The Synthesis And Characterisation Of Some Organic Dicyanomethylene Salts

A thesis presented for the degree of M.Sc.

by

Orla Wilson BSc (Hons)

at

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School of Chemical Sciences

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For my family Una, Sam, Fiona and Kathryn

Declaration

I, the undersigned, hereby declare that this thesis, which I now submit for assessment on the programme of study leading to the award of M.Sc. represents the sole work of the author and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text.

Orla Wilson

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ABSTRACT

As part of our interest in the synthesis of heterocyclic analogues of 7,7,8,8-tetracyano-*p*-quinodimethane (TCNQ), in which the π-electrons of a TCNQ carbon-carbon double bond are replaced by a lone pair of electrons on a heteroatom, we have investigated chemistry related to the synthesis of a saturated heterocyclic analogue.

Condensation of succinic anhydride with malononitrile in the presence of sodium hydride yielded the sodium salt of 4-dicyanomethylene-4-hydroxybutanoic acid. Attempts to cyclise these salts to give the corresponding dicyanomethylene lactones, potential precursors to the desired saturated analogues, by a variety of methods were unsuccessful. The corresponding sodium salt of 5-dicyanomethylene-5-hydroxypentanoic acid was similarly synthesised from glutaric anhydride.

Further investigations into the condensation reactions of succinic anhydride and malononitrile in the presence of a variety of amines of varying basicity have been carried out and the products were isolated and characterised.

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CHAPTER 1
INTRODUCTION

1.A.1 Introduction

There has been much interest in recent years in investigating the anolagy between the compounds of oxygen ie alcohols, carboxylic acids, aldehydes, ketones, acyl compounds, ethers, quinones, amine oxides, sulfoxides and phosphine oxides, and those compounds which contain a $C(CN)_2$ moiety in place of the O atom.

The cyano group is one of the most powerful electronegativity-enhancing groups and as such the more CN groups a carbon atom bears, the greater will be its attraction for electrons. It is this important property that has aroused great interest in exploring the chemistry of structures containing the cyano group. Of particular interest are those compounds which accept one electron to form charge-transfer (C-T) compounds which are highly conducting materials that also exhibit magnetic[1] properties.

In this chapter, the literature dealing with the introduction of a dicyanosubstituted carbon moiety in place of a carbonyl oxygen into a compound will be discussed, with particular emphasis on the Knoevenagel condensation reaction. The importance of the electron-withdrawing ability of the CN group will become clear as electron acceptors are discussed.

1.A.2 Nucleophilic addition reactions of carbonyl compounds

Two types of reactions dominate the chemistry of carbonyl compounds: In one type they are the passive partner of a nucleophilic addition at the carbonyl carbon atom. It is characterized by addition and - after subsequent elimination - substitution. In the other type, initial abstraction of an alpha-proton transforms carbonyl compounds into the active agent of such an addition or addition-elimination reaction.

In a carbonyl group the mobile π-electrons are pulled strongly towards the oxygen atom. Since the important step in nucleophilic addition reactions is the formation of a bond to the electron deficient carbonyl carbon, the carbonyl group is most susceptible to attack by electron-rich nucleophilic reagents such as the malononitrile anion.

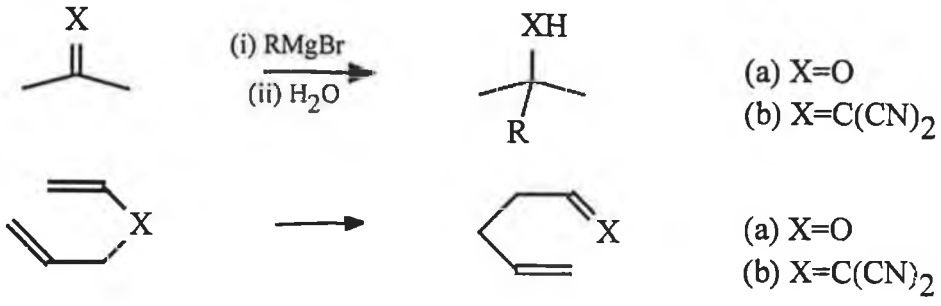
Acyl compounds - carboxylic acids and their derivatives - are made susceptible to nucleophilic attack because of (1) the tendency of the carbonyl oxygen to acquire electrons even at the expense of gaining a negative charge and (2) the relatively unhindered transition state leading from the trigonal reactant to the tetrahedral intermediate.

1.A.3 Analogy between carbonyl compounds and alkylidenemalononitriles

Wallenfels[2] has found, by synthesising a large number of $=C(CN)_2$ substituted compounds by analogy with those containing =O and studying their properties that the two groups of compounds have similar inductive and resonance effects. It is also of interest to note that while there are notable similarities between carbonyl and $C(CN)_2$ compounds, there are also some marked differences that can be brought about to the reactivity and solubility of a particular compound simply by replacing a carbonyl oxygen with a dicyanomethylene moiety.

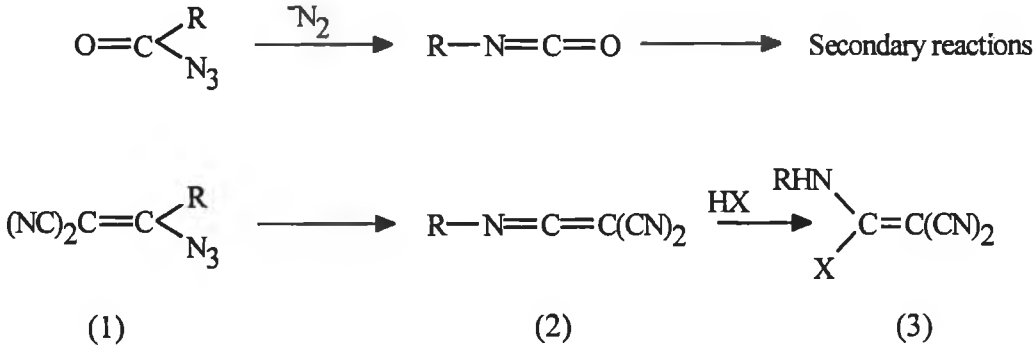
With regard to the analogy between carbonyl compounds and alkylidenemalononitriles, Wallenfels[2] *et al* have also showed that many of the well-known reactions of the carbonyl group have close parallels with the dicyanomethylidene group. Examples of these include the Grignard addition reactions and the sigmatropic 3,3- Cope rearrangement, scheme 1.01.

Another analogous reaction is pyrolysis, where the (1-azidoalkylidene)malononitriles (1) behave like acyl azides and undergo a Curtius-analogous rearrangment, scheme 1.02.



Scheme 1.01

Friedrich[3] had previously used this principle, that structural elements =O and $=C(CN)_2$ are analogous in organic compounds, to show that 2-azidoethylene-1,1- dicarbonitriles (1) decompose rapidly when warmed to 60-70°C, with the loss of one molar equivalent of nitrogen, in accordance with the

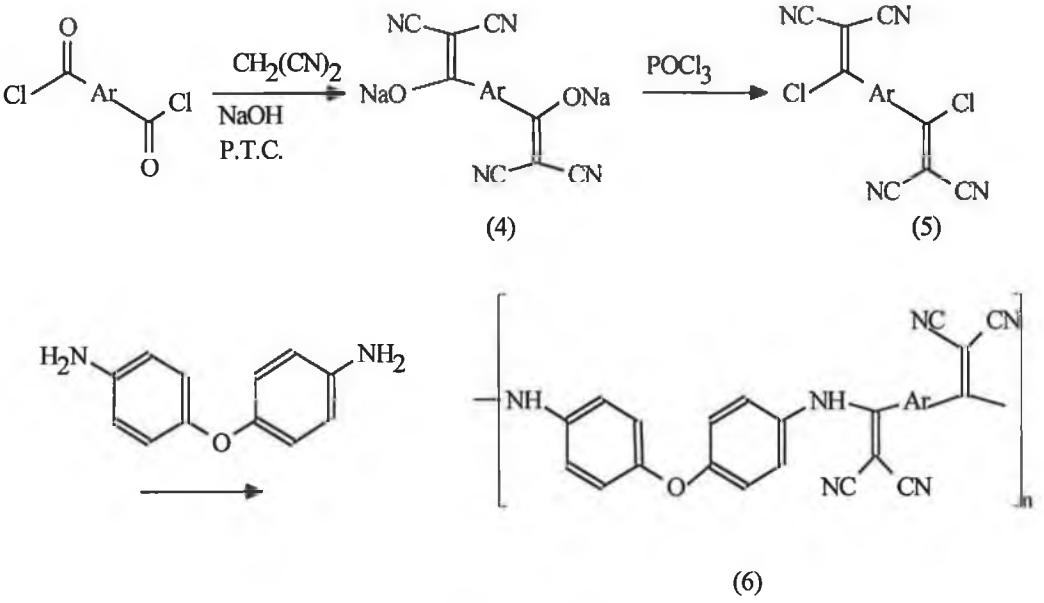


Scheme 1.02

Curtius degradation of acyl azides. It was concluded that, on evolution of the nitrogen, the R group migrates to the N atom that remains attached, with the formation of the 2-imino-ethylene-1,1-dicarbonitriles (2), which were then reacted with HX (X=eg OC_2H_5, OH, SH, Cl, CN) to give the 2-aminoethylene-1,1-dicarbonitriles (3), scheme 1.02.

1.A.3.1 Synthesis of poly(enaminonitriles), thermally stable polymers.

In a more recent paper[4] the analogy has again been used in the synthesis of some moderately high molecular weight poly(enaminonitriles) (6) by vinylic nucleophilic substitution. These polymers exhibited excellent thermal stability, retaining 100% of their mass up to 400°C under nitrogen; and can be "cured" without the emission of volatile byproducts which had been the principal drawback in the curing reaction of polyimides. The monomer (5) was synthesised by reaction of the corresponding acid chloride with malononitrile under basic, phase-transfer conditions to provide the disodium salts of the bis enols (4) which were then reacted with phosphorus oxychloride to give the desired products (5). The bis(chlorodicyanovinyl) monomers (5) were then polymerised with 4,4'-diamino- diphenyl ether to produce the poly(enaminonitriles) (6), scheme 1.03. In the initial reaction, that of the formation of the disodium salt of the bis enols, the malononitrile anion attacks the electron-deficient carbonyl carbon and the dicyanomethylidene moiety replaces the carbonyl oxygen atom.

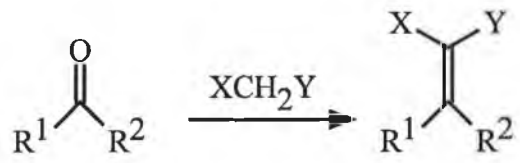


Scheme 1.03

1.A.4 The Knoevenagel condensation reaction

As an active methylene compound, one of the most important reactions that malononitrile takes part in is the Knoevenagel condensation reaction which is a nucleophilic addition reaction related to the aldol condensation.

The Knoevenagel condensation is effected by treating a carbonyl compound (7) with an active methylene compound (XCH_2Y) in the presence of at least catalytic amounts of a base or an acid to give alkylidene- or benzylidene-dicarbonyls or analogous compounds (8), scheme 1.04. Usually methylene groups with two electron-withdrawing moieties, which may or may not be the same, are employed (X,Y=CO_2R, $CONR_2$, COR, CN, $CNNR_2$, Ar, NO_2, $PO(OR)_2$, SO_2OR, SO_2NR_2, SO_2R, SOR, SR and SiR_3); the reaction of an aldehyde or ketone with nitroalkanes in the presence of a weak base, the Henry reaction, is however also considered a variant of the Knoevenagel condensation.



(7)a: R^1=H, R^2=alkyl
b: R^1,R^2=alkyl

(8)a: R^1=H, R^2=alkyl
b: R^1,R^2=alkyl

Scheme 1.04

The active methylene compounds used most frequently are acyclic 1,3-dicarbonyls and analogous substances such as malonates, acetoacetates, acetonitriles and acetylacetones, although the most used active methylene compound in the formation of heterocycles is malononitrile. Cyclic compounds such as 1,3-cyclohexanediones, barbituric acids, Meldrum's acid and 4-hydroxycoumarins may also be used. The aldehydes used in the reaction can be varied over a wide range but the use of ketones is limited due to their low reactivity. The catalyst used is of great importance; the most commonly

used catalysts are primary, secondary or tertiary amines or their corresponding ammonium salts, but many others such as phase transfer catalysts, Lewis acids or potassium fluoride can also be applied. The most widely used catalyst is pyridine, either alone or in the presence of a small amount of piperidine, and ammonium salts such as ammonium or piperidinium acetate.

1.A.4.1 Reaction conditions

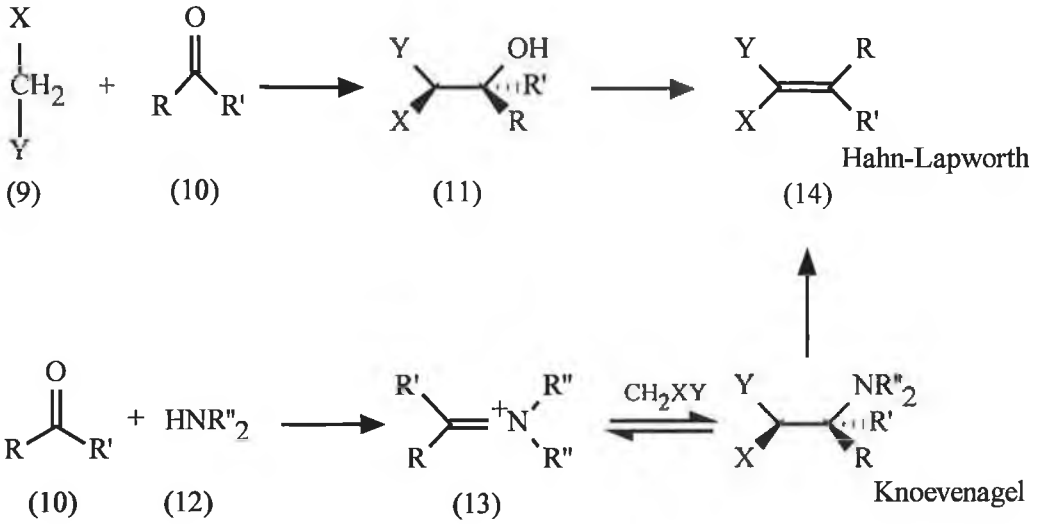
As the methylene compounds are more acidic than the aldehydes and ketones used in the aldol condensation, the bases employed as catalysts are usually weaker than those needed to effect the aldol condensation. The use of the Lewis acid titanium tetrachloride in the presence of pyridine, known as Lehnert's reagent, in tetrahydrofuran has been shown to give good yields of the alkene (8), X=CO_2Et, scheme 1.04, from the condensation of diethyl malonate with aldehydes.[5] This procedure is often superior to standard methods in reactions of sensitive compounds because it can be performed at low temperatures.

Foucaud *et al.* found that Knoevenagel condensations can be achieved in the presence of dry alumina without organic solvents under very mild conditions and the use of similar reaction conditions has increased in recent years as they involve easier workup and higher selectivity than similar reactions in solution. Knoevenagel condensations can be carried out in solid-liquid systems with magnesium oxide or zinc oxide as catalyst at room temperature.[6] Recently, silica-gel bearing amino groups has also found application as a catalyst.[7] The Knoevenagel condensation is strongly solvent-dependant and is facilitated by highly polar solvents.

1.A.4.2 Reaction mechanism

The Knoevenagel condensation reaction belongs to the general class of base-catalysed aldol-type condensations where a carbanion adds to an electron-deficient carbonyl or heterocarbonyl group. Two different mechanisms, depending on the base being used, have been proposed for the reaction of (9)

and (10) to give (14); scheme 1.05. The first, the Hahn-Lapworth mechanism, postulates the formation of a β-hydroxydicarbonyl compound (11). This mechanism is suggested for bases such as tertiary amines and pyridine. The β-hydroxy adduct (11) is also formed as the intermediate when the sodium salt of the active methylene compound is used.



Scheme 1.05

Knoevenagel reasoned that when primary or secondary amines are used as catalysts, the condensation of the aldehyde and amine takes place first to give an iminium salt (13), which then reacts with the active methylene compound. Since an elimination step is involved in both mechanisms, the final product would be the same.

The generalization can be made that in the presence of tertiary amines, with or without acids the Knoevenagel reaction always proceeds according to the Hahn-Lapworth mechanism through a β-hydroxy intermediate. With primary and secondary amines, the two mechanisms can compete, with the formation of the intermediate imine depending on the bulkiness of the amine and the carbonyl compound. With ketones and piperidine as catalyst, with or without acid, normal basic catalysis is found, whereas with hexylamine in the presence of an acid, an intermediate imine is formed. With aldehydes and piperidine, an

intermediate imine is obsereved, whereas with diisopropylamine, the chief intermediate is the β-hydroxy adduct.

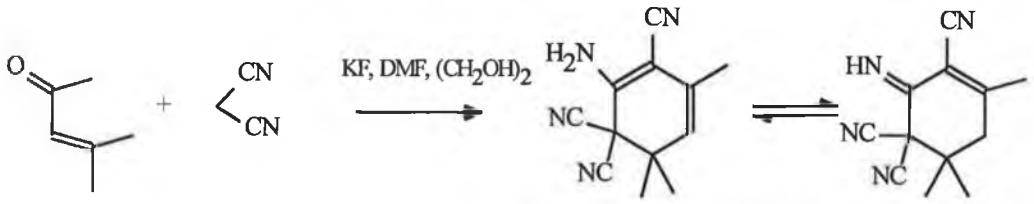
With regard to the kinetics of the Knoevenagel reaction, Patai *et al.* and others have studied the effect the catalyst has on the reaction mechanism.[8-10] For the reaction of malononitrile and 3-methylcyclohexanone in benzene with triethylamine or piperidine, the rate of the reaction was found to be first order in amine, ketone and nitrile[11] and was interpreted in terms of base catalysis by the amine. When a mixture of triethylamine or piperidine and acetic or benzoic acid was used, general acid catalysis was observed, but only showed a very small effect on the overall reaction rate since the acid lowers the concentration of the free amine. With mixtures of primary amines like hexylamine and acetic acid in the same reaction the rate is seen to be zero order in malononitrile. It was argued that, in the rate-determining acid-catalysed step hexylamine forms an imine with cyclohexanone, which then reacts with malononitrile. In the absence of acid, hexylamine acts as a basic catalyst and the reaction proceeds according to the Hahn-Lapworth mechanism.[11] It has also been shown that weak bases producing solutions having a pH 0f 7.5-8.0 are most efficient. With β-alanine the energy of activation is 7.6 kcal mol^{-1}, compared to 11 kcal mol^{-1} for the uncatalysed reaction.[12]

The influence of pressure on the rate of the Knoevenagel reaction has also been investigated and it has been shown that, as expected, the rate of the reaction is directly proportional to the pressure.[13]

1.A.4.3 Competitive reactions

The main problem intrinsic to the application of the Knoevenagel condensation for synthesis is the undesired formation of the so-called bis adduct or Michael adduct, resulting from the Michael addition of a second molecule of the active methylene compound to the initial Knoevenagel product.[14,15] In the reaction of α,β-unsaturated ketones and malononitrile it has been found that the ratio of Knoevenagel and Michael products depends on steric factors. As an example, in the reaction of mesityl oxide (15), Knoevenagel condensation is followed by

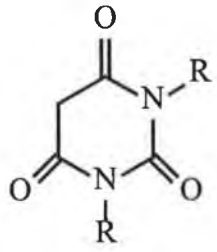
conjugate addition and finally by intramolecular condensation to yield the trinitrile (16), scheme 1.06.



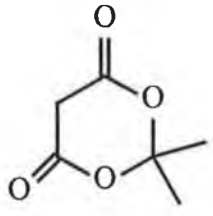
(15) (16)

Scheme 1.06

While the reaction of barbituric acid (17) and *N,N*-dimethylbarbituric acid (18) yields Knoevenagel condensation products with nearly every type of aldehyde,[14,16,17] Meldrum's acid (19) and its derivatives give Knoevenagel products only with aromatic aldehydes and ketones and with hindered aliphatic aldehydes, but yield Michael products upon reaction with simple aliphatic aldehydes.[18]

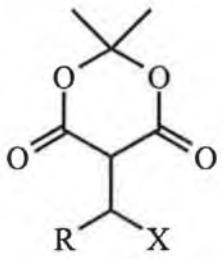


(17) R=H
(18) R=CH_3



(19)

Formation of the undesired Michael adducts can be avoided by trapping the Knoevenagel product with methoxide,[19] secondary amines,[20] or thiols[21] to give the 3-heterosubstituted alkyl-1,3-dicarbonyls (20), (21) and (22), respectively, from which the alkene may be generated by acid or in the case of the thio compound by an oxidative base-catalysed hydrolysis.



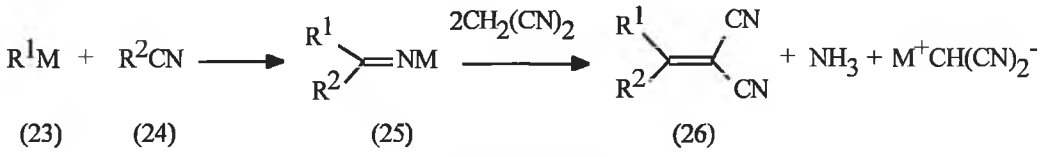
(20) X=OR, (21) X=NR_2 and (22) X=SPh

With some active methylene compounds ($NCCH_2PO(OEt)_2$) competition between Knoevenagel and Wittig-Horner reactions has been observed and in this case the ratio of the products is dependent on the reaction conditions.[6,22]

A further problem involves Knoevenagel compounds that contain a γ-hydrogen atom and their propensity to undergo isomerisation to β,γ-unsaturated products.[23] It has been observed that the ratio of α,β- to β,γ-isomers is dependant upon the nature of the amine catalyst used. While separation of the isomers is difficult, it has been achieved in a few cases.[24]

1.A.4.4 Malononitrile as the active methylene compound

The active methylene compounds XCH_2Y can be divided into cyclic and acyclic, into symmetrical and unsymmetrical compounds and into compounds that contain either carbon or heteroatoms at positions 1 and 3. The acyclic, symmetrical compound malononitrile is one of the most commonly used active methylene compound in synthesis.[25,26] It is one of the most reactive methylene compounds employed in Knoevenagel condensation reactions and alkylidene and arylidene malononitriles are readily available. In many cases the condensation proceeds satisfactorily without any added catalyst, although it is efficiently catalysed by weak bases such as ammonium acetate and pyridinium acetate. Recently ylidene malononitriles (26) have been prepared by reaction of an organometallic reagent (23) with a nitrile (24) to produce a metal ketimate intermediate (25), which gives the desired ylidene malononitrile (26) upon treatment with two equivalents of malononitrile,[27] scheme 1.07.



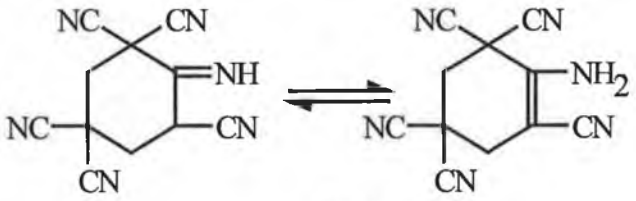
(23) (24) (25) (26)

Scheme 1.07

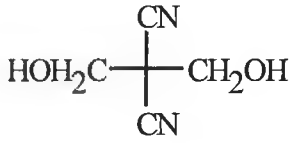
Previous syntheses of ylidedemalononitriles by Campaigne and Ellis[28] involved reaction of the carbonyl compound with a 20% excess of malononitrile using ammonium acetate and glacial acetic acid as the catalyst. In the case of hindered ketones an additional amount of catalyst was used.

1.A.5 Knoevenagel condensation in synthesis

The Knoevenagel condensation of malononitrile with aldehydes and ketones followed by cyclisation has been used widely for the synthesis of a multitude of carbocycles and heterocyclic compounds. The reaction of malononitrile with formaldehyde is unique and is known to give one of five possible products depending on the reaction conditions used:[29] 1,1,3,3-tetracyanopropane, 2,2,4,4-tetracyano-1, 5- pentanediol, 2,2,4,4,6-pentacyanocyclohexanonimine (27) or 2,2-dicyano-1,3-propane diol (28).



(27)

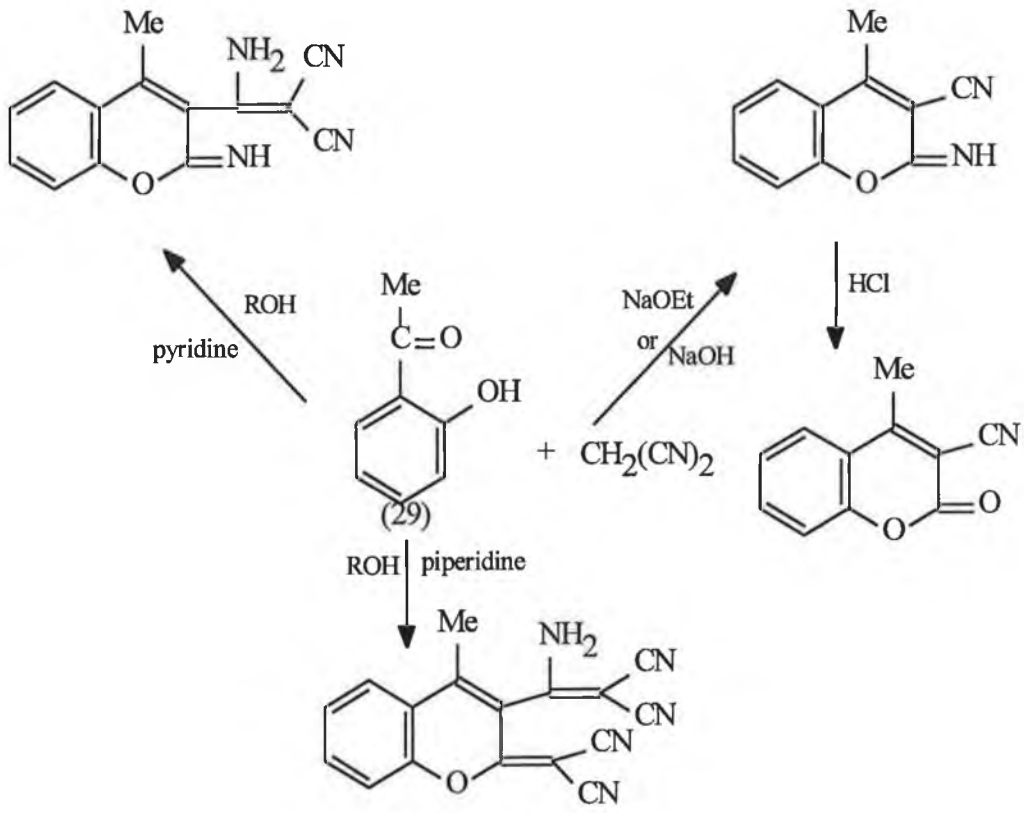


(28)

The reaction of malononitrile with acetaldehyde has been reported to give 1,1,3,3-tetracyano-2,4-dimethylcyclobutane or 1,1,3,3-tetracyano-2-methylpropane.

