NOTTINGHAM POLYTECHNIC

INVESTIGATIONS OF FUSED 1,2,3-TRIAZIN-4-ONES AND RELATED SYSTEMS

A thesis submitted in partial fulfilment of the requirements of the Council for National Academic Awards for the degree of Doctor of Philosophy

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February 1992

I would like to dedicate this thesis to my parents who have not only encouraged me throughout this work, but in everything I have ever done. I owe them many thanks.

PREFACE

The work described in this thesis was carried out by the author in the laboratories of the Department of Physical Sciences, Nottingham Polytechnic, Nottingham, between July 1988 and July 1991.

The author wishes to thank Dr.P.R.Huddleston for his excellent supervision and constant encouragement throughout the course of the work. Thanks are also due to Dr.J.M.Barker for his helpful advice and to Mr.M.L.Wood for spectral determinations.

The author would like to thank Mr.J.Young of Synthetic Chemicals Ltd, for his continued interest during this work.

Elaine Denise Woodland
Nottingham Polytechnic
February 1992

SUMMARY

This thesis describes work carried out on several chemical aspects of fused 1,2,3-triazin-4-ones.

In the first section several substituted 1,2,3-benzotriazinones were prepared with a view to observing their rate of deazoniation. It was envisaged that a kinetic analysis of this reaction would aid the elucidation of the nature of a hitherto controversial reaction intermediate. The rate constants obtained were used to construct Hammett plots and hence calculate the reaction constants. Several pieces of evidence were obtained that suggested the intermediate was of a diradical nature. Unfortunately, this could not be substantiated by Chemically Induced Dynamic Nuclear Polarisation spectroscopy.

The second section involved devising a new synthetic route for the preparation of 1,2,3-thieno-[3,4-d]triazinones since the one existing preparation gave polysubstituted products. A simple thienotriazinone was obtained which was used to study the reaction conditions required to cause its deazoniation. It was envisaged that for this reaction to occur, a potentially undesirable sulphur IV intermediate must be surmounted. As anticipated the thieno[3,4-d]triazinone did not deazoniate under the normal conditions.

The synthetic route used to prepare the thieno[3,4-d]-triazinone also afforded an intermediate aminonitrile. An investigation into the versatility of this compound as a potential precursor to other fused heterocycles was undertaken. Several fused thienopyrimidines were obtained.

The final section of this work was dedicated to devising a synthetic route for the preparation of pyrrolo- and furanotriazinones. Unfortunately these compounds were not obtained due to difficulties of instability and excessive water solubility encountered in the synthesis, several useful intermediates were, however, successfully prepared.

CONTENTS

CHAPTER ONE

I N T R O D U C T I O N

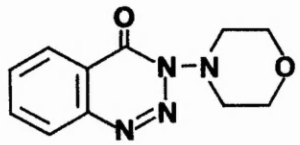
Uses and biochemical aspects of 1,2,3-benzotriazin-4-ones.

1,2,3-Benzotriazin-4-one derivatives show a wide commercial utility.

The medicinal properties of condensed 1,2,3-triazine compounds were demonstrated as early as 1951[1].

1,2,3-Benzotriazinone itself is reported to induce a weak sedative effect[2]. The 3-amino derivative gives rise to a pronounced hypnotic effect coupled with a strong emetic action[2]. A wide range of other 3-alkyl and 3-dialkyl-amino compounds were prepared and their pharmaceutical uses investigated[2]. Modification of the alkyl/dialkyl-amino functionality causes a considerable alteration in pharmacological activity, whereas introduction of substituents onto the benzene ring shows only minor changes.

The types of activity shown by these compounds varies from weakly analgesic to prolonged hypnotic, narcotic, muscle relaxant, diuretic and strongly analgesic. Indeed the 3-morpholino derivative (1) was shown to have superior analgesic activity to either phenacetin or aminopyrine, but with a much lower acute toxicity[3].

(1) 

Other 3-substituted benzotriazinones have been found to possess insecticidal properties. Modification of the 3-substituted side chain is a simple process and can result in selective action against particular insect spread diseases in both fruit and vegetables.
Finally, the ability to act as 'masked' diazonium compounds has led to 1,2,3-benzotriazinones being used as azo-dye equivalents. Their high water solubility, coupled with the ease by which the triazine ring can be opened by thermal methods, has ensured their industrial usefulness as azo-dye precursors.
In view of these useful properties, together with their intrinsic interest, it is not surprising that much work has been done on the preparation and reactions of the 1,2,3-benzotriazin-4-ones.

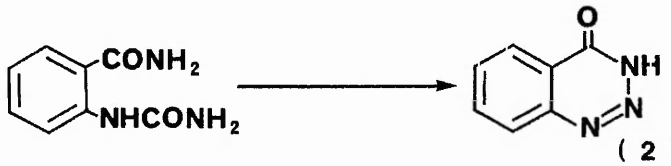
Synthesis of 1,2,3-benzotriazin-4(3H)-ones.

Of the variety of methods described, the diazotization of anthranilamide and its derivatives is the most exploited. This is due to the ease of the reaction, which affords stable products in high yields, coupled with the ready availability of the starting amides.

The parent 1,2,3-benzotriazin-4(3H)-one (2) was first prepared by Finger[4], by diazotization of anthranilamide with nitrous acid. He employed the name benzazimide, suggesting that the compound was an azimide of an o-amino-benzamide.

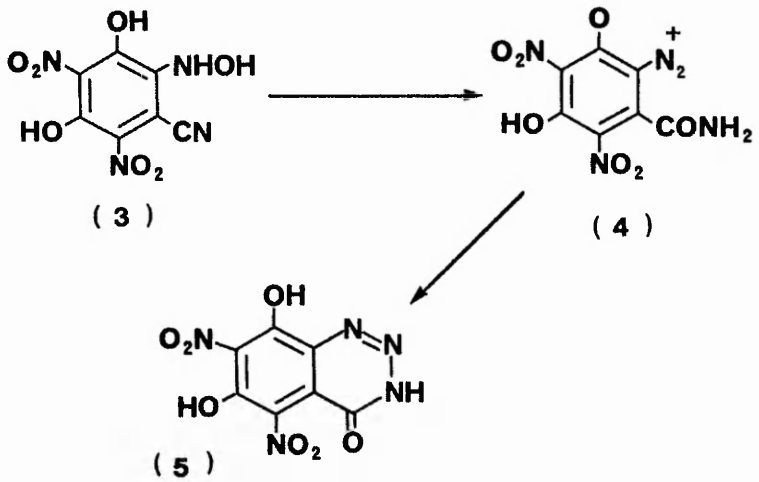
(2)

A similar diazotization of isatoic diamide, carried out by Jacini[5], also gave rise to the parent compound (2).



(2)

The highly substituted benzotriazinone (5) was produced by Fierz and Brutsch[6] by reaction of isopurpuric acid (3) with either nitrous acid or amyl nitrite. The intermediate diazonium compound (4), in which a cyano group has hydrolysed to an amide group, was dissolved in alkali to afford the triazinone.



(3)

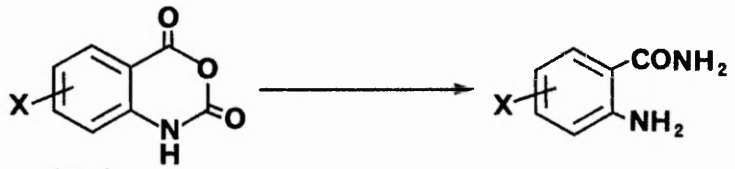
(4)

(5)

(1)

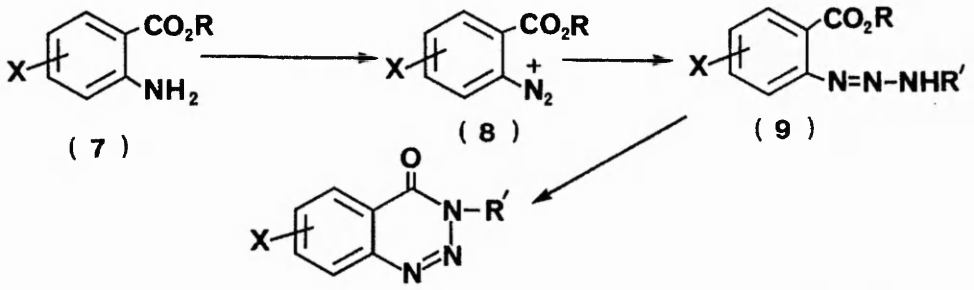
Substituted benzotriazinones are readily prepared from the appropriately substituted anthranilamides[7-10].

Adamson et al[11] extended the availability of the substituted anthranilamides, by their novel ring opening of isatoic anhydrides (6) with concentrated ammonia.



(6)

An alternative, frequently used synthetic route for substituted benzotriazinones, is the diazotization of the anthranilate (7) with nitrous acid followed by reaction of the formed diazonium compound (8) with an amine[12-30]. The triazene (9) thus formed cyclises to the triazinone.

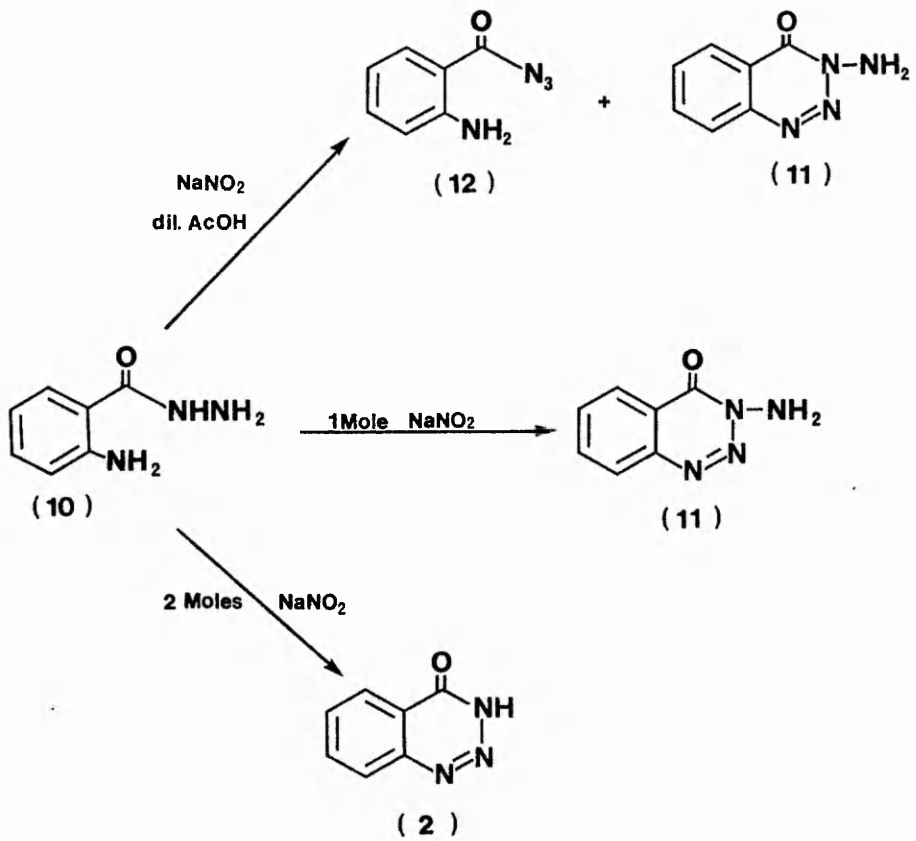


(7) (8) (9)

Initial attempts[29] to prepare 1-alkyltriazenes were unsuccessful due to the low yield and instability of the product. However, Clark and Gilmore[13] demonstrated that under carefully controlled conditions, moderate yields of alkyl triazenes could be obtained. Furthermore, an investigation undertaken by Le Blanc and Vaughan[18] into

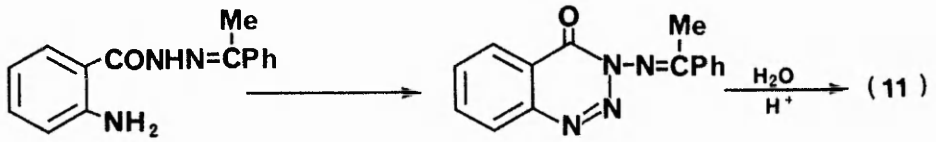
the diazotizability of anthranilates and their subsequent reaction with amines, showed that a variety of alkyl triazenes could be prepared in good to excellent yields. Their cyclisation to 3-alkylbenzotriazinones was easily achieved.

3-Amino-1,2,3-benzotriazin-4(3H)-one (11) can be readily obtained from the diazotization of anthranilic hydrazide (10). Heller and Siller[33] showed this to be a complex reaction since the products obtained depend upon the reaction conditions employed.[31,32]



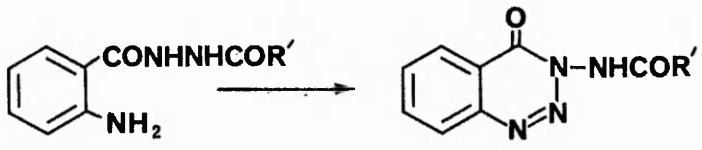
Treatment of the hydrazide with nitrous acid in dilute acetic acid gives a mixture of 3-aminobenzotriazinone and the anthranoyl azide(12). When diazotized with one mole of nitrous acid in dilute hydrochloric acid the hydrazide yields the 3-amino derivative as the sole product. Two moles of nitrous acid cause a further reaction and the parent triazinone is isolated.

An alternative preparation of 3-aminobenzotriazinone is the diazotization and mild acid hydrolysis of acetophenone hydrazone (13)[11,34].



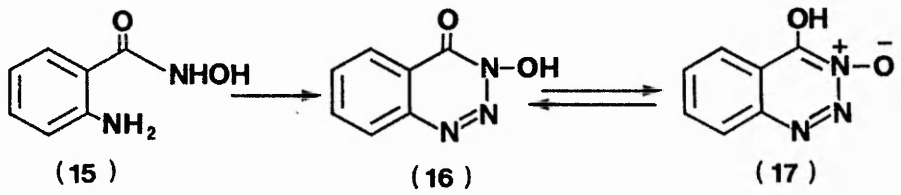
(13)

3-Acylamino-1,2,3-benzotriazinones (14) are readily accessible by the diazotization of the appropriate acyl hydrazide[34].



(14)

Diazotization of 2-aminobenzohydroxamic acid (15)[35] affords 3-hydroxy-1,2,3-benzotriazin-4-one (16) which can be formulated as the tautomeric 4-hydroxy-1,2,3-benzotriazin-3-oxide (17).

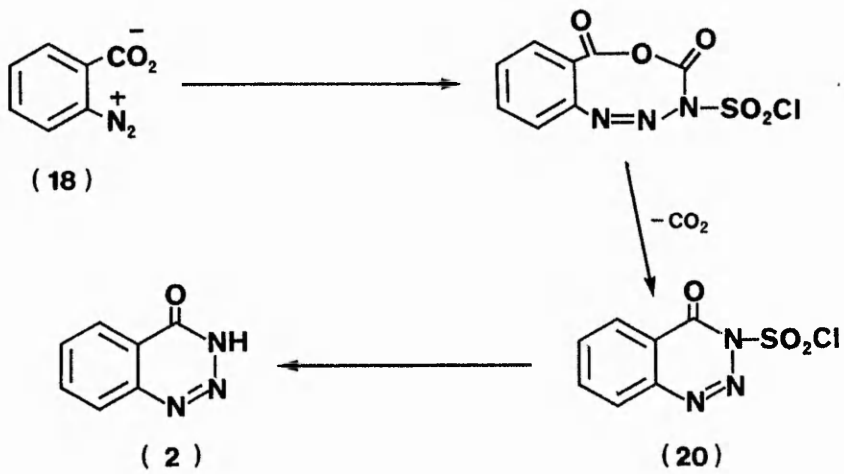


(15) (16) (17)

Treatment of the benzyne precursor (18) with a triphenyl phosphine arylamide[36] affords a 3-aryl-1,2,3-benzotriazin-4-one (19) in poor yield, but the reaction is of mechanistic importance.

(18) (19)

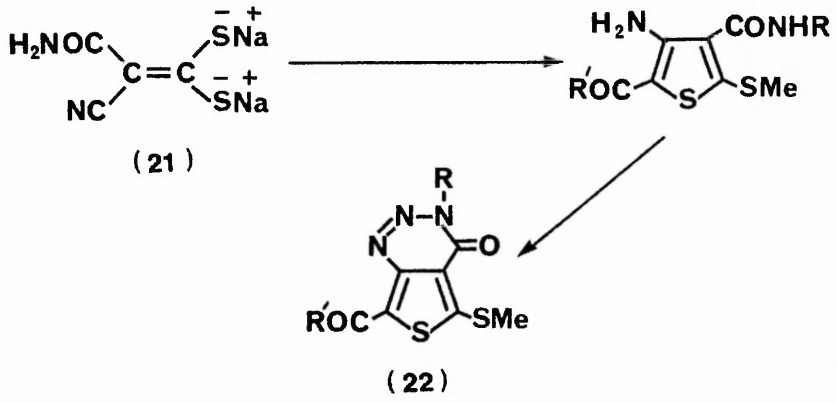
Moriconi and Shimakawa[37] coupled the precursor (18) with chlorosulphonyl isocyanate to give the unstable chlorosulphonyl benzotriazinone (20). Attempts to purify this compound resulted in its conversion to the parent triazinone.



(18) (20) (2)

Preparation of Thieno[3,4-d]-1,2,3-triazin-4-ones.

The method of diazotisation of o-aminoarenecarboxamides was used in the only known preparation of thieno[3,4-d] triazin-4-one[38]. Henriksen and Autrup obtained the aminoamide by α-halogenocarbonyl alkylation of the disodium salt of 2-carbamoyl-2-cyanoethylene-1,1-dithiolate (21), followed by base-induced cyclisation. Subsequent reaction with nitrous acid afforded the novel thieno[3,4-d]triazin-4-one (22) ring system.



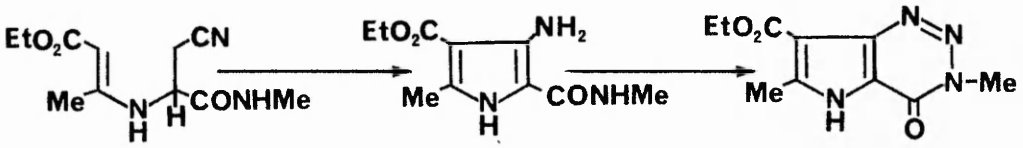
(21)

(22)

Of the six examples prepared all are highly substituted, with both the 2 and 5 positions of the thiophene ring being protected.

Pyrrolo[3,2-d] and [3,4-d]-1,2,3-triazin-4-ones.

Murata and Ukawa[39] prepared the novel pyrrolo[3,2-d] triazin-4-one ring system by diazotisation of 3-amino-2-carboxamidopyrrole (24), obtained from an intramolecular addition of an enamine to a nitrile group. The enamine (23) was formed by condensation of ethyl acetoacetate with an aminocyanoacetamide, base-induced cyclisation affording the pyrrole.



(23) (24)

Although a following paper by the authors[40] extended this work, no other references to the preparation of this pyrrole ring system is mentioned in literature sources.

