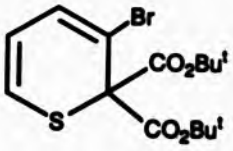


(13)

The intermediate having been positively identified, attention was then turned to the regiochemistry of this rearrangement. The rearrangement of the ylid (5, R=^{t}Bu, R'=Br) gave rise to a thiopyran intermediate as before, the structure of which was proved by X-ray crystallography to be (14)[14].



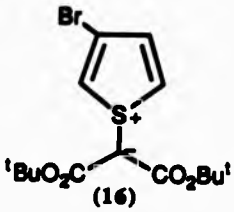
(14)



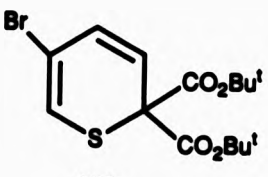
(15)

No (15) was formed, and it is likely that this is due entirely to steric effects.

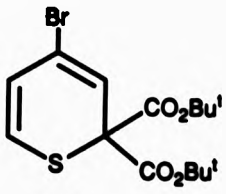
As in the above case, two possible products, (17) and (18), can be formed from the rearrangement of the 3-bromo ylid (16). Reaction of 3-bromothiophene with di-t-butyl diazomalonate under Rh(II) catalysis did not in this case yield the expected ylid (16), but the thiopyran (17) was formed in low yield. None of the isomer (18) was isolated. That the structure was indeed that of (17) was established by X-ray crystallography[14].



(16)



(17)

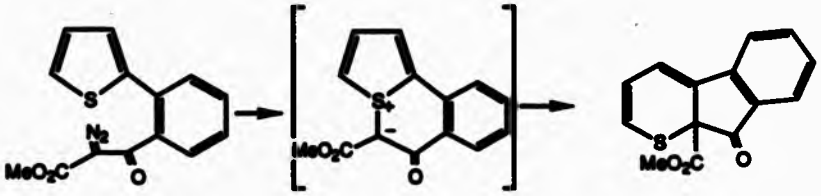


(18)

As in the previous case, the rearrangement appears to take place to maximise the distance between the ester groups and the bulky bromine atom, suggesting that the regiochemistry is sterically controlled.

The mechanisms of the two rearrangements, from ylid to thiopyran and from thiopyran to thiophene-2-malonate, were of some interest. A study of the literature was undertaken to establish whether precedents for these interesting molecular rearrangements existed.

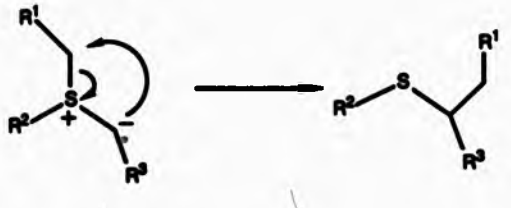
(2H)-Thiopyran (20) formation in the rearrangement of a thiophenium ylid has been observed, by Skramstadt et al[15].



(19) (20)

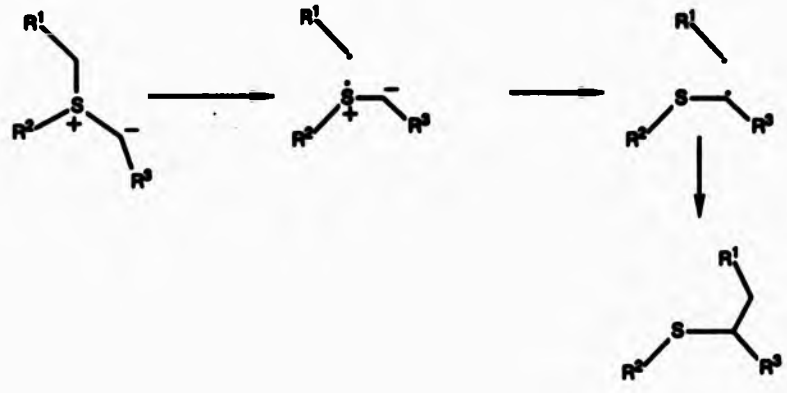
The authors suggested that the thiopyran intermediate in this case was formed by Stevens rearrangement of the intermediate ylid (19). Sulphur ylids are known to undergo Stevens-type rearrangements[16] (scheme 5).

Scheme 5



This rearrangement is a 1,2-migration of an alkyl group, and as such is thermally "forbidden" as a concerted process, and the mechanism has been the source of some puzzlement. In certain cases, CIDNP effects have been observed, implying that a radical mechanism operates[17] (scheme 6).

Scheme 6



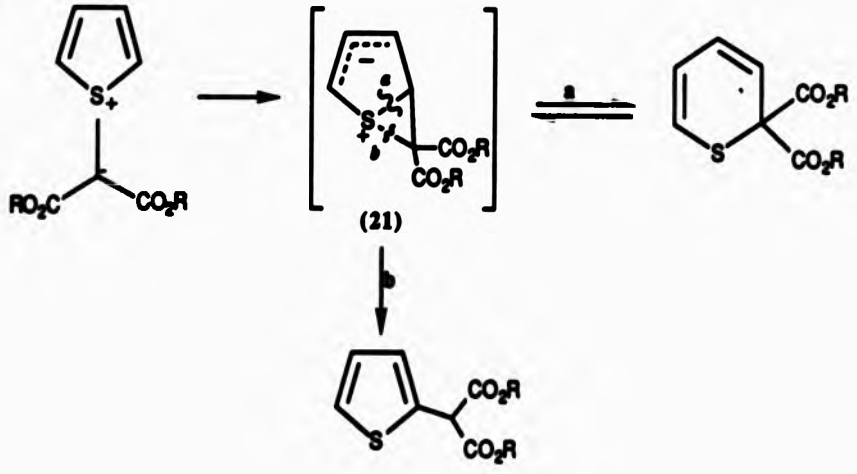
However, CIDNP is not observed in all cases, and migration of the alkyl group can occur with complete retention of stereochemistry[18]. An alternative mechanism has been proposed, at least for the Stevens rearrangement of nitrogen ylids, in which migration occurs in a concerted process, in apparent violation of Woodward-Hoffmann rules[19]. Although in such a concerted process the transition state will be antiaromatic, the loss of charge separation in the course of the reaction suggests that the rearrangement will be strongly exothermic. In accordance with the Hammond postulate, this implies that the transition state will lie close to the starting material on the reaction profile. In these circumstances, the antiaromaticity of the transition state will not be significant.

In a quantitative study of CIDNP effects in the Stevens rearrangement of nitrogen ylids, Dolling et al[20] have concluded that, although radical pair formation does occur, the major pathway is *via* the concerted mechanism. An alternative hypothesis is that the radical pairs formed recombine too rapidly for detection of CIDNP, and too rapidly even for rotation. It is conceded that there is little difference between a radical process this fast and a concerted process.

Whether the rearrangement of thiophenium ylids takes place by a radical or concerted process, the result will be the same. It should be noted that no CIDNP effect has been observed in this rearrangement[21]. However, this does not necessarily preclude radical involvement.

An alternative mechanism for the formation of (2H)-thiopyrans, which could also account for their conversion to thiophene-2-malonates, involves the intermediacy of (21) (scheme 7).

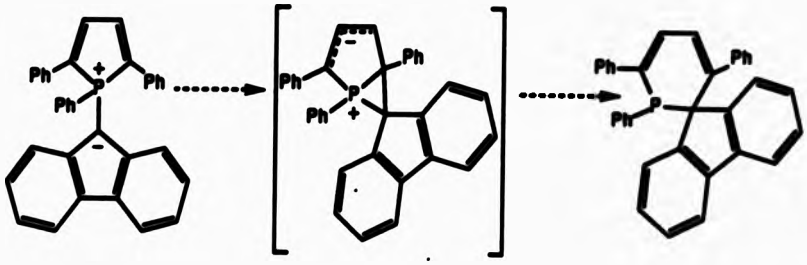
Scheme 7



Cleavage of bond *a* in this intermediate would give rise to the thiopyran, whereas cleavage of bond *b* would give the malonate. Whether this species is a true intermediate or a transition state, this mechanism requires that thiopyran formation is a reversible process. It should also be noted that the only difference between this mechanism of thiopyran formation and a concerted process lies in the timing of bond-breaking and bond-forming.