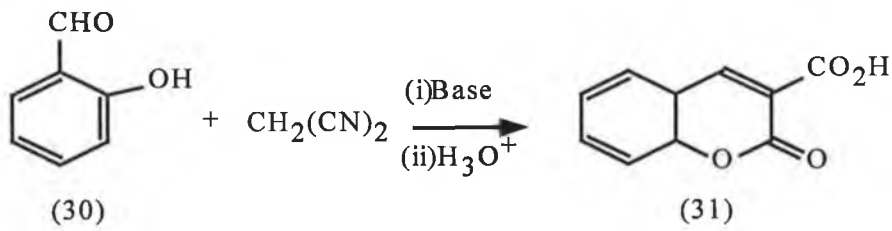
1.A.5.1 Importance of bases

The bases used in the Knoevenagel condendensation are very important. Proof of this[30] lies in investigations of the condensation reaction between hydroxy-acetophenone (29) and malononitrile in the presence of a base. Scheme 1.08 shows the three different products. Each reaction involves a Knoevenagel condensation followed by cyclisation to the coumarin ring structure.



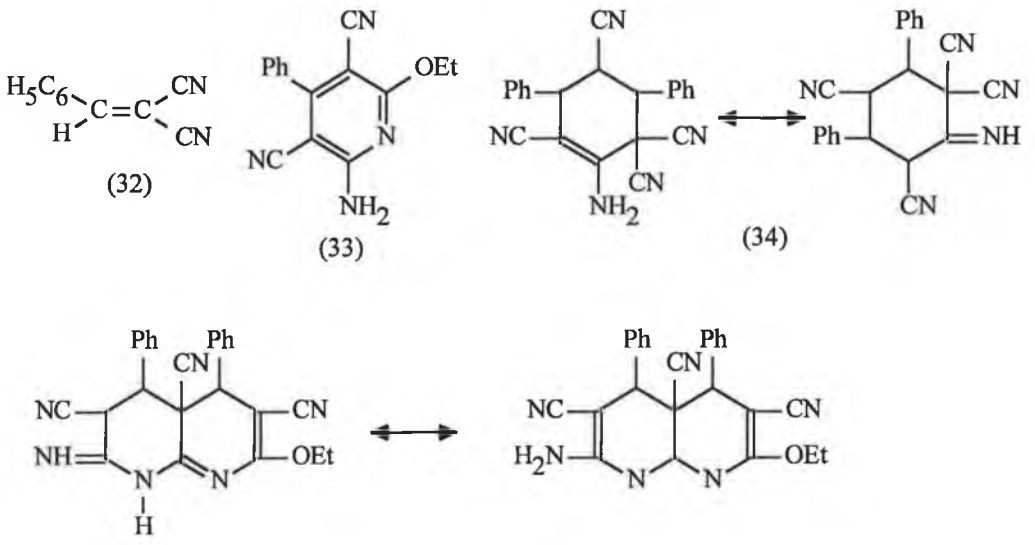
Scheme 1.08

This is also seen in the reaction of salicylaldehyde (30) with malononitrile in piperidine giving the intermediate arylidenemalononitrile which is hydrolysed to the corresponding coumarin-3-carboxylic acid (31), scheme 1.09.



Scheme 1.09

The base that is used is also seen to be of vital importance in the preparation of aryl- and alkylidenemalononitrile dimers. Benzalmalononitrile (32) reacts in ethanolic potassium hydroxide to give 2-amino-6-ethoxy-3,5-dicyano-4-phenylpyridine (33),[31a] while on treatment with *n*-butylamine in ethanolic solution the two crystalline products (34) and (35) were obtained.[31b]

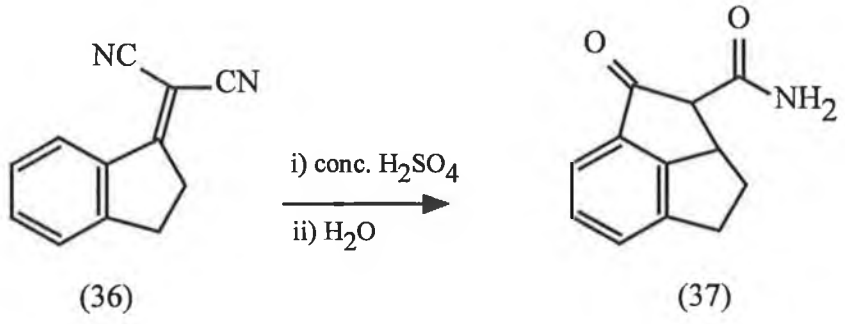


(32) (33) (34)

(35)

1.A.5.2 Synthesis of carbocycles

Cyclisation of the benzylidene malononitrile (36) to form a five-membered carbocyclic ring (37) can be achieved upon treatment with acid and subsequent hydrolysis, scheme 1.10.[27]

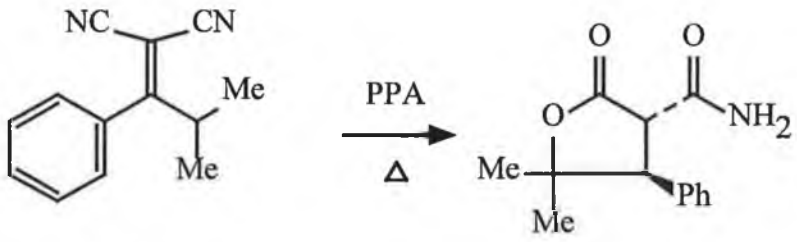


(36) (37)

Scheme 1.10

Such cyclisation reactions were normally carried out in concentrated sulphuric acid in preference to polyphosphoric acid which did not prove as reliable in the

formation of ketones, but it was seen[28] that when α-cyano-β-isopropylcinnamonitrile (38) was cyclised with PPA, α-carboxamido-β-phenyl-γ-methyl-γ-valerolactone (39) was produced, scheme 1.11. On further investigation this reaction was seen as a novel method of preparing γ-substituted-γ-valerolactones, usually in better yields than the previously reported procedures which involved levulinate esters and Grignard reagents.



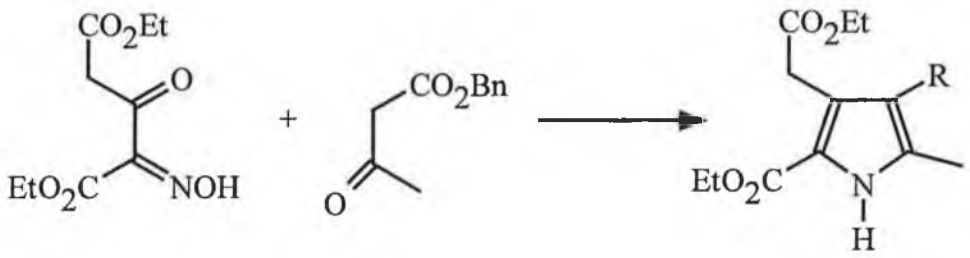
(38) (39)

Scheme 1.11

1.A.5.3 Synthesis of heterocycles

Knoevenagel reactions are used in the synthesis of a wide variety of O- and N-heterocycles. In the typical Knorr pyrrole synthesis a 1,3-dicarbonyl compound is condensed with an oximino- or azimino-1,3-dicarbonyl compound followed by reductive cyclisation. For example, catalytic hydrogenation of benzyl acetoacetate (40) and diethyl oximinoacetonedicarboxylate (41) affords pyrrole (42), which, following transformation into the 4-formyl derivative, can be converted to (43) by another Knoevenagel reaction, scheme 1.12.

Another typical preparation of a heterocycle that involves a Knoevenagel condensation is the Hantzsch 1,4-dihydropyridine synthesis. An aldehyde (44) and two molecules of a 1,3-dicarbonyl compound (45) react in the presence of ammonia or an amine to give the 1,4-dihydropyridine (46) which is readily oxidised with nitric acid to give a pyridine (47), scheme 1.13.

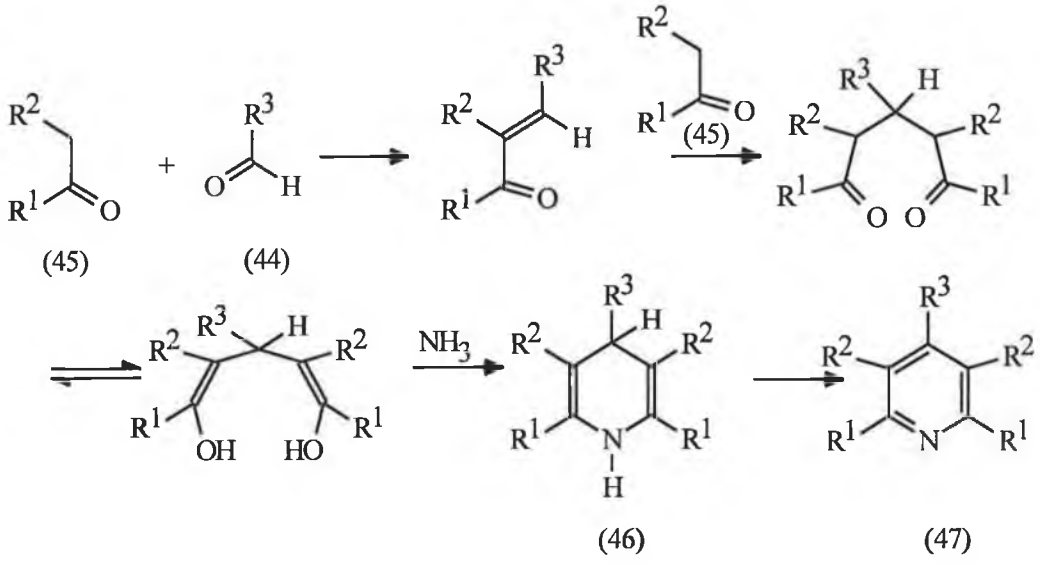


(40) (41) (42)R=CO_2H

(43)R=$CH_2CH_2CO_2Et$

Scheme 1.12

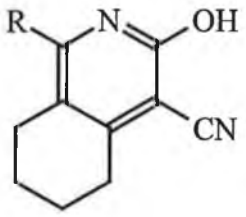
For the synthesis of pyridine derivatives, the Knoevenagel condensation with malononitrile, cyanoacetamide or cyanoacetates followed by an intramolecular addition of an amino function to a C≡N triple bond has found wide application.



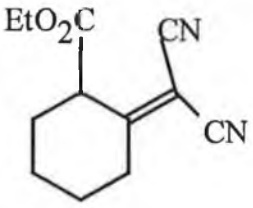
(45) (44) (45) (46) (47)

Scheme 1.13

Hence the formation of 2-hydroxypyridines like (48) is accomplished by Knoevenagel reaction of 1,3-diketones with cyanoacetamide, cyanoacetate and malononitrile, and that of 2,6-dihydroxypyridines like (49), by reaction with β-keto esters and cyanoacetamide followed by direct cyclisation. With malononitrile, the reaction with β-keto esters usually stops at the Knoevenagel stage (50), although, using a mixture of ammonium acetate

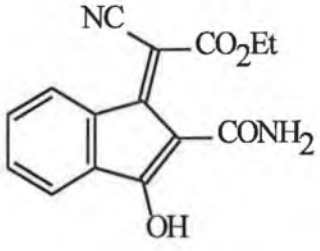


(48) R=alkyl
(49) R=OH
(51) R=O-alkyl

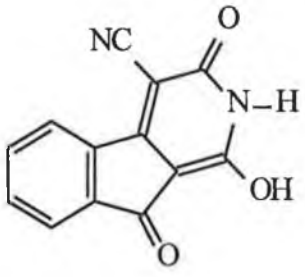


(50)

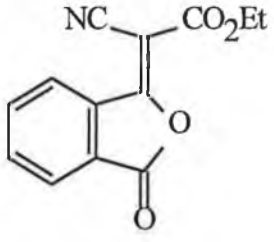
and acetic acid as catalyst, the 6-alkoxy-2-hydroxypyridines (51) are formed exclusively.[32] Knoevenagel condensation of phthalic anhydride with ethyl cyanoacetate in the presence of triethylamine in toluene yields highly reactive benzofulvene (52), which can then be transformed into the indenopyridine-1,3-dione (53) with base. Knoevenagel product (54) is not formed in this reaction if an amine is used as the catalyst, whereas with sodium hydride 9% of (54) can be isolated.[33]



(52)

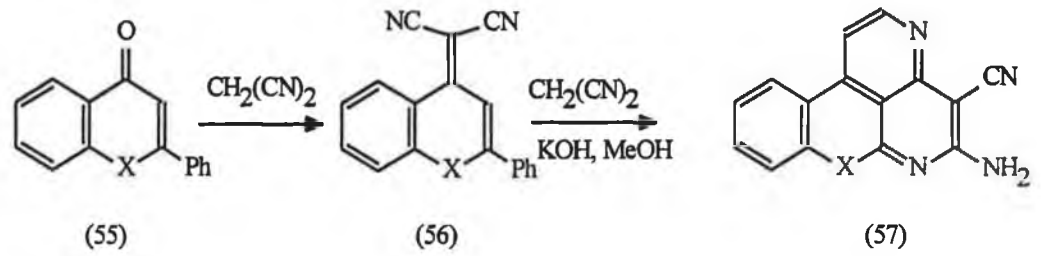


(53)



(54)

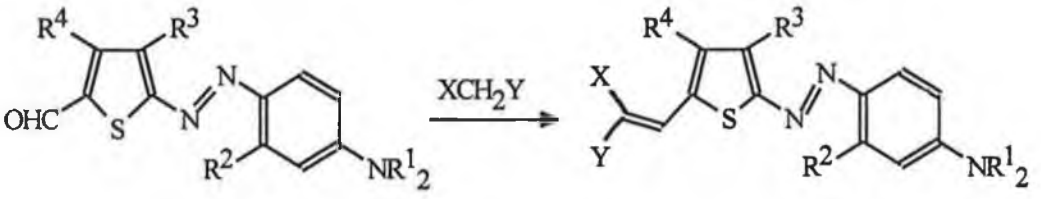
4-Flavones and their thia analogues (55) undergo Knoevenagel condensation with malononitrile to give the corresponding 4,4-dicyanomethylene derivatives (56). These compounds give ready access to pyranonaphthyridine (57; X=O) and its thia analog (57; X=S) by condensation with a second equivalent of malononitrile, scheme 1.14.[34]



(55) (56) (57)

Scheme 1.14

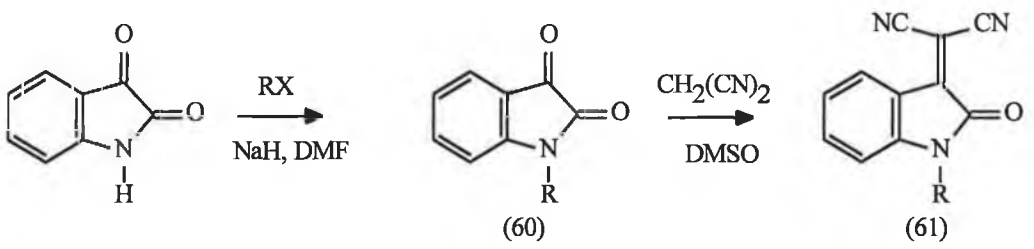
The Knoevenagel condensation has been used in the synthesis of different types of dyes. Thiophene derivatives (59), which may be useful for dyeing synthetic fibres or plastic, have been prepared by condensation of the azo aldehydes (58) with a variety of methylene compounds,[35] scheme 1.15.



(58) (59)

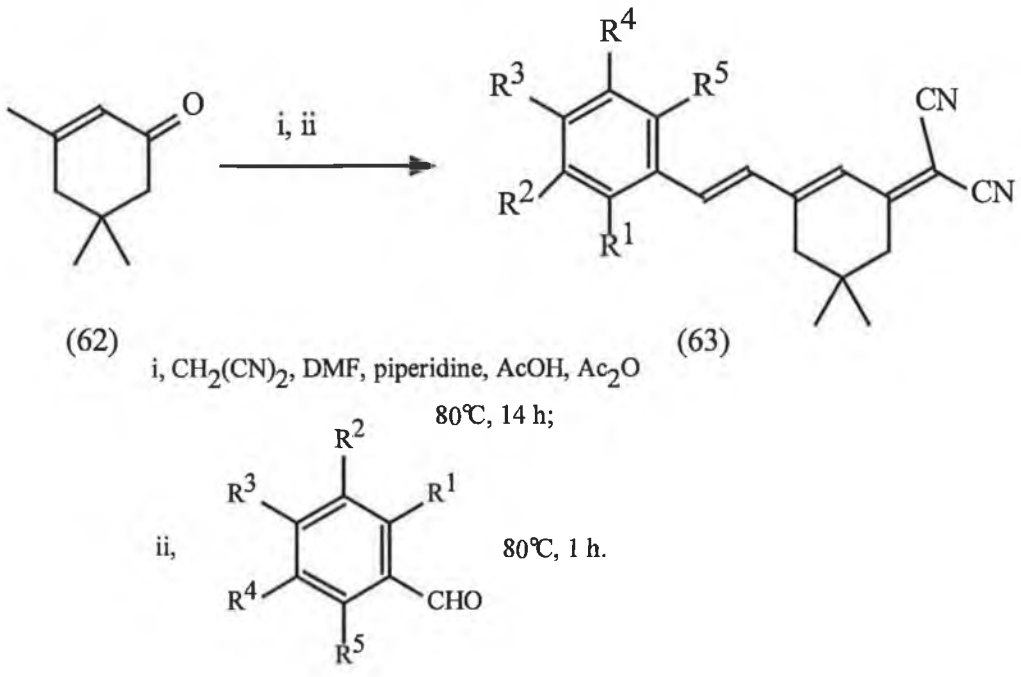
Scheme 1.15

Malononitrile is commonly used in the synthesis of dicyanomethylene derivatives in dyestuff chemistry, as the strong electron acceptor property of the dicyanomethylene group confers chromophoric or highly efficient auxochromic character, and it is known that compounds containing a dicyanomethylene group which is conjugated with another chromophore should be deeply coloured.[36] Katritzky *et al.* have prepared a series of coloured compounds, 1-alkyl-3-dicyanomethylideneindol-2-ones (61), by introducing the dicyanomethylene group into a 1-alkylisatin (60) which causes a dramatic bathochromic shift [80-100 nm red shift from (60) to (61)] together with a small hyperchromic effect, scheme 1.16.[36]



Scheme 1.16

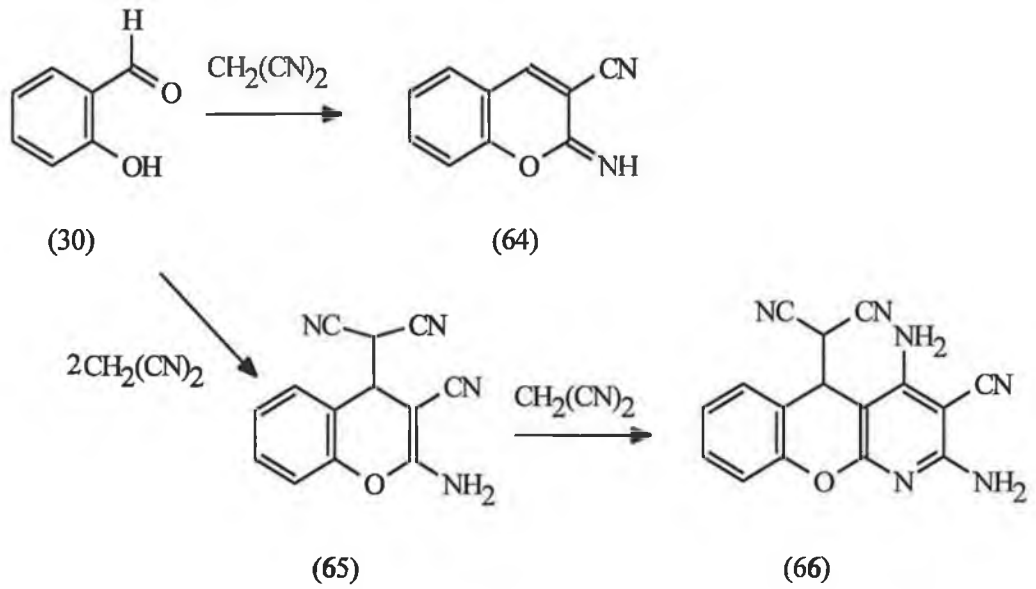
The dyes (63) which exhibit positive solvatochromic and negative thermochromic properties are prepared by Knoevenagel reaction of isophorone (62) and malononitrile followed by an aldol condensation with substituted benzaldehydes, scheme 1.17.



Scheme 1.17

1.A.5.4 Syntheses of trinitrile derivatives of dibenzopyran

While it has been shown that reaction of salicylaldehyde (30) with malononitrile in 1:1 ratio affords the relatively unstable 2-imino-2*H*-[1]benzopyran-3-carbonitrile (64), the same reaction carried out with two molar equivalents of malononitrile



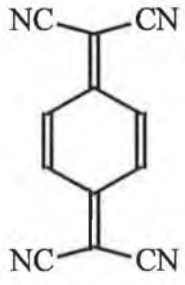
Scheme 1.18

affords the trinitrile derivative 2-(2-amino-3-cyano-4*H*-[1]benzopyran-4-yl)propane-1,3-dinitrile (65).[37] Reaction of (65) itself with malononitrile gives the tricyclic product (66), which can also be formed by prolonged heating of the trinitriles in alcoholic solution,[38] scheme 1.18.

1.B Electron acceptors

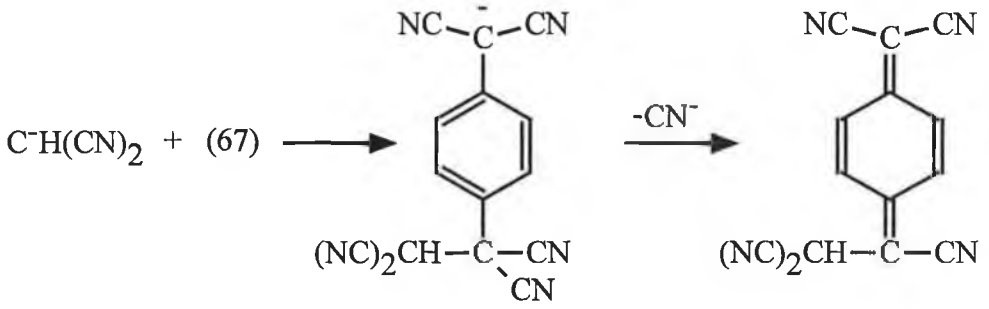
1.B.1 Introduction

While malononitrile, due to its unique reactivity, has found much use in dyestuff chemistry, and in the syntheses of a wide range of carbocycles and heterocyclic compounds as described thus far, the importance of the presence of the two electron withdrawing cyano groups in malononitrile was clearly realised with the discovery of the compound 7,7,8,8-tetracyanoquinodimethane (TCNQ, 67). TCNQ is one of the few stable quinodimethanes and has received extensive study because of its unusual stability and electrical properties.[39] This compound and its analogues are congenial to the development of charge-transfer systems, of organic conductors, and of semiconductors, since tetracyanoquinodimethanes are effective electron acceptors due to the two strongly electron, withdrawing dicyanomethylene groups.

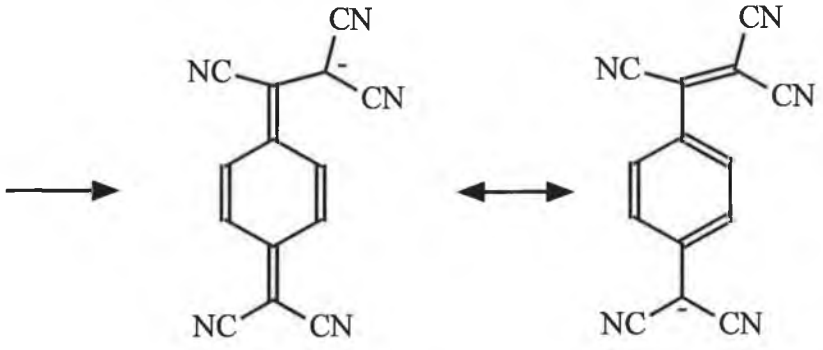


(67)

Malononitrile can itself be added to TCNQ to give the blue anion (68), the mechanism of which probably involves the addition of the dicyanomethyl anion to (67) to form (69). Elimination of a cyanide ion from (69) follows to give the conjugate acid of (68), scheme 1.19.[25]



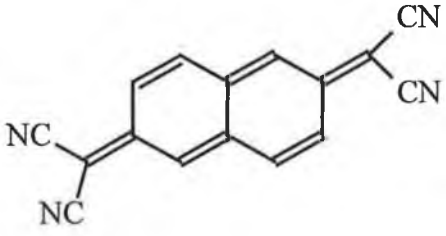
(69)



(68)

Scheme 1.19

Meanwhile the more conjugated 11,11,12,12-tetracyano-2,6-naphthoquinodimethane (TNAP, 70) reacts with malononitrile to give 6-(tricyanovinyl)-2-naphthyldicyanomethanide (71).[40]



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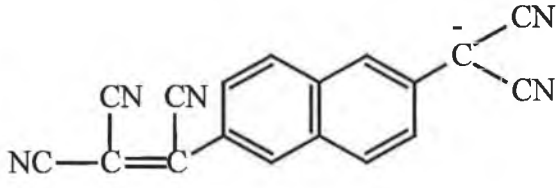
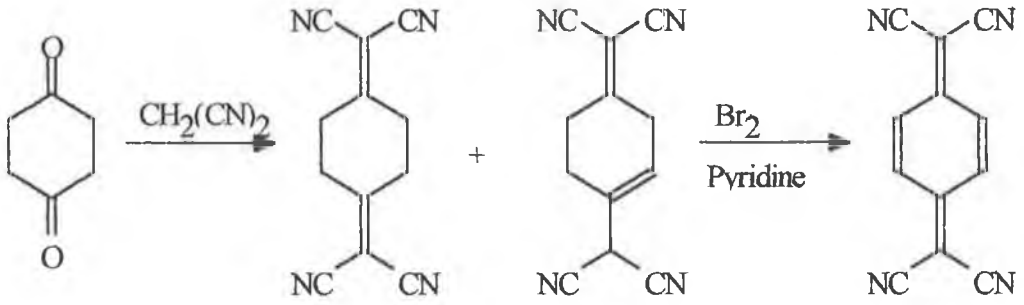


(71)

1.B.2 Synthesis of TCNQ

The synthesis of TCNQ (67) was first described in 1960.[41] It was synthesised by the condensation of malononitrile with cyclohexane-1,4-dione (72), followed by bromination and dehydrobromination of 1,4-bis(dicyanomethylene)cyclohexane in the presence of pyridine, scheme 1.20.