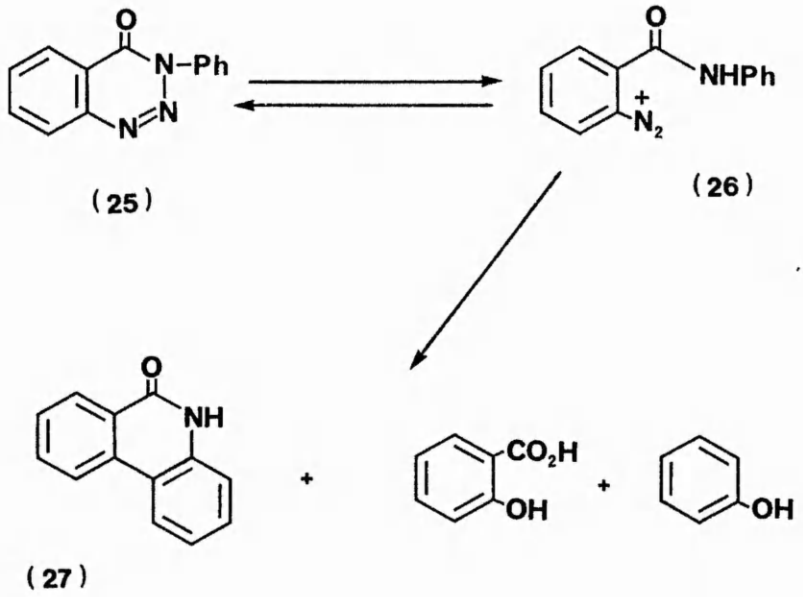
Despite a report in Chemical Abstracts of pyrrolo-[3,4-d]triazin-4-one[41], consultation of the patent failed to reveal any reference to the compound. It must therefore be concluded that this ring system remains novel.

Furano[3,2-d] and [3,4-d]-1,2,3-triazin-4-ones.

No reference to these two ring systems could be found, thus it must be assumed that both are novel compounds.

The thermal and photolytic decomposition of 1,2,3-benzotriazin-4(3H)-ones.

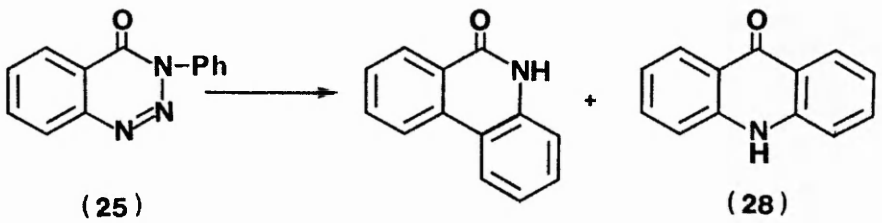
This reaction of 1,2,3-benzotriazin-4-ones has caused interest since it was first reported in 1962 by Gibson[42]. He attempted to show the lability of triazinones towards acid by a reversible protonation and ring-scission of 3-phenyl-1,2,3-benzotriazin-4-one (25) to phenanthridone (27). Decomposition of the triazinone in syrupy phosphoric acid at 200-220°c gave a low yield of the desired product together with salicylic acid and phenol. Gibson explained the reaction products in terms of the diazonium intermediate (26).



(25) (26) (27)

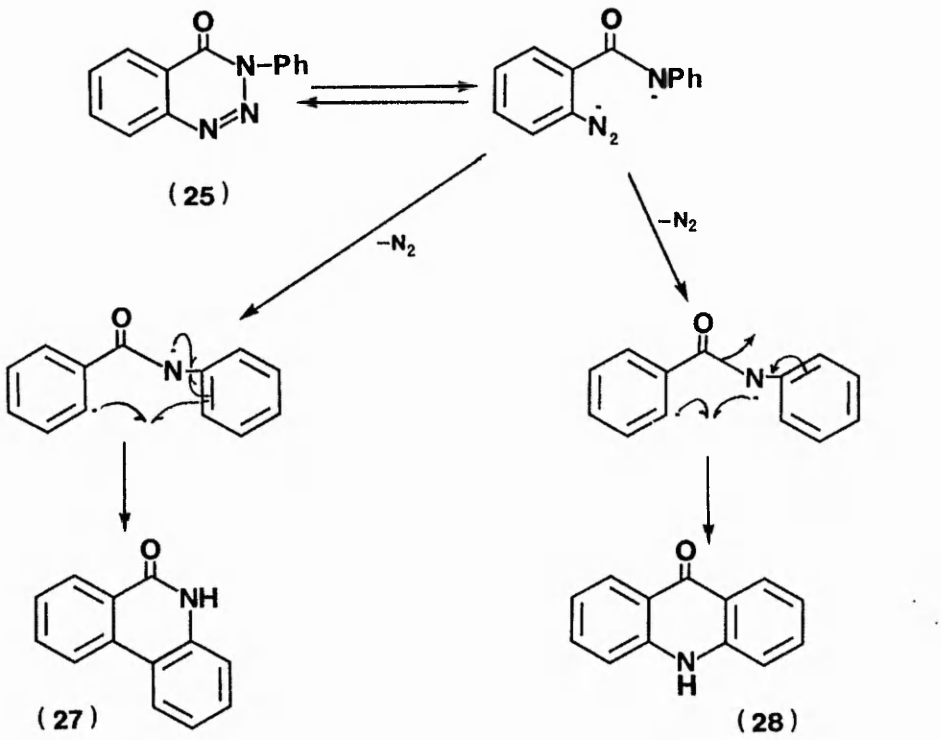
Reversible protonation and ring-scission of the triazinone yields the diazonium intermediate and subsequent loss of nitrogen, followed by rotation and recyclisation with loss of a proton, gives the phenanthridone. Gibson explained the formation of the by-products by way of competing reactions of the diazonium compound. This involves the hydrolytic splitting of the amide group and nucleophilic displacement of the diazonium group by anions or water. The author also demonstrated that the salicylic acid did not decarboxylate at the reaction temperature.

Hey, Rees and Todd[43] independently reported a decomposition of 3-phenylbenzotriazinone (25). Heating the triazinone without solvent at temperatures of 250-280°c gave a mixture of phenanthridone (27) and acridone (28).



(25) (27) (28)

The authors demonstrated that the acridone was not formed by an isomerisation of phenanthridone, which is inert at this temperature, but must have arisen from a rearrangement caused from the loss of nitrogen. The following mechanism was proposed:



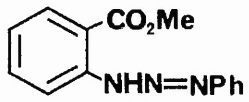
In an attempt to moderate the decomposition by heating the triazinone in liquid paraffin, Hey et al were able to substantiate the free radical nature of the diazonium intermediate, since the benzanilide produced arose from hydrogen abstraction from the solvent by the radical. Although a free radical mechanism was postulated, the analogous ionic mechanism could not be discounted.

Both Ege[44] and Burgess & Milne[45] irradiated 3-phenyl-1,2,3-benzotriazinone in the presence of a variety of nucleophiles to obtain N-phenyl anthranilic acid derivatives.

(25)

R= OH, OMe, NHC_6H_{11}

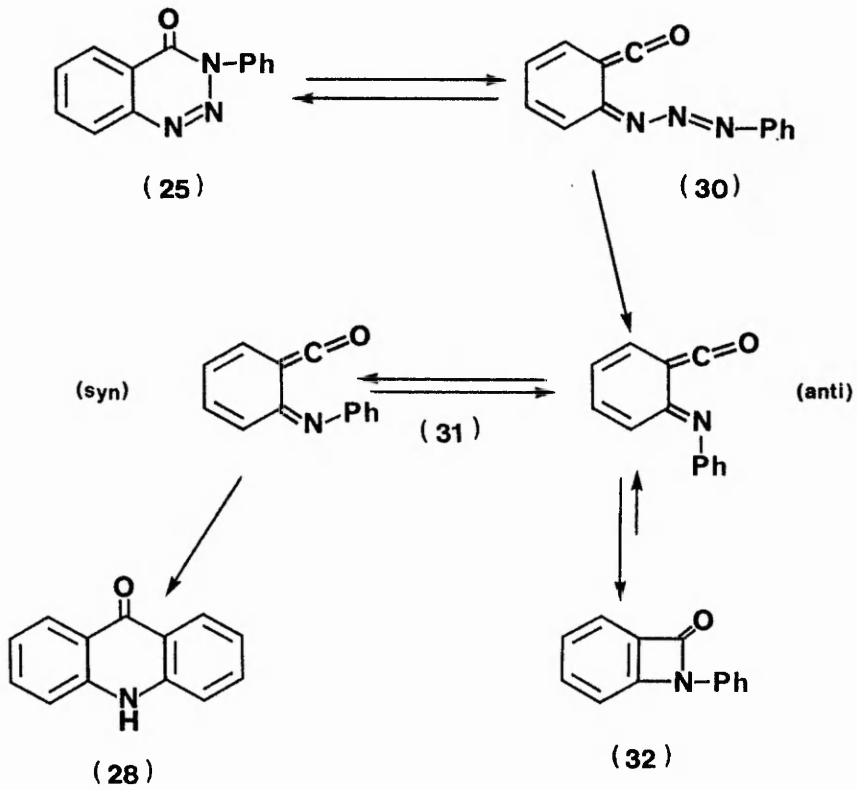
The latter found that decomposition in dry benzene gave rise to the acridone. Quenching with methanol afforded, in addition to unreacted triazinone, a low yield of methyl N-phenylanthranilate and methyl diazoamino-benzene-2-carboxylate (29).



(29)

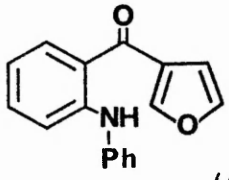
Infra-red scanning of the triazinone after brief irradiation showed strong absorptions at 1830, 1590 and 1500 cm^{-1}, ascribed to the lactam (32). These slowly disappeared to give the characteristic absorption of the acridone.

Addition of methanol converts the spectrum to that of the anthranilic acid derivative. The authors suggested the following mechanism:



The triazinone (25) undergoes photochemical transformation to the trans-ketene (30). Evidence for this is provided by the isolation of (29) on quenching with methanol. Loss of nitrogen and rearrangement gives the anti-configuration of (31), which is valence tautomeric with N-phenyl-benzazetinone (32). Since (32) appears to be the predominant tautomer the subsequent rearrangement to the acridone must be slow.

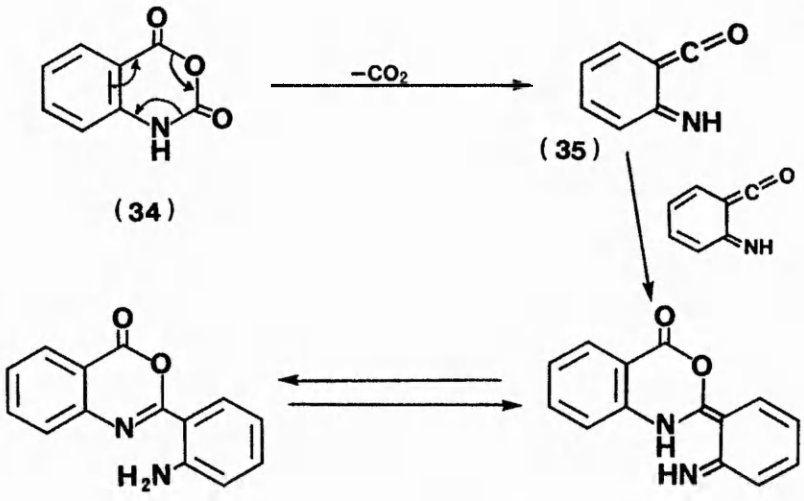
The authors showed that the ketene was implicated in some of the observed reactions since its presence could be demonstrated by trapping with furan to give the adduct (33).



(33)

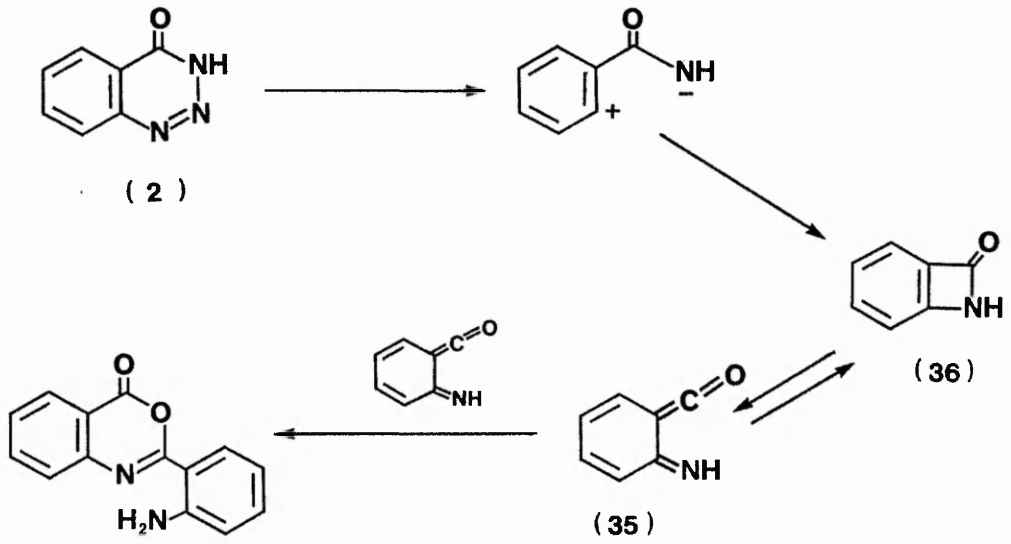
The isolation of the benzazetinone and hence the proof of the existence of the iminoketene became a key factor in the elucidation of the deazoniation mechanism.

Further evidence for the existence of the iminoketene was obtained by Smalley et al[46] in their comparison of the thermolysis of benzotriazinone (2, R=H) with that of isatoic anhydride (34). Thermolysis of isatoic anhydride in a high boiling, inert solvent gives benzoxazinone with liberation of carbon dioxide. The product is formed by a Diels-Alder reaction of two molecules of the iminoketene (35).

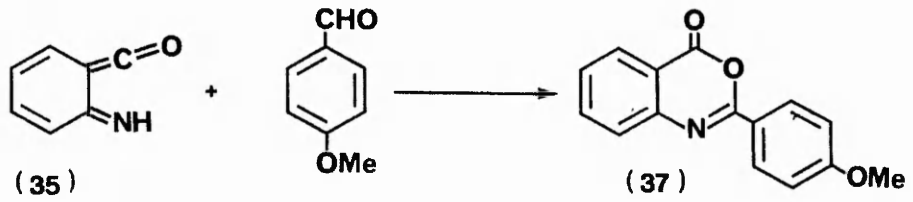


(34) (35) (15)

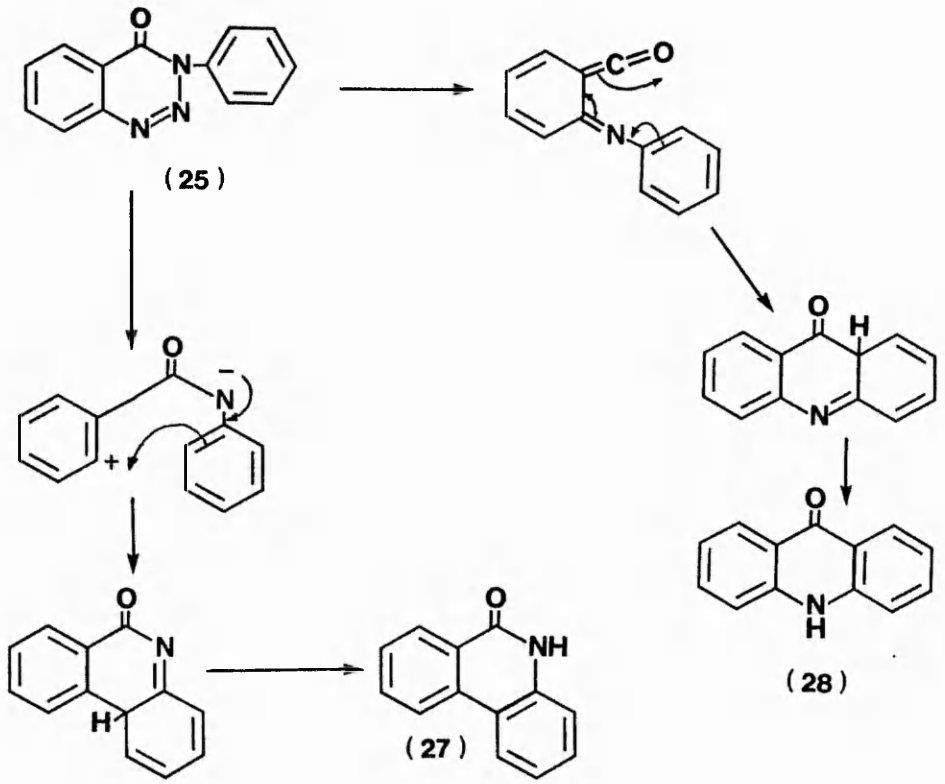
Pyrolysis of 1,2,3-benzotriazin-4-one under identical conditions to those used for the anhydride gave the oxazinone by loss of nitrogen. The mechanism proposed involved the iminoketene structure:



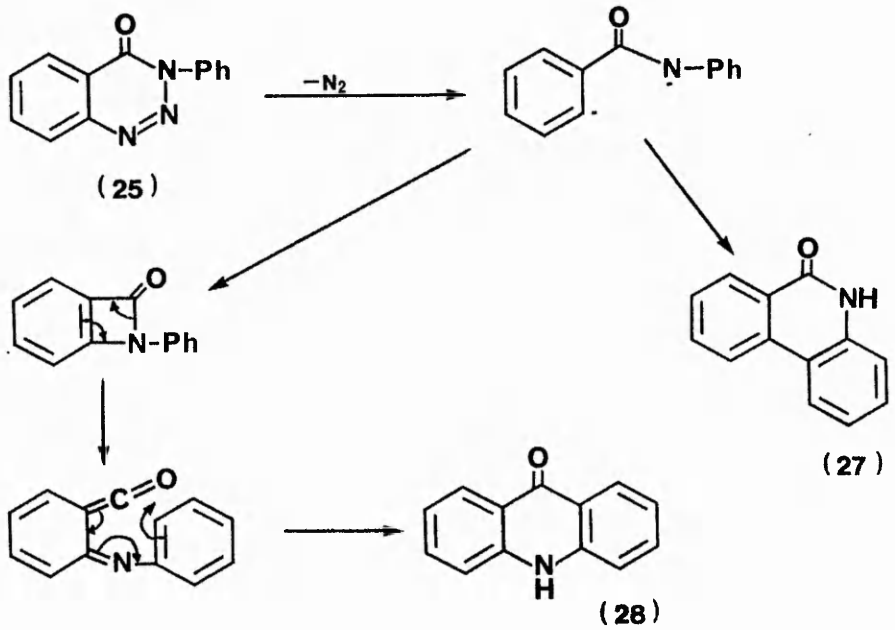
Smalley et al prepared 2(4-methoxyphenyl)benzoxazinone (37) by trapping the iminoketene in a Diels-Alder reaction with p-anisaldehyde.



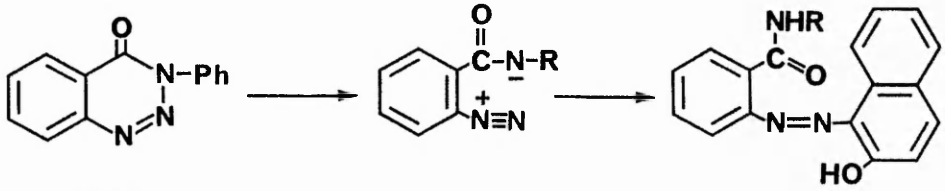
The authors pointed out that the facts were equally well explained with a charged intermediate as by the free radical of Hey et al[43].



Hey, Rees and Todd[14] proposed two alternative mechanisms in which the reaction intermediate was depicted as either a diradical or the corresponding zwitterion. Collapse of this to the lactam, followed by ring opening to the iminoketene and recyclisation would account for the formation of the acridone (28).

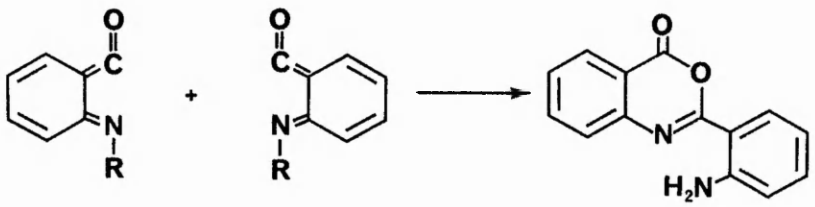


Ege[25] offered further evidence for the mechanism of photolysis of 3-phenylbenzotriazinone in which the intermediate diazonium salt was trapped as an azo-dye (38) by reaction with β-naphthol.