A similar intermediate has been proposed in the rearrangement of a closely related phosphorus system (scheme 8)[22].

Scheme 8



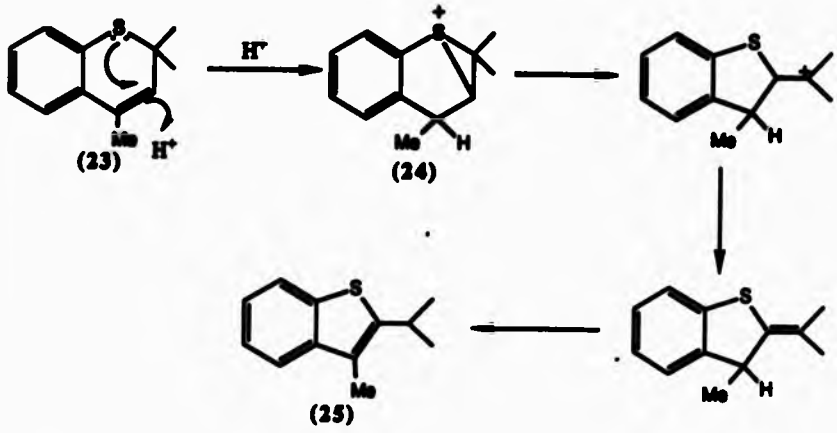
(22)

As was the case with the thiophene system, no CIDNP effect has been observed in this rearrangement, and the bicyclic ylid (22) (cf. (21)) was suggested as an intermediate.

Ring contraction of thiopyrans to thiophenes has been observed in a few cases. For example, thiachromens (eg (23)) react with polyphosphoric acid to form benzothiophenes (25)[23]. A bicyclic intermediate (24) which bears some resemblance to (21) has been suggested, although the important

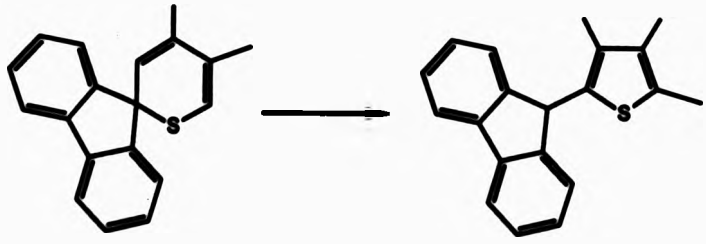
difference is that this is an acid-catalysed process rather than a purely thermal one (scheme 9).

Scheme 9



Ring contraction of a thiopyran to a thiophene has also been observed by Praefke and Weichsel[24], although in this case no mechanistic interpretation was forthcoming (scheme 10).

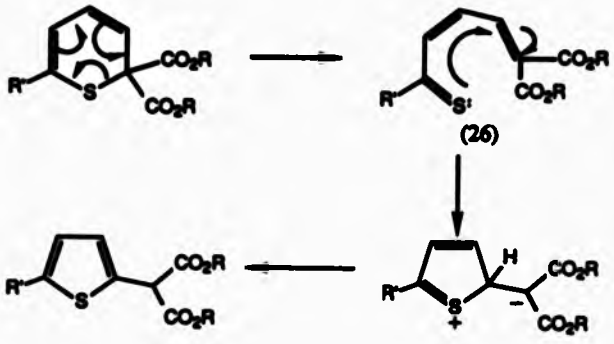
Scheme 10



An alternative mechanism for the conversion of (2H)-thiopyrans to thiophenes is *via* electrocyclic ring-opening to the thioaldehyde (26),

which could then undergo nucleophilic Michael-type ring closure (scheme 11).

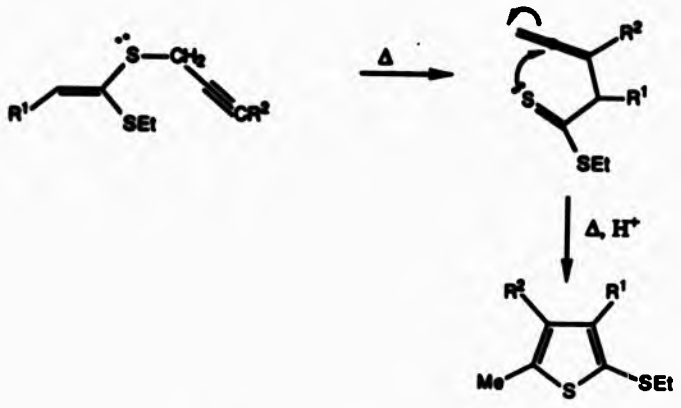
Scheme 11



The final proton transfer is a 1,2-shift, and as such is thermally forbidden in a concerted reaction. However, minute traces of acid contaminants in the reaction would facilitate this process.

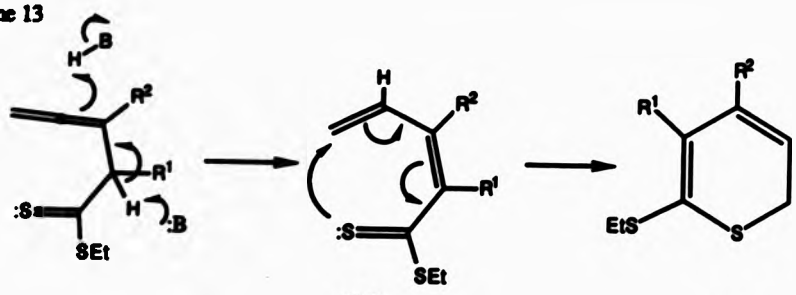
Thioaldehydes, or thials, are extremely reactive species, and have not been isolated. They have, however, been invoked as reactive intermediates in a number of reactions, and have been trapped, mainly as Diels-Alder adducts. Little evidence exists for nucleophilic behaviour of the thial sulphur atom, although Brandsma *et al* have proposed a nucleophilic ring closure to account for thiophene formation in the thermal rearrangement of propargyl vinyl sulphides[24] (Scheme 12).

Scheme 12



Thiophene formation was observed under neutral or acidic conditions, whereas in the presence of triethylamine the thiopyran (28) was formed. It was suggested that, under the influence of the base, the allene rearranges to the conjugated system (27), which then undergoes ring closure. This process is formally the reverse of the electrocyclic ring-opening suggested above (scheme 13).

Scheme 13

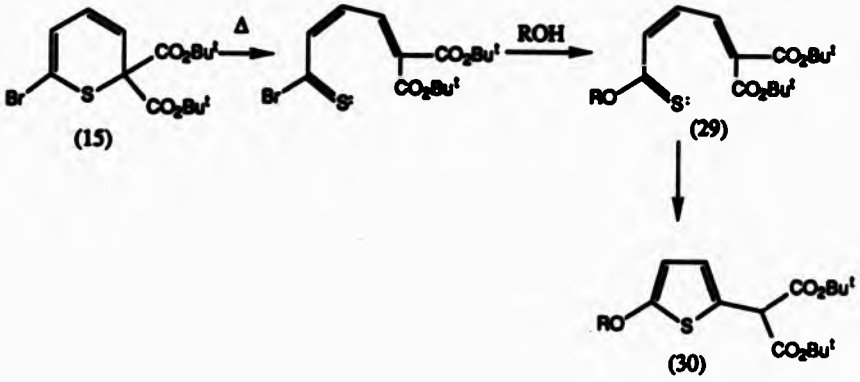


(27) (28)

The question of whether the thiophene originates from rearrangement of the thiopyran was not addressed, but cannot be ruled out.

In the case of the 6-bromo-substituted thiopyran (15), the electrocyclic ring-opening would generate a thio-acid bromide. The thiocarbonyl group in this compound would be expected to be highly susceptible to nucleophilic attack by, for example, alcohols to form thio-esters. Thus, pyrolysis of this thiopyran in an alcoholic medium would be expected to generate either the ester (29) or the ring-closure product (30) (scheme 14).