The reaction can be carried out in benzene in the presence of a small amount of acetic acid and ammonium acetate which affords a mixture of isomers (73a) and (73b), while condensation in aqueous solution in the presence of β-alanine afforded (73a) only.

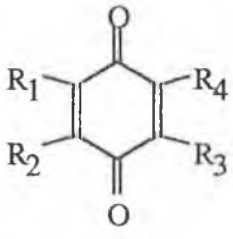


(72) (73a) (73b) (67)

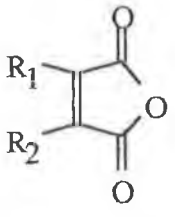
Scheme 1.20

1.B.3 Properties of TCNQ

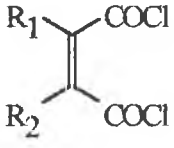
Many organic compounds function as acceptors in charge-transfer (C-T) complexes, the most common being *p*-benzoquinone and its derivatives (74),[42a] maleic anhydride and its derivatives (75) and acid chlorides (76).[42b]



(74)a: $R_1=R_2=R_3=R_4=H$
b: $R_1=R_2=R_3=R_4=Cl$
c: $R_1=R_2=R_3=R_4=Br$
d: $R_1=R_2=R_3=R_4=CN$



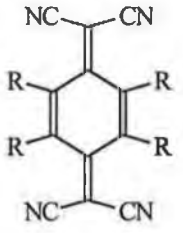
(75)a: $R_1=R_2=H$
b: $R_1=H$, $R_2=Cl$
c: $R_1=R_2=(CH=CH)_2$



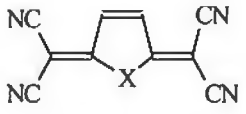
(76)a: $R_1=R_2=H$
b: $R_1=R_2=(CH=CH)_2$

However, it was the presence of the powerful electron-withdrawing cyano group and its inferred high electron affinity that led to cyano-containing molecules being investigated as potential electron acceptors.

In addition to TCNQ a large variety of electron acceptors containing the cyano group have been prepared. These include substituted (77), heterocyclic (78) and π-extended TCNQ derivatives, eg 11,11,12,12-tetracyano-2,6-naphtoquinodimethane (TNAP) (70), along with *N,N'*-dicyanoquinonediimine (79).



(77)



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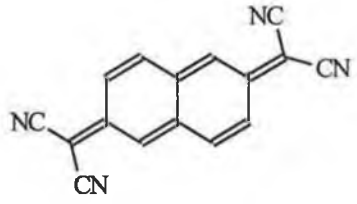
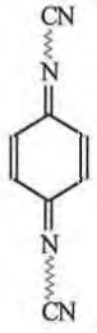


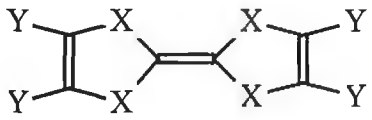
(70)

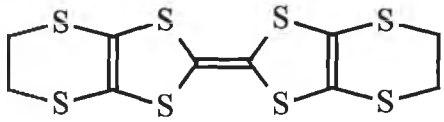


(79)

1.B.4 TCNQ as an electron acceptor

The presence of four electron-withdrawing cyano groups is what gives TCNQ its high electron affinity and therefore its potential as an electron acceptor in charge - transfer (C-T) complexes, for example its amalgamation with tetrathiafulvalene (TTF, 80a)[43] to form the first C-T complex,[44] TTF-TCNQ.

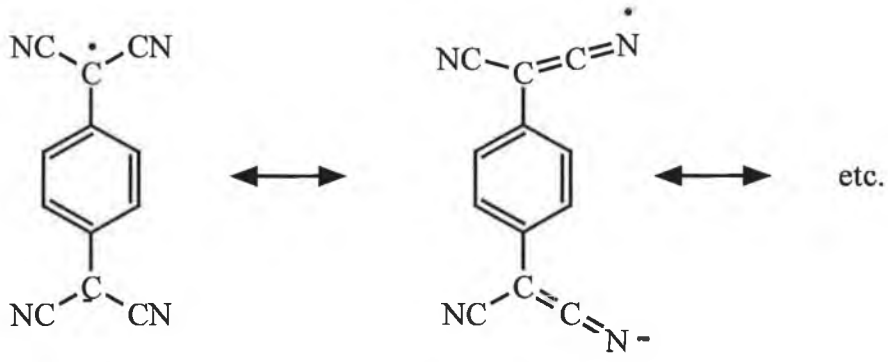




(80) a: X=S, Y=H, TTF
b: X=Se, Y=Me, TMTSF

(80)c

TCNQ (67) undergoes 1,6-addition as well as substitution reactions with nucleophiles.[45] Of particular interest is the ease with which it accepts one electron to form stable anion-radical derivatives. TCNQ forms three types of electrically conducting compounds:[45] (i) crystalline π-complexes (C-T complexes) with aromatic hydrocarbons, amines and polyhydric phenols which have intermediate to high resistivity (10^3 to 10^4 ohm cm) and very weak electron paramagnetic resonance (E.P.R.) absorption, and (ii) and (iii), two series of stable, salt-like derivatives, each involving complete transfer of an electron to TCNQ with the formation of the anion-radical TCNQ·– represented by the resonance hybrid (67X). The first of these salts has intermediate to high resistivity[46] and weak E.P.R. in the solid state[47] while the second and more complex salts are characterised by exceptionally low electrical resistivity and variable E.P.R. absorption.

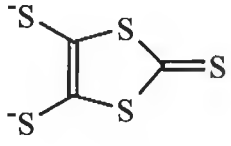


(67X)

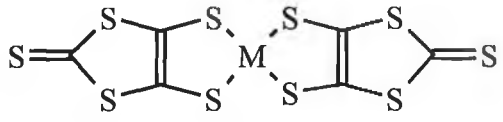
Because of the unusual stability of TCNQ (67), and electrical properties of its anion radical (67X), several alkyl derivatives were prepared for comparison and it was seen that as expected, the alkyl substituents exerted a normal inductive effect which produced a decrease in the oxidation-reduction potentials relative to TCNQ.[45]

Since the discovery of the one-dimensional electrical conductivity in the TCNQ-TTF complex, a lot of effort has been expended in investigating the synthesis of novel donor and acceptor systems, although with the discovery that derivatives of TTF, tetramethyltetraselenafulvalene (TMTSF) (80b), and bis(ethylenedithiolo)- tetrathiofulvalene (BEDT-TTF or ET) (80c), form superconducting salts in the absence of an organic acceptor, attention has been somewhat directed away from acceptor molecules.

The research that has been carried out over the last twenty years on acceptors has primarily centered around the synthesis of derivatives of TCNQ, but also on the development of two novel families of acceptor molecules; those of the metal $M(dmit)_2$ complexes (82) of the 4,5-dimercapto-1,3-dithiole-2-thione ligand (81) and *N,N'*-dicyano-quinone diimine (DCNQI) (79). Both of these form conducting complexes, with the former exhibiting superconductivity - the passage of electric current without resistance.



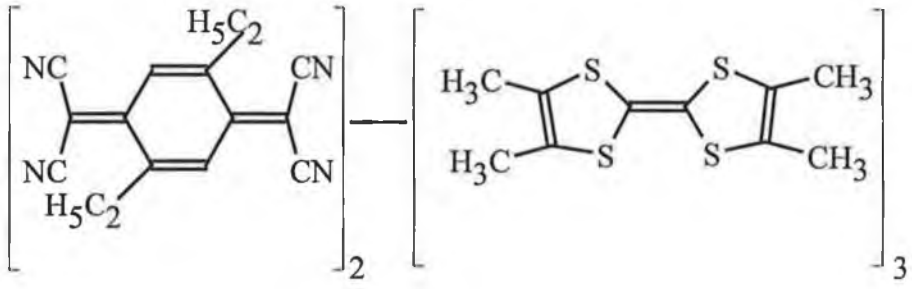
(81)



(82)

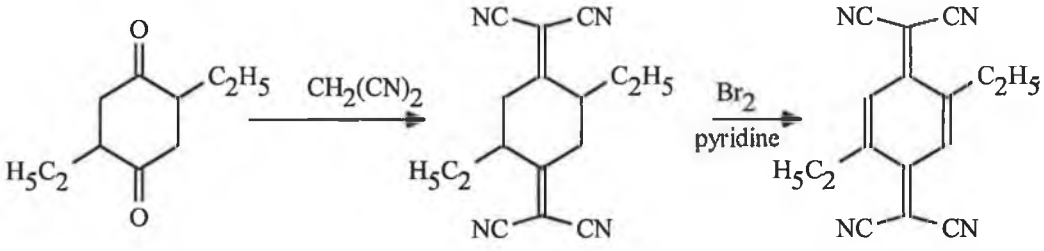
1.B.5 Synthesis of $TMTTF_3$ - $DETCNQ_2$

While the first synthesis of TCNQ was carried out in 1962,[41] and the first π-molecular charge transfer complex, TTF-TCNQ, was discovered in 1973,[44] it was not until 1980 that the first charge transfer salt in the TTF - TCNQ series with a higher stoichiometry was perceived,[48] $TMTTF_3$-$DETCNQ_2$, (83).



(83)

DETCNQ (86) was synthesised in a manner analogous to the preparation of TCNQ - from the condensation of 2,5-diethyl-1,4-cyclohexanedione (84) with two molecules of malononitrile, scheme 1.21.

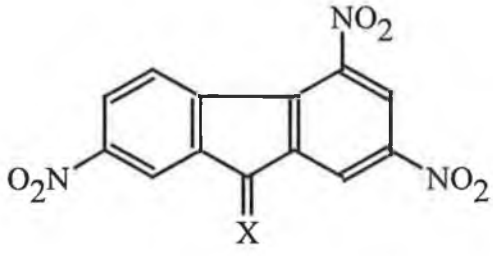


(84) (85) (86)

Scheme 1.21

1.B.6 Synthesis of 9-dicyanomethylene-2,4,7-trinitrofluorene (DTF), (87)

The synthesis of 9-dicyanomethylene-2,4,7-trinitro-fluorene (DTF; 87), was reported by Mukherjee and Levasseur[49] in 1960 as a compound that had complexing properties superior to its precursor, 2,4,7-trinitro-fluorenone (TNF; 88).



(87) X=C(CN)$_2$
(88) X=O

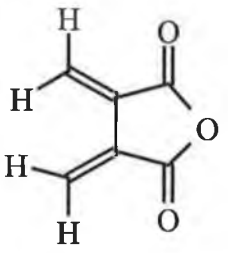
It was also of interest because of its ability to form charge-transfer complexes and stable anion-radical salts of lithium and triethylammonium ions. DTF was synthesised in excellent yield by the piperidine-catalysed condensation of TNF and malononitrile in methanol.

The analogous ammonium acetate-acetic acid catalysed condensation in benzene was attempted but led to recovery of starting material. This fact is attributed to the donor activity of the solvent, which converts TNF completely to its benzene complex.

1.C Fulgides

1.C.1 Introduction

Fulgides are described[50] as compounds which may be obtained by substitution of the hydrogen positions in dimethylenesuccinic anhydride (89). When one of the hydrogens is substituted by an aryl group, the crystals have initially a yellow to reddish shade, which deepens on exposure to light.

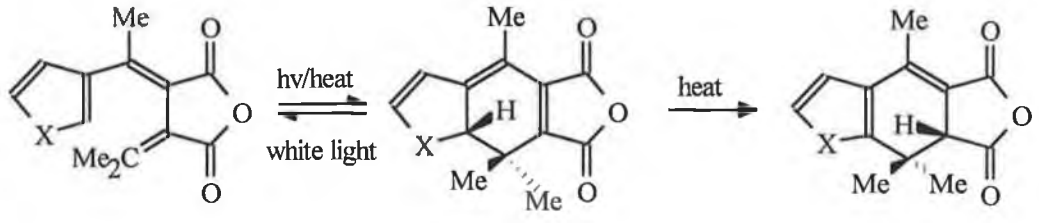


(89)

Much work has been carried out on these photochromic fulgides[51-55] and due to the thermally stable photochemically fatigue-resistant nature of some heterocyclic fulgides they have been found to be suitable for chemical actinometry[51] in the near U.V. and visible spectral regions.

1.C.2 Photochemistry of fulgides

The photochromic properties of the pale yellow (*E*)-α-3-furylethylidene-(isopropylidene)succinic anhydride (90a), an (*E*)-3-furyl fulgide, are shown[52] to result from its photocyclization to give red 7,7a-dihydro-4,7,7-trimethylbenzofuran-5,6-dicarboxylic anhydride (91a), which undergoes the reverse reaction on exposure to white light, scheme 1.22. Compound (91a), can also be formed by heating (90a) above 100°C.



(90) a: X=O
b: X=S

(91) a: X=O
b: X=S

(92) a: X=O
b: X=S

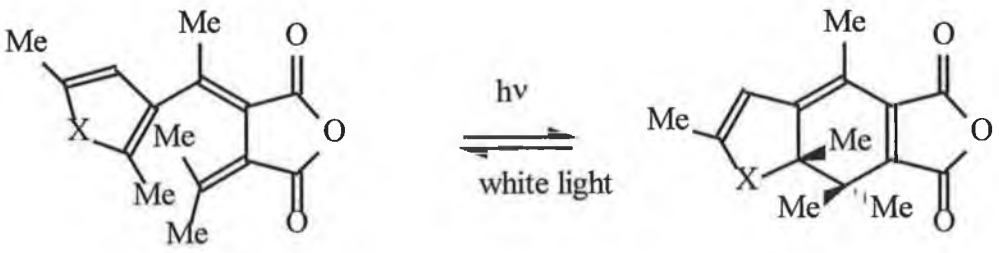
Scheme 1.22

1.C.3 Effects of structure modification

Studies on related (*E*)-thienylfulgides[53a] illustrate how markedly the photochromic properties and photochemical and thermal reactions can be altered by modifications in their structure.

2-Isopropylidene-3-[α-(3-thienyl)ethylidene]succinic anhydride (90b) showed a change from a nearly colourless to a deep red colour on irradiation (366nm) and on heating (180°C for 1 min.). As with the furylfulgide (90a) the colour is due to the 7,7a-dihydrobenzothiophene derivative (91b) which undergoes the reverse reaction on exposure to white light.

When heating time was extended, the E-fulgides (90a) and (90b) were converted quantatively into the 6,7-dihydrobenzo-furans and thiophenes (92a) and (92b), presumably via a 1,5-hydrogen shift in the 7,7a-DHBF and 7,7a-DHBT (91a) and (91b), scheme 1.21. Introduction of a methyl substituent into the 2- and 5-positions of the 3-thienyl group of the (E)-fulgide (91b), giving (93b), while not affecting the reversible photochemical reaction (93b)⇔(94b), does eliminate the thermal hydrogen-shift reactions possible for the 7,7a-DHBT (91b). Also because of the steric interactions which would arise between the 7a-methyl and the 7-methyl group *cis* to it, thermal disrotatory ring opening of a 7,7,7a-trimethyl-7,7a-DHBT (94b) is prevented, scheme 1.23.



(93) a: X=O
b: X=S
c: X=NMe

(94) a: X=O
b: X=S
c: X=NMe

Scheme 1.23

Compound (93a) does not cyclise to the corresponding DHBF derivative on heating. This fulgide turns red but the colour is not reversible on exposure to white light and is attributed to breakdown products. It does, however, undergo quantitative conversion to (94a) on irradiation at 334 and 366 nm.

In a later paper[54] it was illustrated how the colour of the ring-closed forms can be altered to deep blue simply by replacing the 3-furyl or 3-thienyl group by a 3-pyrryl group. Product (94c) is obtained on irradiation of (93c) at 366nm, and once again the thermal stability of the 7,7a-dihydroindole derivatives (7,7a-DHI's) is attributed to the steric interactions between the cis 7- and 7a-methyl groups, which prevent ring opening by the symmetry-allowed disrotatory mode. The photochemical symmetry-allowed conrotatory ring-opening is not subject to steric constraints.

When X=NPh, the coloured form absorbs at a higher wavelength than when X=O or X=S which is of particular interest now with the development of laser diodes which emit radiation at wavelengths as short as λ=670nm. This leads to the possibility of the structure of photochromic fulgides being modified so that their coloured forms absorb in the λ600-700nm region.

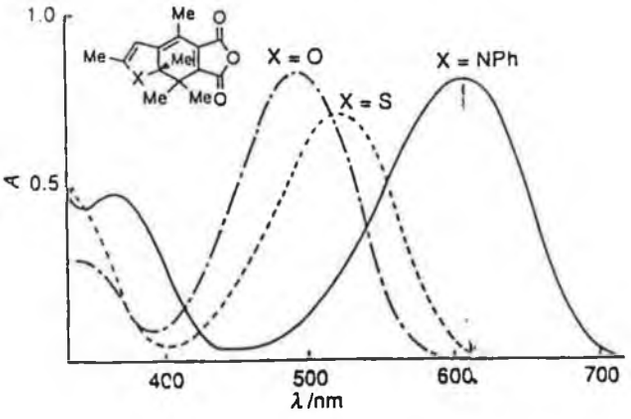
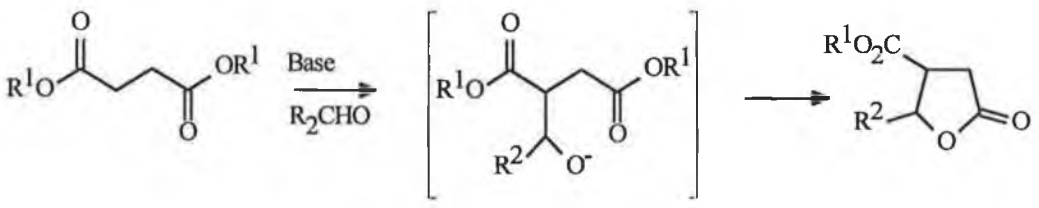


Fig. 1 Absorption spectra of the coloured forms (X=O, S and NPh) obtained on irradiation (λ366nm) of *ca.*1 x 10^{-4} mol dm^{-3} solutions of the corresponding fulgides in toluene to the photostationary states.

1.C.4 Synthesis of fulgides

The furyl fulgides were all prepared via the classical Stobbe condensation reaction,[55] scheme 1.24, where succinic esters (95) are deprotonated and treated with aldehydes or ketones to form, via the unstable adduct (96), the paraconic ester (97).



(95) (96) (97)

Scheme 1.24

(E)-α-3-Furylethylidene(isopropylidene)succinic anhydride (90a) was prepared[52] via the Stobbe condensation of 3-acetylfuran with isopropylidenesuccinate in the presence of sodium hydride followed by cyclisation with acetyl chloride.

(E)-α-2,5-Dimethyl-3-furylethylidene(isopropylidene)succinic anhydride (93a) was synthesised[53b] by reaction of diethyl isopropylidenesuccinate and 2,5-dimethyl-3-acetylfuran in the presence of sodium hydride. The di-acid obtained after work-up was cyclised using acetic anhydride and on selective recrystallisation gave (93a).

2-Isopropylidene-3-[α-(3-thienyl)ethylidene]succinic anhydride (90b) was synthesised[53a] by the Stobbe condensation of 3-acetylthiophene and diethyl isopropylidenesuccinate in the presence of sodium hydride and finally the resulting diacid was treated with acetyl chloride.

(E)-α-1,2-Trimethyl-3-pyrrylethylidene(isopropylidene)succinic anhydride (93c) was prepared[54] in a similar manner from diethyl isopropylidenesuccinate and 3-acetyl-1,2,5-trimethylpyrrole in the presence of potassium *tert*-butoxide in *tert* -butyl alcohol and finally cyclised with acetyl chloride.

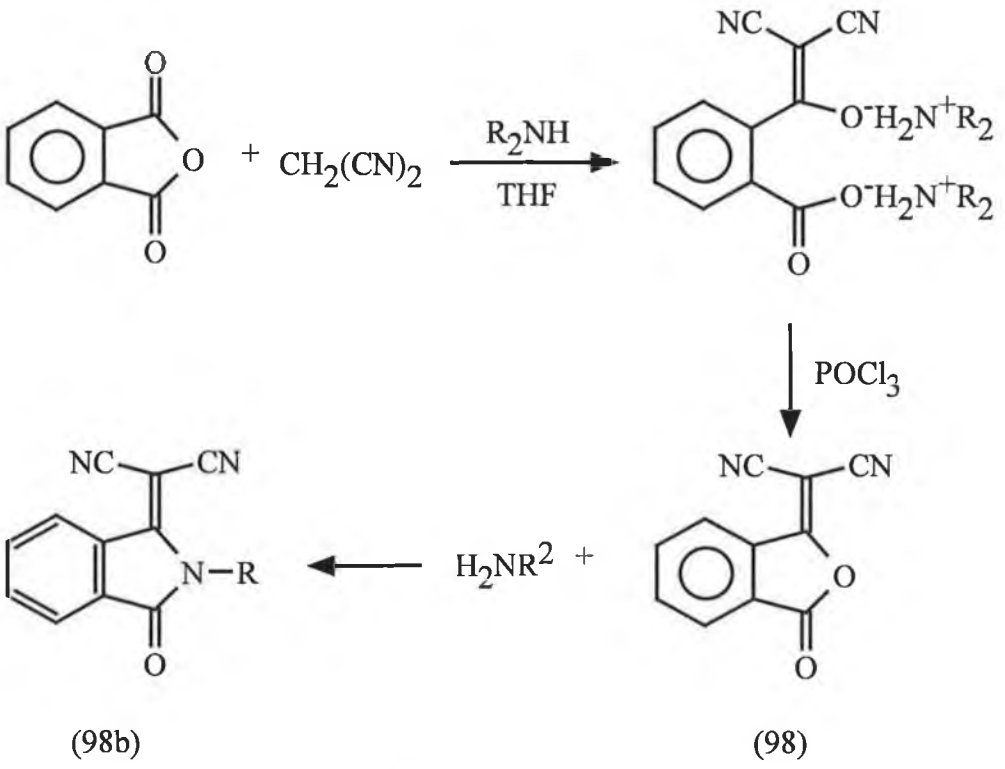
1.C.5 Introduction of the dicyanomethylene group

As already mentioned with regard to the pyrryl fulgides, it was of interest to modify the structure of photochromic fulgides so that their coloured forms absorbed in the 600-700nm region. It was discovered by Heller and co-workers[56] that, by replacing one of the carbonyl groups of the anhydride ring by the powerful electron-withdrawing dicyanomethylene group, the resulting coloured forms absorb at much longer wavelengths, >100nm, than the photocyclised compounds (94a and b) obtained from the corresponding photochromic fulgides (93a and b).

1.C.6 Synthesis of dicyanomethylene derivatives

These new photochromic dicyanomethylene derivatives of fulgides were synthesised based upon the method of Moore and Kim,[57] who reported a novel imide-forming reaction, scheme 1.25, in which 3-(dicyanomethylidene)phthalide (98) reacts with amines at room temperature, to give the corresponding imides (98b). It is the first two steps in this synthesis, i.e. introduction of the dicyanomethylene group, and subsequent ring-closure affording compound (98), that are the steps upon which Heller's method is based.

The phthalic anhydride derivative (98) was prepared in high yield from phthalic anhydride and malononitrile in the presence of diisopropylamine, and the introduction of the dicyanomethylidene group was shown to be a means of modifying the reactivity as well as enhancing the solubility of such materials.

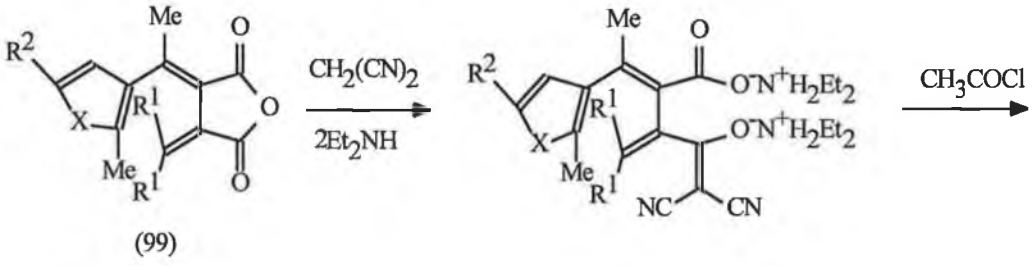


(98b) (98)

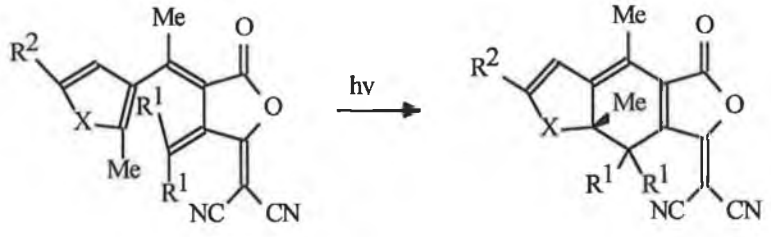
R=Me_2CH, R^2=Ph, PhOPh, NHPh, n-hexyl.

Scheme 1.25

Heller and co-workers used a similar method to synthesise[56] their photochromic dicyanomethylene derivatives (100), scheme 1.26.



(99)



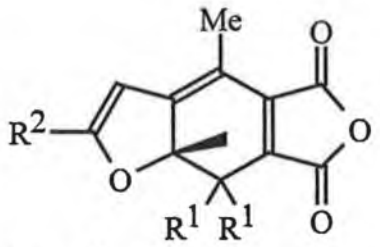
(100) (101)

a: X=O, R^1=R^2=Me
b: X=O, R^1=cyclopropyl, R^2=Ph
c: X=S, R^1=Me, R^2=Ph

Scheme 1.26

In both cases two molar equivalents of the secondary amine were added dropwise to a stirred solution of equimolar portions of the anhydride and malononitrile in tetrahydrofuran at room temperature. The intermediate salt was filtered off after 4-5 hours, and in Heller's case was treated with acetyl chloride to afford ring-closure giving (100), while Moore and Kim's diisopropylamine salt was treated with excess phosphorus oxychloride in dichloroethane to yield 3-(dicyanomethylidene)phthalide (98).

The spectra of compounds (101b), (101c) and (102), ($1x10^{-4}$ mol dm^{-3} solutions in toluene), after irradiation at 366nm to the photostationary state, are shown in Fig. 2 and clearly show the potential of replacing one of the carbonyl functions in fulgides by a dicyanomethylene group in the design of fatigue-resistant thermally stable photochromic systems.