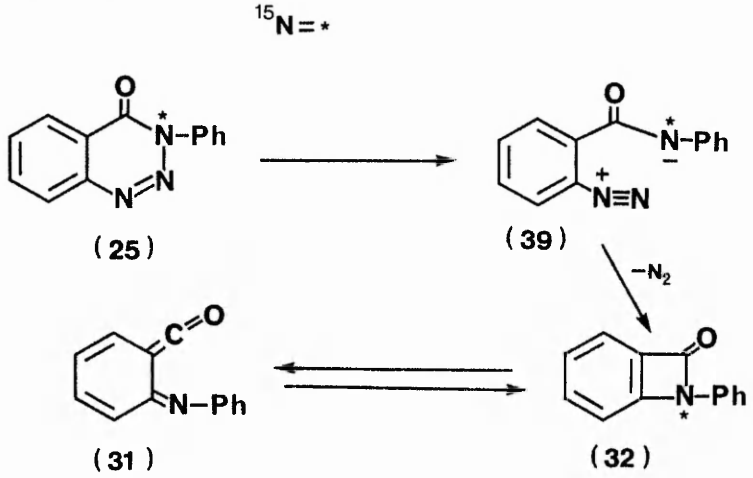
(25) (38)

Interest in the existence and reaction of the iminoketene was extended by Crabtree et al[47] in their attempt to trap the intermediate via Diels-Alder reactions using a variety of dienophiles. Pyrolysis of benzotriazinone in the absence of solvent yields a benzoxazinone by a Diels-Alder coupling of two molecules of the iminoketene.

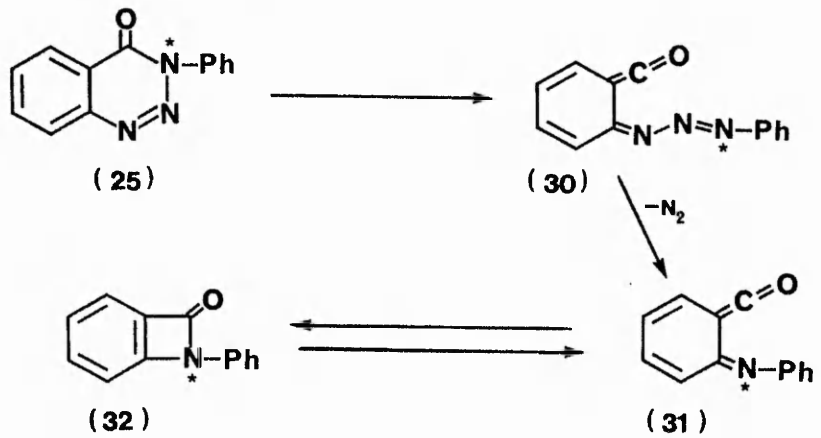


The authors noted that in general the iminoketene showed a preference to reaction with dienophiles other than itself.

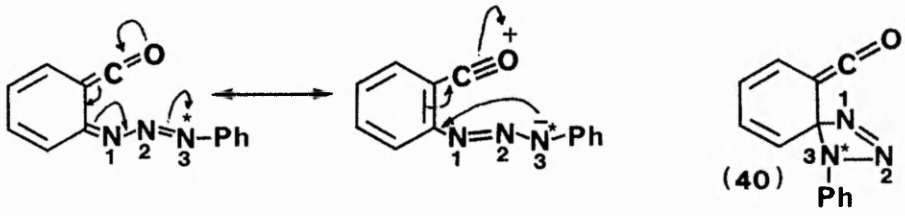
Elucidation of the mechanism of deazoniation by the use of ^{15}N labelling experiments was investigated by Ege and Pasedach[20]. They suggested a mechanism whereby the initial stage of reaction was the heterolysis of the triazinone to the diazonium zwitterion (39). Elimination of nitrogen affords the benzazetinone (32) via the ketene valence isomer (31).



An alternative mechanism proposed by Burgess and Milne[45] involved valence isomerisation of the triazinone to the ketene (30) as the initial stage. Nitrogen is then split off to give the ketene (31) which is tautomeric with (32).

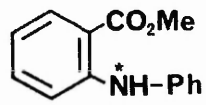


Which nitrogen atoms are eliminated is not clear from this mechanism, but those attached by multiple bonds are most likely to be lost. Thus it would be expected that the nitrogen atoms at positions N2 and N3 would be eliminated. Formation of the triazete form (40) could cause elimination from the N1 and N2 positions.

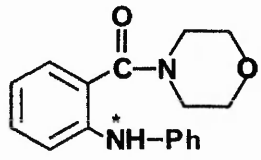


(40)

The authors photolysed 3-^{15}N-labelled phenyltriazinone, (prepared from diazotised methyl anthranilate and ^{15}N-aniline hydrochoride), in methanol and ethyl acetate in the presence of morpholine. The products obtained, (41) and (42), both showed the ^{15}N-label. No label was found in the eliminated nitrogen.

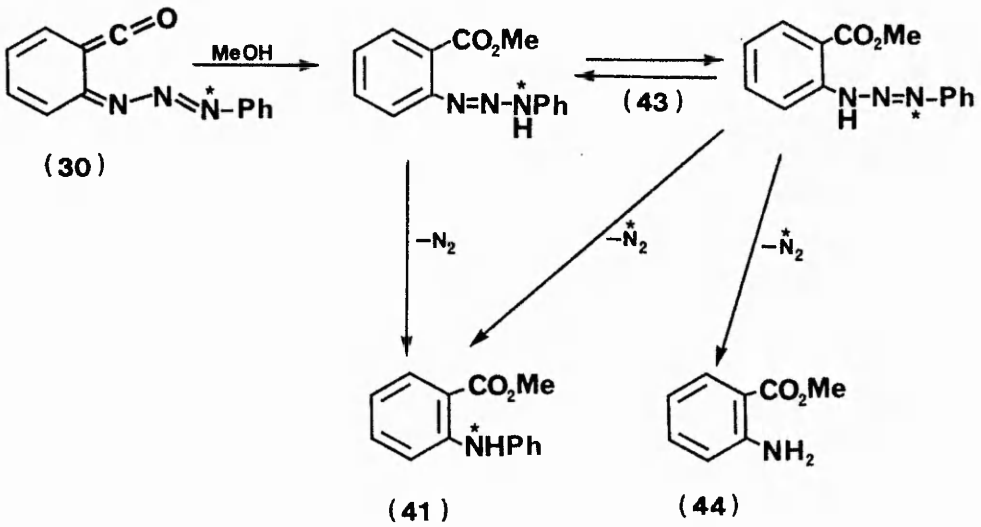


(41)



(42)

Since no differentiation between the two mechanisms was achieved, Ege and Pasedach proposed a variant to mechanism two in which the tautomeric mixture (43) could only eliminate nitrogen from the N1 and N2 position.



The N-phenylanthranilic acid methyl ester (41) obtained showed a different labelling pattern from that of the triazinone and unlabelled methyl anthranilate (44) was also isolated, thus eliminating the triazene ester (43) as an intermediate in the reaction. The existence of this ester could not be verified by the authors.

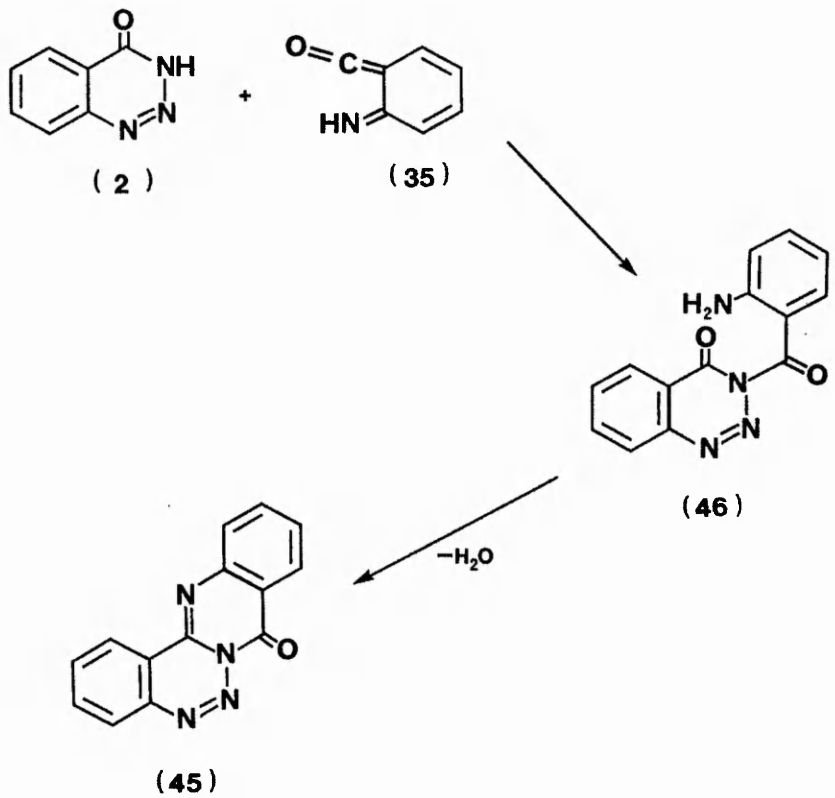
Since the mechanism of Burgess and Milne[45] relies heavily on the participation of the ester after addition of methanol to the irradiated solution, the failure to detect (43) casts doubt on the proposals outlined above. Burgess and Milne reiterated that mechanism one was further supported by the trapping of the diazonium zwitterion (39) as a coupled product with β -naphthol[25].

Decomposition of the parent triazinone (2, R=H) in diethylene glycol dimethyl ether was shown by Murray and Vaughan[48] to afford quinazolino[3,2-c]-1,2,3-benzotriazin-8-one (45) as the product.

(45)

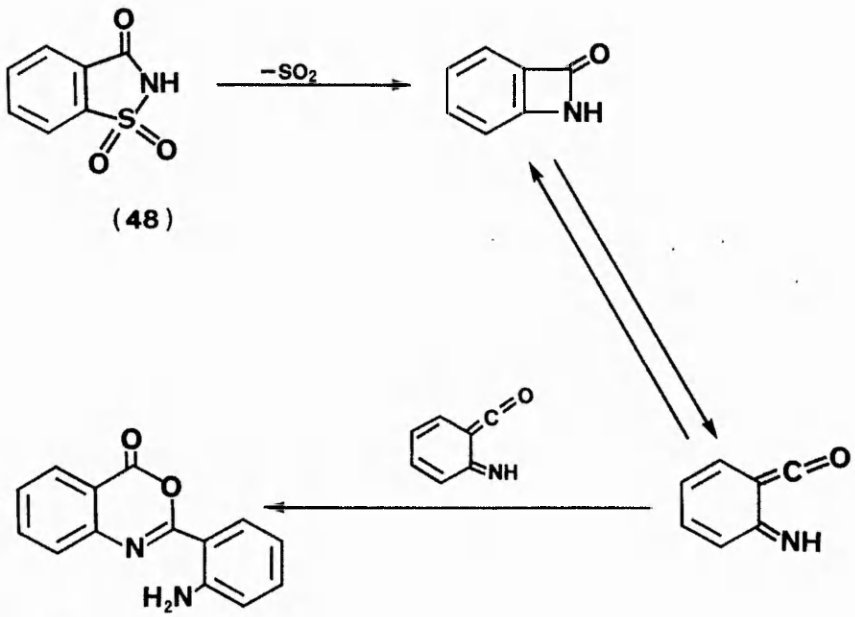
It was suggested that although the benzoxazinone was not obtained, the reaction still involved the intermediate iminoketene.

Murray and Vaughan proposed that the heterodiene reacted with a second molecule of triazinone to give 3-(2-amino-benzyl)benzotriazinone (46) which undergoes cyclodehydration to the quinazolino compound (45).



The authors also suggested that the product could be obtained by one molecule of triazinone acting as a nucleophile and attacking the amide function of a second molecule of triazinone. Loss of nitrogen and cyclodehydration would also give (45). Although this is an unfavourable reaction, the possibility of it occurring as an alternative to the intermediate iminoketene could not be ignored by the authors.

Existence of the heterodiene was also evident in the thermolysis of benzo-1,2-isothiazol-3-one-1,1-dioxide (48). Barker and Smalley[49] thermolysed (48) in diethyl phthalate to obtain 2-(o-aminophenyl)benzo-3,1-oxazin-4-one (49) by loss of sulphur dioxide. The authors proposed the following mechanism:



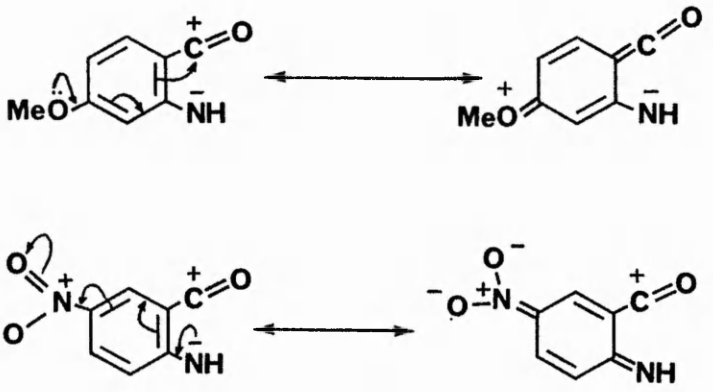
(48)

(49)

Decomposition of (48) in liquid paraffin gave rise to benzamide, with no trace of any oxazinone. This is analogous to the thermolysis of 3-phenyl-1,2,3-benzotriazinone in paraffin[43].

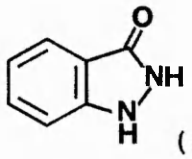
The thermolysis of unsubstituted benzotriazinone in paraffin affords the oxazinone as the sole product. The difference in products for these reactions was explained in terms of the enhanced mesomeric stabilization of the intermediate N-Ph over that of the N-H species.

The initial attempt to isolate the benzazetinone was undertaken by Archer et al[15] in their study of the thermolytic decomposition of nuclear-substituted benzotriazinones. They envisaged that the polar form of the benzazetinone could be stabilized by the mesomeric effects of the functional group thereby permitting its isolation.



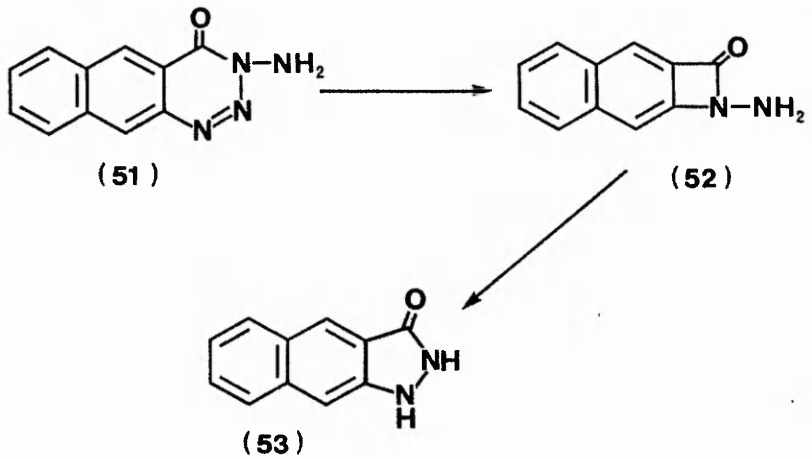
The authors observed that the decomposition temperatures of the 6- and 7-substituted benzotriazinones prepared altered little from that of the parent triazinone. The appropiately substituted oxazinones were the only products isolated.

Unambiguous evidence for the existence of the azetinone intermediate has been demonstrated in the naphtho-triazinone series by Wunsche et al[50]. Initial attempts by Bashir and Gilchrist[51] to prepare benzazetinone by photolysis of 3-aminobenzotriazinone gave indazolin-3-one (50) as the product.



(50)

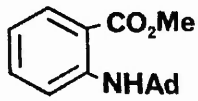
3-Aminonaphthotriazinone (51) under identical conditions, gave the naphthazetinone (52); this, when treated with acid undergoes fragmentation of the four membered ring to yield benz[f]indazol-3-(2H)-one[51] (53).



Although unreactive to photolysis 3-(1-adamantyl)-benzotriazinone (54) gave rise to a multi-component mixture on vapour phase pyrolysis[51], the chief product being N-1-adamantylbenzazet-2(1H)-one (55).

(54) (55)

It was proposed that the by-products, biphenylene and adamantyl isocyanate, were due to a competing minor reaction to that of the formation of the azetinone. The benzazetinone (55) was shown to be stable to thermal decomposition, and was recovered quantitatively after vapour phase pyrolysis at 600°c. Susceptibility to nucleophilic attack was demonstrated by reacting the adamantyl azetinone with methanol. The product, methyl 2-(1-adamantylamino)benzoate (56) was produced by cleavage of the four membered ring.



(56)

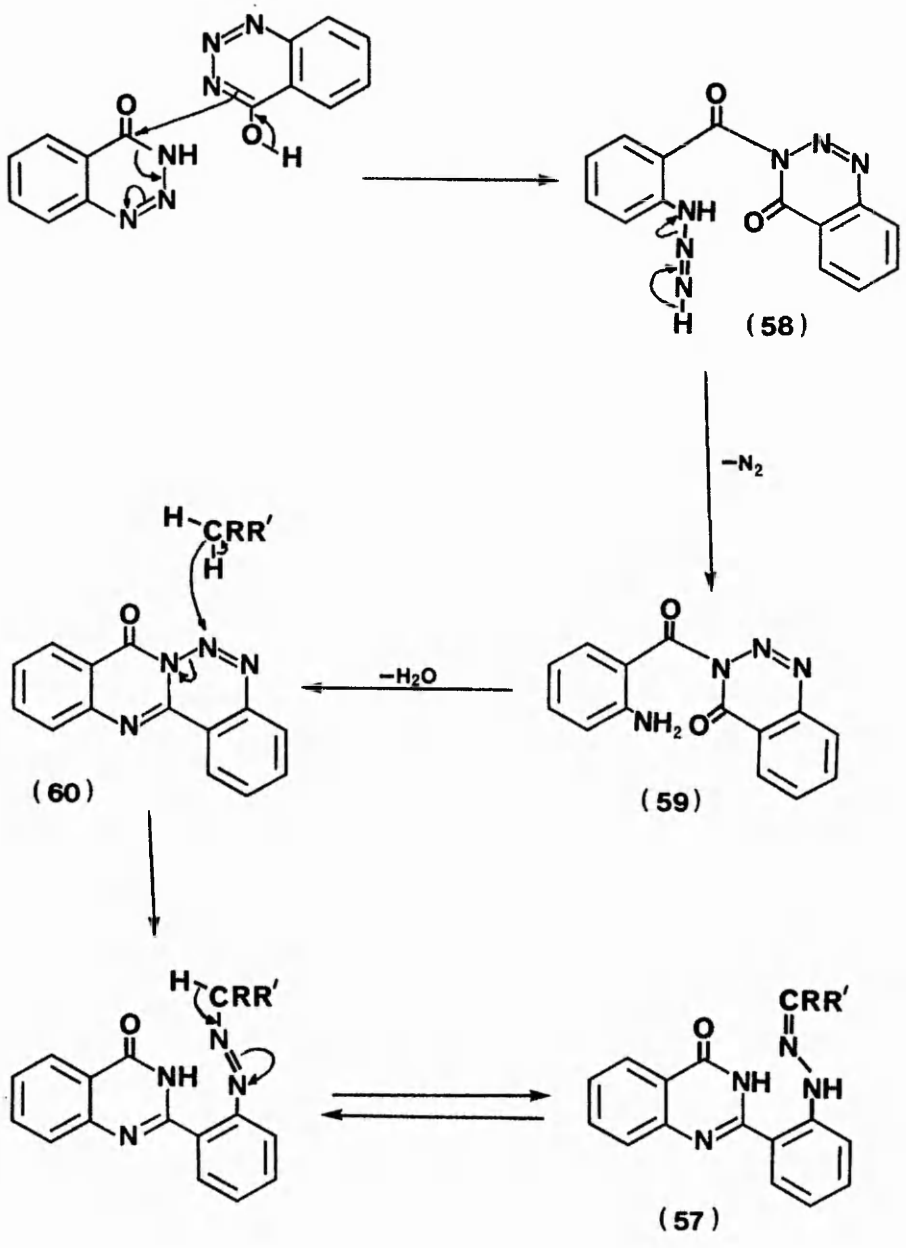
There are several instances reported in the literature where the thermolysis of a benzotriazinone does not give the expected product <u>via</u> the iminoketene route.