Scheme 14



However, thermolysis of (15) in a variety of alcohols at a range of temperatures yielded only the previously observed rearrangement product, with no products arising from trapping of the thio-acid bromide. This does not, however, rule out this species as an intermediate. It is possible that this is indeed formed, but that ring-closure is substantially faster than esterification. If the intermediate is held in the all-*cis* configuration, it is ideally set up for ring-closure, which must occur before bond rotation can take place.

At this point, no definite conclusions could be drawn about the mechanisms of these rearrangements. To obtain further information, which might shed some light on the matter, a kinetic study of both rearrangements was undertaken, the results of which are described in the next section.

METHODS

The kinetics of the rearrangement of thiophenium ylids to 2H-thiopyrans were studied by following the reactions by ultraviolet spectroscopy. The spectra of the thiopyrans showed an absorbance at 320 nm which was absent in the spectra of the ylids. The position of this band was unaffected by solvent.

The reactions were followed spectrophotometrically using a Pye-Unicam SP8-300 UV/Visible spectrophotometer fitted with a thermostatted cell compartment with cell changer. The system was controlled by an Apple IIe microcomputer, which was programmed[26] to record automatically both temperature (T) and absorbance (A) for up to 4 cells at user-specified time intervals. First-order rate constants were calculated using a non-linear least squares method. This procedure could be carried out automatically by the computer on completion of the kinetics run, or at a later time from data input by the user.

The rearrangements were carried out in three solvents - toluene, 1,4-dioxane and acetonitrile in order of increasing polarity. These solvents were chosen because of their reasonably high boiling points coupled with their ability to dissolve the ylids in the necessary concentration. The use of three such different solvents would hopefully enable determination of the effects of solvent polarity on the reaction rates and activation parameters. The rearrangements were carried out at various temperatures in the range 40-80° to enable activation parameters to be determined. Below this range, the reactions were too slow, and the upper limit was the maximum temperature at which the equipment could be operated safely and without damage. This upper limit also approaches the boiling points of acetonitrile and 1,4-dioxane.

Activation parameters were calculated using the Eyring equation (equation 1):

$$k = K \frac{k_B T}{h} e^{-\Delta G^{\ddagger}/RT} \qquad (1)$$

where k_B = Boltzmann constant
h = Plank constant
R = Gas constant
K = Transmission coefficient (assumed = 1)
k = Rate constant
T = Absolute temperature
$\Delta G^{\ddagger}$ = Free energy of activation.

Substituting the expanded term for free energy, $\Delta G = \Delta H - T\Delta S$, this expression can be expanded and expressed logarithmically as equation 2:

$$\ln\left(\frac{k}{T}\right) = -\frac{\Delta H^{\ddagger}}{RT} + \frac{\Delta S^{\ddagger}}{R} + \ln\left(\frac{k_B}{h}\right) \qquad (2)$$

where $\Delta H^{\ddagger}$ = enthalpy of activation
$\Delta S^{\ddagger}$ = entropy of activation

Thus a plot of $\ln(k/T)$ vs $1/T$ will give a straight line with slope = $-\Delta H^{\ddagger}/R$ and intercept = $\Delta S^{\ddagger}/R + \ln(k_B/h)$.

The investigation of the kinetics of the rearrangement of the 2H-thiopyrans to thiophene-2-malonates was less straightforward. The above procedure was not possible as the reactions were too slow at the operating temperatures of the automated system, and a manual, batch system was required.

The appropriate solvent was placed in a three-necked flask equipped with

reflux condenser, thermometer and stopper, and the flask immersed in a thermostatted oil bath preheated to the required temperature. Once the temperature within the flask had reached equilibrium, the thiopyran was added and the flask vigorously shaken. An aliquot of the solution was immediately withdrawn and cooled, and the UV spectrum over the range 200-450 nm recorded. Provided that this spectrum was satisfactory, ie that the absorbance at 320 nm was between 1 and 3, further aliquots were withdrawn at intervals, cooled and the UV spectra recorded. The absorbance at a selected wavelength was then plotted against time.

The selection of the appropriate wavelength was less straightforward than in the previous experiments. In the case of the dimethyl ester (3), the absorbance at 320 nm was absent in the product, and a plot of ln(absorbance) at this wavelength vs time was linear, characteristic of a first-order reaction. However, in the t-butyl esters (12 and 5,R=Bu^t,R'=Br), the product also absorbed at this wavelength and the plot of absorbance vs time was very difficult to interpret. However, in the range 290-300 nm, a trough in the spectra of the thiopyrans corresponded to a shoulder in the spectra of the products. Thus it was possible to follow the reaction by monitoring the increasing absorbance in this range, corresponding to increasing concentration of product. Consequently, whereas in the case of the dimethyl ester (3) the reaction was monitored by following the disappearance of starting material, in the latter cases the formation of product was monitored.

Obviously, the potential errors inherent in this method are somewhat greater than in the automated procedure, particularly with regard to

temperature stability. The automated system was capable of maintaining temperatures constant to within ± 0.1°, whereas the temperature of the oil bath used in the batch system was only constant to within ± 1°. The number of readings obtained for each run (ca. 20) was also considerably less than was used with the automated system (ca. 100).

Due to the more complicated nature of this rearrangement, rate constants could not be obtained for the formation of product, but were obtained graphically for the disappearance of (3) by plotting $\ln(A_{\infty}-A_t)$ vs time, and activation parameters could be estimated using the graphical method described above.

RESULTS

1. Rearrangement of Thiophenium Ylids to 2H-Thiopyrans.

The rate constants (k) for the rearrangements of the ylids (3,12 and 5,R=Bu^t, R'=Br)) to the corresponding thiopyrans in the three solvents are tabulated in the Appendix. Unless otherwise indicated, all reactions were carried out in duplicate. Tabulated below are mean rate constants derived from these data. It should be noted that the rearrangement of (5,R=Bu^t,R'=Br) in acetonitrile was only carried out at 75°, as at lower temperatures the reaction was too slow to be monitored.

Table 1: 1st Order Rate Constants for the Rearrangement of Thiophenium Bis(methoxycarbonyl)methylide (3)

Solvent	T/K	$k/10^{-5}s^{-1}$
Toluene	74.4	99.2 (±11.0)
	64.9	40.2 (± 1.1)
	55.7	13.8 (± 0.5)
	46.3	4.46 (± 0.0)
Dioxane	74.0	71.4 (±10.0)
	64.7	22.7 (± 1.6)
	55.6	8.4 (± 1.1)
	46.3	2.29 (a)
Acetonitrile	75.7	30.8 (± 1.3)
	68.8	14.2 (± 0.1)
	60.2	5.13 (± 0.0)
	55.7	2.79 (± 0.14)

(Figures in parentheses represent estimated error of k.)

a. Only one result was obtained at this temperature.

Table 2: 1st Order Rate Constants for the Rearrangement of Thiophenium Bis(t-butoxycarbonyl)methylide (12).

Solvent	T/K	k/ 10^{-5}s^{-1}	
Toluene	74.34	187	(±1)
	64.95	70.0	(± 0.1)
	55.83	23.6	(a)
	46.58	7.90	(± 0.08)
Dioxane	73.92	119	(a)
	64.80	46.2	(a)
	54.97	15.7	(± 0.1)
	46.25	6.25	(± 0.04)
Acetonitrile	72.82	26.4	(± 1.8)
	63.77	10.4	(± 0.1)
	55.26	3.69	(± 0.09)
	46.13	1.25	(± 0.00)

Table 3: 1st Order Rate Constants for the Rearrangement of 2-Bromo-thiophenium Bis(t-butoxycarbonyl)methylide (5 BrBu^t B'nBr)

Solvent	T/K	k/10^{-5}s^{-1}	
Toluene	73.87	15.6	(± 0.5)
	65.11	6.62	(± 0.01)
	55.82	2.33	(a)
	46.00	0.71	(± 0.01)
Dioxane	74.73	13.8	(± 0.3)
	64.30	4.78	(a)
	56.04	1.86	(± 0.02)
	46.18	0.64	(± 0.01)
Acetonitrile	72.71	0.47	(± 0.09)

(Figures in parentheses represent estimated error in k.)
a. Only one result was obtained at this temperature.