(102) R^1=cyclopropyl, R^2= Ph

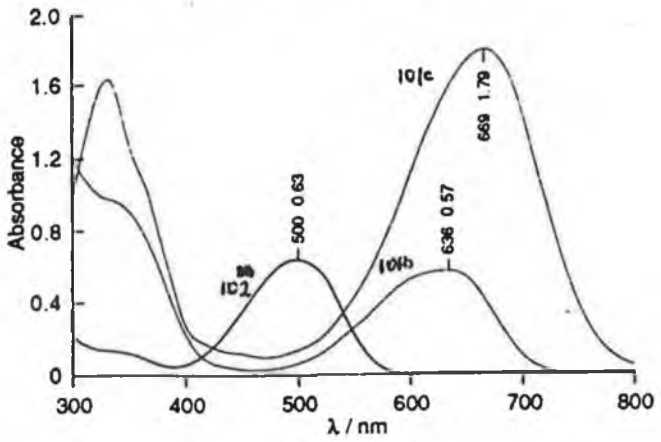
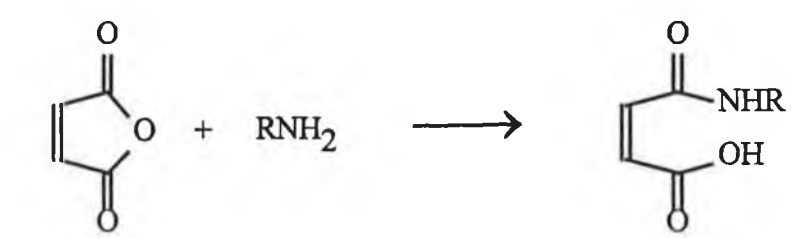


Fig. 2 The spectra of compounds (101b), (101c) and (102) (1 x 10^{-4}mol dm^{-3} solutions in toluene) after irradiation at 366 nm to the photostationary state.

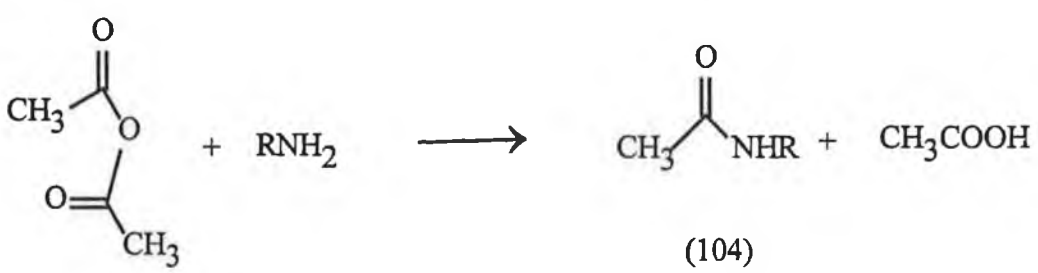
1.D Aminolysis of anhydrides

1.D.1 Introduction

While the Knoevenagel condensation (Section 1.A.4) involves the reaction of a carbonyl compound with an active methylene compound, usually in the presence of an amine, the addition of an amine to a reactive carbonyl compound has also received much attention in recent years. It is the detailed mechanism of this reaction that is a problem of continuing interest. In the reactions between anhydrides and amines the observed mechanism depends greatly on (a) whether the anhydride is cyclic or acyclic, and (b) whether the amine is primary, secondary or tertiary. The most significant of these two factors is (b) which can in fact be reduced to whether the amine is tertiary or not. Primary and secondary amines have at least one hydrogen atom available to take part in the reaction, otherwise proton transfer cannot occur. The reaction of primary or secondary amines with anhydrides, both cyclic and acyclic, is a common and practical approach to the formation of amides,[58] scheme 1.27.



(103)



(104)

Scheme 1.27

Work that has been carried out on the aminolysis of anhydrides has centered around examining the effect of basicity, category of amine, hydrophobic bonding and steric effects[59,60,61] on the rate of reaction, and the sensitivity of the rate-determining step to the reaction conditions.[61]

1.D.2 Aminolysis of phthalic anhydride in water by strongly basic secondary amines.

It was seen[59] that when the aminolysis of phthalic anhydride was carried out in water using strongly basic amines and the total amine concentration, $[amine_T]_0$, was at least five times greater than the initial anhydride concentration, $[anhydride]_0$, the rates of change in ultraviolet absorbance which followed the mixing of the reactants obeyed a first-order rate law. The pseudo-first-order rate constant values were found to have a first-order dependance on $[amine_T]_0$ for reactions of amines containing less than six carbon atoms but they exhibited both a first-order and a zero-order dependance for reactions of amines containing larger numbers of carbon atoms. This transition occurred at high values of $[amine_T]_0$ and the value decreased with increasing numbers of carbon atoms in the amine. The specific value of these amine concentrations is thought to be the critical micelle concentration (CMC) of the amine cations in solutions of ionic strength 1.0M. Once the CMC has been exceeded, the addition of extra amine does not significantly increase the thermodynamic activity of the free amine that is the reactive species in the aminolysis reaction, and consequently the rate of reaction does not increase.

From this work it was seen that no simple relationship exists between the basicity of strongly basic amines toward a proton and their nucleophilicity in the aminolysis reaction. Jencks[60] observed a similar behaviour during the aminolysis of very reactive acylating reagents such as 2,4-dinitrophenyl

acetates by strongly basic amines and concluded that very little positive charge had been generated on the amine nitrogen atom (and consequently very little N-C bond formation had occurred) in the rate-determining transition state for aminolysis. Pitman et al[59] tended to suggest that the rate-determining step occurred earlier along the reaction coordinate than the point where a tetrahedral intermediate was formed or a concerted displacement occurred and suggested mechanisms in which either the reactants are approximated by intermolecular hydrophobic bonds prior to the rate-determining step in which a N-C bond is partially formed or in which the transition states are stabilized by hydrophobic forces.

It was also seen in this study[59] that any catalysis of the hydrolysis of phthalic anhydride by the amines was very small compared to their nucleophilic participation in the aminolysis reaction.

1.D.3 Aminolyses of phthalic and succinic anhydrides by weakly basic primary and secondary amines.

It was of interest to see whether or not the rates of aminolysis of phthalic and succinic anhydrides by weakly basic amines were influenced by the basicity of the amines when the amines are weakly basic primary and secondary amines.

It was seen[61] that, as with the case of the strongly basic amines, the amines in question did not significantly catalyse the hydrolysis reactions of the anhydrides. None of these reactions became zero order in amine concentration even when the initial total amine concentration, $[amine_T]_0$, exceeded 10^{-2} M. This was explained by the fact that the cations of weakly basic aromatic amines are known to have very much higher CMC's than aliphatic amines containing the same number of carbon atoms and hence the CMC of the weaker amines was not exceeded.

The pH dependence of the reactions with the weakly basic amines was identical with that found for the stronger bases and was consistent with the neutral amine molecule being the major species that participated in the reaction.
The sensitivity of the aminolysis rate constants to the pK_a value of the amine cation decreased as the amines became more basic, which concurs with what Jencks and Gilchrist found on investigation of the rate constants of nucleophiles of pK = 3.1-15.8 with a series of acetate esters with leaving groups of pK 10-2. A very small sensitivity to basicity was observed in the reactions of strongly basic amines with the most reactive esters. It was also concluded that due to the similarity in the behaviour of primary, secondary and tertiary amines, no proton transfer occurs or is required in these reactions and that amine attack and leaving-group expulsion can occur through transition states of zero net charge.

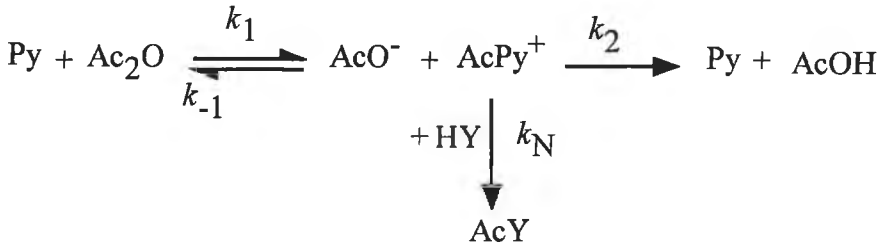
In contrast to the reactions with strongly basic amines, the reactants in reactions with weakly basic aromatic amines are not significantly approximated by hydrophobic forces or the rate-determining transition steps are not stabilized by hydrophobic bonds. This is due to the fact that more positive charge is built up on the nitrogen atom in the case of weakly basic amines and this charge can in turn polarise the benzene ring to which it is attached. This polarised hydrocarbon group would not be expected to strongly interact with other hydrocarbon groups such as those on the anhydride to stabilize the transition state. As the positive charge was built up on the nitrogen atom the hydrophobic forces would break down and little acceleration would result.

Kluger and Hunt[58] found, by examining the variation of the second-order rate constant, k, for the addition of amines to maleic anhydride with the pK_a of the conjugate acids of the amines used, that there was a change in the rate-determining step with variation in basicity of the nucleophile. This was apparent from the non-linear relationship between log k and pK_a. If all the amines react by a common mechanism with a common rate-determining step, a linear relationship would be expected.

The results were interpreted in terms of a mechanism in which proton transfer in the zwitterionic tetrahedral intermediate is the rate-determining step for amines whose conjugate acids have pK_a values less than 7.7 (ie pK_b of amine >6.3), while the reactions of more basic amines, pK_b<6.3, involve rate-determining formation of a tetrahedral unit.

1.D.4 Reactions of acyclic anhydrides with amines

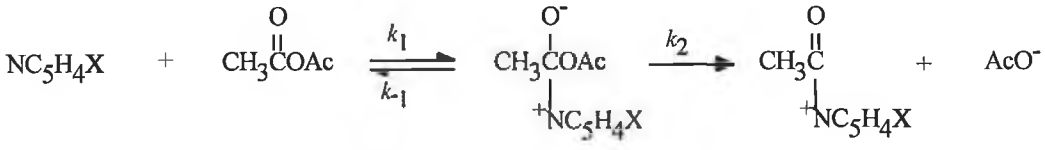
Unlike the reactions of cyclic anhydrides with amines which are subject to specific-acid catalysis and/or general-acid catalysis[58-61] those involving acyclic anhydrides are not subject to acid catalysis. The most extensively studied reaction of acyclic anhydrides with amines is the pyridine-catalysed hydrolysis of acetic anhydride[62] which is believed to proceed through the intermediate formation of the N-acetyl- pyridinium ion scheme 1.27. Bafna and Gold[62a] in 1953 observed that the dependance of the reaction velocity on the concentrations of pyridine and acetic anhydride appeared complex but could be explained if the formation of catalytically inactive pyridinium acetate is allowed for. In the same series Gold and Jefferson[63] observed that there was no evidence of formation of an intermediate by interaction of less catalytically active amines than pyridine with the anhydride. The experimental facts are consistent with the mechanism proposed, in which the transfer of an acetylium group ($CH_3{\cdot}CO^+$) from acetic anhydride to the catalyst is rate-determining, with hydrolysis of the resulting cation being rapid. The pyridine-catalysed hydrolysis of acetic anhydride is orders of magnitude faster than the general-base catalysed hydrolysis by acetate-ion, and must, therefore proceed by a different mechanism. Pyridine-catalysed hydrolyses of other activated acyl compounds with good leaving groups are thought to proceed through the



Scheme 1.28

same intermediate and other pyridine-catalysed acylation reactions presumably involve the same mechanism, with another nucleophile, HY, replacing water as the eventual acyl group acceptor, k_N, scheme 1.28 . Pyridine is an effective catalyst for these reactions because it is a highly effective nucleophile for acyl compounds with a good leaving group and because the presumed intermediate acylated tertiary amine cannot lose a proton to give a resonance-stabilised amide and is, therefore, highly reactive towards water and other nucleophiles.

Castro and Castro,[62c] in examining the reactions of 4-amino- and 4-dimethylamino-pyridine with acetic anhydride explained the results in terms of a tetrahedral intermediate in the reaction path and a change in the rate-determining step from breakdown to formation of the intermediate as the nucleophile increases its basicity, scheme 1.29.

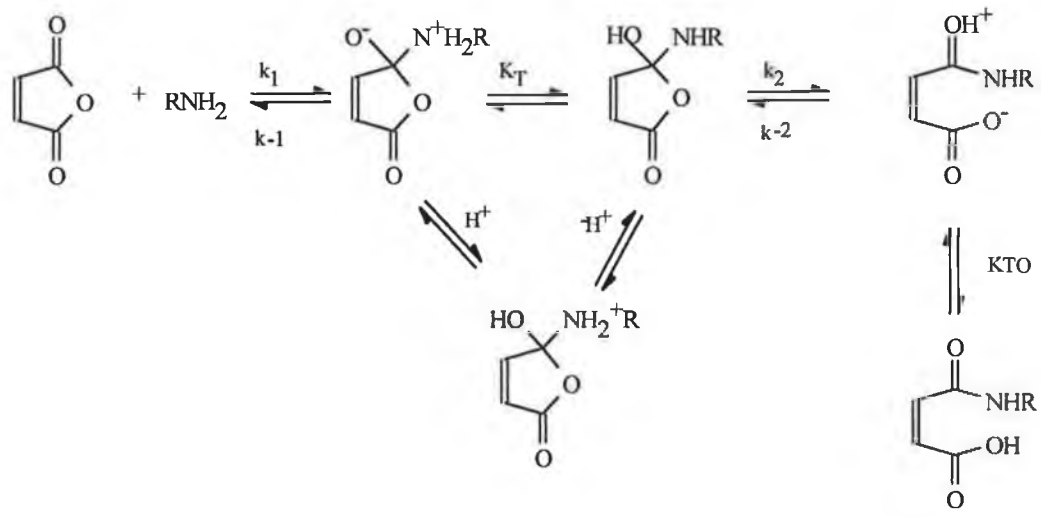


Scheme 1.29

The higher sensitivity of the rate to amine basicity for the less basic nucleophiles compared to the smaller one for the most basic has been explained here in terms of the transition state structures for (i) the less basic nucleophiles and (ii) the most basic nucleophiles. In the former there is full bond formation between the amine nitrogen and carbonyl carbon, whereas in the latter only a "loose" bond occurs between the atoms. This is once again in accordance with what Jencks[60] observed for the aminolysis of 2,4-dinitrophenyl acetates by strongly basic amines.

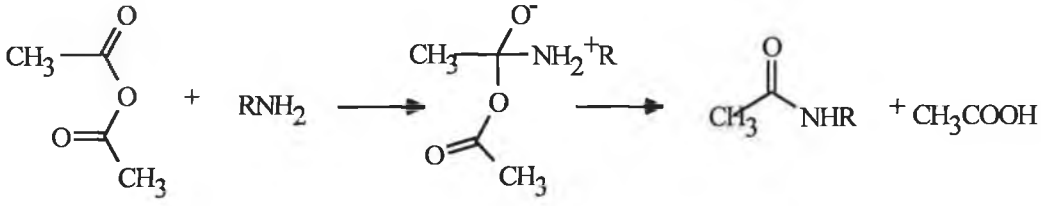
1.D.5 Aminolysis of cyclic anhydrides with tertiary amines.

Aminolysis of cyclic anhydrides by primary or secondary amines is subject to acid catalysis which implies that proton-transfer steps are kinetically significant. Acid catalysis is thought to promote proton transfer between nitrogen and oxygen centers of a tetrahedral intermediate, scheme 1.30.



Scheme 1.30

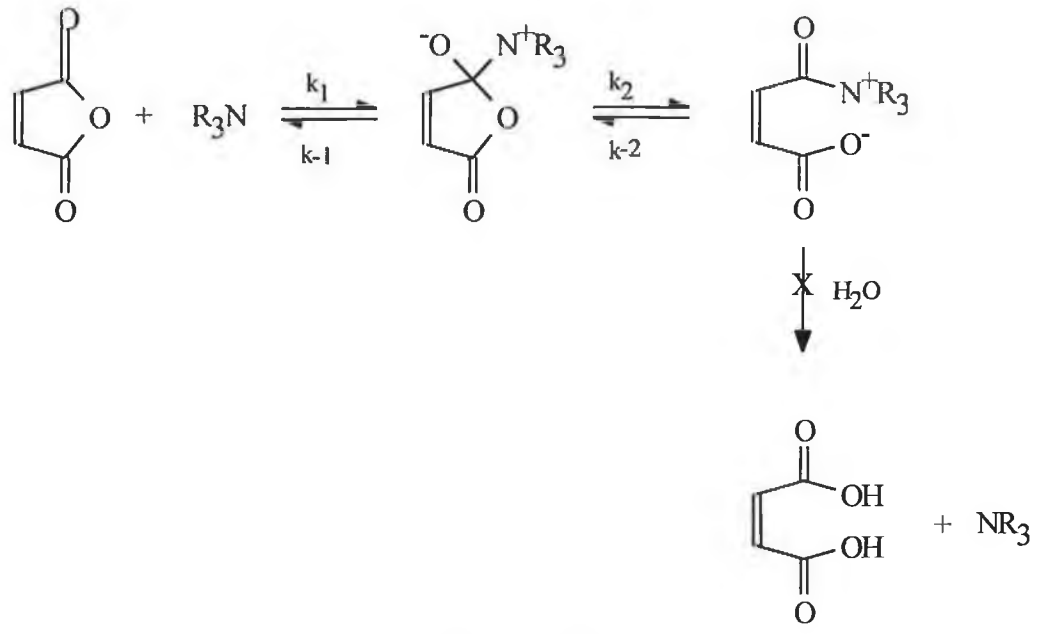
The initially formed tetrahedral intermediate is zwitterionic and the transfer of the proton converts it to the uncharged aminol. The same reaction involving acyclic anhydrides involves addition of an amine to an anhydride to form a zwitterionic intermediate which decomposes directly to the amide and carboxylic acid,[64] scheme 1.31.



Scheme 1.31

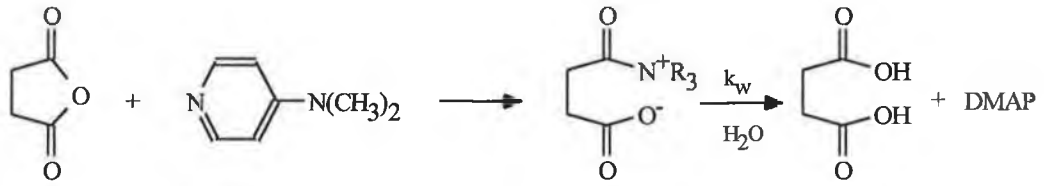
Kluger and Hunt[64] were able to deduce the function of catalysis of proton transfer in the cyclic series by studying the reaction of cyclic anhydrides with tertiary amines - a reaction that does not involve proton transfer. In the reaction of maleic anhydride with water in the presence of pyridine it was

found that the rate of reaction was independant of the concentration of pyridine, which means that if an intermediate acylammonium ion is formed, it must revert to its reactants faster than it can react with water, scheme 1.32.



Scheme 1.32

The reaction of maleic anhydride with a more basic tertiary amine, 4-(dimethylamino)pyridine, which should have reacted more readily with the anhydride, once again showed no significant formation of a complex. These results suggested that the reactions of maleic anhydride and pyridines are readily reversed as a result of the high effective molarity of the intramolecular carboxylate nucleophile produced in the reaction and is consistent with the observed rate supression by common ions in reactions involving acylammonium ion intermediates. The hydrolysis of succinic anhydride was investigated as it is known to cyclise more slowly and to a lesser extent than maleic anhydride and so would provide a better opportunity for the complex to exist in higher concentrations. The hydrolysis of succinic anhydride with pyridine itself could not be studied as pyridine absorbs in the same region (220-230nm) as the spectral change in the anhydride would be observed. The reaction of succinic anhydride with 4-(dimethylamino)pyridine (DMAP) in water was examined and in this case the formation of a complex was observed, scheme 1.33.



Scheme 1.33

While DMAP does not promote the hydrolysis of succinic anhydride, spectroscopic analysis of the reaction products has shown it to be the succinyl-4-(dimethylamino)- pyridinium ion (SDMAP). The reverse reaction of the succinylpyridinium ion is sufficiently slow to permit accumulation of the intermediate. Also, it was seen that the rate of decomposition of the pyridinium ion is independent of the concentration (within the ranges used) of added 4-(dimethylamino) pyridine.

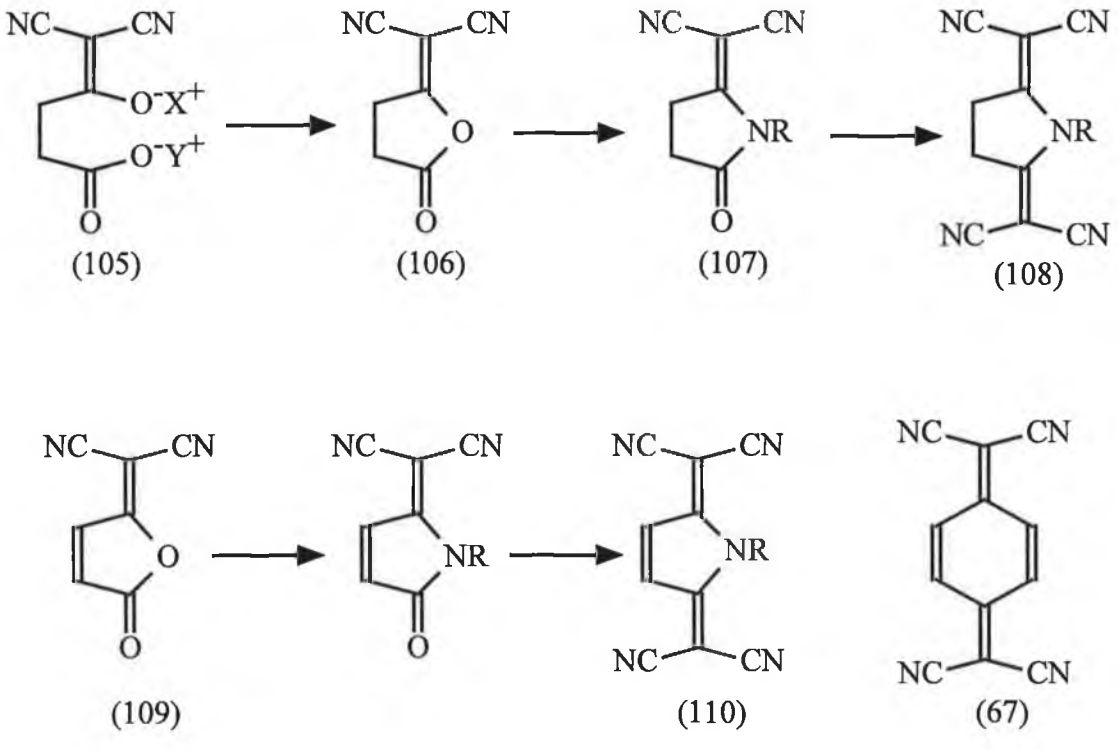
It was concluded from this work that the reaction of pyridine with maleic anhydride is not observed because the reversion competes favourably with the addition of water to the intermediate, while the hydrolysis of succinic anhydride via the intermediate formation of the SDMAP ion is observed.

CHAPTER 2

RESULTS AND DISCUSSION

2.A.1 Introduction

The importance of compounds containing the dicyanomethylene moiety in place of a carbonyl group can be seen from Chapter 1 in particular in investigations directed towards the synthesis of electron acceptors. We have investigated routes directed towards the synthesis of 4-(dicyanomethylene)butanolide (106) as a potential precursor to (107) and ultimately (108), scheme 2.01. The lactone (106) is a saturated analogue of (109) which has recently been synthesised in our laboratory by the Knoevenagel condensation of maleic anhydride with malononitrile, followed by treatment of the resulting sodium salt with thionyl chloride.[65] This lactone (109) was seen as a potential precursor to the heterocyclic TCNQ analogue (110), scheme 2.01, in which isoelectric replacement of a double bond π-electron pair has been achieved by a nitrogen atom carrying a lone pair of electrons capable of π-type conjugation.



Scheme 2.01

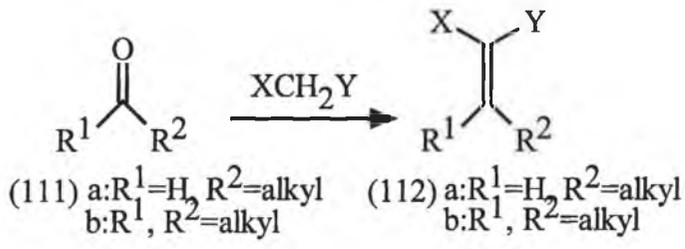
These compounds (110), analogues of 7,7,8,8-tetracyanoquinodimethane (TCNQ, 67), were of interest in order to determine the effects of N-substitution on electron

acceptor ability and on the formation of C-T complexes with various electron-rich donors.

It was decided therefore to investigate a potential analogous synthesis of (106), involving the Knoevenagel condensation of succinic anhydride with the active methylene compound malononitrile in the presence of sodium hydride and also a variety of amines.

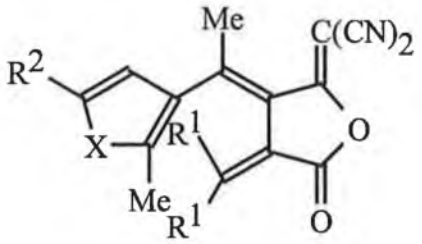
2.A.2 The Knoevenagel Condensation Reaction

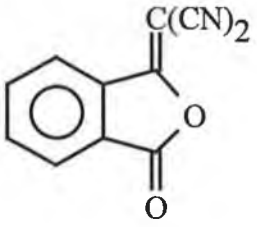
As already described, Section 1.A.4, the Knoevenagel Reaction purports treating a carbonyl compound, usually an aldehyde or ketone not containing an α hydrogen (111), with an active methylene compound of the form XCH_2Y (where X and Y=CN, CO_2Et, CO_2H, SOR, SO_2R, SO_2OR), normally in the presence of at least a catalytic amount of base or acid, to afford an alkene (112), scheme 2.02.