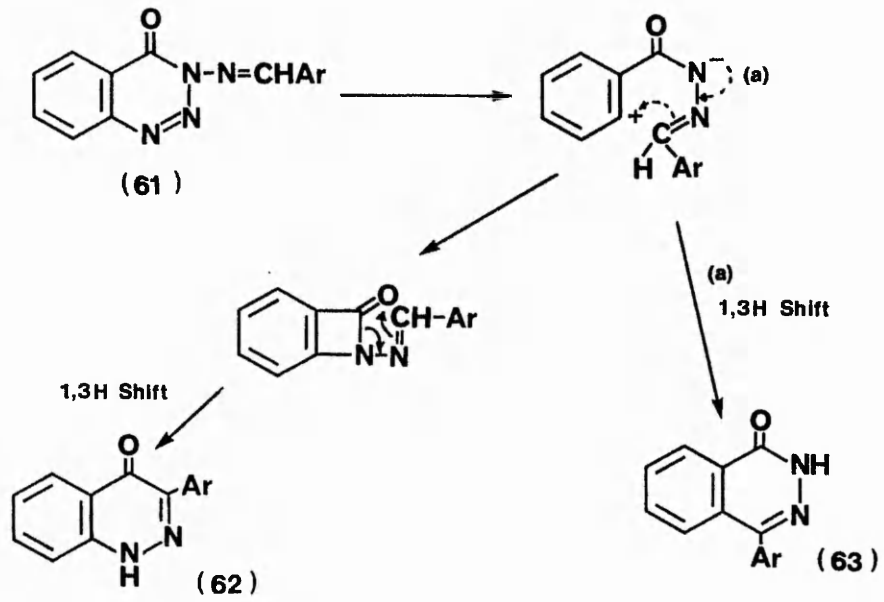
Whilst comparing the behaviour of benzotriazinones with a range of compounds containing reactive methylene groups, Siddiqui and Stevens[52] obtained a yield of quinazolinyl-phenylhydrazone (57). The authors proposed a mechanism whereby the triazinone underwent nucleophilic attack at the exposed and reactive C-4 position by a second molecule of triazinone. The unstable 3-aryltriazene (58) decomposes to the anthraniloyltriazinone (59) by loss of nitrogen. Subsequent cyclodehydration affords the quinazolino[3,2-c]-1,2,3-benzotriazinone (60). Reaction with a reactive methylene system causes cleavage of the N2-N3 bond of the quinazolinotriazinone to yield the hydrazone (57) by a Japp-Klingemann type reaction (scheme one).

Since this reaction occurs at a lower temperature than that of the decomposition of the triazinone, the authors discounted the intermediacy of the iminoketene.

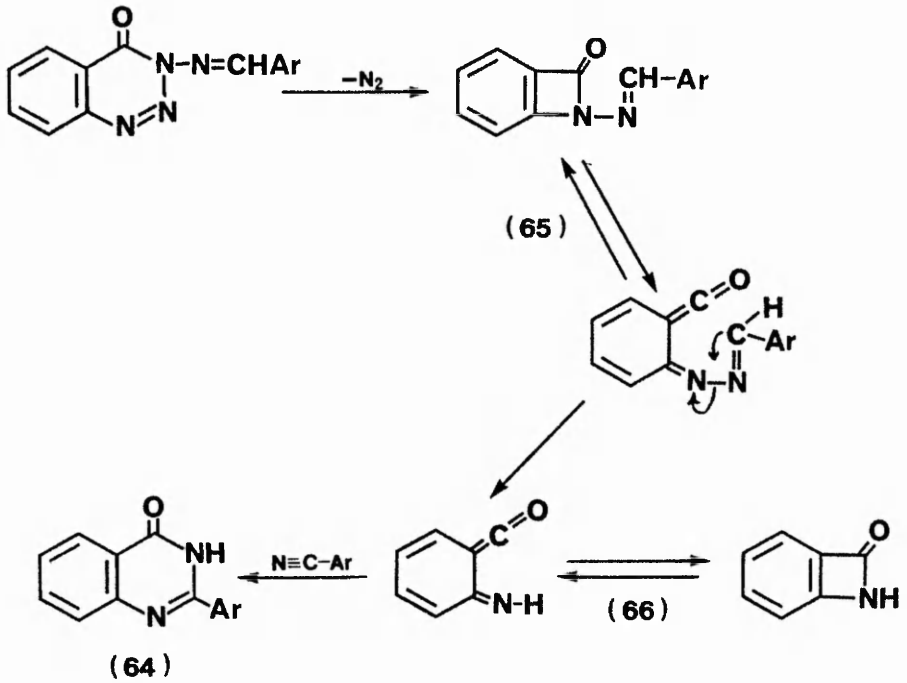
The pyrolysis of the 3-arylideneamino-1,2,3-benzotriazinone (61) was undertaken by McPaterson *et al*[53] with the expectation of obtaining 3-arylcinnolone (62) and 1-arylphthalazinone (63). This was envisaged as being analogous to the formation of acridone (28) and phenanthridone (27) from the thermolysis of 3-phenyl-benzotriazinone (25).

Scheme one:



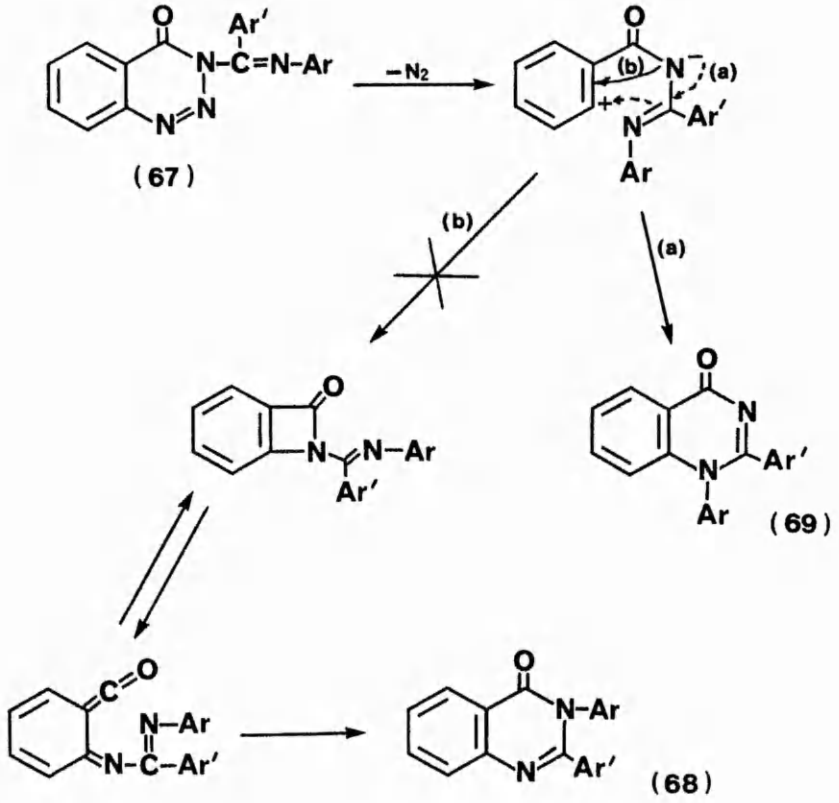


However, in the event, the isomeric 2-arylquinazolin-4-one (64) was obtained. It was suggested that the product arose from an azetinone/iminoketene intermediate (65) which underwent a 1,3-H shift and loss of aryl cyanide to give the valence tautomers (66). A (4+2) cycloaddition with the aryl cyanide would afford the 2-arylquinazolinone (64).

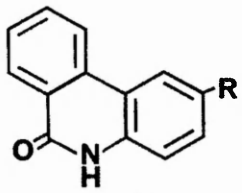


The proposed mechanism for this reaction could not be substantiated by the authors, but they clearly demonstrated that the quinazolinone was not obtained by thermal rearrangement of the cinnolone (62) or phthalazinone (63).

McPaterson et al[54] carried out the thermolysis of 3-imidoyl-1,2,3-benzotriazinone (67) in an inert solvent. The expected product via the benzazetinone route, 2,3-diaryl quinazolin-4-one (68), was not obtained. Instead a moderate yield of 1,2-diaryl-1,4-dihydro-quinazolin-4-one (69) was produced by a competing cyclisation.

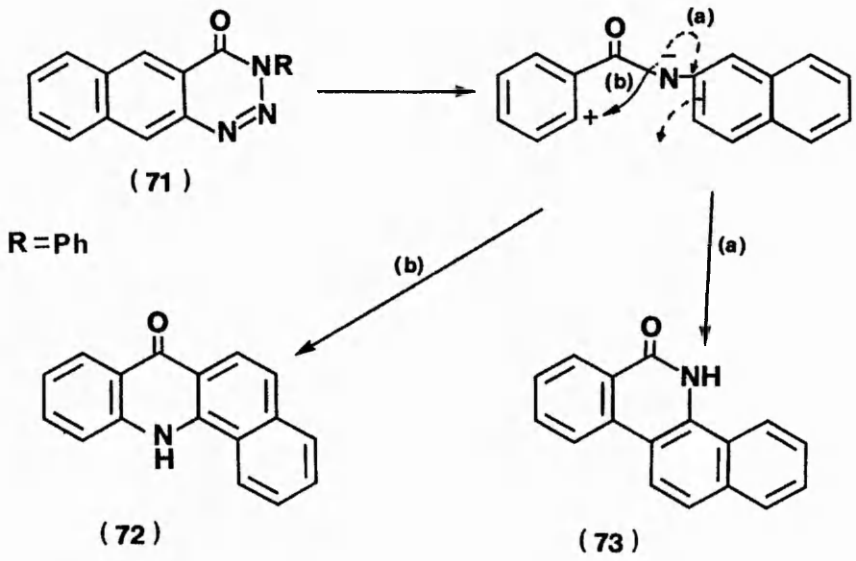


A surprising by-product of the reaction was the substituted 9H-phenanthridone (70). The authors could not suggest a mode of formation for this compound, but demonstrated that it did not occur by thermal rearrangement of either 2,3-diaryl- or 1,2-diaryl-quinazolin-4-one.



(70)

The thermolysis of naphtho[2,3-d]triazin-4-one (71) in liquid paraffin, carried out by Barker and co-workers[55], gave a mixture of benzo[c]acridone (72) and benzo[c]-phenanthridone (73). The authors proposed that the formation of these products was analogous to that of acridone and phenanthridone.



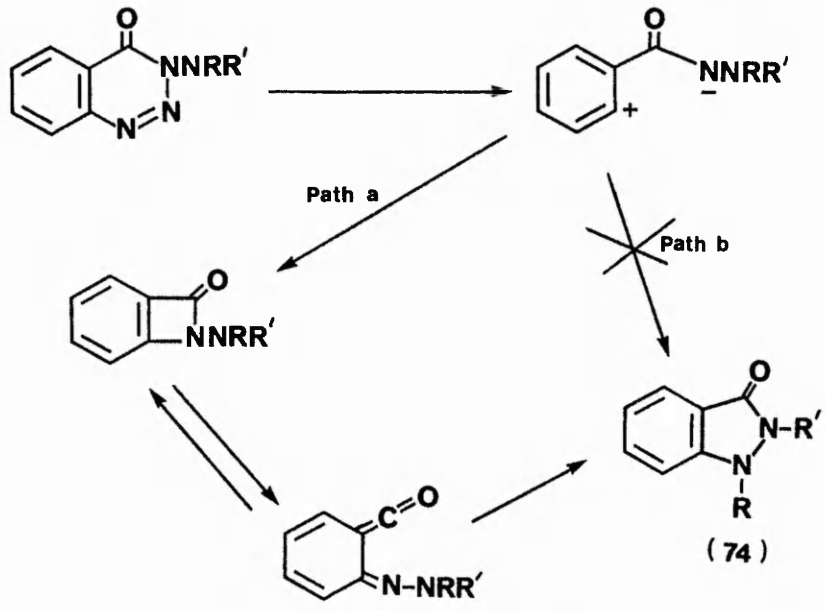
(71)

(72)

(73)

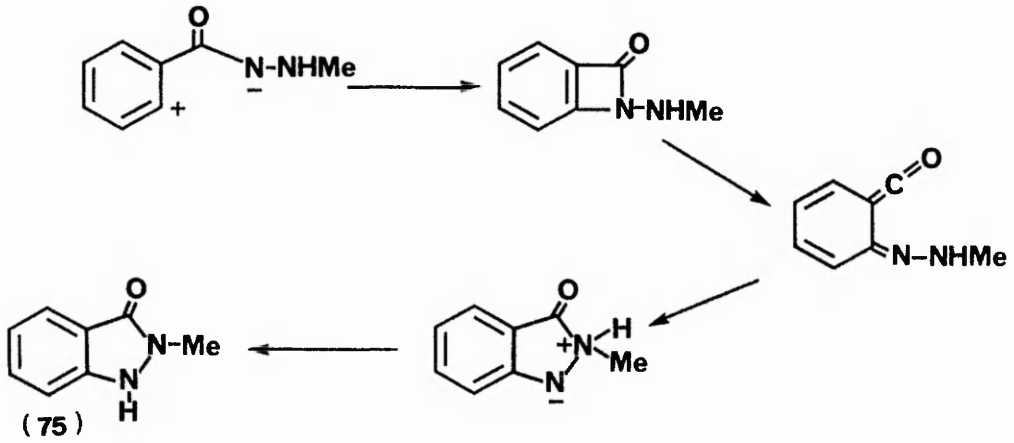
It had been previously noted[49] that in the thermolysis of the parent benzotriazinone the absence of 'anilide' products heralded the formation of the oxazinone. Thermolysis of the parent naphthotriazinone under identical conditions did not yield the expected naphthoxazinone. This discrepancy is thought to be due to the loss of aromaticity involved in forming the iminoketene making the reaction unfavourable.

Further evidence for the participation of the azetinone was supplied by McPaterson and Smalley[56] in their pyrolysis of 3-amino-1,2,3-benzotriazin-4-one. Electrocyclisation of the azetinone/iminoketene, rather than direct cyclisation of the zwitterion, was thought to give rise to the 1,2-dihydroindazol-3-one (74).



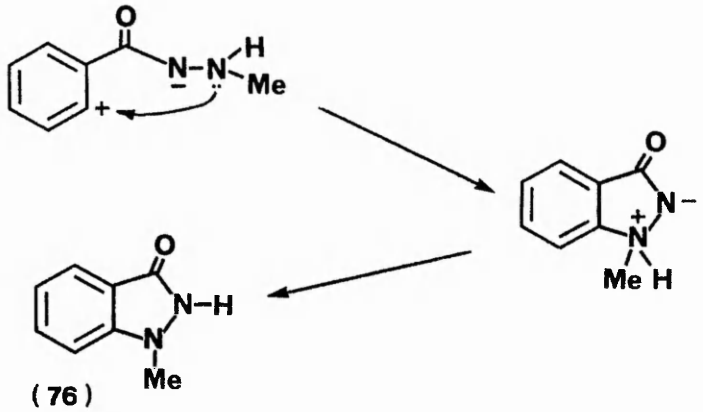
(74)

Confirmation of path (a) was achieved by the decomposition of a variety of 3-substituted benzotriazinones. The isolation of the 2-substituted indazolone (75) in each case proved the existence of the heterodiene intermediate.



(75)

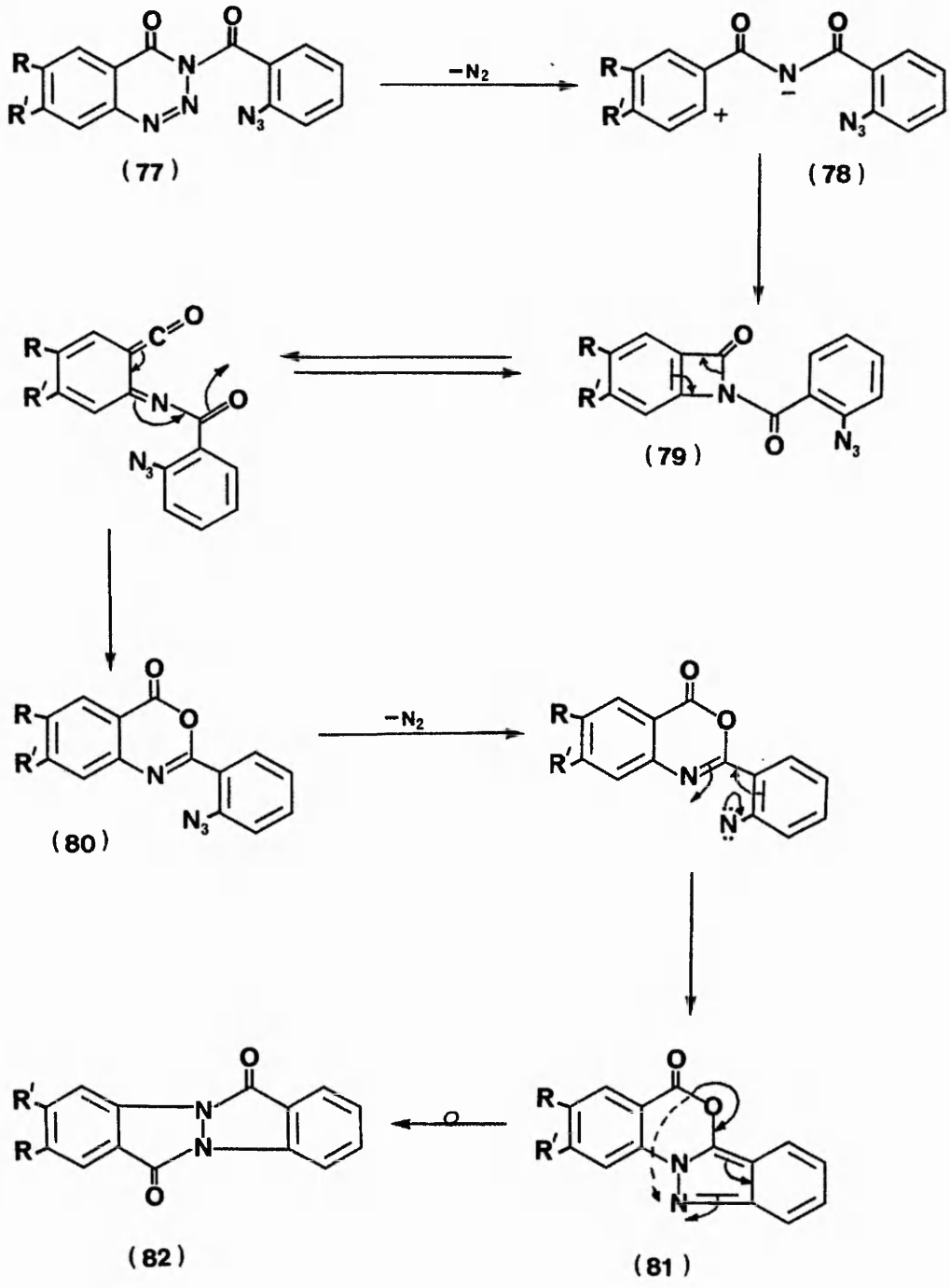
The competing pathway (b) produces the isomeric 1-substituted indazolone (76).



(76)

The decomposition of 3-(2-azidobenzoyl)-1,2,3-benzotriazin-4-one (77) was studied by Alkhader and Smalley[57], and it was shown to undergo the expected deazoniation reaction.