These data are represented graphically as Eyring plots in Figures 1-3 , and the activation parameters derived from these plots are given in Table 4 below.

Table 4: Activation Parameters for the Rearrangements of Thiophenium Ylide to 2H-Thiopyrans.

Ylid	Solvent	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J K^{-1}mol^{-1}	Correlation Coefficient
3	Toluene	99.7	-16.0	0.999
	Dioxane	110.6	12.3	0.999
	Acetonitrile	110.9	4.7	1.000
12	Toluene	102.9	-2.0	1.000
	Dioxane	95.5	-26.8	0.999
	Acetonitrile	99.5	-27.4	0.998
5, R=But	Toluene	99.7	-31.3	0.999
R'=Br	Dioxane	96.0	-44.1	0.999

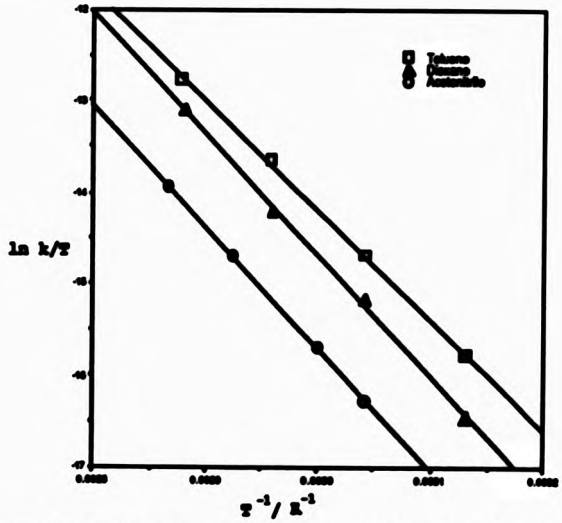


Figure 1: Eyring Plots for the Rearrangement of Thiophenium Bis(methoxycarbonyl)methylide (3).

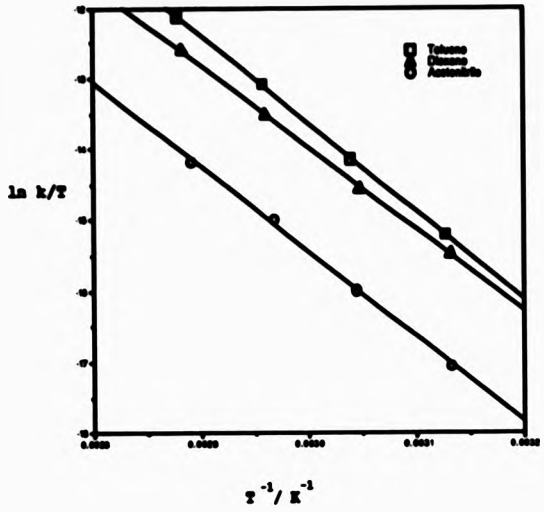


Figure 2: Eyring Plots for the Rearrangement of Thiophenium Bis(t-butoxycarbonyl)methylide (33).

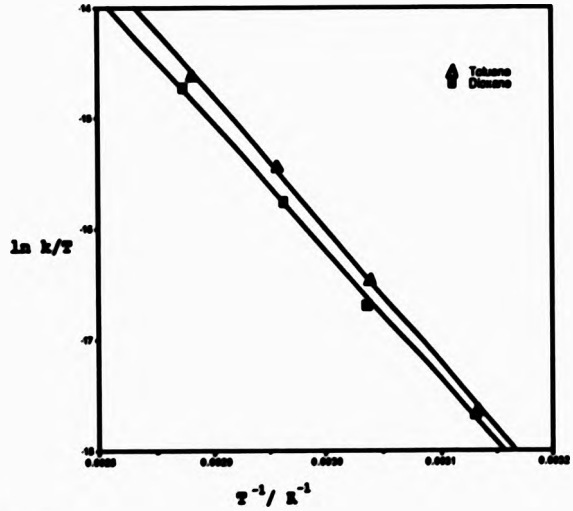


Figure 3: Eyring Plots for the Rearrangement of 2-Bromothiophenium Bis(t-butoxycarbonyl)methylide (34).

2. Rearrangement of 2H-Thiopyrans to Thiophene-2-malonates.

The absorbance values (A) measured during the rearrangements of the thiopyrans are recorded in the Appendix. In the case of the dimethyl ester, the reaction was monitored by following the disappearance of the starting material, and the reaction showed first-order kinetics. The first-order plots for the reactions at 91 and 111° are shown in figures 4 & 5 , and the rate constants, including that determined using the automated system, are given in Table 5.

Table 5: Rate Constants for the Rearrangement of 2,2-Bis(methoxycarbonyl) 2H-thiopyran in Toluene.

T/K	k/s^{-1}
79.4	1.53×10^{-5} a
91	3.4×10^{-5} b
111	5.8×10^{-5} b

a. Obtained by automated system.

b. Obtained by manual batch method.

The 3-point Eyring plot of these data is shown in Figure 6. The activation parameters derived from these data are:

$$\Delta H^{\ddagger} = 43 \text{ kJ mol}^{-1}$$

$$\Delta S^{\ddagger} = -42 \text{ J K}^{-1} \text{ mol}^{-1}$$

However, the correlation coefficient of this plot is very poor, at 0.933, and these figures must be treated with some caution.

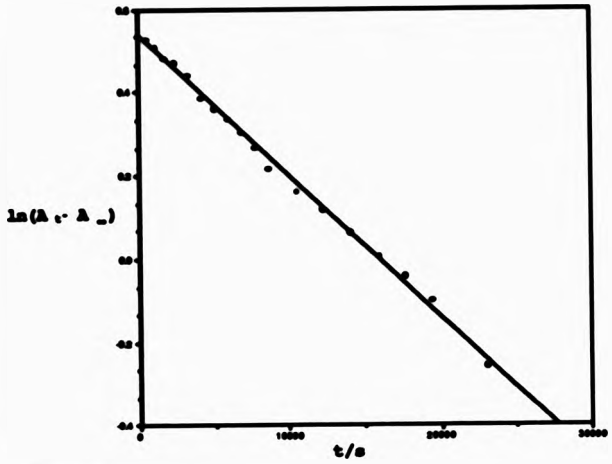


Figure 4: First-Order Plot for the Rearrangement of 2,2-Bis(methoxycarbonyl)-2H-thiopyran in Toluene at 91°.

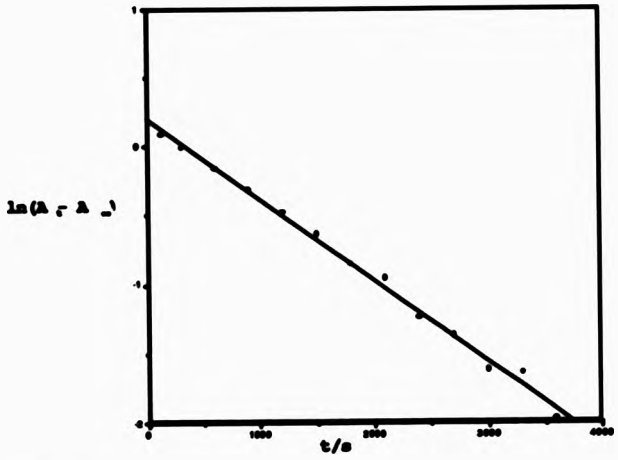


Figure 5: First-Order Plot for the Rearrangement of 2,2-Bis(methoxycarbonyl)-2H-thiopyran in Toluene at 111°.