Scheme 2.02

To date, Knoevenagel condensation of succinic anhydride with the active methylene compound malononitrile has not been reported. The closest related syntheses in the literature are of the photochromic dicyanomethylene derivatives of fulgides (100) reported by Heller *et al,*[56] and of the pseudoanhydride (98) reported by Moore and Kim.[57]





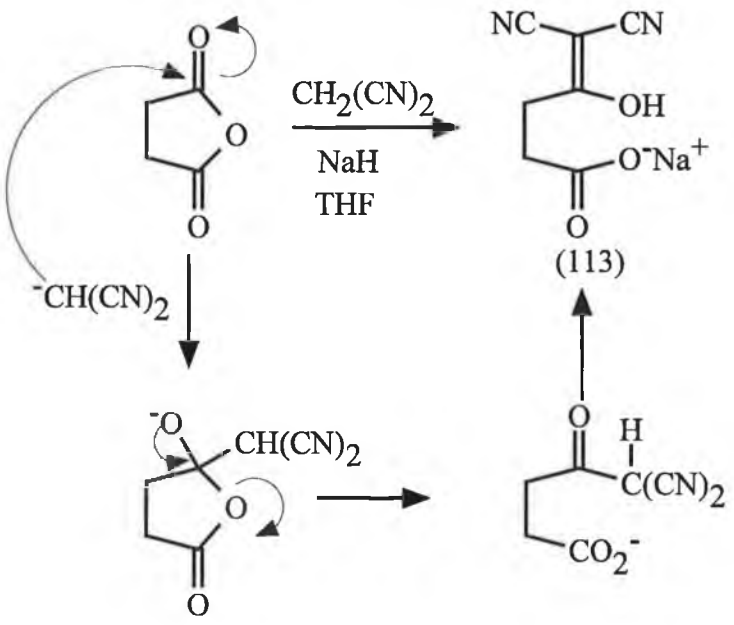
(100) a:X=O, R^1=R^2=Me (98)
b:X=O, R^1=cyclopropyl, R^2=Ph
c:X=S, R^1=Me, R^2=Ph

Both compounds (100) and (98) were synthesised by a base-catalysed condensation of anhydrides with malononitrile. Knoevenagel condensations involving anhydrides and active methylene compounds are much less numerous than those involving aldehydes or ketones.

2.A.3 Knoevenagel condensation reaction using sodium hydride as the base.

When the condensation reaction between succinic anhydride and the active methylene compound malononitrile was carried out using sodium hydride as a base in dry tetrahydrofuran, the sodium salt, sodium 4-dicyanomethylene-4-hydroxybutanoate (113) was obtained as an off-white solid, scheme 2.03.

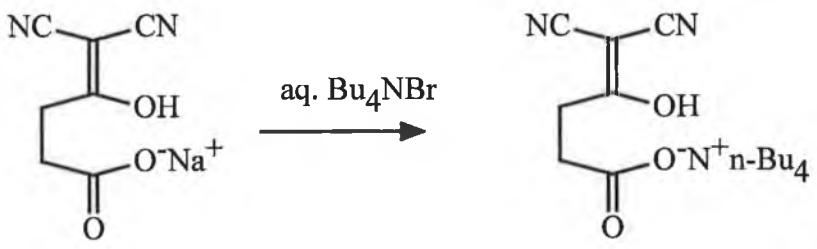
The ^{1}NMR spectrum of sodium 4-dicyanomethylene-4-hydroxybutanoate (113) showed two two-proton multiplets, at 2.28 and 2.48 ppm, corresponding to the two methylene groups of the CH_2-CH_2 backbone. The sodium salt (113) was completely insoluble in organic solvents other than hot methanol, and because of this the NMR spectra were determined in D_2O, which means that the presence or absence of the OH moiety cannot be determined. The ^{13}C NMR spectrum exhibited seven signals in all. The two methylene carbon absorption signals appeared at 35.04 and 36.07 ppm, the dicyanosubstituted carbon absorption at 52.65 ppm, two cyano absorptions at 122.80 and 124.72 ppm, the dicyanomethylene-substituted carbon absorption at 182.00 ppm and the carbonyl absorption appeared at 199.85 ppm.



Scheme 2.03

The IR spectrum of (113) showed a broad hydroxyl band at 3448 cm^{-1}, a C-H stretching band at 2936, two strong nitrile bands at 2216 and 2192 cm^{-1}, and a strong carbonyl band at 1567 cm^{-1}.

The sodium salt proved very difficult to recrystallise due to its insolubility in most organic solvents. It could be dissolved in boiling methanol but only a very small percentage (12%) of the product was recovered. However, it was found that the salt could very easily be converted to the corresponding tetrabutylammonium salt by mixing an aqueous solution of the sodium salt (113) with aqueous tetrabutylammonium bromide to give tetrabutylammonium 4-dicyanomethylene-4-hydroxybutanoate (114), scheme 2.04.



(113) (114)

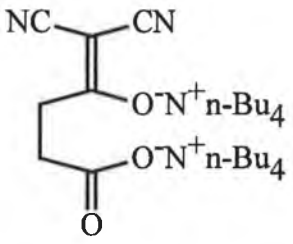
Scheme 2.04

The structure of (114) has been confirmed by IR, ^{1}H and ^{13}C NMR spectra and elemental analysis. The ^{1}H NMR spectrum of the tetrabutylammonium salt (114) showed a twelve proton triplet at 0.98 ppm, J=7.1 Hz, corresponding to the four methyl groups of the tetrabutylammonium cation. There was an eight-proton sextet, J=7.4 Hz, at 1.40 ppm, and two further eight-proton multiplets at 1.61 and 3.17 ppm, each arising from one of the three methylene groups of the cation. There were two two-proton multiplets, at 2.52 and 2.75 ppm, as a result of the two methylene groups of the backbone. The three eight-proton multiplets arising from the butyl side-chains were coupled to each other, with the 3.17 ppm multiplet corresponding to the methylene group α to the nitrogen.

The ^{13}C NMR spectrum of (114) was as expected, with the methyl carbon absorption appearing at 13.54 ppm, the two methylene carbon absorptions of the anion at 30.75 and 32.59 ppm, while the three methylene carbon absorptions of the butyl group appeared at 19.66, 23.80 and 58.86 ppm. These absorptions were assigned conclusively with the aid of a C-H correlation spectrum. The absorption of the dicyanosubstituted carbon appeared at 52.20 ppm, with two cyano absorptions at 118.64 and 120.03 ppm. The dicyanomethylene substituted carbon absorption appeared at 174.78 ppm, with the carbonyl at 195.22 ppm. The IR spectrum of (114) showed a hydroxyl band at 3452 cm^{-1}, C-H stretching between 2976 and 2882 cm^{-1}, two strong nitrile bands at 2214 and 2178 cm^{-1} and a strong carbonyl band at 1702 cm^{-1}.

Attempts were made to synthesise the corresponding bis-tetrabutylammonium salt (115). Addition of two molar equivalents of aqueous tetrabutylammonium bromide to a solution of the sodium salt (113) in water gave only the mono-tetrabutylammonium dicyanovinyl salt (114).

The synthesis of (115) was also attempted by dissolving (114) in methanol, adding it to a solution of sodium methoxide in methanol, and finally adding an equimolar



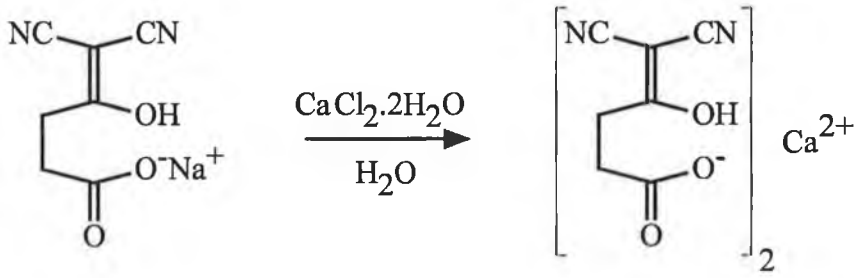
(115)

methanolic solution of tetrabutylammonium bromide. It was only on addition of water to the mixture that a solid precipitated out of the solution but this was found, to be the mono-salt (114).

This appeared to suggest that while the mono-salt (114) was completely insoluble in water, the more crowded bis-analogue (115) was considerably more soluble.

Attempts to carry out analogous reactions using a variety of shorter chain tetraalkylammonium halides, namely tetramethyl- and tetraethylammonium chloride, and tetrapropylammonium iodide, proved unsuccessful so it was concluded that the solubility of the mono- salt in water decreases as the alkyl chain length increases, but, in the case of tetrabutylammonium bromide, increases again on addition of a second equivalent of the tetraalkylammonium halide.

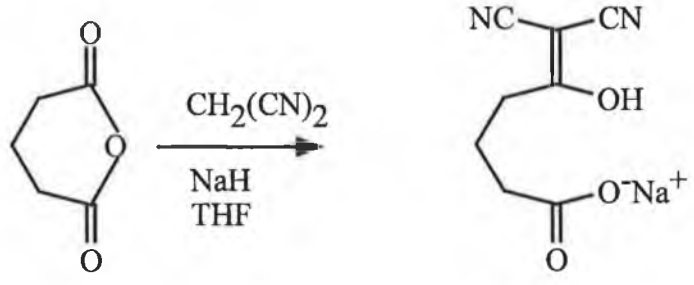
It was however found that, on treating the sodium salt (113) with aqueous calcium chloride a white solid precipitated, scheme 2.05. The ^{1}H and ^{13}C NMR spectra of the product were identical to that of the sodium salt and it was assumed to be the corresponding calcium salt (116). Its IR spectrum showed a broad hydroxyl band between 3200 and 3600 cm^{-1}, two strong nitrile bands at 2245 and 2220 cm^{-1} and a strong carbonyl band at 1560 cm^{-1}. The analogous reactions, using barium- and strontium chloride were also carried out and yielded the corresponding salts.



(113) (116)

Scheme 2.05

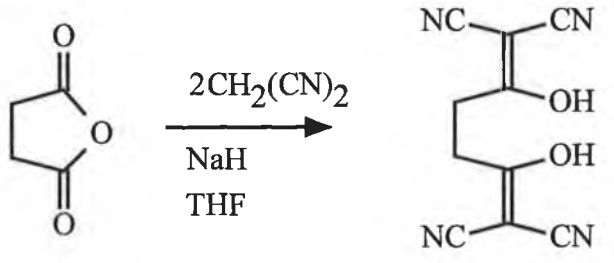
The condensation reaction of the active methylene compound malononitrile with glutaric anhydride in the presence of sodium hydride was carried out in THF in a manner analogous to that used for the reaction involving succinic anhydride. The product obtained was found to be the corresponding sodium salt, sodium 5-dicyanomethylene-5-hydroxypentanoate (117), scheme 2.06. The ^{1}H NMR spectrum of (117) showed a two hydrogen quintet, J=7.8 Hz, at 1.59 ppm, corresponding to the central methylene derived from the anhydride being split by the two adjacent methylenes, and two two-proton triplets, J=7.6 Hz, at 2.00 and 2.20 ppm, corresponding to the remaining two methylene groups each being split by the central methylene protons. The ^{13}C NMR and IR spectra of (117) were analogous to those of the sodium salt (113) derived from succinic anhydride, the ^{13}C spectrum showing an extra methylene absorption at 25.17 ppm as a result of the third methylene group in the compound (117).



(117)

Scheme 2.06

It was of interest to investigate the possibility of synthesising the tetracyano compound 1,4-bis(dicyanomethylene)-1,4-dihydroxybutane (118) by using two molar equivalents of malononitrile in the Knoevenagel condensation with succinic anhydride. The reaction was carried out as before, i.e. initial formation of an excess of malononitrile anion followed by addition of the succinic anhydride. However, the off-white solid obtained showed two triplets, at 2.41 and 2.56 ppm, in the ^{1}H NMR spectrum, inconsistent with symmetrical structure (118), scheme 2.07.



(118)

Scheme 2.07

The ^{13}C NMR was also in discord with the expected structure (118), but both ^{1}H and ^{13}C NMR spectra were in accordance with the structure (113). The IR spectrum and melting point confirmed that the product was, in fact, sodium 4-dicyanomethylene-4-hydroxybutanoate (113).

2.A.4 Knoevenagel condensation reaction using amines as bases

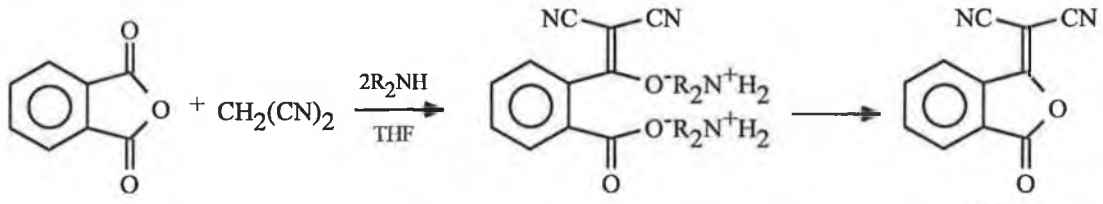
In sections 2.A.4.1 and 2.A.4.2 alkyl amines were used while section 2.A.4.3 examines reactions of succinic anhydride and malononitrile using aromatic and heterocyclic amines.

2.A.4.1 Secondary amines

In an effort to find further suitable precursors to lactone (40), the Knoevenagel reaction of malononitrile with succinic anhydride was also attempted using a variety of amines as bases.

Since both Heller[56] and Moore and Kim[57] used secondary aliphatic amines as bases in their respective Knoevenagel reactions it was first decided to investigate the reaction of succinic anhydride and malononitrile in the presence of (i) diisopropylamine and (ii) diethylamine, as well as the analogous reactions of phthalic anhydride.

The method of Moore and Kim[57] involved reaction of phthalic anhydride and malononitrile in the presence of two molar equivalents of diisopropylamine giving the bis(diisopropylammonium)phthalate salt (119a) which then was subjected to ring-closure to give the pseudoanhydride (98), scheme 2.08.



Scheme 2.08

This reaction was repeated and the bis(diisopropylammonium) salt obtained (119a) had physical and spectral properties identical to those previously reported.[57] The previously unreported bis(diethylammonium) salt (119b) was prepared by the analogous reaction using diethylamine as the base.

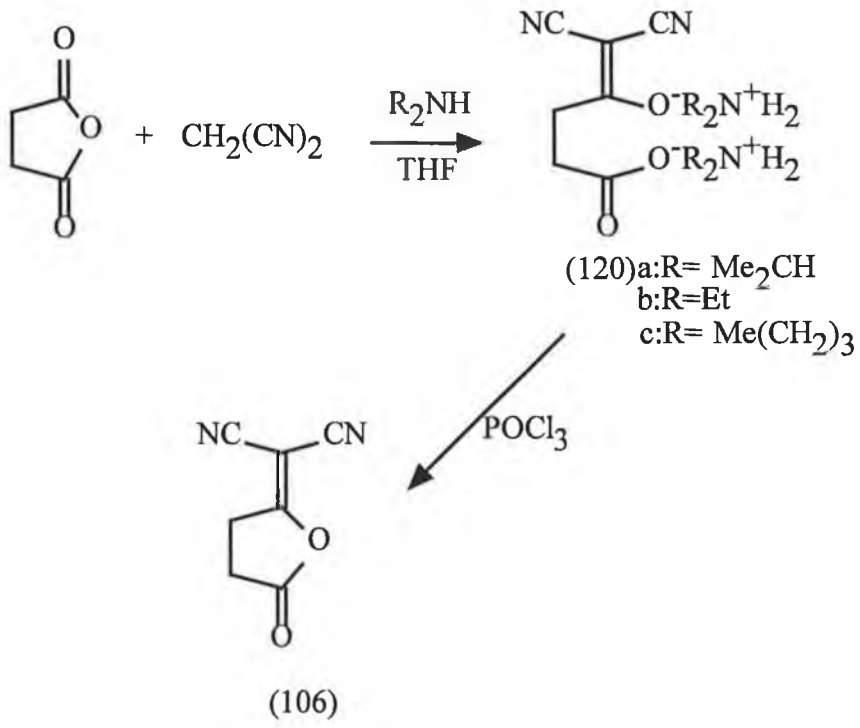
The ^{1}H NMR spectrum of (119b) showed a twelve proton triplet, J=7.4 Hz, at 1.05 ppm, due to the methyl protons, an eight proton quartet, J=7.4 Hz, at 3.82 ppm corresponding to the four methylene groups, and a four proton aromatic multiplet between 6.78 and 7.12 ppm. The ^{13}C NMR spectrum showed the methyl and methylene carbon absorptions of the ethyl group at 13.21 and 44.40 ppm respectively, a signal at 53.79 ppm corresponding to the dicyanosubstituted carbon absorption, two cyano absorptions at 122.63 and 12.80 ppm, six aromatic carbon absorptions between 129.20 and 141.01 ppm, and two absorptions at 177.30 and 198.11 ppm due to the dicyanomethylene substituted and carbonyl carbons respectively. The IR spectrum of (119b) showed a strong NH stretching band, and

both aromatic and aliphatic C-H stretching between 3100 and 2840 cm^{-1}, strong nitrile bands at 2199 and 2178 cm^{-1}, with a weaker nitrile band at 2160 cm^{-1} due to malononitrile, a strong carbonyl band at 1623 cm^{-1} and an aromatic C-H bend at 745 cm^{-1}. Elemental analysis of this solid was consistent with the molecular formula proposed ($C_{19}H_{28}N_4O_3$) and a molecule of water which may have been due to the methanol used in the recrystallisation being slightly wet.

When the Knoevenagel condensation was carried out according to the method of Moore and Kim[57] using succinic anhydride in place of phthalic anhydride, the diisopropylammonium salt (120a), scheme 2.09, was obtained in 90% yield.

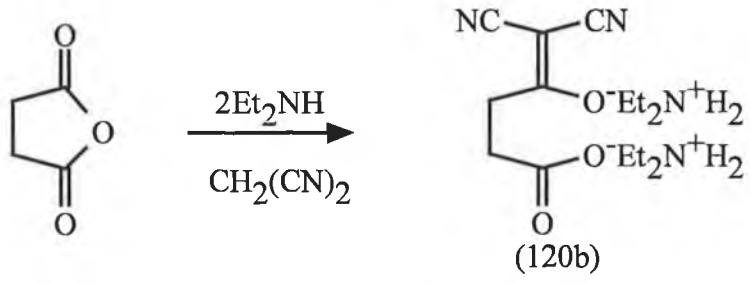
Its ^1H NMR spectrum showed a twenty four proton doublet, J=6.4 Hz, at 1.09 ppm, due to eight methyl groups, two two-proton multiplets at 2.16 and 2.42 ppm representing the two methylene groups derived from the anhydride, and a four proton septet, J=6.4 Hz, at 3.48 ppm corresponding to the two CH moieties of the isopropyl groups. The ^{13}C NMR spectrum showed the methyls at 16.41 ppm, with the methylenes at 31.52 and 32.53 ppm and the methine absorption at 45.35 ppm. The dicyanosubstituted carbon appeared at 48.37 ppm, the two cyano absorptions at 118.64 and 120.65, the dicyanomethylene substituted carbon at 179.31 ppm and the carbonyl at 196.69 ppm. The IR spectrum exhibited a broad N-H band at 3445 cm^{-1}, aliphatic C-H stretching between 2968 and 2719 cm^{-1}, two strong nitrile bands at 2214 and 2185 cm^{-1} and a carbonyl band at 1559 cm^{-1}. Elemental analysis of this compound was consistent with the molecular formula $C_{23}H_{41}N_3O_3$.

The analogous reaction was carried out using diethylamine as the base and in this case the product obtained was a dark viscous oil which on analysis was seen to contain the anticipated product (120b), scheme 2.09, as well as a further product.



Scheme 2.09

The peaks representing (120b) in the ^1H NMR spectrum appeared as a twelve proton triplet, J=7.4 Hz, due to the methyl protons of the diethylammonium cation, with the corresponding methylene protons appearing as an eight proton quartet, J=7.4 Hz, at 2.80 ppm.

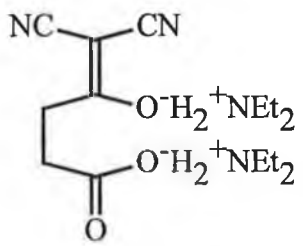


Scheme 2.10

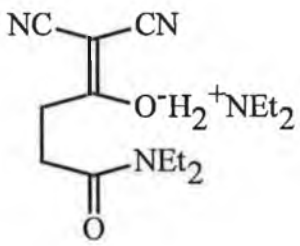
The methylene protons derived from succinic anhydride appeared as two multiplets at 2.22 and 2.39 ppm. The ^{13}C NMR spectrum of (120b) displayed the methyl carbon absorption at 12.90 ppm, with the corresponding methylene carbon appearing at 44.40 ppm. There were two further methylene carbon absorptions at 31.01 and 33.94 ppm due to the $-CH_2-CH_2$ backbone derived from the anhydride. The dicyanosubstituted carbon absorption signal appeared at 51.65 ppm, with two nitrile

absorptions at 122.75 and 124.60 ppm, and two further signals at 175.66 and 199.41 ppm due to the dicyanomethylene and carbonyl substituted carbons. The IR spectrum of the oil displayed C-H stretching between 3200 and 3000 cm^{-1} with an N-H peak at 3118 cm^{-1}, two strong nitrile bands at 2190 and 2224 cm^{-1} and a strong carbonyl band at 1563 cm^{-1}.

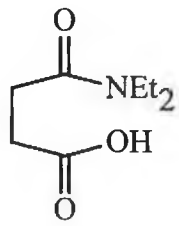
The second product was assigned the structure (121) based on the ^{1}H and ^{13}C NMR spectra of the oil. The peaks corresponding to (121) in the ^{1}H NMR spectrum included two triplets, J=6.9 Hz, at 0.82 and 0.94 ppm and two quartets, J=7.4 Hz, at 3.06 and 3.14 ppm. There was also seen to be corresponding peaks under the two methylene multiplets of (120b) at 2.22 and 2.39 ppm. The ^{13}C NMR spectrum confirms the presence of more than just two further, different ethyl groups. There were two methyl absorption signals at 14.66 and 15.65 ppm, with the corresponding methylenes at 42.95 and 44.86 ppm, two signals at 34.36 and 36.08 ppm due to the two methylene groups derived from the anhydride ring, a signal at 56.75 corresponding to a dicyanosubstituted carbon, and two weak cyano absorptions at 118.79 and 120.14 ppm. There were two further peaks, as before, at 166.73 and 181.57 ppm due to the dicyanomethylene substituted and carbonyl carbons. It proved impossible to separate the mixture and attempts to crystallise out the desired product (119b) were unsuccessful. From the ^{1}H NMR spectrum it was calculated that (120b) was present as 31% of the mixture while (121) was the major product present as 69%. The ^{13}C NMR spectrum exhibits many similarities between the minor and major products apart from those corresponding to an extra ethyl group. The most likely structure for the second product has to be (121) where the diethylammonium cation is identical to (120b) and the two ethyl groups on the diethylamide will manifest themselves as two nonequivalent three-proton triplets and two-proton quartets. This structure would account for the extra peaks in the ^{1}H NMR spectrum and also the two dicyanosubstituted and dicyanomethylene substituted carbon absorptions in the ^{13}C NMR spectrtum.



(120b)

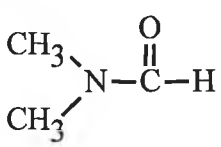


(121)



(121b)

The reaction of diethylamine and succinic anhydride alone yielded the acid-amide (121b) as expected from the reaction between a primary or secondary amine and a cyclic anhydride.[58] The ^{1}H NMR spectrum of (121b) exhibited two different ethyl groups as two three-proton triplets, J= 7.1 Hz, at 0.73 and 0.85 ppm, and two two-proton quartets, J=7.1 Hz, at 2.99 and 3.06 ppm. There was a further two triplets at 2.14 and 2.28 ppm due to the two nonequivalent methylene groups derived from the anhydride. The non-equivalence of the ethyl groups is in accordance with the case of *N,N*-dimethylformamide (121c) where the methyl groups appear as two unique singlets in the ^{1}H NMR spectrum.[66] This non-equivalent resonance is due to the π-overlap arising from the double bond.



(121c)

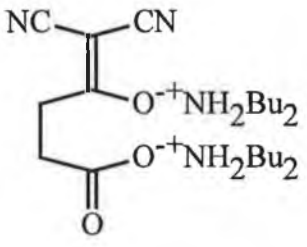
The ^{13}C NMR spectrum of (121b) displayed two methyl absorptions at 12.74 and 15.42 ppm with the two methylenes of the ethyl groups appearing at 42.78 and 44.22 ppm. There were a further two methylenes at 30.79 and 33.71 ppm due to the two nonequivalent CH_2 moieties derived from the anhydride ring. The two carbonyl absorptions appeared at 175.47 and 181.32 ppm.

The reaction between succinic anhydride, malononitrile and diethylamine was also carried out in an NMR tube with gradual addition of the amine. From ^{1}H NMR spectroscopic analysis of the reaction mixture it was observed that the anhydride reacts first with the amine. This was apparent from the decrease in the relative intensity of the singlet corresponding to succinic anhydride compared to the malononitrile two proton singlet and also the appearance of two nonequivalent

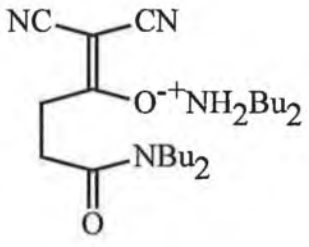
triplets due to the two methylene groups derived from the anhydride present in the final mixture. The ^{1}H NMR spectrum obtained after addition of the remainder of the amine showed that all the malononitrile and succinic anhydride had reacted and that the mixture of products, including the salt (120b), had been formed.

While di-n-butyl amine is a base of similar strength to diisopropylamine, it does, however, have a longer alkyl chain so it was of interest to investigate the consequences this would have on the synthesis of the bis(dibutylammonium) salt (120c). It has been shown that longer chain amines (> 6 carbon atoms) cause a change from first order to zero order dependance on amine concentration in the k_{obs} values[59] in the reactions of amines with cyclic anhydrides. The reaction between succinic anhydride and malononitrile in the presence of di-n-butyl amine yielded a dark, very viscous oil after removal of the solvent.

The ^{1}H NMR spectrum of this oil suggested the presence of a mixture of the anticipated product (120c) and another product whose structure was (122).



(120c)



(122)

The ^{1}H NMR spectrum of compound (120c) exhibited a twelve proton multiplet at 0.69 ppm due to the presence of four methyl groups, with the three methylene groups of each dibutylammonium cation appearing as three eight-proton multiplets at 1.10, 1.40 and 2.65 ppm, the latter being due to the methylene group α to the nitrogen atom. The two methylene groups derived from succinic anhydride appeared as two two-proton triplets, J=6.9 Hz, at 2.19 and 2.35 ppm.