Scheme two:



The initial loss of nitrogen comes, as expected, from the triazinone ring, rather than the azido function. The polar intermediate (78) cyclises to the azetinone (79), the valence tautomer of which can undergo a 6 π electrocyclisation to 2-(o-azidophenyl)3,1-benzoxazin-4-one (80). As reported in a previous communication[58] decomposition to the indazolo[2,3-a][3,1]benzoxazin-5-one (81) and the subsequent rearrangement to the indazoloindazolinone (82) is a favourable reaction (scheme two).

CHAPTER TWO

D I S C U S S I O N

This discussion section is divided into three areas of study.

The first part incorporates the work carried out on the elucidation of the mechanism for the deazoniation of C-6 and C-7-substituted benzotriazinones. The experimental results obtained from this study will be considered in this section.

The second area discussed will be that of the preparation of thieno[3,4-d]-1,2,3-triazin-4-one. During this synthesis a versatile intermediate was obtained, and some time was spent in assessing its potential usefulness as a precursor to other fused heterocycles.

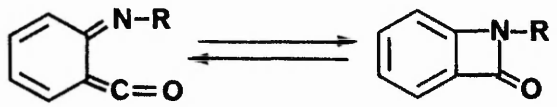
Finally, an exploratory study into the feasibility of synthesising [3,2-d] and [3,4-d] pyrrolo- and furano-1,2,3-triazin-4-ones was investigated.

A study of the deazoniation of C-6 and C-7 substituted benzotriazin-4-ones.

Hitherto, the elevated temperatures necessary to bring about the deazoniation of 1,2,3-benzotriazin-4(3H)-ones have precluded any possibility of kinetic study of the reaction sequence.

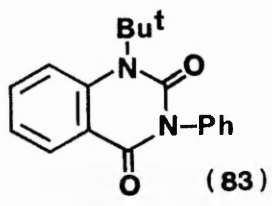
Elucidation of the proposed mechanisms has been centred upon corroborative evidence for the iminoketene (35) from Diels-Alder trapping experiments[46] and the isolation of an adamantyl derivative of the benzazetinone (36)[51].

Further indirect evidence for the existence of the heterodiene, established by Olofson et al[59] in their study of the reaction of benzazetinones with nucleophiles, has shown a ring-chain tautomer equilibrium between (35) and (36) at room temperature.



(35) (36)

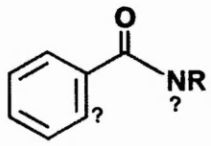
Attempts to trap the iminoketene with maleic anhydride were unsuccessful. However, the azetinone[60] reacted with phenyl isocyanate to give the adduct (83).



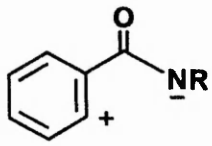
(83)

The authors pointed out that although (83) would be the expected product from a Diels-Alder reaction with (35), a pathway involving nucleophilic attack of the isocyanate on the azetinone could not be excluded.

Efforts to establish the identity of the intermediate (84) have been limited.



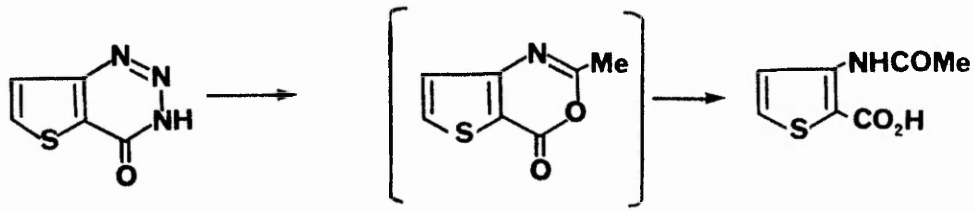
(84)



(84a)

In an endeavour to demonstrate[15] the effect of substituents on the proposed dipolar intermediate (84a), an examination of the decomposition temperatures of nuclear substituted benzotriazinones in comparison to the parent triazinone was undertaken. No significant temperature variation was observed.

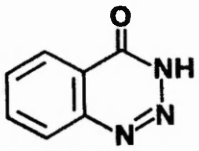
During attempts to acetylate thieno[3,2-d]triazin-7(6H)-one[61] (85) the unexpected 3-acetylaminothiophene-2-carboxylic acid (86) was obtained.



(85)

(86)

This reaction, analogous to the deazoniation of benzotriazinones, occurred at a relatively low temperature of 100°c. Under identical conditions, benzotriazinone (2) underwent deazoniation to give N-acetylanthranilic acid (87).



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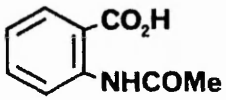
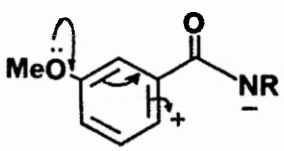


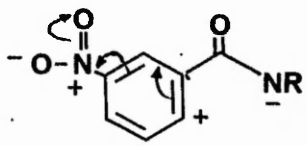
(87)

This novel, low temperature procedure has been applied in this work to the accumulation of kinetic data from the deazoniation reaction of substituted benzotriazinones. A key factor in the clarification of the mechanism is the identity of the intermediate (84).

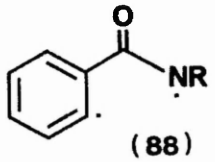
It was envisaged that a kinetic study of the effect of C-6 and C-7 substituents on the rate of deazoniation of the triazinones would define the nature of (84). In the case of a dipolar intermediate, as proposed by Smalley et al[46], the positive charge situated on the aromatic ring would be stabilized by C-6 para and C-7 meta electron releasing groups, thus enhancing the rate of reaction.

Conversely, electron withdrawing groups at these positions would cause a retardation of the rate.





The diradical intermediate (88), suggested by Hey et al[43] would not be expected to show a very large change in the rate from the effects exerted by the substituents.



(88)

Preparation of C6 and C7 substituted benzotriazinones.

The substituted benzotriazinones were prepared by literature methods, diazotisation of o-aminobenzamides being the preferred route.

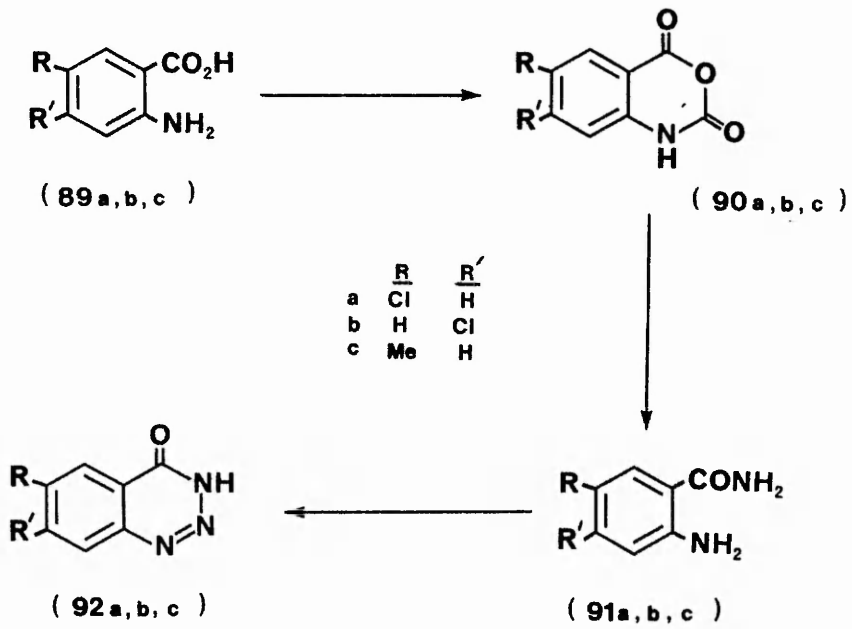
Scheme Three:

The commercially available 5-chloro, 4-chloro- and 5-methylanthranilic acids (89a,b,c) were converted to their respective isatoic anhydrides (90a,b,c) by reaction with 20% phosgene in toluene. Treatment with ammonia[11] afforded the amino benzamides (91a,b,c) which cyclised to the triazinones (92a,b,c) on diazotisation.

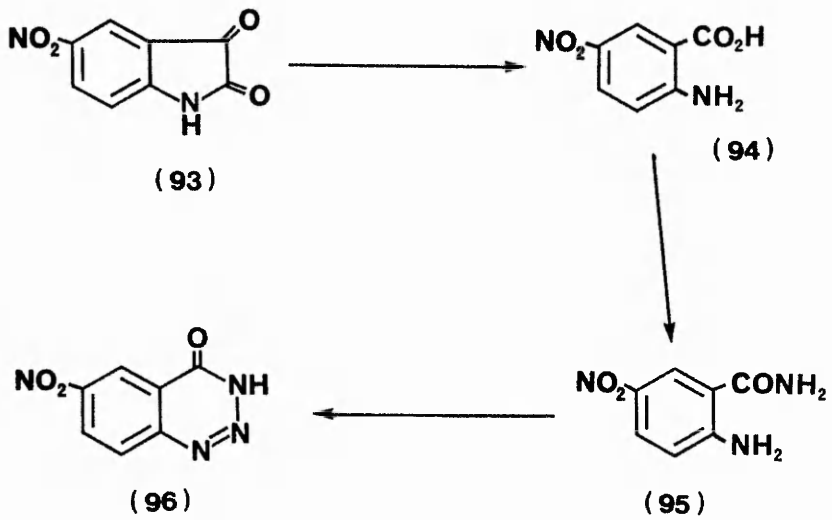
Scheme Four:

5-Nitroisatin (93) was oxidised to 5-nitro anthranilic acid (94) by hydrogen peroxide[62]. Treatment with thionyl chloride, followed by neutralisation with ammonia gave the aminobenzamide (95), which readily gave the required triazinone (96) on diazotisation.

Scheme three:



Scheme four:



Scheme Five:

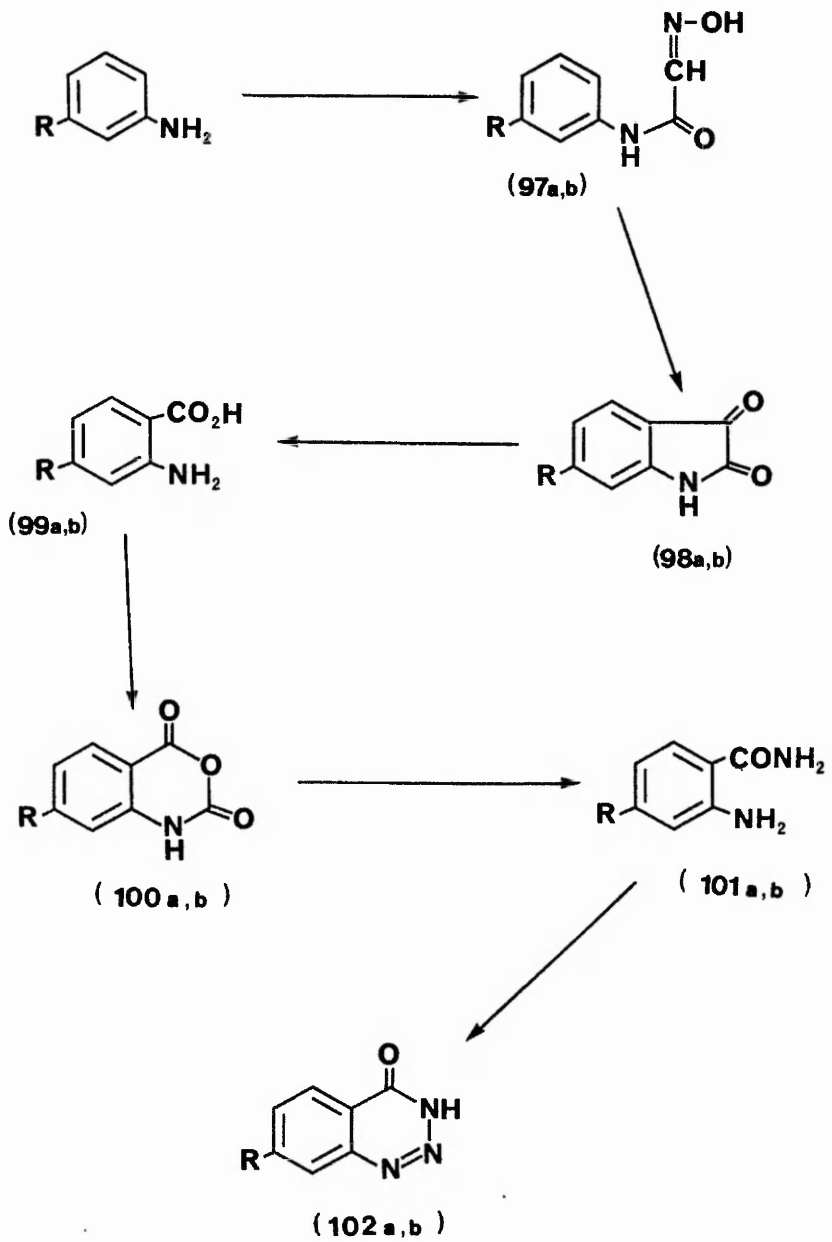
m-Anisidine and m-toluidine reacted readily with chloral hydrate and hydroxylamine hydrochloride[63] to give their respective m-isonitrosoacetanilides (97a,b). Cyclodehydration to the isatin (98a,b) with polyphosphoric acid gave good yields of the ring closed product. Chromium trioxide oxidation[64] to the isatoic anhydride could not be achieved. Oxidation to the anthranilic acid by hydrogen peroxide[62] gave moderate yields of the required 4-methoxy and 4-methylanthranilic acids (99a,b). Reaction with phosgene afforded the isatoic anhydrides (100a,b) and subsequent treatment with ammonia gave the anthranilamides (101a,b). The desired benzotriazinones (102a,b) were prepared in excellent yield by diazotisation.

Scheme Six:

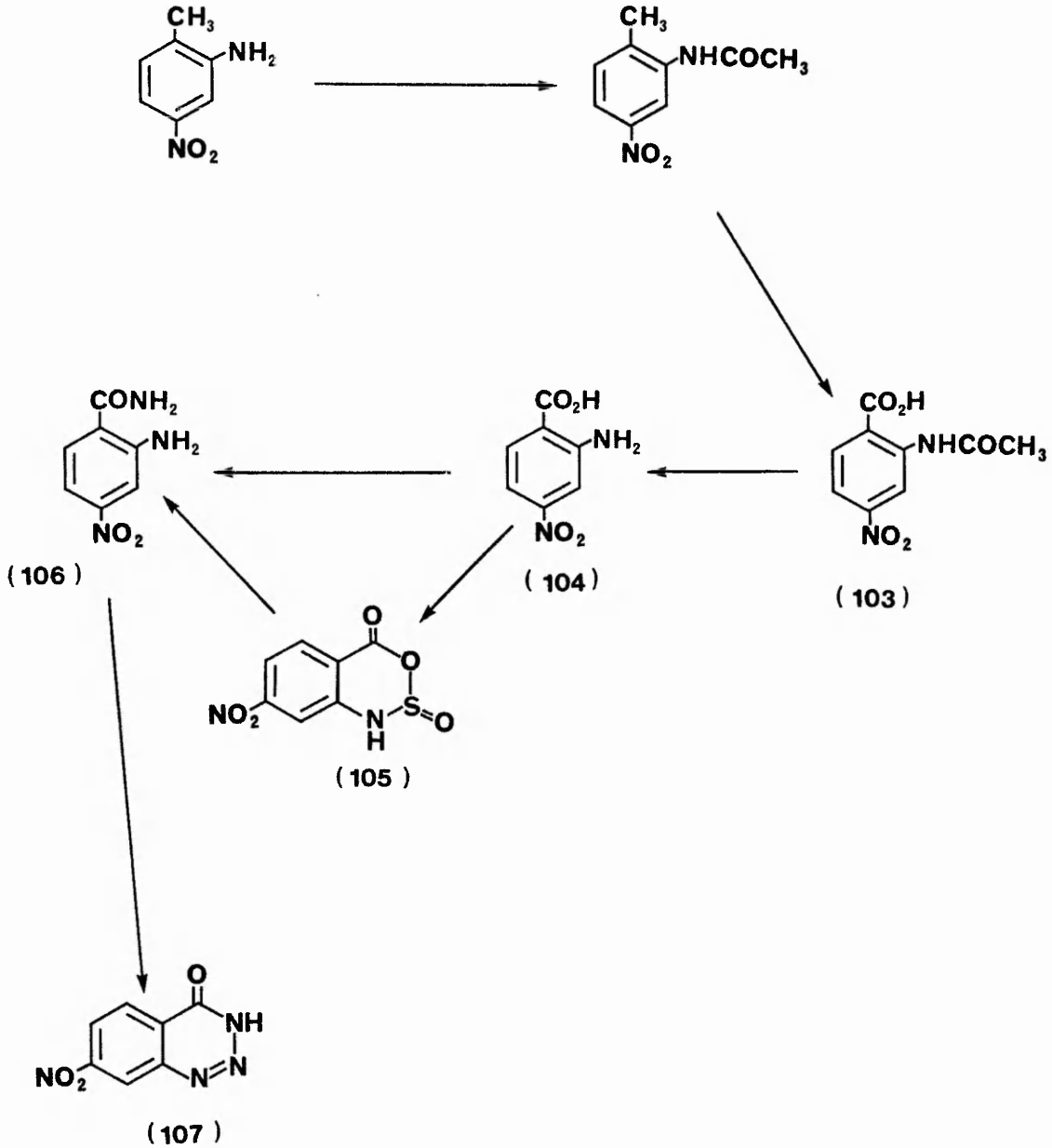
4-Nitrotoluidine was acetylated and then oxidised to 4-nitroacetamidobenzoic acid (103) with potassium permanganate[65]. Removal of the protecting group gave rise to 4-nitroanthranilic acid (104). Conversion to the isatoic anhydride could not be achieved. Reaction of the acid with thionyl chloride, catalysed by dimethyl-formamide, followed by ammonia gave the required amide (106). A cyclic intermediate (105), similar to that proposed by Parker and Fedynyshyn[66] was removed by refluxing in ammonia. Diazotisation of the pure amide afforded 7-nitrobenzotriazinone (107) in high yield.

Scheme five:

a R=OMe , b R=Me



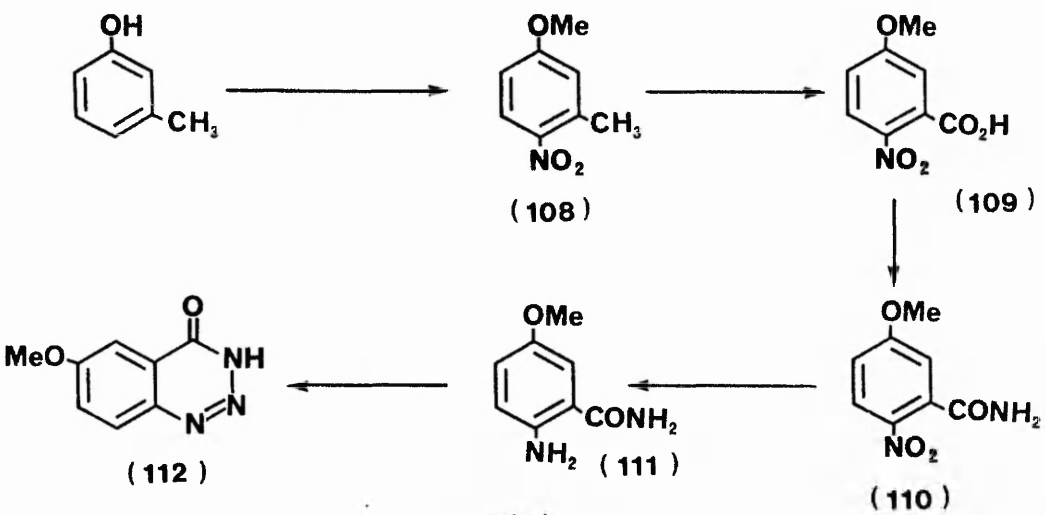
Scheme six:


CH3
NH2
NO2
CH3
NHCOCH3
NO2
CO2H
NHCOCH3
NO2
(103)
CO2H
NH2
NO2
(104)
CONH2
NH2
NO2
(106)
O
O
NO2
N
H
S
O
(105)
O
NH
NO2
N
N
(107)

Scheme Seven:

3-Methyl-4-nitroanisole (108), obtained from m-cresol[67], was oxidised with alkaline potassium permanganate to 5-methoxy-2-nitrobenzoic acid (109). Reaction of the acid with thionyl chloride and then ammonia gave 5-methoxy-2-nitrobenzamide (110) in high yield. Attempts to reduce the nitro group with Raney nickel/hydrogen[15] failed, starting material being recovered. Several other reducing systems were explored, $NaBH_4/Pd/C$[68], Fe_2O_3/NH_2NH_2[69] and Fe/AcOH[70]. Starting material was recovered except for the latter case where reductive acetylation took place. The reducing system of nickel(II) chloride-sodium borohydride[71] converted the nitroamide into 5-methoxy-2-aminobenzamide (111) in good yield. Diazotisation with sodium nitrite afforded the desired 6-methoxy-1,2,3-benzotriazinone (112) (scheme seven).