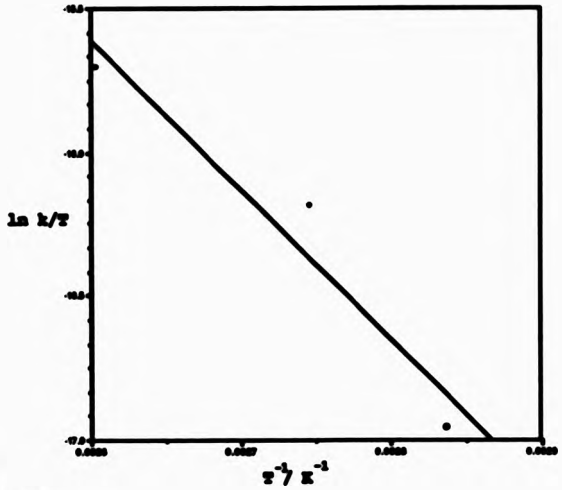


Figure 6: Eyring Plot for the Rearrangement of 2,2-Bis(methoxycarbonyl)-2H-thiopyran in Toluene.

The measured absorbance values for the rearrangements of the other two thiopyrans, (13) and (14), given in the Appendix, are plotted vs time in Figures 7 and 8 respectively. Due to the complicated nature of these rearrangements, which do not have simple first-order kinetics, no rate constants were determined.

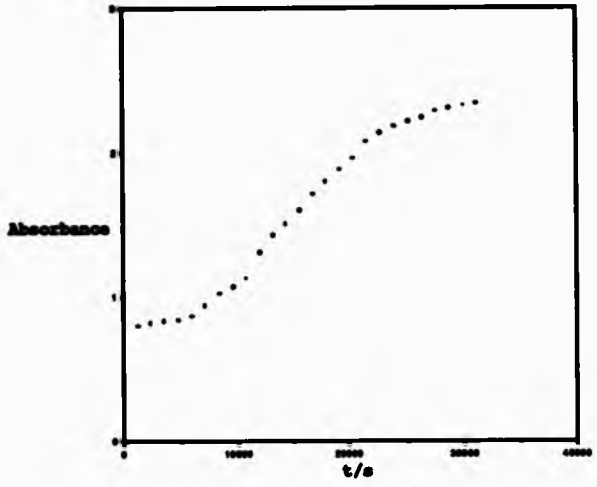


Figure 7: Plot of Absorbance vs Time for the Rearrangement of 2,2-Bis(t-butoxycarbonyl)-2H-thiopyran.

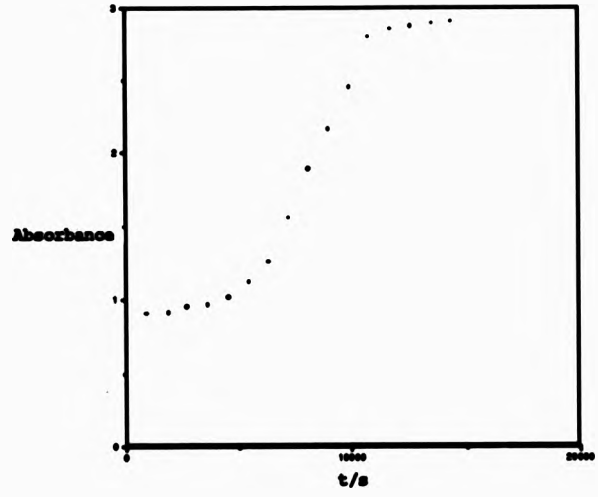


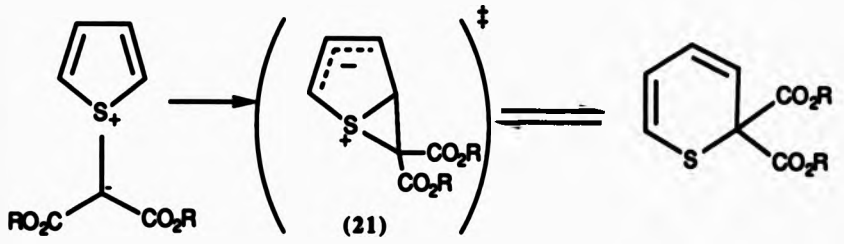
Figure 8 : Plot of Absorbance vs Time for the Rearrangement of 2,2-Bis(t-Butoxycarbonyl)-6-bromo-2H-thiopyran

Discussion

1) Rearrangement of Ylids to 2H-thiopyrans.

The formation of 2H-thiopyrans from thiophenium ylids in the three examples studied showed simple first-order kinetics. This is conclusive evidence that no long-lived intermediates are formed in this reaction, ie that it is probably a one-step process. Thus, if the mechanism proposed initially (see Scheme 15, below) is correct, the species (21) cannot be a long-lived intermediate, and is proposed here as the transition state in a single step process.

Scheme 15



The rate of rearrangement of each of the ylids showed a decrease with increasing solvent polarity (Tables 1-3, pp 154-155). However, this decrease in rate was in general only marginal, and any conclusions drawn from the limited experimental data available must be treated with some caution. Nevertheless, such a solvent effect, although slight, does suggest that more polar solvents are able to solvate the starting material more effectively than the transition state. This lends some support for the existence of (21) as the structure of the transition state, this being less polar than the ylid, and thus less well solvated by polar solvents.

The enthalpies of activation for the various rearrangements show no obvious trend (Table 4, p156). In the rearrangement of the dimethyl ester (3), the enthalpy of activation is significantly (ca. 10%) greater in dioxane than in toluene, whereas in the rearrangements of the di-t-butyl esters (12 and 5, R=Bu^t, R'=Br) the value in dioxane is some 5% lower than that in toluene. The enthalpy of activation does not change significantly in the rearrangements of either (3) or (12) on changing the solvent from dioxane to acetonitrile.

Although the C-S bond dissociation energies for thiophene derivatives are not available, the values for dialkyl sulphides are of the order of 290 kJ mol^{-1}.[27] The observed enthalpies of activation are appreciably lower than this, providing support for the hypothesis that a radical mechanism does not operate in this rearrangement. If such a mechanism were in operation, activation would in all likelihood involve C-S bond scission, which would require an enthalpy input comparable with the bond dissociation enthalpy. Delocalisation of the resultant radical would be unlikely to account for a reduction in enthalpy of activation to the observed value of ca. 100 kJ mol^{-1}.

If the rearrangement does proceed *via* the transition state (21), a number of factors are likely to contribute to the enthalpy of activation. Whereas the starting ylid is aromatic, (21) is not, and loss of aromatic stabilisation energy is likely to make a substantial contribution to $\Delta H^{\ddagger}$. In addition to this, (21) contains a highly strained thiabicyclo-[3.1.0]-hexane system. Introduction of this ring strain is likely to raise the activation enthalpy further. These factors will be

offset to some degree by the enthalpy liberated by formation of a new σ-bond. A figure of 100kJ mol^{-1} does not therefore seem unreasonable for the conversion of the ylid to (21). It is worth noting that the energy difference between (3) and (21) has been calculated[28] as 128 kJ mol^{-1}. Given that this figure is for the gas phase reaction, and therefore takes no account of the effects of differential solvation, it is in reasonable agreement with the observed figure.

The entropy of activation of this rearrangement is somewhat more difficult to predict. The substantial loss of conformational freedom experienced on formation of the rigid bicyclic system in (21) would suggest that the entropy of activation would be large and negative. However, the degree of solvation and therefore the degree of order in the solvent, will also affect $\Delta S^{\ddagger}$. As mentioned above, it is likely that the transition state will be less well solvated than the starting material in polar solvents, and this would lead to a positive contribution to the entropy of activation. These two opposing factors would be expected to give rise to a low value for the entropy of activation, although the sign is more difficult to predict.

The experimental values obtained for the entropies of activation for these rearrangements (Table 4, p156) are in general small and negative. In the rearrangements of the two di-t-butyl esters, a slight trend is observed for $\Delta S^{\ddagger}$ to become more negative with increasingly polar solvents. However, as the differences between the values are not appreciably greater than the possible experimental error, this trend may not be real or significant.

2. Rearrangement of 2H-Thiopyrans to Thiophene-2-malonates.

The rearrangement of the thiopyran dimethyl ester was monitored by following the disappearance of the starting material. Not surprisingly, the results were consistent with a first order process. The rate of this rearrangement is considerably slower than that for the formation of the thiopyran. Due to the poor correlation coefficient of the Eyring plot (figure 6, p160), any mechanistic interpretations based on the activation parameters can only be tentative.