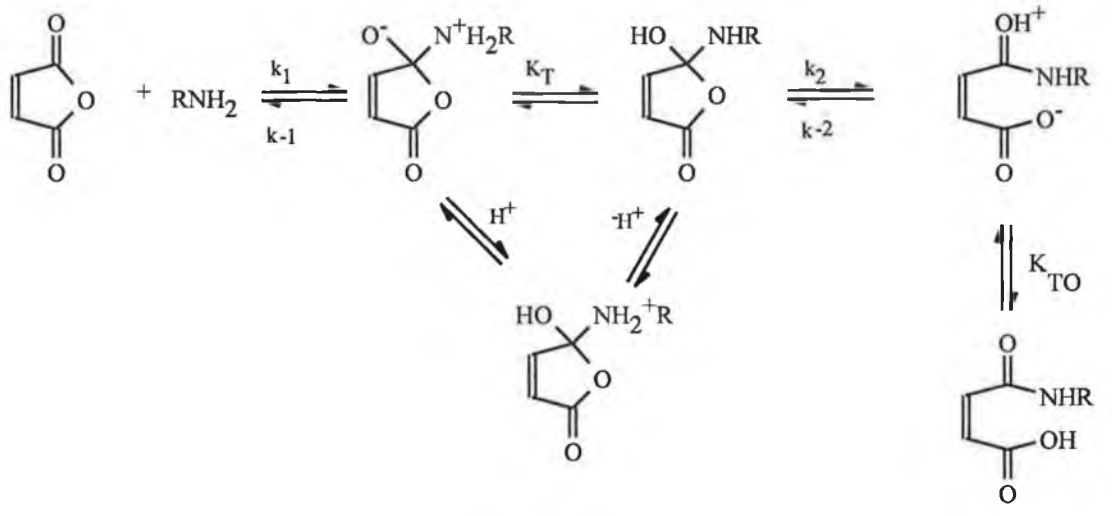
The ^{13}C NMR spectrum of (120c) exhibited the methyl carbon absorption at 15.21 ppm and the three corresponding methylenes of the dibutylammonium cation at

21.56, 29.68 and 49.16 ppm. The two remaining methylenes derived from the anhydride appeared at 31.32 and 31.67 ppm, with the dicyanosubstituted carbon absorption at 51.35 ppm. There were two nitrile absorptions at 122.36 and 124.01 ppm, and two absorptions at 175.48 and 198.70 ppm due to the dicyanomethylene substituted and carbonyl carbons respectively.

In addition to these peaks corresponding to the bis(dibutylammonium) salt (120c) of 4-(dicyanomethylene)-4-hydroxybutanoic acid, there were further peaks present in the NMR spectra due to the presence of the other component of the mixture which was assigned the structure (122). The product (119c) was present as the minor component of the mixture - 30% - with (122) appearing as the major constituent (70%). Separation of the mixture into its components proved impossible so further investigations were not carried out.

2.A.4.2 Tertiary amines

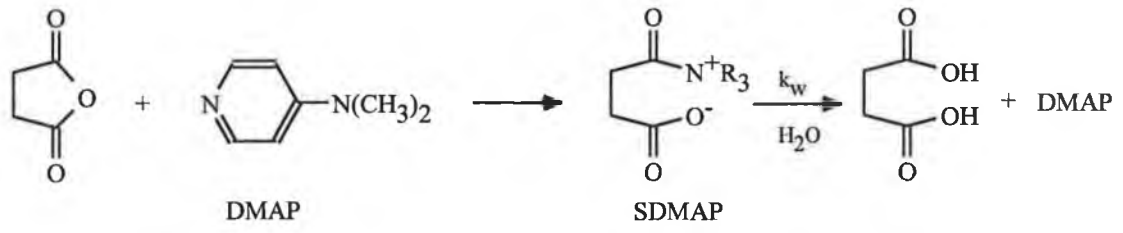
The reaction between a cyclic anhydride and a tertiary amine is known to follow a different mechanism from that with a primary or secondary amine. In the case of the aminolysis of maleic anhydride by primary or secondary amines the reaction is subject to acid catalysis which implies that proton-transfer steps are kinetically significant, scheme 2.11.[64]



Scheme 2.11

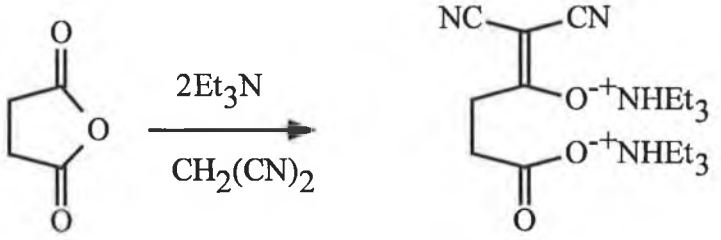
The reaction between cyclic anhydrides and tertiary amines does not involve proton transfer and when the hydrolysis of succinic anhydride with 4-(dimethylamino)pyridine in water was examined[64] the formation of the complex succinyl 4-(dimethylamino)pyridinium carboxylate, SDMAP, was observed, scheme 2.12. In the reaction of maleic anhydride with DMAP, there was no significant formation of a complex, suggesting that if one is formed it must revert to its reactants faster than it can react with water.

It was of interest to see how the Knoevenagel condensation reaction of succinic anhydride with malononitrile in the presence of a tertiary amine would compare with that in the presence of secondary amines diisopropylamine, diethylamine and dibutylamine.



Scheme 2.12

It was expected that the triethylammonium dicyanovinyl salt (123), scheme 2.13, would be formed, corresponding to the dialkylammonium salts (120 a, b and c).



(123)

Scheme 2.13

The ^{1}H NMR spectrum of the oil that separated out from the reaction mixture showed an eighteen proton triplet, J=7.4 Hz, at 1.05 ppm due to the six methyl groups, two

two-proton triplets, J=6.9 Hz, at 2.25 and 2.40 ppm corresponding to the methylene protons derived from the anhydride ring and a twelve proton quartet, J=7.4 Hz, at 2.92 ppm due to the methylene protons of the ethyl groups. The ^{13}C NMR spectrum exhibited nine signals, one at 10.58 ppm due to the methyl absorption of the ethyl group with the corresponding methylene signal at 48.82 ppm, two further methylene absorptions at 33.06 and 35.32 ppm corresponding to the two methylenes derived from the anhydride, the dicyanosubstituted carbon absorption at 51.49 ppm, two nitrile absorptions at 122.67 and 124.46 ppm, and two absorptions at 180.23 and 198.76 ppm due to the dicyanomethylene substituted and carbonyl carbons. A C-H correlation spectrum of (123), table 2.1, showed, conclusively the expected correlations between the sp^3 hybridised carbon atom signals in the ^{13}C NMR spectrum and the four signals present in the ^{1}H NMR spectrum. A 2-D COSY obtained of this oil shows only coupling between the triplet at 1.05 ppm and the quartet at 2.92 ppm, and between the two triplets at 2.25 and 2.40 ppm. These results confirm that the oil contained exclusively the bis(triethylammonium) salt (123) of 4-(dicyanomethylene)-4-hydroxybutanoic acid.

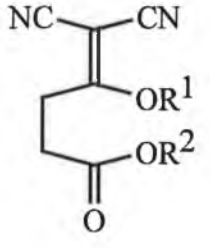
Table 2.1 showing the correlating peaks from the C-H correlation spectrum

^{1}H NMR peaks (ppm)	**^{13}C NMR peaks (ppm)**
1.05	10.58
2.25	33.06
2.40	35.32
2.92	48.82

In a further attempt to ascertain the mode of reaction of succinic anhydride with malononitrile in the presence of triethylamine the reaction was carried out in an NMR tube, with gradual addition of the amine to the succinic anhydride/malononitrile mixture. After addition of half of the amine solution (i.e.

one molar equivalent) it was clear from the ^{1}H NMR spectrum that the malononitrile had all reacted, while there was still unreacted succinic anhydride (59%) present. The ^{1}H NMR spectrum displayed a three proton triplet, J=6.9 Hz, at 1.25 ppm due to the methyl group with the corresponding methylene protons appearing as a two-proton quartet, J=6.9 Hz, at 3.10 ppm. The two methylene groups derived from the anhydride ring appeared as two multiplets at 2.46 and 2.68 ppm. Unreacted succinic anhydride appeared as a singlet at 2.95 ppm. On addition of the remainder of the triethylamine to the tube and subsequent ^{1}H NMR analysis, the same peaks were again seen, but the intensity of the succinic anhydride peak had decreased. This leads to the conclusion that it is the malononitrile that reacts first with the tertiary amine, as opposed to what was observed with the secondary amine diethylamine in which case the anhydride reacted with the amine first.

The bis(triethylammonium) salt (123) of 4-(dicyanomethylene)-4-hydroxybutanoic acid was acidified in an effort to obtain the compound (124a), (124b) or ultimately (124c). Acidification was carried out by adding 20% hydrochloric acid to an aqueous solution of the salt (123) until the solution was just acidic to blue litmus paper. Subsequent extraction with dichloromethane and removal of the solvent resulted in a sticky solid which had lost the peaks due to the two nitrile groups from the ^{13}C

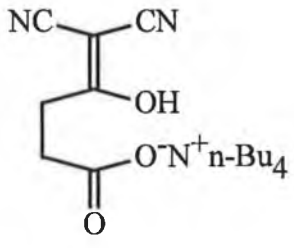


(124)a:R_1=H, R_2=N^+HEt_3
b:R_1=N^+HEt_3, R_2=H
c:R_1=H, R_2=H

NMR spectrum which also showed two different methyl carbon absorptions at 12.85 and 13.91 ppm, four different methylene carbon absorptions at 27.83, 29.71, 40.62 and 42.10 ppm, and two absorptions at 171.22 and 176.41 ppm due to two carbonyl carbons. The ^{1}H NMR spectrum exhibited two three-proton triplets at 1.05 and 1.18 ppm suggesting two different methyl groups, a four proton multiplet at 2.62 ppm due to two different methylene groups, with another four proton multiplet at 3.29 ppm

corresponding to another two methylene groups. Therefore it would seem that there are two different methylene groups - one pair originating from the succinic anhydride backbone, and the other pair arising from the ethyl group, with the non-equivalent methyl groups also coming from the two different ethyl groups. These results suggest that the product resulted from the bis(triethylammonium) salt (123) of 4-(dicyanomethylene)-4-hydroxybutanoic acid being hydrolysed in the presence of the acid and losing the dicyanomethylene moiety but further analysis was not carried out on the product.

Aqueous tetrabutylammonium bromide was added to an aqueous solution of the oil in order to compare and contrast the reaction of (a) bis(triethylammonium)salt (123) of 4-(dicyanomethylene)-4-hydroxybutanoic acid and (b) sodium 4-dicyanomethylene-4-hydroxybutanoate with the tetraalkylammonium halide. It has previously been shown (Section 2.A.2.3) that adding aqueous tetrabutylammonium bromide to an aqueous solution of (113) gave tetrabutylammonium-4-dicyanomethylene-4-hydroxybutanoate. In the case of the oil (123), though there are obvious differences in structure from (113), an off-white product precipitated from the aqueous solution and was confirmed as tetrabutylammonium 4-dicyanomethylene-4-hydroxybutanoate (114) (IR, NMR and m.p.).



(114)

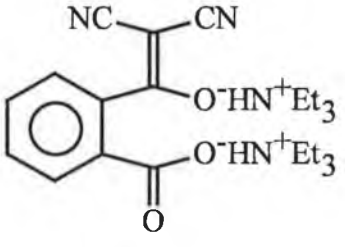
Knoevenagel condensation of phthalic anhydride and malononitrile in the presence of triethylamine was carried out and as with the analogous reaction involving succinic anhydride an oil separated from the THF solution. Its ^{1}H NMR spectrum displayed an eighteen-proton triplet at 0.98 ppm due to the six methyl groups of the equivalent ethyl groups present in the product, with the corresponding twelve-proton methylene

quartet appearing at 2.38 ppm. There were three aromatic multiplets between 7.10 and 7.56 ppm integrating for one, two and one protons respectively, due to the three different types of aromatic protons present. The multiplet that integrated for two protons corresponded to the protons on C_4 and C_5 of the benzene ring.

The ^{13}C NMR spectrum exhibited thirteen signals in total; the methyl absorption appeared at 10.57 ppm, with the corresponding methylene absorption appearing at 48.67 ppm. The dicyanosubstituted carbon appeared at 52.82 ppm with the two nitrile signals at 122.90 and 124.43 ppm, six aromatic carbon absorption signals between 129.45 and 142.54 ppm, a signal at 174.37 ppm due to the dicyanomethylene substituted absorption and the carbonyl absorption at 196.77 ppm.

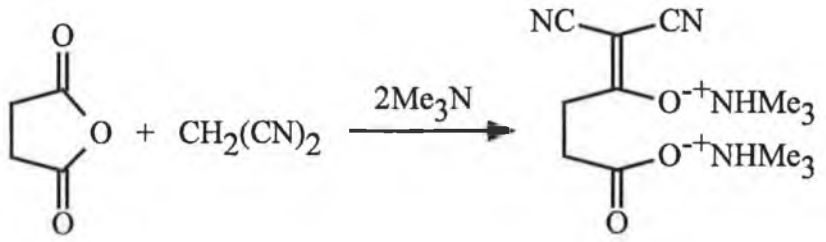
The IR spectrum of the oil showed the N-H stretch of a tertiary amine salt between 2515 and 2700 cm^{-1} with the expected nitrile bands at 2213 and 2192 cm^{-1}, and the carbonyl band at 1566 cm^{-1}.

These results clearly suggest that the oil that separated from the THF solution was the bis(triethylammonium) salt (125) of 2-(1-hydroxy-2,2-dicyano-methylene) benzoic acid.



(125)

In a further attempt to investigate the reactivity of tertiary amines in the Knoevenagel condensation reaction trimethylamine (pK_b=4.2) was employed as the amine in the reaction of succinic anhydride and malononitrile in THF. The anticipated product was the bis(trimethylammonium) salt (126) of 4-(dicyanomethylene)-4-hydroxybutanoic acid, scheme 2.14. However, unlike the case of triethylamine, no oil precipitated out of the reaction mixture and on removal of the solvent by rotary evaporation, an oil remained from which a solid immediately began to separate. On analysis (IR, NMR, and m.p.) this was found to be succinic anhydride.

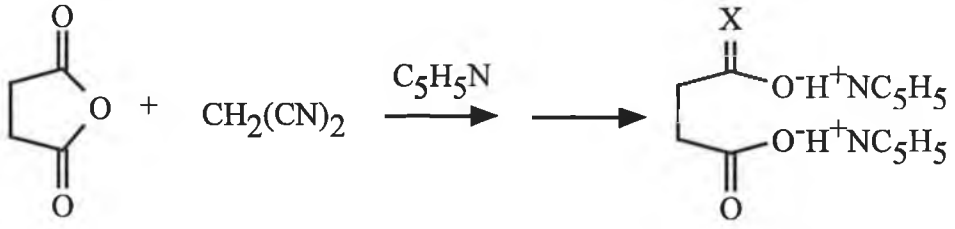


(126)

Scheme 2.14

2.A.4.3 Heterocyclic and aromatic amines

Pyridine (pK_b = 8.75) is a considerably weaker base than triethylamine (3.25). The Knoevenagel condensation of succinic anhydride and malononitrile using pyridine as a base was carried out in THF and it became obvious that malononitrile anion had played no part in the reaction. Removal of the solvent from the reaction mixture yielded a dark red oil which was readily soluble in water but on analysis did not contain the expected product (127b), scheme 2.15.



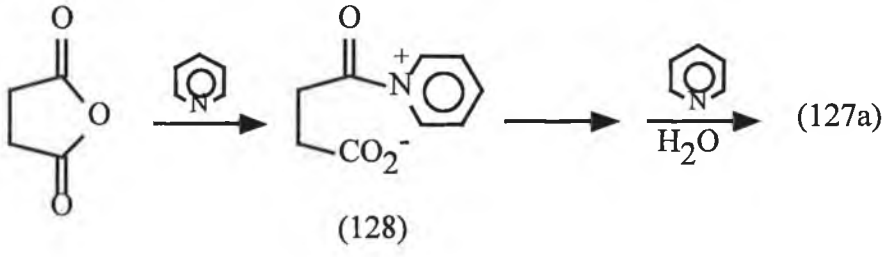
(127)a: X=O
b: X=C(CN)$_2$

Scheme 2.15

The ^{1}H NMR spectrum of the oil exhibited a four proton singlet at 1.99 ppm in accordance with the two, in this case identical, methylene groups derived from succinic anhydride, a four proton triplet at 7.23 ppm corresponding to the four equivalent aromatic protons derived from the two pyridine rings β to the nitrogen atom, each being split by two adjacent hydrogens. A two proton triplet appeared at 7.72 ppm allied to the single aromatic proton on both rings para to the nitrogen atom and each being split by the hydrogens on either side. The remaining four equivalent aromatic protons α to the nitrogen atom appeared as a four proton doublet at 8.08 ppm. The ^{13}C NMR spectrum exhibited a methylene signal at 33.12 ppm, two aromatic absorption signals at 128.30 and 145.59 ppm, and a carbonyl absorption

signal at 181.05 ppm. There was also two signals confirming the presence of unreacted malononitrile - a methylene at 23.85 ppm and a nitrile at 113.50 ppm.

Clearly the structure of the product is (127a) arising from attack of the lone pair of electrons on the nitrogen atom of pyridine on the electron deficient carbonyl carbon atoms of the succinic anhydride to give (128), which then picks up a molecule of water as a result of the solvent not being completely dry, and a further pyridine to give (127a), scheme 2.16.



(128)

Scheme 2.16

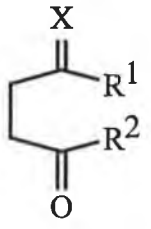
Previous investigations carried out into the reaction between succinic anhydride and 4-(dimethylamino)pyridine have shown[64] the formation of the succinyl 4-(dimethylamino)pyridinium ion (SDMAP), scheme 2.12. The hydrolysis of succinic anhydride in the presence of pyridine could not be studied due to the high background absorbance of pyridine in the region in which the spectral change would be observed.

The SDMAP ion in scheme 2.17 corresponds to (128) scheme 2.16, in the reaction of pyridine and succinic anhydride.

Since the oil did not contain the desired precursor (127b) to 4-dicyanomethylenebutanolide (106) that was being sought, further separation and purification of products from the oil was not undertaken.

Benzyl amine ($pK_b = 4.67$), while not as strong a base as triethylamine ($pK_b = 3.25$),

is considerably stronger than pyridine. When the Knoevenagel condensation reaction of malononitrile and succinic anhydride was carried out using benzyl amine as the base a white solid was collected which on analysis was not the expected product (129). Spectroscopic analysis (^{1}H and ^{13}C NMR and IR) suggested that the structure of the product was (130) but further characterisation was not carried out once it was seen that the product did not contain the dicyanovinyl- moiety.

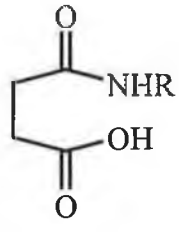


(129) $R^1=R^2=O^{-+}NH_3CH_2Ph$
$X=C(CN)_2$

(130) $R^1=NHCH_2Ph$
$R^2=O^{-+}NH_3CH_2Ph$
$X=O$

Previously it has been shown that the reactions of cyclic primary and secondary amines with anhydrides leads to an amide and a carboxylic acid scheme 2.11 which would imply that the amic-acid (130a) is formed here initially.

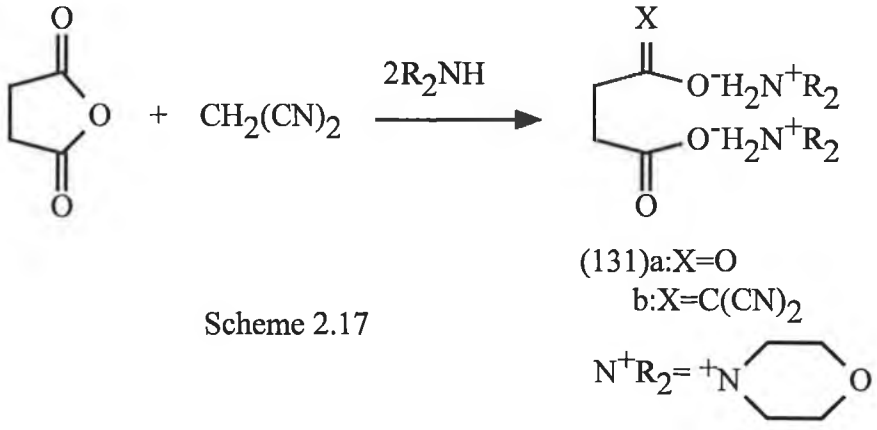
Compound (130a) then reacts with the excess benzyl amine to give the proposed reaction product (130).



(130a)

Morpholine (pK_b = 5.67) is a relatively weak base so it was of interest to ascertain if it would be strong enough to cause the malononitrile to become involved in the reaction, scheme 2.17. Once again from analysis of the spectra (^{1}H and ^{13}C NMR and IR) it was clear that there were no cyano groups present in the product. The ^{1}H NMR spectrum of the solid obtained displayed a four proton singlet at 2.18 ppm due to the two methylene groups derived from the anhydride, with an eight proton multiplet at 3.05 ppm attributed to the two pairs of methylenes on each of the morpholine rings that are α to the oxygen atom with the other four equivalent

methylene groups appearing as an eight proton multiplet at 3.70 ppm. The ^{13}C NMR spectrum shows three unique methylene carbon absorption signals at 36.18, 45.27 and 65.77 ppm, and one carbonyl carbon absorption at 184.37 ppm. The IR spectrum displayed an NH stretch at 3144 cm^{-1} with CH stretching appearing at 3095 cm^{-1} and a strong carbonyl band at 1610 cm^{-1}.



(131)a:X=O
b:X=$C(CN)_2$

N^+R_2=

Scheme 2.17

From the results of the analysis carried out the conclusion that was reached was that the structure of the product was probably (131a) but as the product was not what we were interested in further investigation into the Knoevenagel reaction of succinic anhydride and malononitrile using morpholine as the base was not pursued and the structure suggested was not confirmed.

2.A.5 Discussion and Conclusion

Having carried out Knoevenagel condensations of succinic, phthalic and glutaric anhydrides and the active methylene compound malononitrile using a variety of bases it is clear from the results obtained that the bases used are of particular importance. Sodium hydride, the only non-amine base used, gave the expected results based on work carried out previously on maleic anhydride. However, when a variety of primary, secondary and tertiary amines was used it quickly became apparent that the strength of the base being used would have implications on what products were obtained.

From the results obtained it seems that benzylamine, morpholine, and pyridine are not sufficiently strong bases to remove one of the protons from the malononitrile to form the anion, as the products obtained from these reactions did not have cyano groups present. While malononitrile is a relatively weak cyanocarbon acid with a pK_a of 11.2,[29] it appears that amines with a $pK_b > 3.25$ will not abstract one of the acidic protons.

Table 2.2 Strength of bases used (pK_b=-$\log_{10}K_b$)

BASE USED	pK_b
diisopropylamine	2.95
diethylamine	2.98
triethylamine	3.25
trimethylamine	4.2
benzylamine	4.67
morpholine	5.67
pyridine	8.75

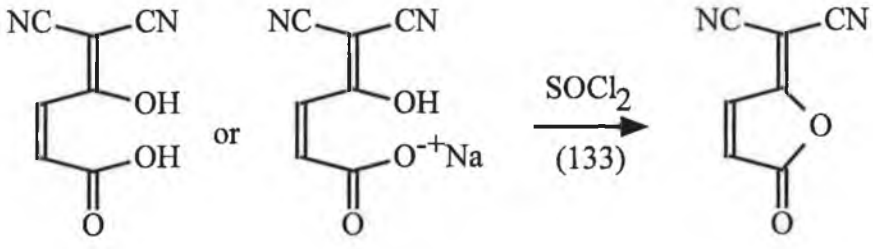
While dependence on the strength of the amine used seems to be large, the effect of the type of amine, i.e. primary, secondary or tertiary, being used does not seem to be of such paramount importance. Both Heller et al[56] and Moore and Kim[57] used secondary amines, diethylamine and diisopropylamine respectively, in their work, but we saw that the expected product was also obtained when the base used was triethylamine.

From the work carried out by Pitman et al[61] on the aminolysis of acid anhydrides in water by both strong and weak amines, it was seen that when a stronger base is used (ie. lower pK_b) the rate at which the reaction occurs depends less on the strength of the amine.

Section 2.B Investigations directed towards the synthesis of 4-(dicyanomethylene)-butanolide (106)

2.B.1 Introduction

As mentioned previously (section 2.A.1), the lactone (109) is readily obtained[65] by treating sodium salt (132b) with thionyl chloride (133) scheme 2.18.



(132a) (132b) (109)

Scheme 2.18

A higher yield of the lactone (109) was obtained when the hydroxy acid (132a) was treated with thionyl chloride in the same way. The difference in the yield (53% vs. 71%) may be due to the low solubility of the sodium salt in thionyl chloride. In the work of Heller,[56] it is acetyl chloride that is used to afford ring closure, scheme 1.25, to give the photochromic dicyanomethylene derivatives of fulgides (100) from the diethylamine salt. Meanwhile Moore and Kim[57] used phosphorus oxychloride to carry out the related pseudoanhydride-forming step in their synthesis of (98), scheme 1.24, from the diisopropylammonium salt. It was decided to investigate the reaction between sodium 4-dicyanomethylene-4-hydroxybutanoate (113) and thionyl chloride in an attempt to synthesise the lactone (106), as it had been shown to work in the case of the maleic anhydride analogue.

Meyer[67] observed that thionyl chloride converts maleic and succinic acids into anhydrides while in the presence of a catalytic amount of zinc chloride the anhydrides are converted into chlorides by the action of thionyl chloride.

2.B.2 Attempted synthesis of 4-(dicyanomethylene)butanolide (106) from (113) or (120a)

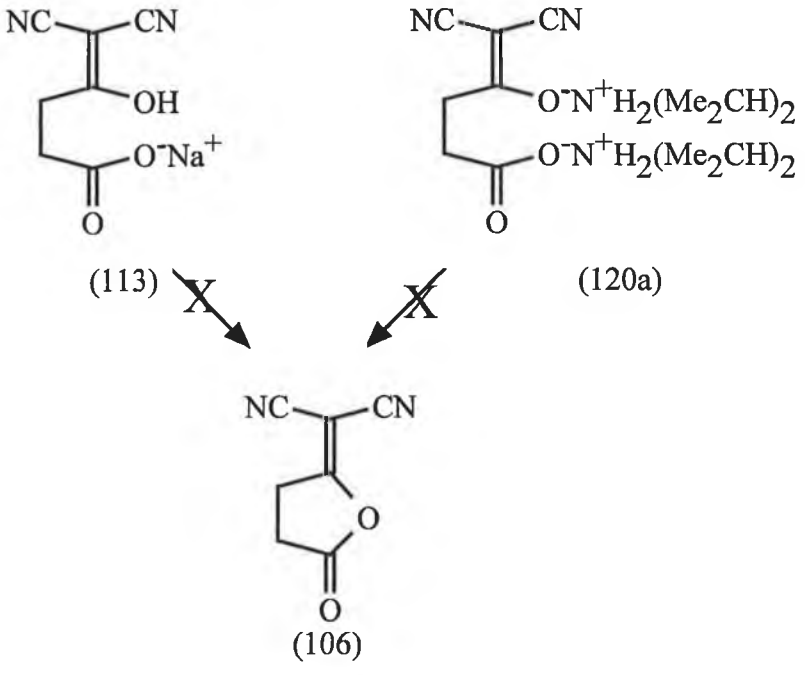
The reaction between sodium 4-dicyanomethylene-4-hydroxybutanoate (113) and thionyl chloride was investigated under a variety of reaction conditions, as well as the analogous reaction of the bis(diisopropylammonium) salt (120a) of 4-(dicyanomethylene)-4-hydroxybutanoic acid. The reaction of (120a) with phosphorus oxychloride was also examined. The reaction conditions that were used are summarised in Table 2.3 below.