Scheme Seven:



Kinetic analysis of the deazoniation of C-6 and C-7 substituted benzotriazin-4-ones.

A preliminary investigation into the deazoniation of the prepared benzotriazinones was undertaken. The procedure involved heating the triazinone with acetic anhydride and pyridine on a steam bath for one hour. Isolation of the product, by pouring into ice/ hydrochloric acid, produced a hydrolysis-stable oxazinone, the N-acetylanthranilic acid or a mixture of both products.

The low temperature procedure enabled a detailed kinetic study to be performed on the rate of deazoniation of the prepared triazinones. The decompositions were carried out in a sealed reaction vessel, heated to 82.5°c, and the increasing pressure of the nitrogen evolved was measured as a function of time using a pressure transducer.

Initial results showed the reaction to follow first order kinetics, thus permitting the use of Guggenheim's method[72] to analyse the data. This had the advantage that the initial and final concentrations of the reacting species need not be known, and also that the reaction need only be studied for about two half lives, thus greatly reducing the problems of gas leakage from the reaction vessel.

The rate constants for each compound, detailed in the appendix, were obtained by linear regression analysis of the experimental data (duplicate determinations were carried out). The standard deviations from these results were used to represent the limit of error for each run. Hammett plots were obtained by plotting log k/k_o against the appropriate substituent constant σ (see table one). Table two shows the percentage error for each plot. As expected the lowest errors were obtained for the C-6 para and C-7 meta substituted triazinones.

Table 1.

Subs	Rate const.(k) min	σ-Value meta	σ-Value para	$\log k/k_o$
None	0.020+0.001	-	-	-
6-Me	0.012+0.001	-0.07	-0.17	-0.22
7-Me	0.012+0.001	-0.07	-0.17	-0.22
6-Cl	0.076+0.002	0.37	0.23	0.58
7-Cl	0.102+0.001	0.37	0.23	0.71
6-OMe	0.007+0.0002	0.12	-0.27	-0.46
7-OMe	0.020+0.001	0.12	-0.27	0.00
6-NO_2	0.456+0.013	0.71	0.78	1.36
7-NO_2	0.309+0.006	0.71	0.78	1.18

Table 2.

Figure	Best fit slope value	% Error
1	2.29 + 0.57	24.8
2	1.71 + 0.11	6.5
3	1.87 + 0.22	11.7
4	1.21 + 0.26	20.4

Graphs of Log K/K_o against σ for C-6 and C-7 meta/para substituted benzotriazinones.

Figure 1

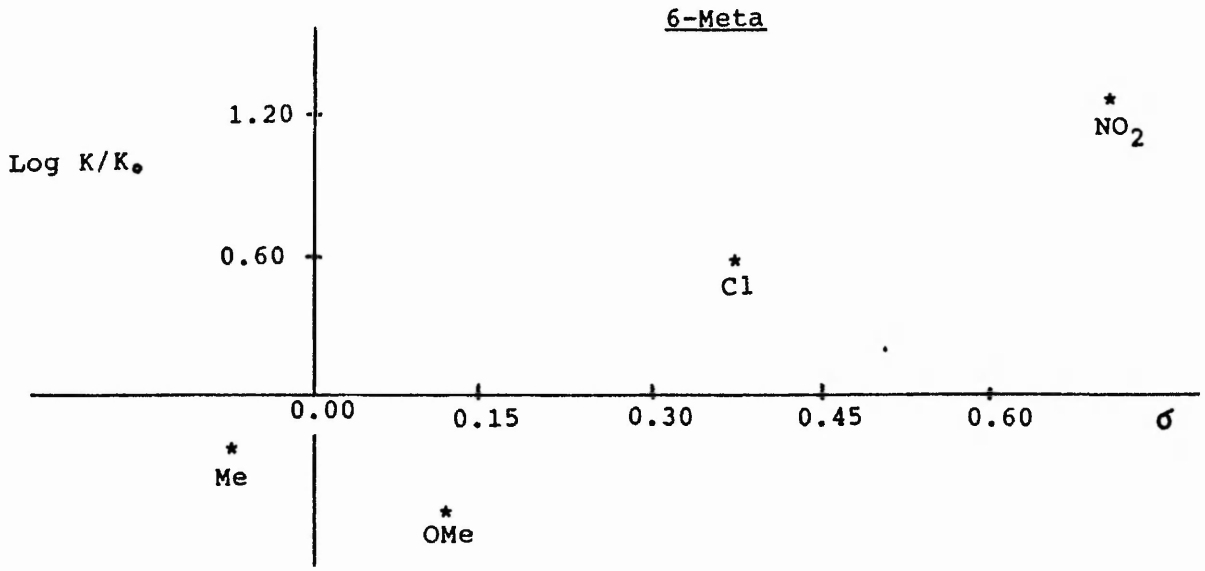


Figure 2

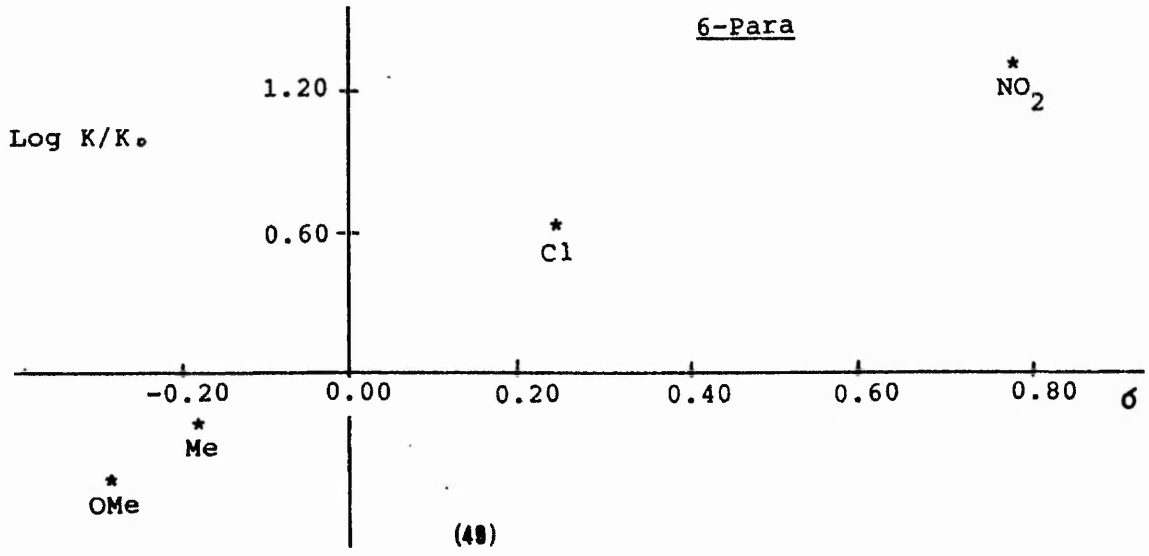


Figure 3

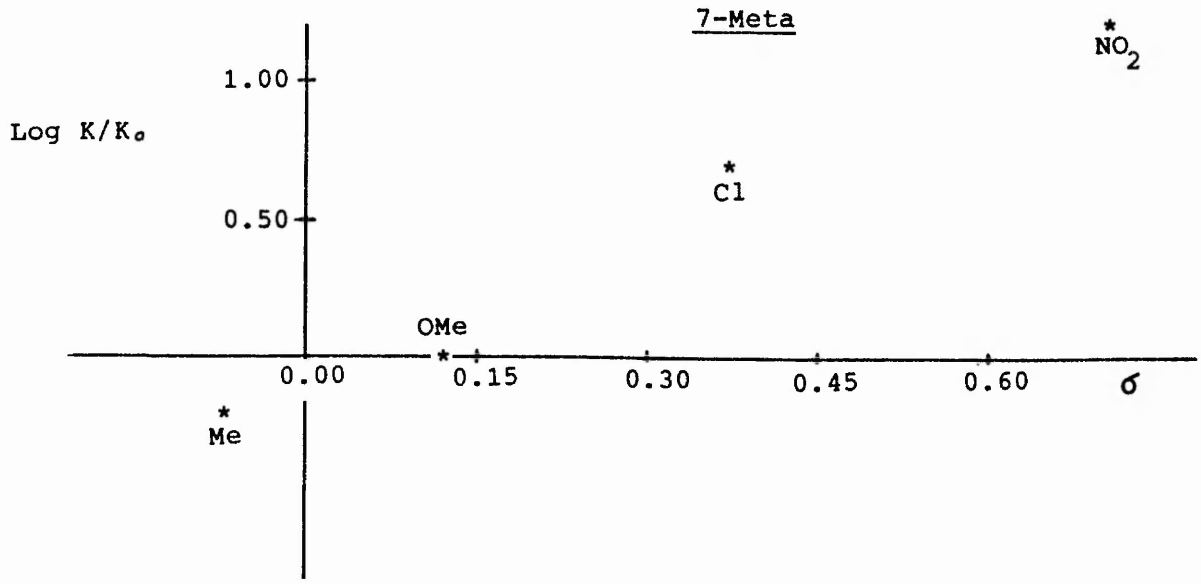
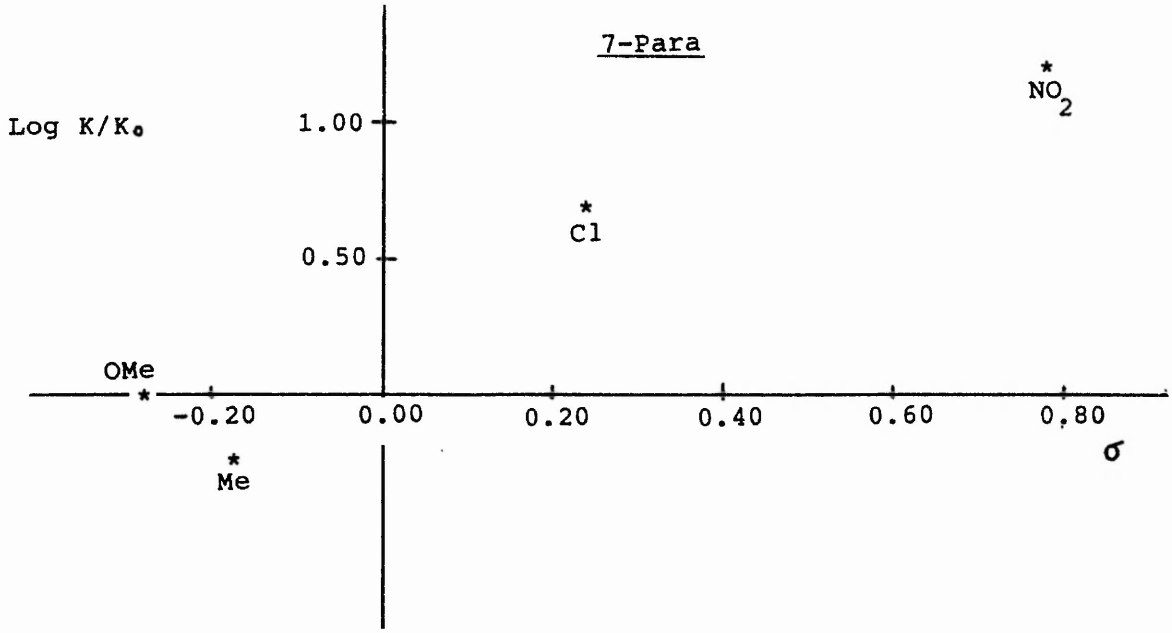
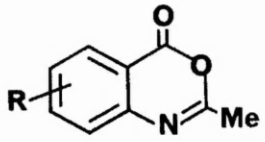


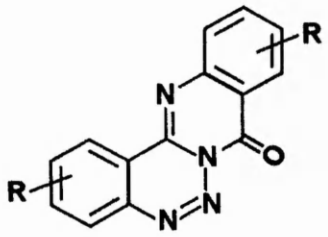
Figure 4



All the C-6 and C-7 substituted benzotriazinones were sucessfully deazoniated by the low temperature procedure. Indeed, a reduction to a reaction temperature of 82.5°C was necessary to obtain ideal kinetic conditions. During this study it was not felt necessary to isolate all the products of deazoniation. Thus, in some cases the insoluble products isolated were minor components. The absence of dienophiles in the reaction mixture dictated that the iminoketene underwent either self cycloaddition to form a 2-methyl-1,3-oxazin-4-one (113) or reacted with another molecule of triazinone to give the oxazinone (114).



(113)

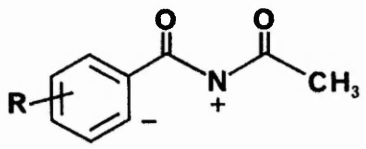


(114)

1,3-Oxazinone or its hydrolysis product, N-acetyl-anthranilic acid, were the products isolated. Although several of the oxazinones were stable to hydrolysis, this stability did not seem to be attributable to the electronic effect of the substituent present.

The Hammett plots obtained from the deazoniation reaction showed a positive slope thereby indicating the reaction site to be negative. This immediately excludes the possibility of the intermediacy of the dipolar species proposed by Smalley *et al*[46].

A dipolar intermediate with a negative charge on the ring is equally unacceptable, since the unfavourable situation of a positive charge being shared between the three electronegative atoms of the side chain would occur.

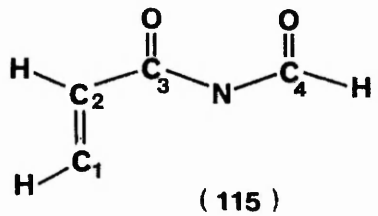


It is therefore proposed that the intermediate is of a diradical nature as suggested by Hey, Rees and Todd[43]. The Hammett plots substantiate this, since the positive gradient indicates excess electron density at the site of reaction and the reaction constants ρ are within the range of free radical reactions.

In an attempt to trap the free radical, deazoniation was carried out in the presence of styrene. No polystyrene was detected. Subsequent trapping experiments, using diphenylsulphide, diphenyl selenide and tetraphenyl hydrazine, all led to the isolation of the normal deazoniation product. The diradical intermediate, being exceedingly short lived , does not survive long enough to react with the trapping agents.

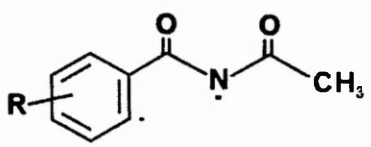
To delineate further the nature of the intermediate ab initio self-consistent field molecular orbital calculations[73] were performed on the fragment CH=CHCONCOH, the C_6H_5 moiety being replaced by HC_2H. The calculations were carried out on both the singlet and triplet states with complete geometry optimisation using the Gaussian 86 programme[74]. The results showed that no stable singlet state existed for either a planar or a non-planar molecule and any attempt at optimisation led to the elimination of the ethyne fragment HC≡CH.

However, the triplet state showed a minimum for both the planar and non-planar structures; the preferred geometry being the non-planar species (115).

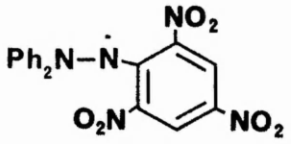


(115)

Spin densities and Fermi contact interaction terms obtained from molecular orbital analysis using Gaussian 86, showed the unpaired electron density to be associated mainly with C1. This would be in agreement with the radical being situated on the aromatic ring in the benzo-triazinone case.



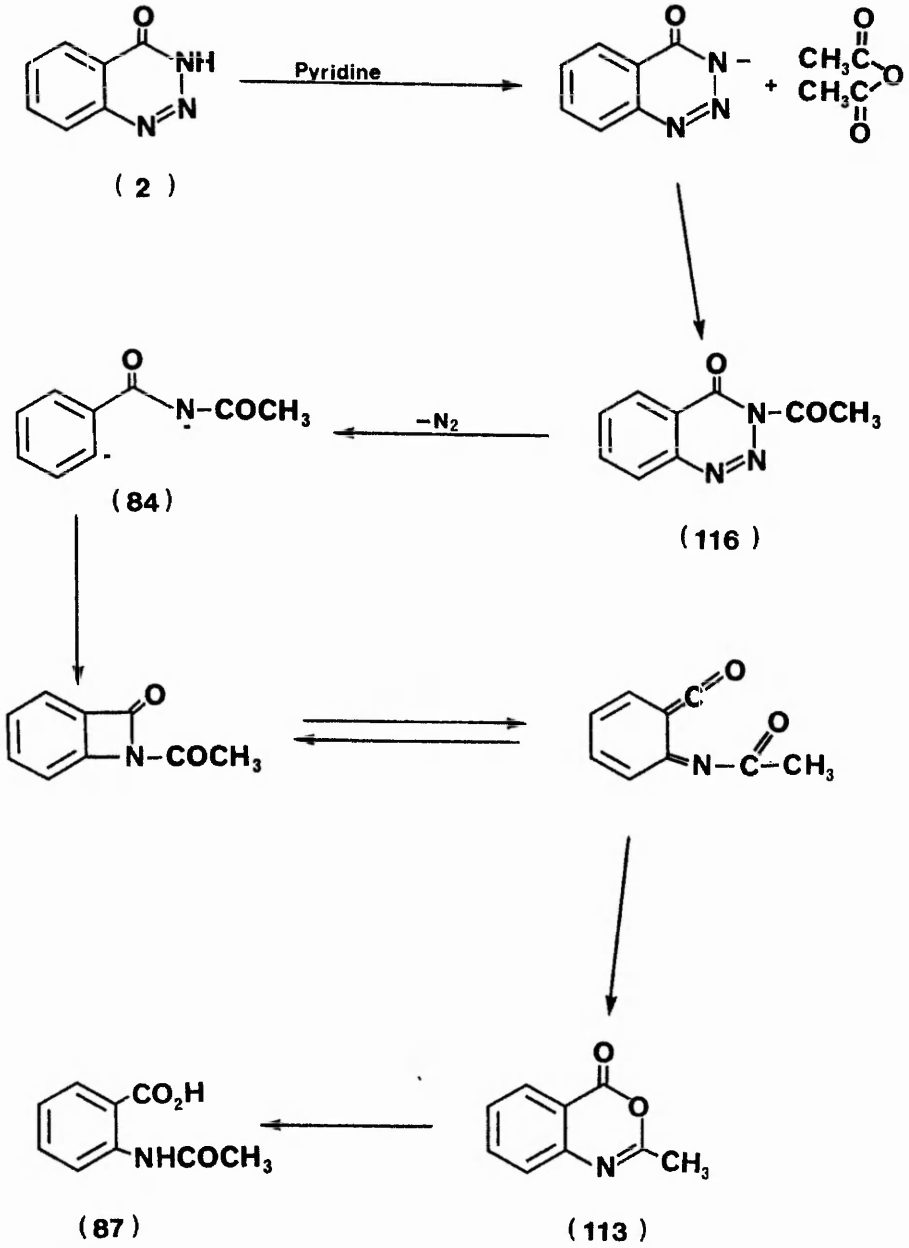
Futher evidence[75] for the free radical nature of the intermediate was obtained by reaction with the diphenyl picrylhydrazyl radical (DPPH).