The results obtained for the rearrangements of the two di-t-butyl esters (13) and (14) were more complicated, and potentially more informative. Due to the complexity of the UV spectra obtained during these reactions, the disappearance of starting material could not be monitored, and the reactions were followed by monitoring the total absorbance. This process did not show first-order kinetics. The absorbance vs time curves (Figures 7 & 8, p 161) were sigmoid in shape. This type of curve is characteristic of a process in which two consecutive reactions occur.

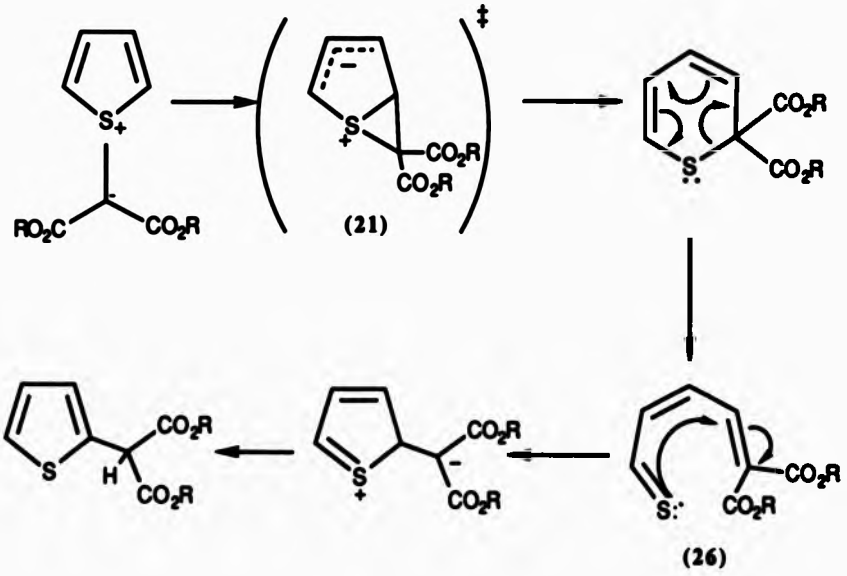
For such a process to operate, a relatively long-lived intermediate must be formed. This immediately rules out the mechanism proposed in Scheme 7 (p 143). As described above, the rearrangement of the ylids to the thiopyrans is a straightforward first-order process, with no long-lived intermediates intervening. The two processes therefore cannot share a common intermediate.

The data obtained above are consistent with the mechanism proposed in Scheme 11 (p 146), in which the intermediate is the thiocarbonyl compound (26).

However, without further evidence, this can but remain speculation.

In conclusion, the evidence gathered to date on the two rearrangements is consistent with the following reaction scheme:

Scheme 15



Further work is required before any firm conclusions can be drawn. Thiones are considerably less reactive than thials. It follows that if the thiopyran contains an alkyl residue at position 6, the intermediate, if the above mechanism is correct, should be somewhat longer lived. It may thus be possible for this intermediate to be trapped, or detected spectroscopically. It is also possible that a sufficiently stable thione intermediate might be isolable.

Further evidence to support this mechanism (or otherwise) could be furnished by attempted synthesis of α,β-γ,δ-unsaturated thials, to determine whether ring-closure to thiophenes does indeed take place.

APPENDIX

Given in tables 1 to 3 below are the rate constants for the rearrangements of the three ylids (3,12 and 5,R=But,R'=Br) to the corresponding 2H-thiopyrans, as determined using the computer-driven system described in the Methods section. Included in Table 1 is the rate constant for the rearrangement of (3) in toluene at 64.85° determined by graphical methods, as an illustration of the accuracy of the automated system.

Table 1: Rate constants for the rearrangement of thiophenium bis(methoxycarbonyl)methylide (3)

Solvent	Temperature/°C	Rate Constant/s^{-1}
Toluene	74.34	1.103×10^{-3}
	74.35	8.812×10^{-4}
	64.86	3.912×10^{-4}
	64.85	4.128×10^{-4}
	64.85	4.110×10^{-4} a
	55.67	1.433×10^{-4}
	55.67	1.327×10^{-4}
	46.26	4.469×10^{-4}
	46.26	4.445×10^{-5}
Dioxane	73.97	8.145×10^{-4}
	73.97	6.141×10^{-4}
	64.70	2.426×10^{-4}
	64.70	2.109×10^{-4}
	55.64	7.353×10^{-5}
	55.63	9.648×10^{-5}
	46.26	2.279×10^{-5}
Acetonitrile	75.70	3.216×10^{-4}
	75.70	2.951×10^{-4}
	68.84	1.422×10^{-4}
	68.85	1.418×10^{-4}
	60.18	5.126×10^{-5}
	60.18	5.123×10^{-5}
	55.66	2.952×10^{-5}
	55.66	2.635×10^{-5}

a. Determined by graphical methods. For first-order plot see Figure 1 overleaf.

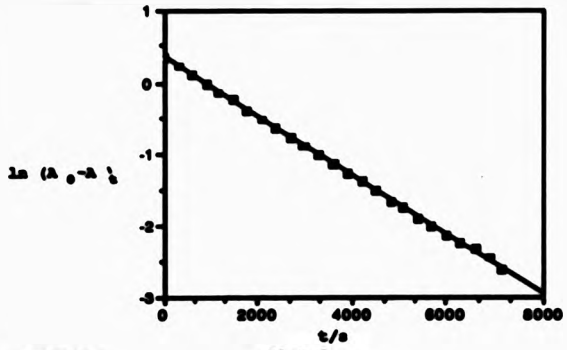


Figure 1: First-Order Plot for the Rearrangement of Thiophenium Bis(methoxycarbonyl)methylide (3) in Toluene at 64.85°

Table 2: Rate constants for the Rearrangement of Thiophenium Bis(t-butoxycarbonyl)methylide

Solvent	Temperature/°C	Rate Constant/s^{-1}
Toluene	74.34	1.964×10^{-3}
	74.34	1.868×10^{-3}
	64.95	7.014×10^{-4}
	64.95	6.989×10^{-4}
	55.83	2.362×10^{-4}
	46.58	7.975×10^{-5}
	46.58	7.818×10^{-5}
Dioxane	73.92	1.185×10^{-3}
	64.80	4.623×10^{-4}
	54.97	1.558×10^{-4}
	54.97	1.578×10^{-4}
	46.25	6.278×10^{-5}
	46.25	6.218×10^{-5}
Acetonitrile	72.82	2.813×10^{-4}
	72.83	2.462×10^{-4}
	63.77	1.053×10^{-4}
	63.77	1.030×10^{-4}
	55.26	3.783×10^{-5}
	55.26	3.604×10^{-5}
	46.13	1.258×10^{-5}
	46.13	1.246×10^{-5}

Table 9: Rate Constants for the Rearrangement of 2-Bromothiophenium Bis(t-butoxycarbonyl)methylide

Solvent	Temperature/°C	Rate Constant/s^{-1}
Toluene	73.87	1.514×10^{-4}
	73.87	1.607×10^{-4}
	65.11	6.631×10^{-5}
	65.11	6.612×10^{-5}
	55.82	2.331×10^{-5}
	46.00	7.282×10^{-6}
	46.00	6.864×10^{-6}
Dioxane	74.73	1.359×10^{-4}
	74.73	1.407×10^{-4}
	64.30	4.784×10^{-5}
	56.04	1.887×10^{-5}
	56.04	1.822×10^{-5}
	46.18	6.313×10^{-6}
	46.18	6.424×10^{-6}
Acetonitrile	72.71	5.587×10^{-6}
	72.71	3.812×10^{-6}

Recorded in Tables 4 & 5 are the measured absorbance values for the rearrangements of the thiopyrans (13) and (14) in refluxing toluene (111°). These data are represented graphically Figures 7 & 8 in the results section (p 161).

Table 4: Absorbance values For the Rearrangement of 2,2-Bis-(t-butoxycarbonyl)-2H-thiopyran.