Table 2.3 *showing a summary of the reaction conditions used in the attempted ring-closure steps.*

RXN.	SALT	REACTION CONDITIONS			
		Ratio (Salt : $SOCl_2$)	**Time** (Hrs)	**Solvent**	**Triturated with**
(a)	113	1:26	5		Light Petroleum
(b)	113	1:26	1.5		Diethyl ether
(c)	113	1:26	5		Ethyl Acetate
(d)	113	1:1	2.5	Dry THF	Diethyl Ether
(e)	120c	1:33	1.5		Ethyl acetate
(f)	120c	(Salt:$POCl_3$) 1:15	3.5	Dichloroethane	

None of the reactions listed in Table 2.3 above gave the desired product (106). While all the methods are similar, especially (a), (b) and (c) where it is only the triturant used and the reaction time that differ, spectroscopic analysis of the product

obtained from each of the reactions did show some anomalies. However, the most unambiguous fact presented was that there were not two different cyano groups present in the products from any of the reactions (a) - (e) above. This was clear from both the ^{13}C NMR and IR spectra. While there were two nitrile absorption signals in the ^{13}C NMR spectrum of the crude product obtained in (f), it was clear that these signals were due to unreacted salt (120a).



Scheme 2.19

It was obvious after carrying out the reactions (a) and (b) that the products obtained were complex mixtures and uncharacterisable. It was anticipated that by suspending the crude product in ethyl acetate and washing with water a cleaner product would be obtained which could be more characterisable. This was due to the fact that both the sodium salt (113) and any other salts present in the reaction mixture would go into the aqueous layer leaving the product in the organic layer. However, removal of the ethyl acetate by rotary evaporation yielded a black solid which on spectroscopic analysis was once again seen to be a complex mixture similar to what had been obtained by methods (a) and (b).

In the case of reaction (d) where only a molar equivalent of thionyl chloride was used with THF as the solvent, the lactone (106) still proved elusive. Once again it had

been thought that carrying the reaction out in THF as opposed to using a large excess of thionyl chloride as the solvent, might lead to a cleaner product. In this case it was only on addition of the thionyl chloride to the reaction vessel containing (113) suspended in dry THF, that the salt (113) was seen to dissolve. This suggested that some reaction had taken place as it is known that the sodium salt (113) is not soluble in THF even on heating. However spectroscopic analysis once again showed a mixture of products.

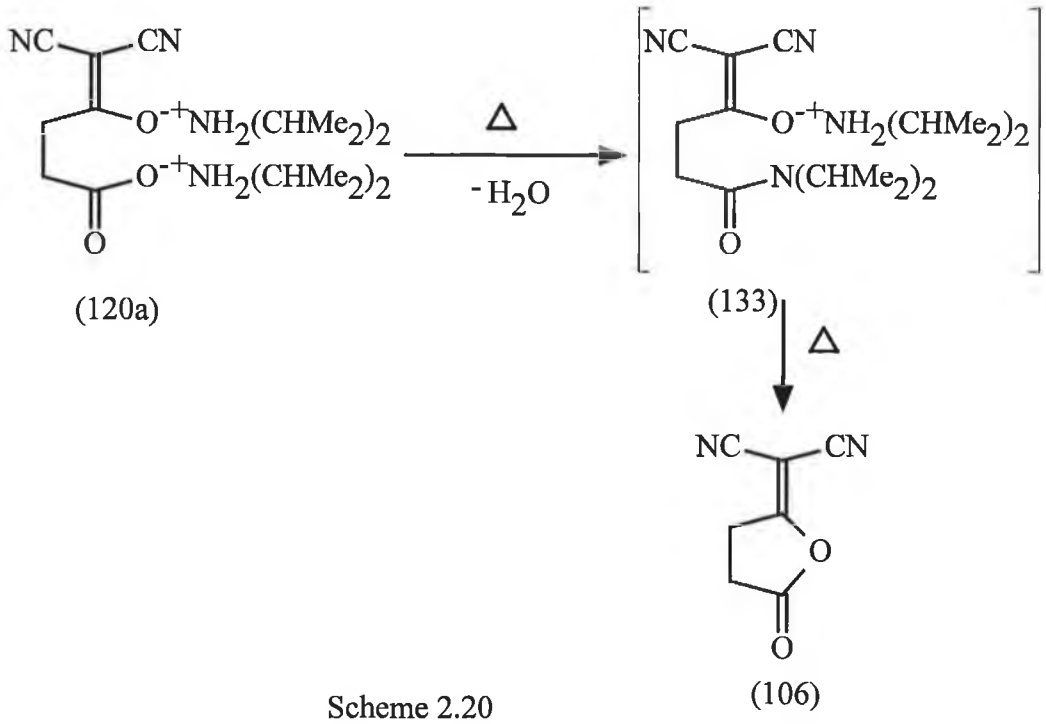
Both (e) and (f), table 2.3, involved reaction of the bis(diisopropylammonium) salt (120a) of 4-(dicyanomethylene)-4-hydroxybutanoic acid with thionyl chloride or phosphorous oxychloride respectively. The latter method, reaction of the salt with $POCl_3$, was the method of ring-closure used in the synthesis of the pseudoanhydride (98),[57] scheme 1.24. After reaction of the salt (120a) with phosphorous oxychloride and subsequent attempted purification of the product by flash chromatography, the ^{13}C NMR spectrum of the resulting sticky brown solid lacked cyano, carbonyl and dicyanovinyl carbon absorptions.

The reaction (e) of the salt (120a) again yielded a complex mixture of products that proved impossible to separate and characterise.

2.B.3 Pyrolysis of the bis(diisopropylammonium) salt (120a) of 4-(dicyanomethylene)-4-hydroxybutanoic acid

Since the methods of ring-closure that were attempted with the diisopropylammonium salt (120a) failed to give the desired lactone (106), it was decided to pyrolyse it as a possible route to 4-(dicyanomethylene)butanolide (106), scheme 2.20.

The diisopropylamine salt (120a) was heated above its melting point (120-122°C) and was seen to bubble slightly as heating was continued at 200°C over two hours. On cooling the oily liquid did not resolidify and spectroscopic analysis (^1H and ^{13}C NMR, IR) showed it to be the unaltered salt (120a).



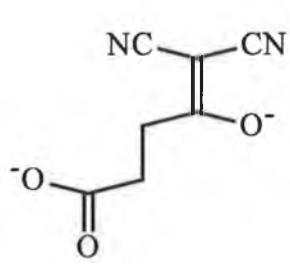
(120a) (133) (106)

Scheme 2.20

2.B.3 Discussion and Conclusion

It is obvious from the attempted synthesis of 4-(dicyanomethylene)butanolide (106) by a variety of methods, that the seemingly analogous, straight forward ring- closure reactions leading to the dicyanomethylene derivatives of fulgides (100), the pseudoanhydride (98) and the lactone (109) cannot be applied to the system under investigation. This difference may arise from the nature of the single bond between C_2 and C_3 in (113) and (120a).

The conformational mobility about the carbon-carbon single bond may militate against the desired ring-closure, the molecule perhaps preferentially adopting an *s*-trans conformation (134) to minimise unfavourable electrostatic interactions.



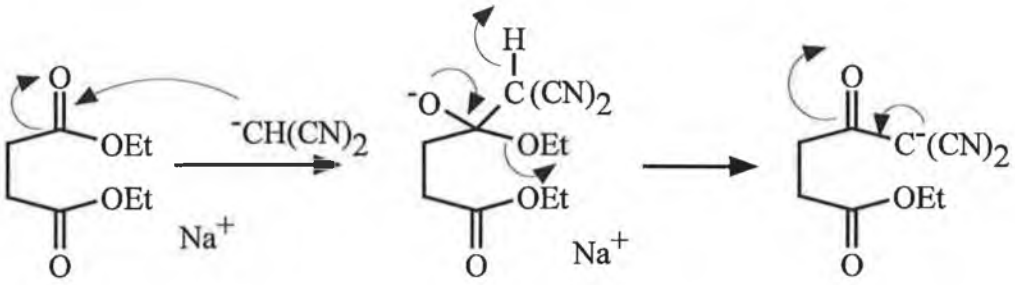
(134)

In contrast, the aromatic ring and the vinyl group in the precursors to the pseudoanhydride (98) and the lactone (109), respectively, ensure the required spatial arrangement for ring-closure. It may also be that the substitution pattern in the precursor to (100) achieves a similar arrangment.

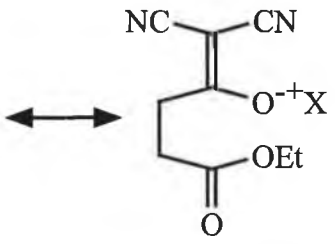
Section 2.C Knoevenagel condensations of diethyl succinate and malononitrile

2.C.1 Introduction

The Knoevenagel condensation of diethyl succinate (135) with malononitrile was investigated as a potential route to the desired product (106). Like succinic anhydride, diethyl succinate (135) has two electron deficient carbons where nucleophilic attack could occur. It was anticipated that attack by malononitrile anion would take place at one of the carbonyl carbons and displace the ethoxy group to give the dicyanovinyl ethyl ester (138) scheme 2.21.



(135) (136) (137)



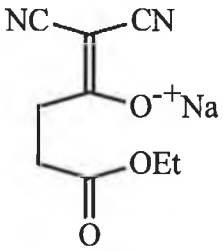
(138) a:X=Na
b:X=H
c:X=Et

Scheme 2.21

2.C.2 Knoevenagel Condensation using sodium hydride as the base

The condensation reaction of diethyl succinate and malononitrile was carried out using sodium hydride as the base. Abstraction of a proton from malononitrile forms the anion capable of attacking the carbonyl carbon. When the equimolar reaction

mixture was refluxed for one and a half hours and then left to cool a solid was collected by filtration. The structure assigned to this solid was (138a).

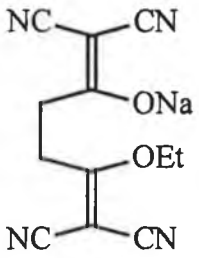


(138a)

The ^{1}H NMR spectrum of (138a) exhibited a three proton triplet at 1.21 ppm due to the methyl protons with the corresponding two methylene protons of the ethoxy group appearing as a two-proton quartet at 4.10 ppm. Two two-proton triplets at 2.48 and 2.54 ppm corresponded to the two non-equivalent methylene groups derived from the ester. There were also peaks that confirmed the presence of diethyl succinate as 8% of the product although the solid had been washed with THF to ensure removal of any starting material. The ^{13}C NMR spectrum of (138a) exhibited a methyl carbon absorption signal at 15.58 ppm, two methylenes, at 32.86 and 34.22 ppm, due to the two non-equivalent methylene moieties on the backbone. There was a signal at 59.89 ppm due to the dicyanosubstituted carbon and the methylene carbon absorption signal of the ethoxy group appeared at 63.87 ppm. There were two further signals at 178.37 and 183.40 ppm due to the dicyanomethylene substituted and carbonyl absorption signals respectively. While no nitrile signals were observed in the ^{13}C spectrum, the IR showed two distinctive CN stretching bands at 2210 and 2160 cm^{-1} and a carbonyl band at 1650 cm^{-1}.

The reaction was repeated using a 0.1 molar equivalent of base and 0.9 equivalents of malononitrile to examine the effect this would have on the outcome. The structure assigned to the product obtained from this reaction was (139) with diethyl succinate present as 90% of the mixture.

The ^{1}H NMR spectrum of sodium 1,4-bis(dicyanomethylene)-1-hydroxy-4-ethoxybutane (139) displayed two symmetrical triplets at 2.45 and 2.58 ppm each due to one of the methylene groups on the backbone derived from the ester. The ethyl group manifested itself as a three proton triplet at 1.19 ppm due to the methyl protons with the methylene protons appearing as a two proton quartet at 4.10 ppm. The ^{13}C NMR spectrum showed two methylenes at 32.89 and 34.06 ppm, a signal at 61.29



(139)

due to the dicyanosubstituted carbons and four nitrile absorption signals at 118.34, 120.52, 125.87 and 128.17 ppm. There were a further two absorption signals at 178.56 and 182.27 due to the two different dicyanomethylene substituted carbons. The IR spectrum displayed four nitrile stretching bands between 2200 and 2320 cm^{-1}.

2.C.3 Knoevenagel Condensations using ammonium acetate/acetic acid and pyridine

It was decided to investigate an alternative method of carrying out the condensation reaction between malononitrile and diethyl succinate in an effort to reach an intermediate salt that could undergo ring-closure to give the desired compound (106). The products obtained from the reaction thus far cannot be recrystallised to a satisfactory degree and the mixtures isolated at the end of the reaction contain diethyl succinate. A commonly used method for condensing aldehydes and ketones (R^1COR^2) with active methylene compounds embodies an ammonium acetate - acetic acid catalysed condensation of the reactants in refluxing benzene, the water formed during the condensation being removed continuously. Under these conditions, large numbers of aldehydes and ketones gave good yields of condensation products[68a] and this method has been used successfully in the preparation of ylidenemalononitriles by refluxing 0.5 mole of carbonyl compound with 0.6 mole of malononitrile in the presence of anhydrous ammonium acetate and glacial acetic acid in benzene. Another related method[68b] involves heating the dicarbonyl compound with the active methylene compound in toluene in the presence of pyridine. It was decided to try both these methods with diethyl succinate and malononitrile to ascertain whether condensation would occur.

The ammonium acetate-acetic acid catalysed condensation of diethyl succinate and malononitrile was carried out in refluxing toluene until the collection of water was complete. The product obtained after vacuum distillation of the oil, on analysis (^{1}H, ^{13}C NMR and IR) was seen to be diethyl succinate. There was water collected during the course of the reaction but this was due to the ammonium acetate that was used.

The reaction was also carried out using pyridine in place of the ammonium acetate - acetic acid catalyst and once again the reaction did not yield the desired product. In this case the oil remaining after removal of the solvent by rotary evaporation was analysed and both ^{1}H and ^{13}C NMR spectra confirmed that the main component was diethyl succinate.

2.C.4 Conclusion

Initially it seemed that this may have been a successful route to a precursor that would undergo the desired ring-closure step but as was the case with sodium 4-dicyanomethylene-4-hydroxybutanoate (113) recrystallisation of the products obtained was not possible due to the insolubility of (138a) and (139) in most organic solvents and their solubility in water. It also became apparent that the quantity of product obtained was very much dependant on the reaction conditions used and the ratio of reactants. This was particularly the case in the synthesis of (139) where the crude product contained (139) as only a 10% solution in diethyl succinate.

When an alternative method of carrying out the reaction between diethyl succinate and malononitrile, using ammonium acetate/acetic acid or pyridine as the catalyst, was investigated all that was recovered was unreacted starting material.

The use of diethyl succinate in the Knoevenagel condensation reaction with malononitrile was not investigated any further.

CHAPTER 3

EXPERIMENTAL

Introductory remarks

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker ACF 400 instrument operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet and m = multiplet). Chemical shifts are given in parts per million (ppm) and coupling constants (*J*) are given in Hertz (Hz).

Infra-red (IR) spectra were recorded on a Perkin-Elmer 983G IR spectrophotometer, or a Nicolet 205 FT-IR spectrometer, for KBr pellets unless otherwise stated.

Melting point determinations were recorded using a Griffin or Gallenkamp melting point apparatus and are uncorrected.

Elemental analyses were carried out by the Microanalytical Laboratory at University College Dublin.

Thin Layer Chromatography was carried out using silica gel TLC plates containing a fluorescent indicator (Riedel de Haen, layer thickness 0.2mm).

Tetrahydrofuran was dried prior to use by heating under reflux over benzophenone and sodium metal until the mixture developed a deep purple colour (sodium benzophenone ketyl) followed by distillation.

Synthesis of sodium 4-dicyanomethylene-4-hydroxybutanoate (113)

Dry light petroleum (b.p. 40-60°C) (10 cm^3) was added to sodium hydride (80 % dispersion in oil; 2.40 g, 0.08 moles), the suspension swirled and the solvent/oil solution removed with a Pasteur pipette once the mixture had settled. The sodium hydride was dried under argon before dry tetrahydrofuran (50 cm^3) was added gradually to the solid. Dry tetrahydrofuran (30 cm^3) was added to malononitrile (6.61 g, 0.1 moles) and the resulting solution was added dropwise to the suspension of sodium hydride in THF with constant stirring. The resultant solution was wine in colour. Succinic anhydride (10.01 g, 0.1 moles) was dissolved in hot dry tetrahydrofuran (50 cm^3) and added to the solution with stirring under reflux. The reaction mixture was heated under reflux for two and a half hours and the crude product was collected by vacuum filtration and washed with hot THF to yield (113) as an off-white solid (10.53 g, 56%), m.p.185°C (dec); IR: ν_{max} 3448 (OH), 2936 (C-H), 2216 and 2192 (CN), 1567 (C=O) cm^{-1}; δ_H (D_2O): 2.28 (m, 2H, CH_2) and 2.48 (m, 2H, CH_2) ppm; δ_C (D_2O): 35.04 and 36.07 (CH_2-CH_2), 52.65 (=CCN), 122.80 and 124.72(CN), 182.00 (C=CCN) and 199.85 (C=O) ppm.

Synthesis of tetrabutylammonium 4-dicyanomethylene-4-hydroxybutanoate (114)

Sodium 4-dicyanomethylene-4-hydroxybutanoate (113), (4.00 g, 0.021 moles) was dissolved in water (15 cm^3) and tetrabutylammonium bromide (3.40 g, 0.015 moles) dissolved in water (50 cm^3) was added slowly with stirring at room temperature to the aqueous sodium salt solution. The precipitated solid was collected by vacuum filtration, washed with water and recrystallised from methanol to yield white crystalline tetrabutylammonium 4-dicyanomethylene-4-hydroxybutanoate (114) (1.10g, 12%); m.p. 73-75°C; Microanalysis: Found: C, 68.04; H, 10.25; N, 10.44%. $C_{23}H_{41}N_3O_3$ requires C, 67.78; H, 10.14; N, 10.31%;

IR: ν_{max} 3452 (OH), 2976-2882 (C-H), 2214 and 2178 (CN) and 1702 (C=O)cm^{-1}; δ_H ($CDCl_3$): 0.98 (t, *J* 7.1, 12H, CH_3), 1.40 (sextet, *J* 7.4, 8H, CH_2), 1.61 (m, 8H, CH_2), 2.52 (m, 2H, CH_2), 2.75 (m, 2H, CH_2) and 3.17 (m, 8H, CH_2) ppm; δ_C ($CDCl_3$): 13.54 (CH_3), 19.66 , 23.80 , 30.75 and 32.59 (CH_2), 52.20 (=CCN), 58.86 (CH_2), 118.64 and 120.03 (CN), 174.78 (C=CCN) and 195.22 (C=O) ppm.

Attempted synthesis of bis(tetrabutylammonium) salt (115) of 4-(dicyanomethylene)-4-hydroxybutanoic acid

(a) Using 2 equivalents of tetrabutylammonium bromide

The reaction between the aqueous sodium salt solution (4.01 g, 0.021 moles) and aqueous tetrabutylammonium bromide was carried out as above but with two molar equivalents (13.60 g, 0.042 moles) of the tetraalkylammonium halide. As previously, the product precipitated from solution before all of the tetrabutylammonium bromide had been added, but the whole two molar equivalents was added despite this. A solid (3.21 g) was collected by vacuum filtration and was found to be the mono-tetrabutylammonium dicyanovinyl salt (114) by comparison (IR, NMR, m.p.) with an authentic sample..

(b) From tetrabutylammonium 4-dicyanomethylene-4-hydroxybutanoate (114)

The mono-salt (0.3 g, $7.36x10^{-4}$ moles) was dissolved in methanol (3 cm^3), and this was added to a solution of sodium methoxide made by adding sodium hydride (0.024 g, $1x10^{-3}$ moles, 35% excess) to methanol (5 cm^3). This solution was kept stirring while an eqimolar equivalent of tetrabutylammonium bromide (0.24 g, $7.36x10^{-4}$ moles) in methanol (5 cm^3) was added. The methanolic solution was left stirring for one hour but no solid precipitated. On addition of water the mono-salt (114) precipitated and was identified by comparison (IR, NMR, m.p.) with an authentic sample..

(c) From tetrabutylammonium 4-dicyanomethylene-4-hydroxybutanoate (114)

The reaction was carried out as in (b) above but the tetrabutylammonium bromide solution was added to the sodium methoxide solution first. On addition of the

mono-tetrabutylammonium dicyanovinyl succinic anhydride salt in methanol no solid precipitate formed. On addition of water to the solution, the product that did precipitate out was the mono-salt (114).

Synthesis of calcium 4-dicyanomethylene-4-hydroxybutanoate (116)

Sodium 4-dicyanomethylene-4-hydroxybutanoate (113), (1.03 g, 0.0055 moles) was dissolved in the minimum amount (~15 cm^3) of water. A solution of calcium chloride (0.41 g, 0.0027 moles) in water (10 cm^3) was added to the stirred solution. The white solid which precipitated was collected by vacuum filtration, washed with water and dried to yield 0.58 g (59%) of calcium 4-dicyanomethylene-4-hydroxybutanoate (116); m.p. 260°C (dec); IR: ν_{max} 3200-3600 (O-H), 2245 and 2220 (C≡N), and 1560 (C=O) cm^{-1}; δ_H (DMSO-d_6): 2.25 (m, 2H, CH_2) and 2.49 (m, 2H, CH_2) ppm; δ_C (DMSO-d_6): 31.94 (CH_2), 33.27 (CH_2), 47.89 (=<u>C</u>CN), 121.25 and 124.60 (C≡N), 178.90 (<u>C</u>=CCN) and 194.97 (C=O) ppm.

Synthesis of sodium 5-dicyanomethylene-5-hydroxypentanoate (117)

Dry light petroleum (b.p. 40-60°C) (15 cm^3) was added to sodium hydride (80% dispersion in oil; 0.90 g, 0.03 moles), the suspension was swirled and the solvent/oil solution removed with a Pasteur pipette once the mixture had settled. The sodium hydride was dried under argon and dry tetrahydrofuran (30 cm^3) was added gradually to the solid. Dry THF (15 cm^3) was added to malononitrile (1.98 g, 0.03 moles) and this solution was added dropwise to the suspension of sodium hydride in THF with constant stirring. The resultant solution was wine in colour. Glutaric anhydride (4.01 g, 0.03moles) was dissolved in warm dry THF (15 cm^3) and added to the stirring solution under reflux. The reaction mixture was heated under reflux for one hour and the crude product was collected by vacuum filtration, washed with hot THF and dried to yield a grey solid (117), (3.95 g, 65%) m.p. 240°C (dec); IR: ν_{max} 3445 (OH), 2926 (C-H), 2227 and 2190 (CN) and 1571 (C=O) ppm; δ_H (D_2O): 1.59 (qn, *J* 7.8, 2H, CH_2), 1.99 (m, 2H, CH_2) and 2.20 (m,

2H, CH_2) ppm; δ_C: 25.17 (H_2C-$\underline{C}H_2$-CH_2), 38.92 and 39.48 ($\underline{C}H_2$-CH_2-$\underline{C}H_2$), 53.40 (=$\underline{C}$CN), 122.48 and 124.51 (C≡N), 184.94 ($\underline{C}$=CCN) and 201.83 (C=O) ppm.

Attempted synthesis of 1,4-bis(dicyanomethylene)-1,4-dihydroxybutane (118)

Dry light petroleum (b.p. 40-60°C) (20 cm^3) was added to sodium hydride (80% dispersion in oil, 2.40 g, 0.08 moles), the suspension swirled and the solvent/oil solution removed with a Pasteur pipette when the mixture had settled. The sodium hydride was dried under a stream of argon before dry tetrahydrofuran (50 cm^3) was added gradually to the solid. Dry tetrahydrofuran (50 cm^3) was added to malononitrile (6.61 g, 0.1moles) and this solution was added dropwise to the suspension of sodium hydride in THF with constant stirring. Succinic anhydride (5.01 g, 0.05 moles) was dissolved in hot dry tetrahydrofuran (25 cm^3) and added to the stirring solution under reflux. Reflux was maintained for one and a half hours and the crude product which had precipitated was collected as an off-white solid (7.85 g), and was identified (IR, ^{1}H NMR, ^{13}C NMR and m.p.) as the monosodium salt (113).

Synthesis of the bis(diisopropylammonium) salt (119a) of 2-(1-hydroxy-2,2-dicyanoethenyl)benzoic acid

This compound was prepared using the method of Moore and Kim.[57]
Malononitrile (3.30 g, 0.05 moles) was dissolved in tetrahydrofuran (15 cm^3) and added dropwise to a stirred solution of phthalic anhydride (7.41 g, 0.05 moles) in tetrahydrofuran (15 cm^3). Diisopropylamine (10.10 g, 0.10 moles) was added slowly to the stirring solution and the reaction mixture was stirred at room temperature for two hours, by which time a solid had precipitated. This was filtered off, washed with tetrahydrofuran, dried and recrystallised from methanol to yield yellow crystalline bis(diisopropylammonium) salt (119a) of 2-(1-hydroxy-2,2-dicyanoethenyl) benzoic acid (18.88 g, 90 %); m.p.138°C (dec) (lit.,[57] 140°C) ; IR: ν_{max} 3100-2719 (NH and aromatic and aliphatic CH), 2213, 2178 and 2150

(CN), 1623 (C=O) and 735 and 770 (o-disubstituted benzene) cm^{-1}; δ_H (D_2O): 1.08 (d, *J* 6.4, 24H, CH_3), 3.25 (sep, *J* 6.4, 4H, CH), 7.12-7.45 (m, 4H, aromatic) ppm; δ_C (D_2O): 20.46 (CH_3), 49.38 (CH), 53.75 (=CCN), 122.67 and 124.87 (CN), 140.98, 138.99, 131.64 (2C), 130.68 and 129.15 (aromatic), 177.30 (C=CCN) and 198.09 ppm (C=O).