When added to the deazoniation reaction, the deep violet colouration, produced by the DPPH radical, decolourised as it was trapped by the diradical intermediate.
This direct indication of a free radical prompted an investigation[75] using Chemically Induced Dynamic Nuclear Polarisation (CIDNP) spectroscopy. Unfortunately, no evidence of the diradical could be detected by this method.
This does not, however, exclude the possibility of the intermediate (84) having a diradical nature.

The initial steps of the deazoniation sequence are deprotonation of the triazinone by the base, followed by acylation of the resulting anion (scheme eight).
The rate determining step is assumed to be the loss of nitrogen. As a verification, it was proposed to prepare the N-acetyl derivative of the benzotriazinone (116) and subject it to kinetic analysis.

Scheme eight:



Under the conditions of Gibson and Murray [76] the silver salt of the triazinone is reacted with acetyl chloride to afford the N-acetylbenzotriazinone. In our hands all attempts to repeat this work led to the recovery of the parent triazinone. Table 3 outlines other endeavours to prepare the acetyl derivative. Failure to produce the derivative suggests that acetylation of the anion is unlikely to be the rate determining step. Furthermore, the decrease in negativity that ensues during acetylation is in direct contradiction to the positive gradients of the Hammett plots.

Table 3.

Solvent	Triazinone	Reagents	Conditions	Product
MeOH	0.01 mol	0.001m Ac_2O 0.1m Bn_4NOH	RT	Oxazinone
MeOH	0.01 mol	0.001m Ac_2O 0.1m Bn_4NOH	0°c	SM
PhMe	0.01 mol Na Salt	0.01m CH_3COCl	Reflux	SM
C_5H_5N	0.01 mol	0.01m CH_3COCl	0°c	SM
C_5H_5N	0.01 mol	N-acetylimidazole	RT	SM
C_5H_5N	0.01 mol	0.015m CH_3COCl in C_5H_5N	0°c	SM
C_6H_6	0.01 mol	0.014m CH_3COCl in α-pinene	100°c	SM
--	0.01 mol	0.01m CH_3COCl in C_5H_5N	-5°c	SM
--	0.0034 mol	0.04m Ac_2O	Reflux	SM
--	0.0034 mol	0.04m Ac_2O, cat amount of H_2SO_4	Reflux	N-acetyl anthranilic acid
--	0.0034 mol	0.04m Ac_2O & Sodium Acetate	Reflux	N-acetyl anthranilic acid
C_5H_5N & DCM	0.0068 mol	0.0068m Ac_2O	0°c	SM

The synthesis of 7-methylthieno[3,4-d]-1,2,3-triazin-4-one and the subsequent investigation of its behaviour under deazoniation conditions.

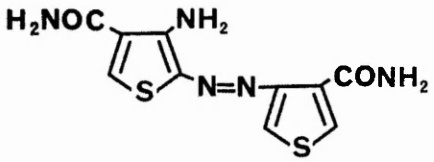
The literature procedure[38] for the preparation of this [3,4-d] ring system affords a highly substituted triazinone. The work described here offers an alternative synthesis resulting in a less substituted triazinone which lends itself to simplifying the analysis of the deazoniation reaction.
This route also afforded an aminonitrile (119) which was seen as a useful precursor to other fused heterocycles. A brief study of the versatility of this intermediate was undertaken.

Preparation of the thieno[3,4-d]triazinone ring system.

Scheme Nine:

The base promoted Michael addition of methyl thioglycolate and acrylonitrile afforded the tetrahydrothiophene (117), subsequent reaction with hydroxylamine produced the aromatic thiophene (118). Initial attempts to hydrate the nitrile of the free base (119) with boron trifluoride /glacial acetic acid[77] failed to produce the amide.

However, hydration using potassium fluoride on alumina[78] converted the aminonitrile to the amide (120) in good yield. Attempts to ring close (120) by reaction with nitrous acid did not yield the desired thieno[3,4-d]-1,2,3-triazin-4-one (121), but gave a high melting solid presumed to be the coupled product (122).



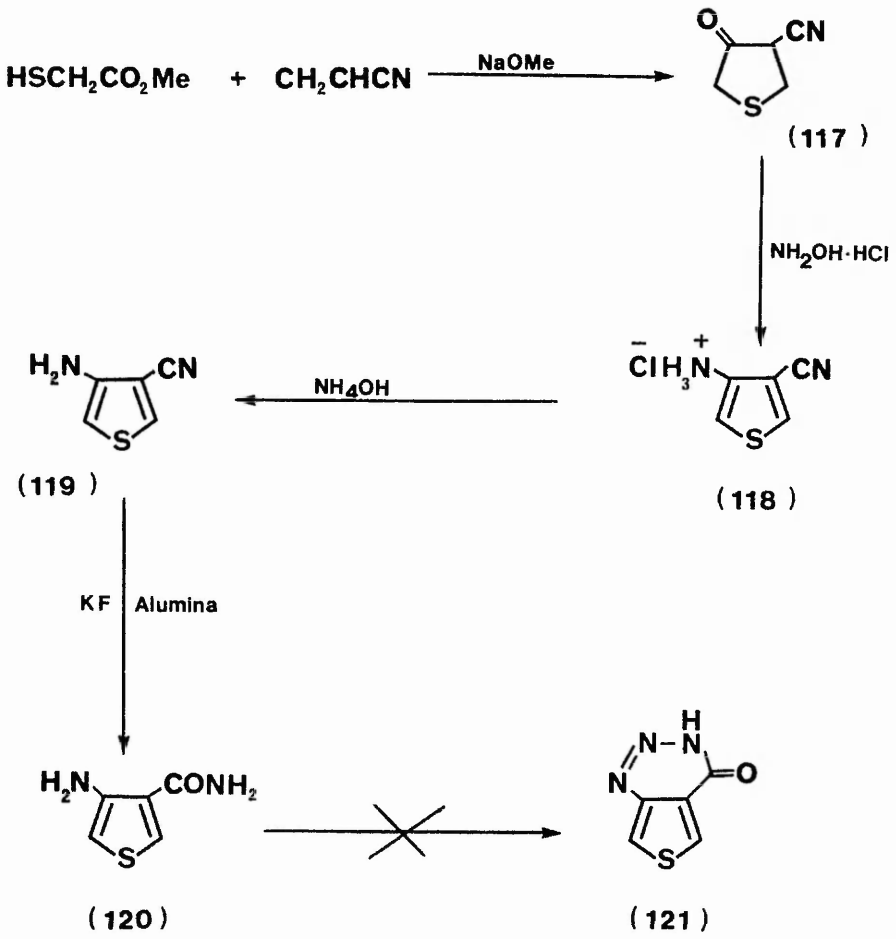
(122)

This compound arises from the electron-donating power of the amino group activating the C-5 position of the thiophene ring towards electrophilic attack. A competing reaction between ring closure to the triazinone and attack from the C-5 position arises. The faster coupling reaction predominates and the azo-compound is formed preferentially to the triazinone.

Deactivation of the amino function, by introduction of a protecting group, would obstruct the ring closure to the triazinone. Thus it was necessary to block the C-5 position of the thiophene ring before diazotisation to the triazinone.

To test the feasibility of this the C-5 hydrogen atom was replaced with a methyl group.

Scheme nine:


HSCH2CO2Me + CH2CHCN
NaOMe
CN
O
S
(117)
NH2OH·HCl
ClH3N
CN
(118)
NH4OH
H2N
CN
(119)
KF Alumina
H2N
CONH2
(120)
N–N
H
N
O
(121)

Scheme Ten:

The Michael addition of methyl thiolactate and acrylonitrile, followed by aromatisation and liberation of the free base afforded 4-amino-3-cyano-5-methylthiophene (126) in good yield. Initial attempts to hydrate the nitrile function with potassium fluoride/alumina[78] produced the amide (127) in very low yield. 4-Amino-3-carboxamido-5-methylthiophene (127) was produced in good yield by hydrolysis with potassium hydroxide in t-butanol[79]. The use of excess hydroxide enabled direct hydration from the amine hydrochloride (125). Diazotisation with nitrous acid afforded the thieno[3,4-d]-1,2,3-triazin-4-one (128) in excellent yield.

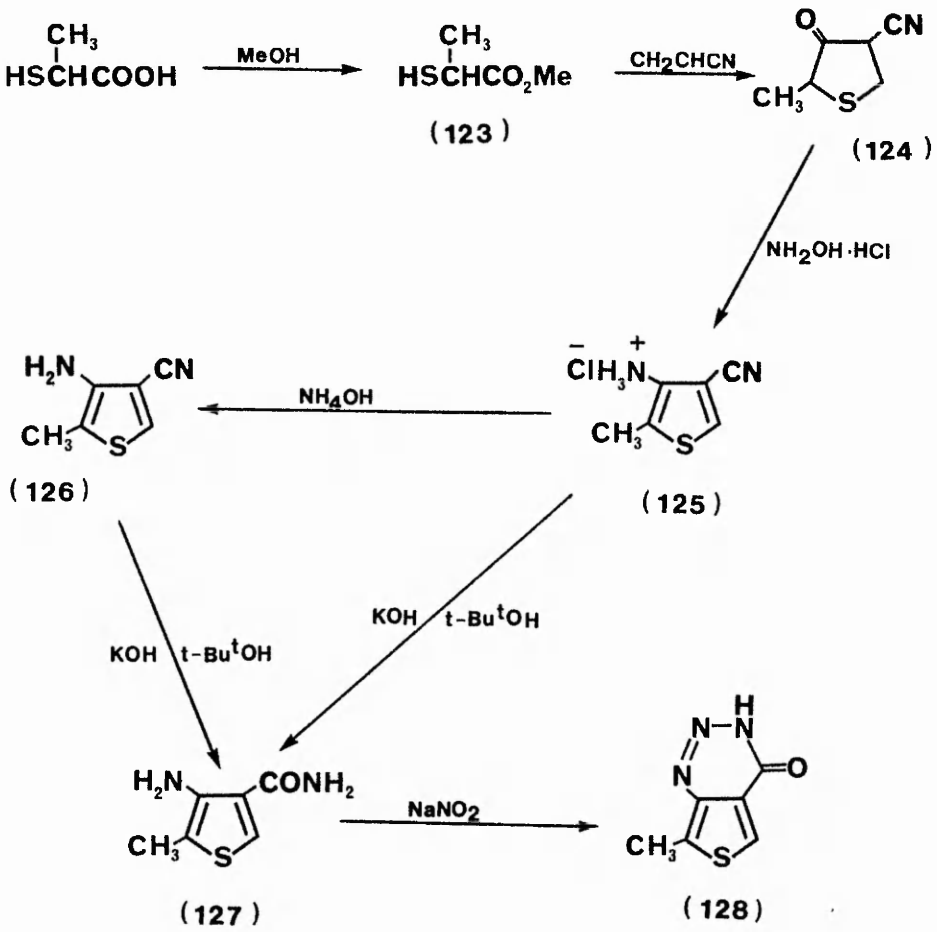
Replacement of the C-5 blocking group with a moiety that could be removed after triazinone formation was envisaged as a method of preparation of the unsubstituted parent triazinone.

The initial attempt utilized the aminonitrile (119) described in scheme nine.

Scheme Eleven:

The amino-function was deactivated by acetylation and the acetyl derivative brominated to give 3-acetylamino-2-bromo-4-cyanothiophene (130).

Scheme ten:


MeOH
CH2CHCN
NH2OH·HCl
NH4OH
KOH t-BuOH
KOH t-BuOH
NaNO2
(123)
(124)
(125)
(126)
(127)
(128)

Attempts to remove the protecting group at this stage by acid hydrolysis did not afford the amino-amide (133) *via* the aminonitrile (131) as was hoped, but caused decomposition of the thiophene ring. Hydrolysis to the N-acetylamino amide (132) was achieved by the procedure of Katritz ky *et al*[80], the potassium hydroxide/t-butanol[79] method being unsucessful. Removal of the acetyl function by acid hydrolysis again caused breakdown of the thiophene ring.

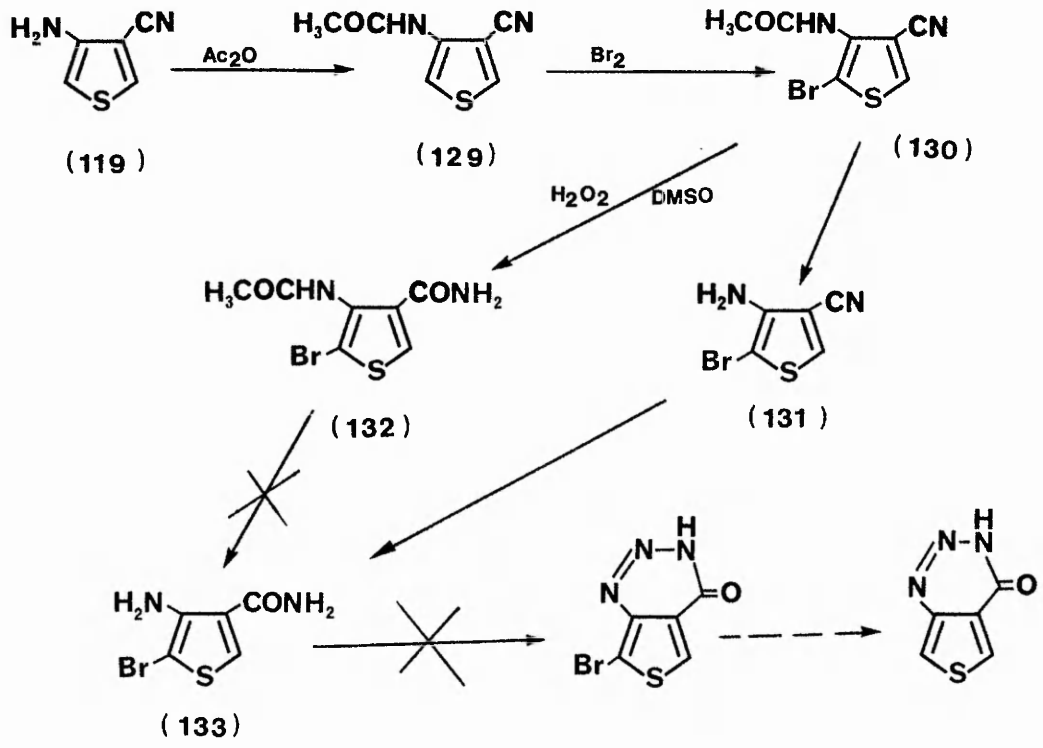
Since the aminoamide appeared to be unstable under these conditions, an alternative protecting group, which could be removed under very mild conditions was employed.

The trifluoroacetyl group can be easily cleaved by very mild alkaline agents. It is so sensitive toward basic hydrolysis that it can be removed by using a weakly basic ion exchange resin[81]. It was envisaged that under these conditions the 4-amino-5-bromo-3-carboxamidothiophene would be isolated.

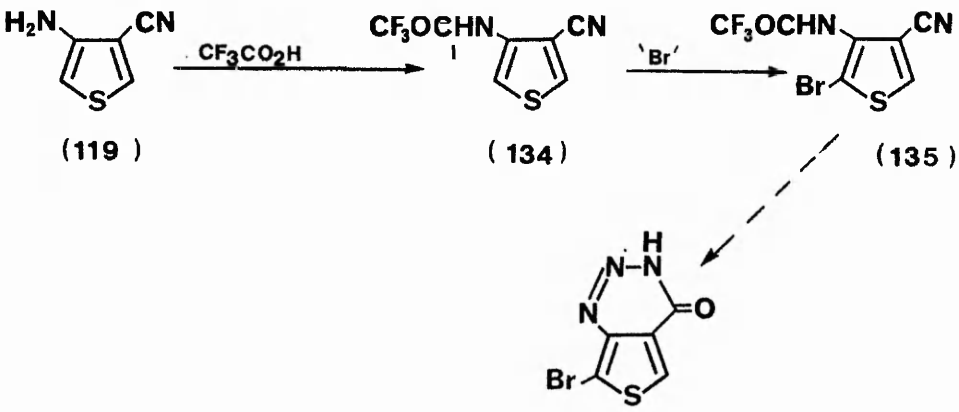
Scheme Twelve:

The trifluoroacetyl derivative (134) of the aminonitrile (119) was readily prepared in moderate yield. Reaction with elemental bromine in glacial acetic acid failed to give the bromo-compound (135). The small scale of the reaction was thought to be the main reason for this failure.

Scheme eleven:



Scheme twelve:



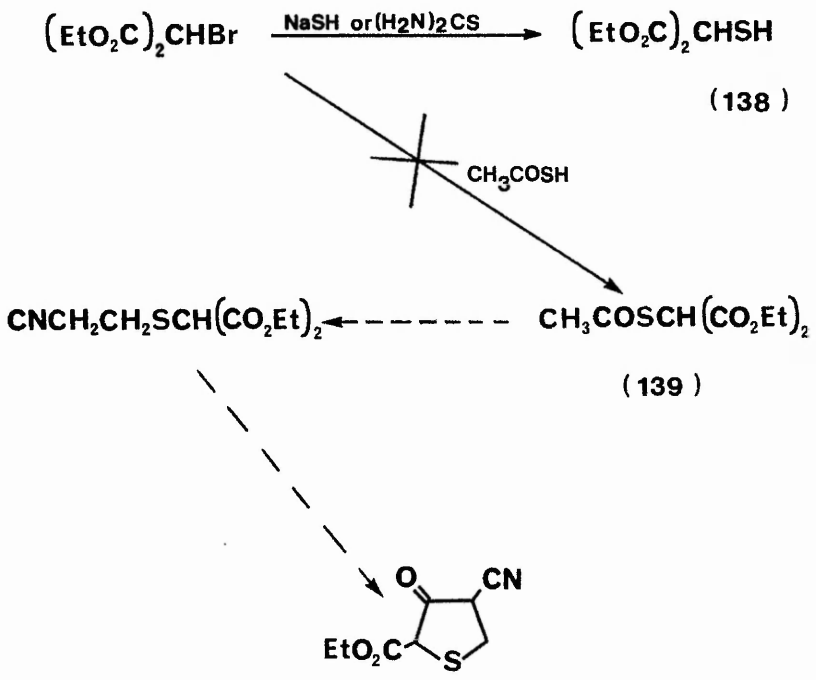
A more convenient reagent for adding small quantities of bromine is available in pyridinium bromide perbromide. However, bromination did not take place and starting material was recovered. Reaction with N-bromosuccinimide also failed to give the desired bromo compound. The reason for this is thought to be a combination of steric hindrance and deactivation of the C-5 position by the strong electronegative nature of the trifluoroacetyl group.

A new approach using a carboxyl group as a blocking species at C-5 was envisaged, since removal by decarboxylation after ring closure should produce the parent triazinone. An initial attempt at preparing the acid by potassium permanganate oxidation of 3-acetylamino-4-cyano-2-methylthiophene (136) was unsuccessful and starting material was recovered.

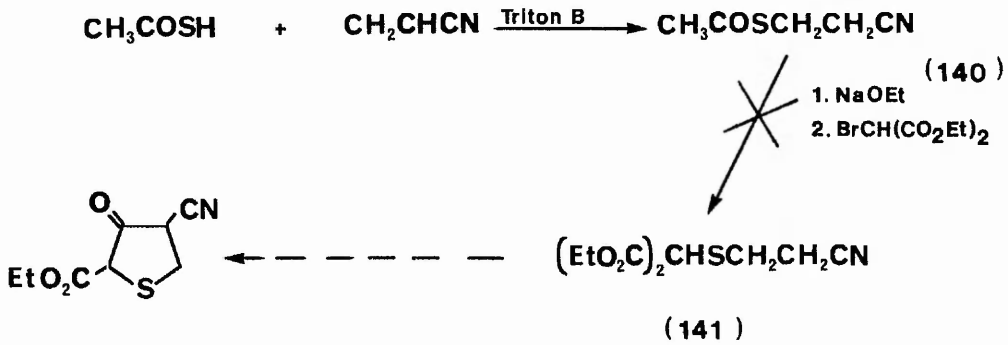
(136) (137)

An alternative possibility was to introduce an ester function at C-5. Removal, by a mild hydrolysis method to give the acid, would perhaps leave the triazinone linkage intact. Decarboxylation would then afford the unsubstituted triazinone.