Time/s	Absorbance	Time/s	Absorbance
0	0.793	12000	1.307
1200	0.806	13200	1.431
2400	0.828	14400	1.502
3600	0.836	15600	1.595
4800	0.843	16800	1.713
6000	0.870	18000	1.797
7200	0.942	19200	1.880
8400	1.024	20400	1.959
9600	1.073	21600	2.081
10800	1.136	22800	2.194

Table 5: Absorbance Values for the Rearrangement of 2,2-Bis-(t-butoxycarbonyl)-6-bromo-2H-thiopyran.

Time/s	Absorbance	Time/s	Absorbance
0	0.892	8100	1.891
900	0.906	9000	2.17
1800	0.916	9900	2.453
2700	0.651	10800	2.8
3600	0.968	11700	2.845
4500	1.021	12600	2.866
5400	1.124	13500	2.887
6300	1.263	14400	2.899
7200	1.558		

EXPERIMENTAL

Dimethyl diazomalonate

To a solution of 143g p-toluenesulphonyl azide and 96g dimethyl malonate in 1 l toluene was added 150 ml triethylamine. The solution was stirred overnight, and the precipitate of p-toluenesulphonamide removed by filtration. The solvent was removed at reduced pressure, and the residue dissolved in 400 ml ether. The ether solution was washed with 4 X 100 ml 20% w/v sodium hydroxide solution and dried over magnesium sulphate. The ether was removed and the product distilled (84°/1 mm).

Yield 73.8g (64%)

Di-t-butyl diazomalonate[29]

21.6g Di-t-butyl malonate, 19.2g p-toluenesulphonyl azide, and approximately 50 mg "Aliquot 366" were dissolved in 800 ml benzene, and 20 ml 10M NaOH solution was added with vigorous stirring. The stirring was continued at room temperature for 15 hours, after which time the organic layer was separated and washed with water. The organic layer was dried over magnesium sulphate and the solvent removed. The product was distilled (80°/0.5 mm).

Yield 18g (74%)

Rhodium bis(methoxycarbonylmethanolate) (2)

A catalytic quantity of rhodium (II) hexanoate was dissolved in 500 ml thiophene. To the well-stirred solution was added 79g dimethyl diazomalonate over a period of 30 minutes. The mixture was stirred at room temperature for 24 hours. The precipitated product was filtered

off, and a further quantity of catalyst was added. Stirring for a further 24 hours led to the formation of a second crop of precipitate. The combined crops were recrystallised from acetonitrile.

Yield 103g (96%).

M.Pt. 145° (Lit.145-146°)[7]

Thiophenium bis(t-butoxycarbonyl)methylide

5g Thiophene and a catalytic quantity of rhodium (II) hexanoate were dissolved in 25 ml methylcyclohexane. To the stirred solution was added 10.2g di-t-butyl diazomalonate, and the mixture was stirred for 2 hours. The precipitated ylid was filtered off and the solution stirred for a further 24 hours. A second crop of ylid was collected, and the combined products were recrystallised from acetonitrile.

Yield 13.2g (93%)

M. Pt. 140-142° dec.

NMR ^{1}H (CDCl$_3$) δ 1.4 (18H,s); 7.05 (4H,m)

IR (KBr) (cm^{-1}) 3080; 2960; 1650; 1475; 1440

$C_{15}H_{22}O_4S$ requires C = 60.40%; H = 7.38%

found C = 60.65%; H = 7.50%

2-Bromothiophenium bis(t-butoxycarbonyl)methylide

5g 2-Bromothiophene was dissolved in 30 ml methylcyclohexane and a catalytic quantity of rhodium (II) hexanoate was added. From a dropping

funnel was added 7.4g di-t-butyl diazomalonate with stirring. The mixture was stirred for 2 hours, filtered and stirred for a further 24 hours. The combined products were recrystallised from benzene.

Yield 10.14g (87%)

M. Pt. 140-143° dec.

NMR ^1H ($CDCl_3$) δ 1.4 (18H,s); 7.0 (3H,m)

IR (KBr) (cm^{-1}) 3060; 2900; 1690; 1640; 1570; 1490

$C_{15}H_{21}BrO_4S$ requires C = 47.80%; H = 5.72%

found C = 48.05%; H = 5.80%

Attempted synthesis of 3-bromothiophenium bis(t-butoxycarbonyl) methylide.

3.03g 3-Bromothiophene was dissolved in 30 ml methylcyclohexane and a catalytic quantity of rhodium (II) hexanoate was added. To the stirred solution was added 4.5g di-t-butyl diazomalonate from a dropping funnel over a period of 15 minutes. The solution was stirred overnight at room temperature. The solvent was evaporated to leave a brown oil. This was loaded onto a silica column and eluted with 20% ethyl acetate in petroleum ether to give 0.52g (21.7%) 2,2-bis-t-butoxycarbonyl -5-bromo-2H-thiopyran (17).

M. Pt. 92-94° (EtOH)

NMR ^1H ($CDCl_3$) δ 1.4 (18H,s); 5.5-6.3 (3H,m).

$C_{15}H_{21}SO_4Br$ requires C = 47.75%; H = 5.61%

found C = 47.64%; H = 5.77%

Dimethyl 2-thienylmalonate

1g of the ylid (3) in 20 ml toluene was heated to reflux for 3 hours and cooled. Evaporation of the solvent left a yellow oil which was purified on a silaca column to yield 0.96g (96%) of the title compound.

NMR ^1H ($CDCl_3$) δ 4.7 (6H,s); 5.0 (1H,s); 71. (3H,m)

IR (thin film) (cm^{-1}) 2950; 1740; 1430; 1240.

2,2-Bis(methoxycarbonyl)-2H-thiopyran

A solution of 0.5g thiophenium bis(methoxycarbonyl)methylide in 5ml xylene was heated to reflux for 2 minutes, and quenched rapidly by immersion in ice. The solvent was removed to leave a yellow oil which was loaded onto a silica chromatography column. Elution with dichloromethane gave the title compound.

Yield 0.11g (22%)

NMR ^1H ($CDCl_3$) δ 3.8 (6H,m); 5.6-6.4 (4H,m)

IR (thin film) (cm^{-1}) 3000; 2940; 1730; 1430

$C_9H_{10}SO_4$ requires m/e = 214.0300

found m/e = 214.0292

2,2-Bis(methoxycarbonyl)-6-bromo-2H-thiopyran (10)

0.5g 2-Bromothiophenium bis(methoxycarbonyl)methylide in 10 ml xylene was heated under reflux for 15 minutes, and cooled by immersion in ice. Evaporation of the solvent left a deep red oil, which was purified by

chromatography on a silica column eluted with 30% ethyl acetate in petroleum ether.

Yield 0.37g (74%).

NMR ^1H ($CDCl_3$) δ 3.75 (6H,s); 5.7-6.5 (3H,m)

IR (thin film) (cm^{-1}) 2950; 1740; 1540; 1430

$C_9H_9BrSO_4$ requires m/e = 291.9406

found m/e = 291.9413

Dimethyl 2-(5'-bromothienyl)malonate

1g 2-Bromothiophenium bis(methoxycarbonyl)methylide in 10 ml toluene was refluxed for 3 hours, and the solvent evaporated. The residue was purified by chromatography on silica to yield the title compound as a yellow oil.

Yield 0.77g (77%)

NMR ^1H ($CDCl_3$) δ 3.75 (6H,s); 5.05 (1H,s); 6.9-7.3 (3H,m)

Attempted Cycloaddition Reactions of (10)

1. With maleic anhydride.

To 200 mg (10) and 92 mg maleic anhydride were dissolved in 10 ml ethyl acetate, was added a catalytic quantity of zinc iodide. The mixture was stirred for 2 days, after which time no reaction had occurred. The mixture was heated to reflux for 8 hours, after which time t.l.c. revealed that the result was a mixture of the thiophene-2-malonate (above) and maleic anhydride. No isolation was attempted.