Synthesis of the bis(diethylammonium) salt (119b) of 2-(1-hydroxy-2,2-dicyanoethyenyl)benzoic acid

Phthalic anhydride (7.40 g, 0.05 moles) was dissolved in dry tetrahydrofuran (15 cm^3). A solution of malononitrile (3.30 g, 0.05 moles) in dry THF (15 cm^3) was added to the stirring solution. Two molar equivalents of diethylamine (7.31 g, 0.10 moles) was slowly added to the reaction vessel and the reaction mixture was stirred at room temperature for four hours at which stage the salt had precipitated. It was filtered off, washed with THF, dried and recrystallised from methanol to yield the bis(diethylammonium) salt (119b) of 2-(1-hydroxy-2,2-dicyanoethenyl) benzoic acid (6.24 g, 34%); m.p.108-110 °C; Microanalysis: Found: C, 60.21; H, 7.84%; N, 14.62%. $C_{19}H_{28}N_4O_3.H_2O$ requires C, 60.26; H, 8.00; N, 14.79%; IR: ν_{max} 3100-2840 (NH, aliphatic and aromatic CH), 2199, 2178 and 2160 (CN), 1623 and 1566 (C=O) cm^{-1}; δ_H (D_2O): 1.05 (t, *J* 7.4, 12H, CH_3), 3.82 (q, *J* 7.4, 8H, CH_2), 6.78-7.12 (m, 4H, aromatic); δ_C (D_2O): 13.21 (CH_3), 44.40 (CH_2), 53.79 (=CCN), 122.63 and 124.80 (CN), 129.20, 130.70, 131.68, 131.73, 138.89 and 141.01 (aromatic), 177.30 (C=CCN) and 198.11 (C=O) ppm.

Synthesis of the bis(diisopropylammonium) salt (120a) of 4-(dicyanomethylene)-4-hydroxybutanoic acid

Malononitrile (3.30 g, 0.05 moles) was dissolved in tetrahydrofuran (15 cm^3) and added dropwise to a stirred solution of succinic anhydride (5.00 g, 0.05 moles) in tetrahydrofuran (20 cm^3). Diisopropylamine (10.11 g, 0.10 moles) was added gradually to the solution and the reaction mixture stirred at room temperature for

three hours after which time a solid had precipitated. The solid was filtered off, washed with tetrahydrofuran, dried and recrystallised from methanol to yield a white crystalline product, the bis(diisopropylammonium) salt (120a) of 4-(dicyanomethylene)-4-hydroxybutanoic acid (16.61 g, 90%), m.p. 120-122°C; Microanalysis: Found: C, 61.75; H, 10.01; N, 14.95%. $C_{19}H_{36}N_4O_3$ requires C, 61.92; H, 9.85; N, 15.21%; IR: ν_{max} 3445 (NH), 2968-2719 (CH), 2214 and 2185 (CN) and 1559 (C=O) cm^{-1}; δ_H (D_2O): 1.09 (d, *J* 6.4, 24H, CH_3), 2.16 (m, 2H, CH_2), 2.42 (m, 2H, CH_2), and 3.48 (sep, *J* 6.4, 4H, CH) ppm; δ_C (D_2O): 16.41 (CH_3), 31.52 and 32.53 (CH_2), 45.35 (CH), 48.37 (=CCN), 118.64 and 120.65 (C≡N), 179.31 (C=CCN) and 196.69 (C=O) ppm.

Synthesis of the bis(diethylammonium) salt (120b) of 4-(dicyanomethylene)-4-hydroxybutanoic acid

Malononitrile (3.30 g, 0.05 moles) was dissolved in THF (15 cm^3) and added to a solution of succinic anhydride (5.0 g, 0.05moles) in THF (25 cm^3). Diethylamine (7.29 g, 0.10 moles) was added slowly to the solution and the reaction mixture was stirred at room temperature for four and a half hours at which stage the reaction was stopped. The solvent was removed by rotary evaporation and a dark, very viscous oil remained. On ^1H and ^{13}C NMR analysis it appeared to contain the expected salt (120b) as the minor constituent (31%) of a mixture with the diethylammonium salt (121) of 4-(dicyanomethylene)-4-hydroxy-diethylsuccinamide as the principal constituent (69%). Isolation of (120b) was not possible. IR ($CHCl_3$): ν_{max} 3200-3000 (C-H), 3118 (NH), 2190 and 2224 (CN) and 1563 (C=O) cm^{-1}; δ_H (D_2O) (120b): 1.04 (t, *J* 7.4, 6H, CH_3), 2.22 (m, 2H, CH_2), 2.39 (m, 2H, CH_2) and 2.80 (q, *J* 7.4, 4H, CH_2) ppm; δ_C (D_2O) (120b): 12.90 (CH_3), 31.01, 33.94 and 44.40 (CH_2), 51.65 (=CCN), 122.75 and 124.60 (CN), 175.66 (C=CCN) and 199.41 (C=O) ppm; δ_H (D_2O)(121): 0.82 (t, *J* 6.9, 3H, CH_3), 0.94 (t, *J* 6.9, 3H, CH_3), 3.06 (q, *J* 7.4, 2H, CH_2) and 3.14 (q, *J* 7.4, 2H, CH_2) ppm; δ_C (D_2O)(121):12.90, 14.66 and 15.65 (CH_3), 34.36, 36.08, 42.95, 44.40 and

44.86 (CH_2), 56.75 (=CCN), 118.79 and 120.14 (CN), 166.73 (C=CCN) and 181.57 (C=O) ppm.

Synthesis of 4-diethylamidobutanoic acid (121b)

The reaction of succinic anhydride and diethylamine was carried out as described above for the synthesis of (120b) but no malononitrile was added. Removal of the solvent by rotary evaporation yielded a dark oil (5.67 g, 76%); δ_H (D_2O): 0.73 (t, *J* 7.1, 3H, CH_3), 0.85 (t, *J* 7.1, 3H, CH_3), 2.14 (t, *J* 7.1, 2H, CH_2), 2.28 (t, *J* 7.1, 2H, CH_2), 2.99 (q, *J* 7.1, 2H, CH_2) and 3.06 (q, *J* 7.1, 2H, CH_2) ppm; δ_C(D_2O): 12.73 and 15.42 (CH_3), 30.79, 33.71, 42.78 and 44.22 (CH_2), 175.47 and 181.32 (C=O) ppm.

Synthesis of the bis(dibutylammonium) salt (120c) of 4-(dicyanomethylene)-4-hydroxybutanoic acid

Malononitrile (3.31 g, 0.05 moles) was dissolved in THF (15 cm^3) and was added to a THF solution of succinic anhydride (5.00 g, 0.05 moles). Di-n-butylamine (12.91 g, 0.10 moles) was added dropwise to the solution and the reaction mixture was left stirring at room temperature for two hours. Removal of the solvent by rotary evaporation yielded a dark viscous oil (8.72 g), containing a mixture of products. The bis(dibutylammonium) salt (120c) of 4-(dicyanomethylene)-4-hydroxybutanoic acid was present as 30% of the mixture with the dibutylammonium salt (122) of 4-(dicyanomethylene)-4-hydroxy-dibutylsuccinamide constituting 70%; IR ($CHCl_3$): ν_{max} 2995-2800 (NH and CH), 2221 and 2198 (CN) and 1561 (C=O); δ_H (D_2O) (120c): 0.69 (m, 12H, CH_3), 1.10 (m, 8H, CH_2), 1.40 (m, 8H, CH_2), 2.19 (m, 2H, CH_2), 2.35 (m, 2H, CH_2) and 2.65 (m, 8H, CH_2) ppm; δ_C (D_2O) (120c):15.21 (CH_3), 21.56, 29.68, 31.32, 31.67 and 49.16 (CH_2), 51.35 (=CCN), 122.36 and 124.01 (CN), 175.48 (C=CCN) and 198.70 (C=O) ppm; δ_H (D_2O) (122): 0.69 (m, 12H, CH_3), 1.05 (m, 8H, CH_2), 1.15-1.35 (m, 8H, CH_2), 2.14 (m, 2H, CH_2), 2.41 (m, 2H, CH_2) and 3.02 (m, 8H, CH_2); δ_C

(D_2O) (122): 15.21 and 15.59 (CH_3), 21.56, 21.87, 22.03, 29.68, 32.85, 34.43, 35.00, 36.38, 47.92 and 49.94 (CH_2), 58.35 (=CCN), 116.58 and 117.81, (CN) and 181.23 (C=O).

Synthesis of the bis(triethylammonium) salt (123) of 4-(dicyanomethylene)-4-hydroxybutanoic acid

Malononitrile (3.30 g, 0.05 moles) was dissolved in THF (15 cm^3) and added to a stirring slution of succinic anhydride (5.02 g, 0.05 moles) in THF (20 cm^3). Triethylamine (10.07 g, 0.10 moles) was added dropwise to the solution and the reaction mixture was left stirring at room temperature for one hour by which stage a dark yellow oil that was immiscible with tetrahydrofuran had appeared. The two layers were separated and the layer containing the product (lower layer) was put on the rotary evaporator to ensure all the THF had been removed, leaving 9.03 g (49%) of a yellow oil (123); IR ($CHCl_3$): ν_{max} 3025 (C-H), 2699 (NH), 2206 and 2164 (CN) and 1552 (C=O) cm^{-1}; δ_H (D_2O): 1.05 (t, *J* 7.4, 18H, CH_3), 2.25 (t, *J* 6.9, 2H, CH_2), 2.40 (t, *J* 6.9, 2H, CH_2) and 2.92 (quartet, *J* 7.4, 12H, CH_2) ppm; δ_C (D_2O): 10.58 (CH_3), 33.06 and 35.32 (CH_2), 48.82 (CH_2), 51.49 (=CCN), 122.66 and 124.46 (CN), 180.23 (C=CCN) and 198.76 (C=O) ppm.

Table 3.1 showing the correlating peaks from the C-H correlation spectrum

^{1}H NMR peaks (ppm)	^{13}C NMR peaks (ppm)
1.05	10.58
2.25	33.06
2.40	35.32
2.92	48.82

Acidification of the bis(triethylammonium) salt (123) of 4-(dicyanomethylene)-4-hydroxybutanoic acid

The bis(triethylammonium) salt (123) of 4-(dicyanomethylene)-4-hydroxybutanoic acid (3.23 g, $8.8x10^{-3}$ moles) was dissolved in water (10 cm^3) and 20% v/v dilute hydrochloric acid was added until the solution was acidic to blue litmus paper (~5 cm^3). This aqueous solution was then extracted with dichloromethane (3 x 10 cm^3) and the combined organic extracts were combined and dried over anhydrous magnesium sulphate. The solvent was removed by rotary evaporation to yield a sticky solid (0.12 g) and IR, ^1H and ^{13}C NMR analysis confirmed that it was not the anticipated product. There were no nitrile carbon absorption signals present in either the ^{13}C NMR or IR spectra. δ_H ($CDCl_3$): 1.05 (t, 3H, CH_3), 1.11 (t, 3H, CH_3), 2.60 (m, 4H, CH_2) and 3.29 (m, 4H, CH_2) ppm; δ_C ($CDCl_3$): 12.85 and 13.91 (CH_3), 27.83, 29.71, 40.61 and 42.10 (CH_2), 171.41 and 171.22 (C=O) ppm.

Synthesis of tetrabutylammonium 4-dicyanomethylene-4-hydroxybutanoate (114)

The triethylamine salt (123) (0.43 g, $1.2x10^{-3}$ moles) was dissolved in water (5 cm^3) and tetrabutylammonium bromide (0.25 g, $9.0x10^{-3}$ moles) in water (10 cm^3) was added slowly with stirring at room temperature to the salt solution. The precipitated solid was collected by filtration, washed with water and recrystallised from methanol to yield white solid (114) (0.08 g, 15%), confirmed by comparison of its IR, ^1H NMR and ^{13}C NMR spectra with those of an authentic sample.

Synthesis of the bis(triethylammonium) salt (125) of 2-(1-hydroxy-2,2-dicyanoethenyl)benzoic acid

Malononitrile (4.46 g, 0.07 moles) in tetrahydrofuran (8 cm^3) was added to a stirring solution of phthalic anhydride (10.03 g, 0.07 moles) in THF (15 cm^3). Triethylamine (13.67 g, 0.14 moles) was added slowly to the reaction mixture and

this was left stirring at room temperature for one hour. The oil that separated out from the THF was collected and any remaining solvent was removed by rotary evaporation to yield 27.92 g (95%) of the bis(triethylammonium) salt (125) of 2-(1-hydroxy-2,2-dicyanoethenyl)benzoic acid as a clear yellow oil; IR (neat): ν_{max} 3025-2889 (aromatic and aliphatic C-H), 2515-2700 (s, NH), 2213 and 2192 (CN) and 1566 (C=O); δ_H (D_2O): 0.98 (t, 18H, CH_3), 2.38 (q, 12H, CH_2), 7.10 (m, 1H, aromatic), 7.27 (m, 2H, aromatic) and 7.56 ppm (m, 1H, aromatic); δ_C (D_2O): 10.57 (CH_3), 48.67 (CH_2), 52.82 (=CCN), 122.90 and 124.43 (CN), 129.45, 131.65, 132.85, 136.16 and 142.54 (aromatic), 174.37 (C=CCN) and 196.77 (C=O) ppm.

Attempted synthesis of the bis(trimethylammonium) salt (126) of 4-(dicyanomethylene)-4-hydroxybutanoic acid

Succinic anhydride (2.5 g, 0.025 moles) was dissolved in warm tetrahydrofuran (15 cm^3) and malononitrile (1.65 g, 0.025 moles) in tetrahydrofuran (10 cm^3) was added gradually to the stirring solution. Trimethylamine (2.95 g, 0.05 moles) was added gradually and the reaction mixture was stirred at room temperature for three hours. Removal of the solvent by rotary evaporation yielded an orange oil from which a white solid precipitated. This was found to be succinic anhydride by comparison (IR, NMR, m.p.) with an authentic sample.

Knoevenagel condensation reaction of succinic anhydride and malononitrile using pyridine as the base

Malononitrile (1.65 g, 0.025 moles) in THF (7 cm^3) was added to a stirring solution of succinic anhydride (2.50 g, 0.025 moles) in THF (15 cm^3). Pyridine (4.20 g, 0.05 moles) was added slowly to the reaction mixture which was then left stirring at room temperature for a further three hours. Removal of the solvent by rotary evaporation yielded a dark red oil (6.32 g, 96%); δ_H(D_2O): 1.99 (s, 4H, CH_2), 7.23 (t, 4H, arom), 7.72 (t, 2H, arom) and 8.08 (d, 4H, arom) ppm; δ_C(D_2O): 33.12 (CH_2), 128.30 and 145.59 (aromatic CH), and 181.05 (C=O) ppm.

Knoevenagel condensation reaction of succinic anhydride and malononitrile using benzylamine as the base

Malononitrile (3.3 g, 0.05 moles) in THF (15 cm^3) was added dropwise to a solution of succinic anhydride (5.0 g, 0.05 moles) in THF (20 cm^3). Benzylamine (10.7 g, 0.10 moles) was added slowly to the stirring solution and within fifteen minutes stirring at room temperature a solid had appeared which was filtered off under vacuum, washed with THF, recrystallised from methanol and dried to yield a white solid (14.37 g); m.p. 107-109 °C; IR (KBr): ν_{max} 3294 (N-H and C-H), 3000-2200 (1^o amine salt NH), 1644 (C=O), 1552 (NH_3^+ bend), 1182 (C-N stretch of 1^o amine salt), and 694 and 729 (monosubstituted aromatic ring) cm^{-1}; δ_H (D_2O): 2.11 (m, 4H, CH_2), 3.80 (s, 2H, CH_2), 3.98 (s, 2H, CH_2), 6.93-6.99 (t, 4H, arom), 7.04 (t, 2H, arom) and 7.12 (q, 4H, arom) ppm; δ_C(D_2O): 34.47, 35.14 and 45.01 (CH_2), 129.30, 129.45, 130.83, 130.89, 134.72, 140.08 (aromatic) 177.57 and 182.90 (C=O) ppm.

Knoevenagel condensation reaction of succinic anhydride and malononitrile using morpholine as the base

Malononitrile (1.65 g, 0.025 moles) was dissolved in dry tetrahydrofuran (5 cm^3) and added to a solution of succinic anhydride (2.5 g, 0.025 moles) in THF (10 cm^3) in a round-bottomed-flask. Morpholine (4.36 g, 0.05 moles) was added slowly to the solution. By the time this addition was complete a solid had appeared which was collected by vacuum filtration, washed with THF and dried to yield 4.08 g of product; m.p. 126-128°C; IR: ν_{max} 3144 (NH), 3095 (CH) and 1610 (C=O); δ_H (D_2O): 2.18 (s, 4H, CH_2), 3.05 (m, 8H, CH_2) and 3.70 (m, 8H, CH_2) ppm; δ_C (D_2O): 31.15, 34.61, 36.18, 44.28, 45.27, 48.10, 65.77 and 68.46 (CH_2) and 184.37ppm (C=O).

Attempted synthesis of 4-dicyanomethylenebutanolide

From (113) using thionyl chloride as solvent and light petroleum

Sodium 4-dicyanomethylene-4-hydroxybutanoate (113), (1.00 g, 5.32 mmol) was placed in a 25ml round-bottomed-flask. Thionyl chloride (10 cm^3, 138 mmol) was added very gradually to the flask from a dropping funnel at room temperature. The reaction mixture was heated under reflux on a water-bath until evolution of gases had ceased (five hours). The excess thionyl chloride was removed from the mixture by ambient pressure distillation and the brown oil that remained after the distillation was triturated with light petroleum (b.p. 40-60°C) to remove any remaining thionyl chloride. A brown solid was filtered off, washed with light petroleum and dried to give 0.36 g of product, m.p. 74-77°C, but recrystallisation was not possible and as ^1H and ^{13}C NMR spectroscopic analyses suggested a complex mixture was present further purification was not attempted.

From (113) using thionyl chloride as solvent and diethyl ether

The reaction was carried out as described above but the crude oil was triturated with diethyl ether to remove any remaining thionyl chloride. A solid was collected from this ethereal solution but analysis showed that it was not the expected product.
The solvent was removed from the ethereal filtrate to yield a very viscous brown oil which was seen to contain a complex mixture of products on analysis by ^1H and ^{13}C NMR spectroscopy.

From (113) using thionyl chloride as solvent and ethyl acetate

The reaction was carried out as in A.1 above. Removal of the thionyl chloride was carried out by vacuum distillation. Ethyl acetate (10 cm^3) was added to the flask containing the brown solid that remained. The resulting solution was carefully washed with three portions of water (3 x 10cm^3) and the organic layer was

collected and dried over magnesium sulphate, before removal of the solvent by rotary evaporation, to yield a black solid (0.21 g) which was uncharacterisable

From (113) using thionyl chloride and tetrahydrofuran as solvent

Sodium 4-dicyanomethylene-4-hydroxybutanoate (1.5 g, 0.008 moles) was suspended in dry THF (10 cm^3) in a round-bottomed-flask fitted with a reflux condenser and stirring bar. Thionyl chloride (0.95 g, 0.008 moles) was added very gradually to the stirring suspension. The reaction mixture was heated under reflux until the evolution of gas ceased (2-3hrs) after which time a small amount of undissolved material was filtered off. The THF was removed under vacuum and a dark orange oil remained from which a small amount of solid material precipitated on cooling. This was filtered off under vacuum, washed with diethyl ether, and dried to yield 0.69 g of a sticky solid. Attempts at recrystallisation were not successful and analysis (^1H and ^{13}C NMR) repeatedly showed a complex mixture of products.

On evaporating the ethereal filtrate which remained after filtering off the solid, a dark orange oil was obtained which was almost completely soluble in $CHCl_3$. The insoluble matter was filtered off and the solvent was removed from the filtrate to yield an oily solid which on analysis (^1H and ^{13}C NMR) suggested degradation of the products to a complex mixture.

From bis(diisopropylammonium) salt (120a) of 4-(dicyanomethylene)-4-hydroxybutanoic acid using $POCl_3$ with dichloroethane

The bis(diisopropylammonium) salt (120a) of 4-(dicyanomethylene)-4-hydroxy-butanoic acid (8 g, 0.022moles) was weighed into a round-bottomed-flask and was treated with phosphorous oxychloride (30 cm^3) in dichloroethane (15 cm^3). The solution was heated under reflux for three and a half hours after which time the excess $POCl_3$ and dichloroethane were removed by distillation at reduced pressure to yield a very viscous black oil. Analysis of the oil showed it to be a complex mixture of products. Attempts were made to isolate these products by

columnchromatography on silica-gel using dichloromethane as the eluent, but without success.

From (120a) using thionyl chloride and ethyl acetate

The salt (120a) (1.54 g, 4.2mmol) was weighed into a round-bottomed-flask and thionyl chloride (10 cm^3, 138 mmol) was added slowly to the reaction vessel. The reaction mixture was heated on a boiling water-bath for one and a half hours after which the excess thionyl chloride was removed under vacuum leaving a brown viscous oil. Ethyl acetate (10 cm^3) was added to the oil and this was left stirring for 15 mins before water (15 cm^3) was slowly added, over ice, to the round-bottomed-flask. The layers were separated and the ethyl acetate layer was washed with two more portions of water. The organic layers were combined and the extract was dried over magnesium sulphate. Removal of the solvent gave a black solid which proved to be a complex mixture of products. Attempts to separate the products by column chromatography were unsuccessful.

Pyrolysis of bis(diisopropylammonium) salt (120a) of 4(dicyanomethylene)-4-hydroxybutanoic acid

The salt (120a) (0.05 g, 0.14 mmol) was placed in a 25 cm^3 round-bottomed flask and heated at *ca.* 200°C on an oil bath under a nitrogen atmosphere for two hours. During this time the compound changed from a white solid to a dark orange/brown oil and a small amount of gas appeared to be given off. This was basic to red litmus paper. The resulting oil (0.049 g, 98%) did not resolidify on cooling and was identified as the unreacted salt (120a) by comparison of its IR, ^1H NMR and ^{13}C NMR spectra with those of an authentic sample.

Synthesis of sodium ethyl 4-dicyanomethylene-4-hydroxybutanoate (138a)

Dry light petroleum (b.p. 40-60°C) (10 cm^3) was added to sodium hydride (80% dispersion in oil; 1.21 g, 0.04moles), the suspension swirled and the solvent/oil solution removed with a Pasteur pipette once the mixture had settled. The sodium hydride was finally dried under argon before dry THF (25 cm^3) was added gradually to the solid. Dry THF (15 cm^3) was added to malononitrile (2.64 g, 0.04moles) and this solution was added dropwise to the suspenson of sodium hydride in THF with stirring. Diethyl succinate (6.96 g, 0.04 moles) in dry THF (20 cm^3) was added to the reaction mixture and the resulting dark solution was refluxed for one and a half hours. After cooling the solution was filtered under vacuum and an orange solid was collected, washed with THF and dried to give sodium ethyl 4-dicyanomethylene-4-hydroxybutanoate (138a) (0.85 g); m.p. 255°C (dec); IR: ν_{max} 3000 (CH), 2160 and 2210 (CN) and 1750 (C=O) cm^{-1}; δ_H (D_2O): 1.21 (t, 3H, CH_3), 2.48 (t, 2H, CH_2), 2.54 (t, 2H, CH_2) and 4.10 (quar, 2H, CH_2) ppm; δ_C (D_2O): 15.58 (CH_3), 32.86, 34.22 and 36.33 (CH_2), 59.89 (=CCN), 126.87 and 129.92 (CN), 178.37 (C=CCN) and 184.71 (C=O) ppm.

Removal of the solvent from the filtrate yielded unreacted diethyl succinate and (138a).

Synthesis of sodium 1,4-bis(dicyanomethylene)-1-hydroxy-4-ethoxybutane (139)

Dry light petroleum (b.p. 40-60°C) (5 cm^3) was added to sodium hydride (80% dispersion in oil; 0.3 g, 0.01moles), the suspension swirled and the solvent/oil solution removed with a Pasteur pipette once the mixture had settled. The sodium hydride was finally dried under argon before dry THF (10 cm^3) was added gradually to the sodium hydride.

Dry THF (10 cm^3) was added to malononitrile (2.38 g, 0.036moles) and this solution was added dropwise to the sodium hydride/THF suspension with constant stirring. Diethyl succinate (6.95 g, 0.04moles) in dry THF (15 cm^3) was added to the reaction mixture and this was left stirring at room temperature for one and a half hours, after which time the solvent was removed by rotary evaporation to yield

a dark brown oil from which a solid precipitated. The brown solid, sodium 1,4-bis(dicyanomethylene) 4-ethoxybutane (139), was collected by vacuum filtration and was left to dry. IR: ν_{max} 3600 - 2800 (CH) and 2100 - 2500 (4xCN stretches) cm^{-1}; δ_H (D_2O): 1.19 (t, 3H, CH_3), 2.45 (t, 2H, CH_2), 2.58 (t, 2H, CH_2) and 4.10 (quar, 2H, CH_2) ppm; δ_C (D_2O): 19.85 (CH_3), 32.92, 34.27 and 63.92 (CH_2), 59.58 and 61.29 (=CCN), [118.34, 120.52, 125.87 and 128.17] (CN), 178.56 and 182.27 (C=CCN) ppm.

Reaction of diethyl succinate with malononitrile in ammonium acetate/acetic acid catalyst

A mixture of diethyl succinate (8.71 g, 0.05 moles), malononitrile (3.3 g, 0.05 moles), acetic acid (3.0 g, 0.05 moles), ammonium acetate (2.0 g, 0.024 moles), and toluene (50 cm^3) in a flask fitted with a Dean-Stark trap and a reflux condensor, was refluxed until collection of water (approximately 1cm^3) was complete. The cooled mixture was washed with brine and dried over magnesium sulphate. Removal of toluene by rotary evaporation yielded a red/orange oil which was distilled under vacuum to give a colourless liquid (5.01 g) which on analysis by ^1H and ^{13}C NMR was seen to be diethyl succinate.

Reaction of diethyl succinate with malononitrile using pyridine as the catalyst.

A mixture of diethyl succinate (4.88 g, 0.028 moles), malononitrile (1.98 g, 0.03 moles), pyridine (10 cm^3) and toluene (50 cm^3), placed in a flask fitted with a Dean-Stark trap and condenser,was refluxed until collection of water (approximately 1cm^3) was complete, and then for a further hour. The cooled mixture was washed with brine and dried over magnesium sulphate. The toluene was removed by rotary evaporation to yield a dark red oil, which, on NMR analysis seemed to contain a mixture of products, of which a large percentage (>95%) was diethyl succinate.

CHAPTER 4

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