2. With N-phenylmaleimide.

0.88g Of the thiopyran (10) and 6.71g N-phenylmaleimide were dissolved in 5 ml xylene and the solution placed in Carius a tube which was then evacuated and sealed. The tube was immersed in an oil bath heated to 150° for 2 hours, after which time the tube was cooled and opened. Evaporation of the solvent left a mixture of the thiophene-2-malonate and N-phenylmaleimide, and no separation was attempted.

Attempted preparation of 6-bromo-2H-thiopyran-2,2-carboxylic acid.

1. By saponification

200 mg (10) Was dissolved in 10 ml 90% ethanol and 5 ml 20% sodium hydroxide solution was added. The mixture was stirred for 2 hours, and 20 ml water added. The mixture was extracted with ethyl acetate, and the organic fraction dried and evaporated to leave a black tarry mixture which defied separation.

2. With Trimethylsilyl Iodide[12]

200 mg (10) Was dissolved in 10 ml carbon tetrachloride and the solution stirred under nitrogen. 0.15g trimethylsilyl iodide in 5 ml carbon tetrachloride was added, and the mixture warmed to 50°. The solution was stirred for 2 days, and then 10 ml water was added. The aqueous phase was separated, dried and evaporated. T.l.c. of the residue confirmed that no reaction had taken place.

3. With Boron Tribromide[13]

200 mg (10) In 10 ml dichloromethane was cooled under nitrogen to -10°,

and 0.2g boron tribromide in dichloromethane was added slowly. The solution was stirred as the temperature was allowed to rise to room 20°. The mixture was stirred at this temperature for 3 days, during which time no reaction was observed to take place.

[redacted] (10) with Lithium Aluminium [redacted]

0.61g Lithium aluminium hydride was suspended in 25 ml dry ether, and 3g (10) in 25 ml ether was added slowly with stirring. The mixture was stirred for 2 days, and 20ml ethyl acetate was added, followed by 20 ml water. The mixture was filtered through Celite, and the organic fraction separated and dried. Evaporation of the solvent left 2.85g (10).

2,2-Bis(t-butoxycarbonyl)-2H-thiopyran (13)

0.5g Thiophenium bis(t-butoxycarbonyl)methylide (12) in 10 ml xylene was heated to reflux for 2 minutes, and cooled rapidly in ice. The solvent was removed to leave a cream solid, which was recrystallised from methanol.

Yield 0.41g (82%)

M. Pt. 93-94°

NMR ^1H ($CDCl_3$) δ 1.4 (18H,s); 5.6-6.4 (4H,m)

IR (KBr) (cm^{-1}) 2980; 1725; 1550; 1450; 1390.

$C_{15}H_{22}SO_4$ requires C = 60.40%; H = 7.38%

found C = 60.15%; H = 7.45%

2,2-Bis(t-butoxycarbonyl)-6-bromo-2H-thiopyran (14)

0.5g 2-Bromothiophenium bis(t-butoxycarbonyl)methylide in 10 ml xylene was heated to reflux for 5 minutes, and then rapidly cooled in ice. The solvent was removed and the residue chromatagraphed on silica, eluted with ethyl acetate, to yield the title compound, which was recrystallised from ethanol.

Yield 0.38g (75%)

M. Pt. 75°

NMR ^{1}H ($CDCl_3$) δ 1.44 (4H,s); 5.85 (1H,d,J=10.07Hz); 6.09 (1H,dd, J=10.07 and 6.53Hz); 6.48 (1H,d,J=6.53Hz).

^{13}C ($CDCl_3$) (ppm) 27.64; 83.66; 113.85; 115.47; 122.06; 126.23; 165.23

IR (KBr) (cm^{-1}) 2975; 1735; 1550; 1370; 1250; 1150

$C_{15}H_{21}BrSO_4$ requires m/e = 376.0345

found m/e = 376.0345

Attempted Reaction of (14) with Alcohols

1. Under acid catalysis

A solution of 0.5g (14) and a catalytic quantity of p-toluenesulphonic acid in 20 ml isopropanol was stirred for 4 weeks, after which time no reaction had occured. The mixture was heated to reflux for 1 hour, after which time t.l.c revealed the product to be the thiophene-2-malonate (6, R= ^{t}Bu, R'=Br).

2. Under base catalysis

A solution of 0.5g (14) and a few drops of pyridine in 20 ml isopropanol

was stirred for 4 weeks, after which time no reaction had occurred. The mixture was heated to reflux for 1 hour, after which time t.l.c revealed the product to be the thiophene-2-malonate (6, R= ^{t}Bu, R'=Br).

3. Without catalysis

The above procedure was repeated without a catalyst, in isopropanol, ethanol and ethylene glycol. In each case, the only isolable product after heating was the thiophene-2-malonate (6, R= ^{t}Bu, R'=Br).

REFERENCES

1. H W Hartough, "Thiophene and its Derivatives", Interscience, New York, 1952.
2. G C Brumlick, A I Kosak and R Pitcher, J. Am. Chem. Soc., 1964, 86, 5360.
3. J A Hashmall, V Horak, L E Khoo, C O Quicksall and M K Sun, J. Am. Chem. Soc., 1981, 103, 289.
4. A E A Porter in "Thiophene and its Derivatives", Ed. S Gronowitz, John Wiley and Sons, Inc, London, 1985.
5. W L Mock, J. Am. Chem. Soc., 1970, 92, 7610.
6. W Ando, H Higuchi and T Migita, J. Org. Chem., 1977, 42, 3365.
7. R J Gillespie, J Murray-Rust, P Murray-Rust and A E A Porter, J. Chem. Soc., Chem. Commun., 1978, 83.
8. T Bowles, A E A Porter, J A Rechka and H S Rzepa, J. Chem. Soc., Chem. Commun., 1984, 859.
9. R J Gillespie, A E A Porter and W E Willmott, J. Chem. Soc., Chem. Commun., 1978, 85.
10. J Cuffe, R J Gillespie and A E A Porter, J. Chem. Soc., Chem. Commun., 1978, 641.
11. W Steinkopf and H Augestad-Jansen, Justus Liebigs Ann. Chem., 1922, 428, 154.
12. J Pless and W Bauer, Angew. Chem. Int. Ed., 1973, 12, 147.
13. T-L Ho and G A Olah, Angew. Chem. Int. Ed., 1976, 16, 744.
14. T Bowles, R Jones, A E A Porter, J A Rechka, H S Rzepa and D J Williams, J. Chem. Soc., Chem. Commun., 1985, 1590.
15. H Storflor, J Skramstad and S Nordenson, J. Chem. Soc., Chem. Commun., 1984, 208.

16. G M Blackburn, W D Ollis, J D Plackett, C Smith and I O Sutherland, J. Chem. Soc., Chem. Commun., 1968, 186.

17. W Ando, T Yagihura, S Tozune, I Imai, J Suzuki, T Toyama, S Nakaito and T Migita, J. Org. Chem., 1972, 37, 1721, and references therein.

18. A. Campbell, A H J Houston and T Kenyon, J. Chem. Soc., 1947, 93. J H Brewster and M W Kline, J. Am. Chem. Soc., 1952, 74, 5179.

19. J E Baldwin, W F Erickson, R E Hackler and R M Scott, J. Chem. Soc., Chem. Commun., 1970, 576.

20. U H Dolling, G L Closs, A H Cohen and W D Ollis, J. Chem. Soc., Chem. Commun., 1975, 545.

21. A E A Porter, private communication.

22. D C Gilheany, J F Malone and B J Walker, J. Chem. Soc., Chem. Commun., 1984, 1217.

23. D C MacNicol and J J McKendrick, J. Chem. Soc. Perkin Trans. I, 1974, 2493.

24. K Praefke and C Weichsel, Liebigs Ann. Chem., 1980, 1604.

25. P J W Schuijl, H J T Bos and L Brandsma, Rec. Trav. Chim. Pays-Bas, 1969, 88, 30.

26. J T Thompson, "Apple Data Acquisition System", revised by R Ferguson.

27. H Mackle, Tetrahedron, 1963, 19, 1159.

28. A E A Porter and H S Rzepa, J. Chem. Soc. Perkin Trans. I, 1988, 809.

29. H Ledon, Synthesis, 1974, 347.