Scheme thirteen:



Scheme fourteen:



Introduction of the ester group was thought to be most convenient before cyclisation to the tetrahydrothiophene.

Scheme Thirteen:

Formation of the mercapto ester (138) was not achieved upon reaction of diethyl bromomalonate with either sodium hydrogen sulphide or thiourea; starting material was recovered in both cases. The S-acetylmercapto ester (139) was not obtained by addition of potassium thiolacetate to diethyl bromomalonate.

An alternative route was envisaged, in which 2-cyanoethyl thiolacetate (140) upon esterification would give the desired mercapto ester.

Scheme Fourteen:

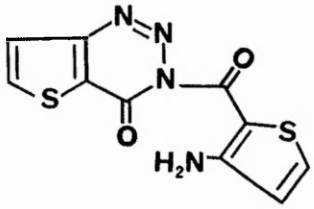
By modifying the conditions of Crouch and Werkman[82], the cyanoethylation of thiolacetic acid, catalysed by Triton B, afforded a high yield of 2-cyanoethylthiolacetate (140). Formation of the anion followed by reaction with diethyl bromomalonate did not produce the required 2-cyanoethylmercapto ester (141), starting material being recovered.

The results expected from this part of the work did not warrant the expenditure of time necessary for its completion, therefore this section was abandoned.

An investigation into the reaction conditions required to achieve the deazoniation of 7-methylthieno[3,4-d]-1,2,3-triazin-4(3H)-one.

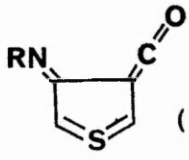
The low temperature deazoniation procedure has been successfully employed for both 1,2,3-benzotriazin-4-one (in the present work) and thieno[3,2-d]-1,2,3-triazin-4-one[61]. The isolated products under these conditions are the N-acetylanthranilic acid and the N-acetyl(amino)thenoic acid respectively, the oxazinones being unstable to the aqueous workup.

The thieno[3,2-d]triazinone[61] when deazoniated at higher temperatures in the absence of dienophiles, undergoes a condensation of the iminoketene with starting material to give the product (142).



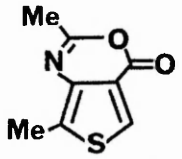
(142)

For the thieno[3,4-d]triazinone to undergo deazoniation, via the azetinone and the iminoketene, the potentially unfavourable sulphur IV tautomer (143) of the azetinone must be an intermediate.

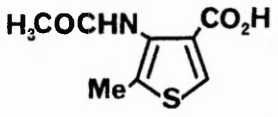


(143)

The products expected from the low temperature method would be either the oxazinone (144) (if it were stable to hydrolysis) or the N-acetyl acid (145).

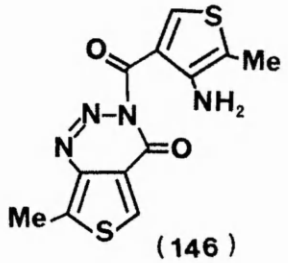


(144)

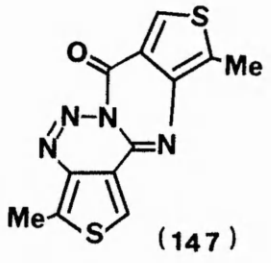


(145)

If higher temperatures are required to bring about deazoniation, then a condensation reaction leading to the product (146) or the dehydrated derivative (147) would be anticipated products.



(146)



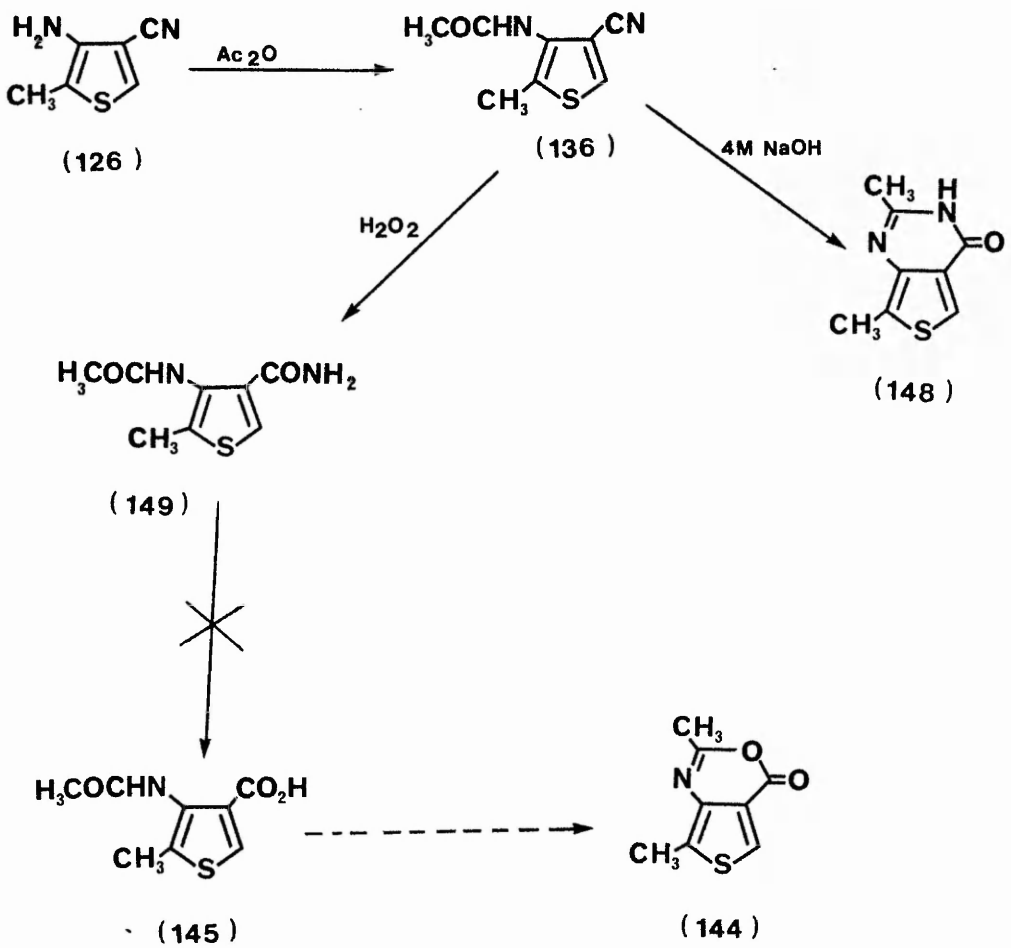
(147)

To aid identification of the products formed it was decided to prepare reference samples of both the acid (145) and the oxazinone (144).

Scheme Fifteen:

4-Amino-3-cyano-5-methylthiophene (126) was acetylated (136) and then hydrolysed with 4M sodium hydroxide. The product obtained was not the expected amide but a pyrimidine (148) formed by intramolecular dehydration of the amide.

Scheme fifteen:



Hydrolysis with potassium hydroxide in t-butanol[79] also afforded the pyrimidine. 3-Acetylamino-4-carboxamido-2-methylthiophene (149) was obtained by hydration of the nitrile function with hydrogen peroxide in dimethyl sulphoxide[80]. Preparation of the acid (145) by diazotisation of the amide failed to give the desired product, starting amide being recovered.

Scheme Sixteen:

A more suitable mode of preparation of the oxazinone (144) was envisaged beginning with the Michael addition of methyl acrylate and methyl thiolactate to give the diester (150). A base induced Dieckmann condensation afforded the tetrahydrothiophene (151). Aromatisation and liberation of the free base (153) were followed by protection of the amino function to give 4-acetylamino-5-methyl-3-methoxycarbonylthiophene (154). Hydrolysis of the ester was achieved by reaction with potassium bicarbonate in methanol. Ring closure of the acid (145) by refluxing in acetic anhydride afforded the 2,7-dimethylthieno[3,4-d]-1,3-oxazin-4-one (144) in moderate yield.

The initial attempt to deazoniate the thieno[3,4-d]-1,2,3-triazinone (128) at low temperature resulted in a compound being formed which did not spectroscopically resemble any of the expected products (table four).

Scheme sixteen:

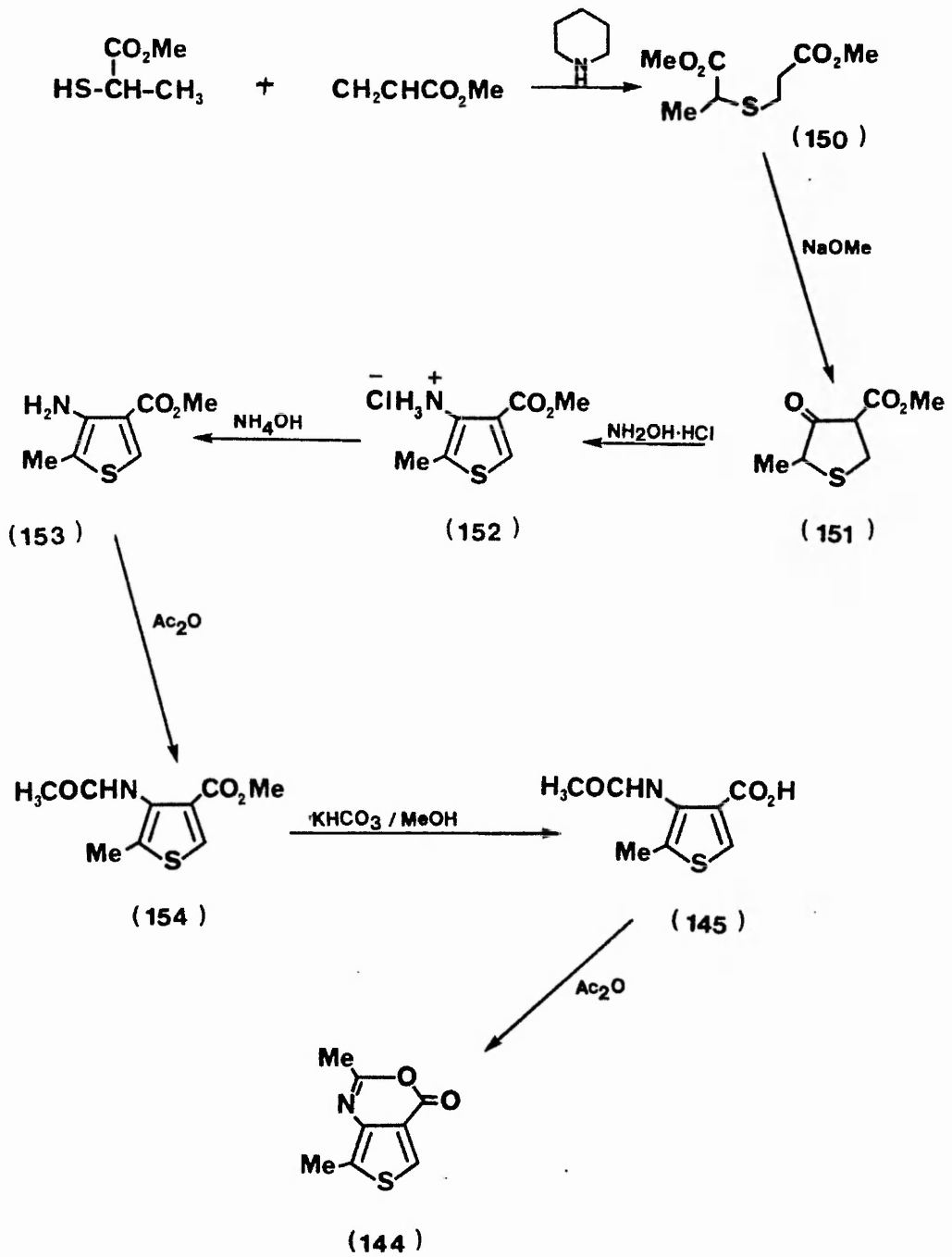


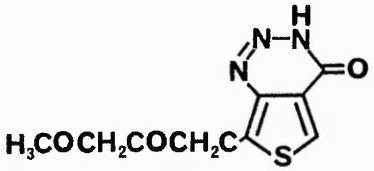
Table 4.

Comparison of the spectral data obtained from the unknown product Vs 7-methylthieno[3,4-d]triazinone.

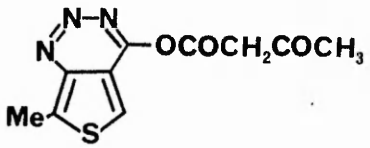
	Thienotriazinone	Unknown
Rmm	167	251
Mpt	217-218°c	200-201°c
IR	3100cm sharp (NHst) 1660cm broad, strong (C=O) 1540cm medium (NHdef)	3350cm sharp, medium 3100cm sharp, medium 1750cm sharp, strong 1730cm broad, strong 1530cm medium
^{1}H	3.0(3H, s, $ArCH_3$) 3.5(1H, br, exchanges with D_2O, NH) 8.2(1H, s, ArH)	2.5(3H, s) 2.8(3H, s) 7.9(1H, s) 8.1-8.2(1H,s)
^{13}C	11.95 - CH_3 141.03 - C2 143.37 - C3 122.98 - C4 122.98 - C5 153.68 - CO	21.56 25.39 120.77 121.87 123.37 149.53 157.07 158.23 169.40 171.54
Mass Spec.	CI 168 M+H 140 124	CI: 252 M+H, 238, 210, 193, 168, 151, 141, 125 EI: 251, 209, 168, 151, 141, 124, 94, 70, 43, 28

Elemental analysis and mass spectroscopic fragmentation data of the unknown compound indicated that deazoniation had not taken place. A molecular formula of $C_{10}H_9N_3O_3S$ was assigned. A positive Lassaigne's test for sulphur was obtained and comparison of the spectroscopic data of the unknown compound against that of the starting material suggested that the triazinone ring was intact. The molecular formula of the extra fragment must be $C_4H_5O_2$. This fragment could easily be introduced to the triazinone molecule as either an acetoacetyl group or two acetyl moieties.

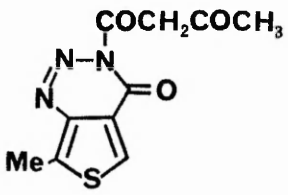
Of the four acetoacetyl structures possible (155a) is the most unlikely, since it would involve acylation of the least electronegative atom. Compound (155b) involving O-acylation of the thienotriazinone is also an unlikely candidate for this reaction product.



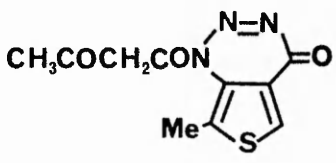
(155a)



(155b)



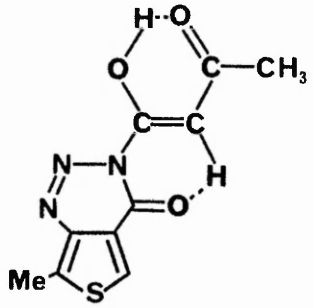
(155c)



(155d)

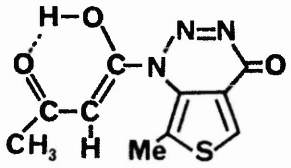
O-Acylation of benzotriazinone[83] was proposed but the author could not provide evidence substantiating this suggestion. A later study by Gibson and Murray[76] proved that acylation occurs solely at the N-3 nitrogen. Neither of the stuctures (155a) or (155b) are likely to be the unknown as their expected spectra would not agree with that observed.

The N-3 acetoacetyl compound (155c) could arise from the N-acetylation of the thienotriazinone. Abstraction of an acidic proton on the acetyl methyl by the base causes a further acetylation to form the acetoacetyl group. The keto-enol tautomerisation exhibited by this molecule makes a reasonable fit with the experimental data (3350cm^{-1} enolic OH_{st}), although correlation of the ^{13}C nmr with that of the starting material shows a deviation for the peaks corresponding to the C4-N1 junction and the aromatic methyl.



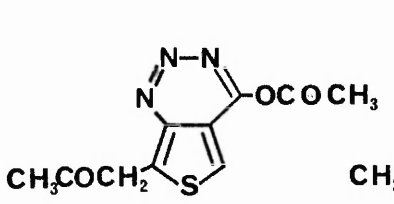
This infers that the new fragment must affect these positions. Clearly this would be difficult for the acetoacetyl group at N-3.

The final acetoacetyl structure (155d) involves acylation at the N-1 nitrogen. The spectral data for this compound would be expected to compare closely to that of the unknown compound, as again an enolic form would exist.

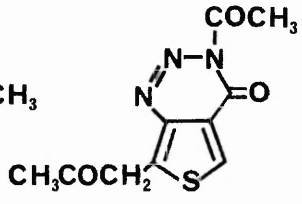


The ^{13}C nmr peak positions of the C4-N1 junction and the aromatic methyl would clearly be affected in this case. However, acylation in the N-1 position has never been reported and this must cast some doubt on the validity of this structure.

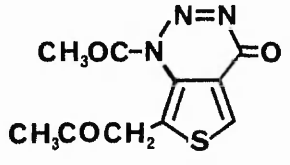
Introduction of the extra fragment to form a diacetyl compound can give three possible structures:



(156a)



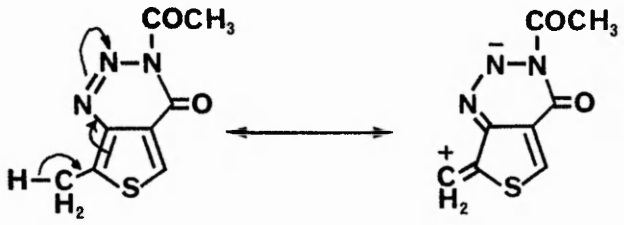
(156b)



(156c)

The unfavourable situation of O-acylation taking precedence over N-acylation would exist for the formation of structure (156a). As already mentioned there are no reports of selective O-acylation in the benzotriazinone series. This, along with the expected spectral data for the compound, makes this unlikely as a candidate structure.

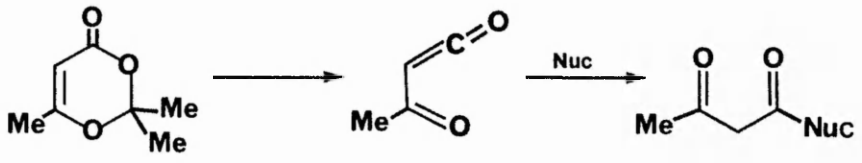
Formation of (156b) could involve either, initial acylation of N-3 followed by a second attack caused by the electron withdrawing effect exerted by the azo function on the methyl group:



or, by the azo function causing initial attack at the methyl group, followed by a subsequent attack at N-3. Neither of these routes can be applied to (156c), thereby making its formation unlikely.
Thus, of the two structures the N-3 acetyl (156b) is the most plausible, but the N-1 acetyl compound (156c) would be expected to give a closer correlation to the experimental data since an enolic structure can also be envisaged.

In an attempt to resolve this problem of identification of the unknown 'deazoniation' product, it was proposed to prepare the acetoacetyl compound by reaction of the thienotriazinone with diketene. The initial experiment was carried out using the residue of an old batch of diketene, which, although it had deteriorated, was thought usable. A two-spot mixture was obtained which, when

compared by tlc, was shown to be mostly starting material. The second tlc spot had an identical rf value to that of the 'acetoacetyl' product. Unfortunately, it was not possible to obtain further supplies of diketene commercially, and a substitute had to be used.
The diketene acetone adduct, 2,2,6-trimethyl-1,3-dioxen-4-one (157) is stable at room temperature, but decomposes when heated above 100°c to provide acetyl ketene (158) and acetone.



(157) (158)

Heating the triazinone and diketene adduct in high boiling solvents, such as xylene, diphenyl ether and 3,5-lutidine, to temperatures ranging from 130-180°c, did not afford the desired acetoacetyl compound. Starting material was recovered in each case. Due to the inability to obtain the acetoacetyl compound, it was proposed to prepare the N3-acetylthienotriazinone (159). Addition of a second mole of acetylating agent would then either attack the existing acetyl group to form the acetoacetyl compound, or substitute the aromatic methyl to give the diacetyl compound (156b). The action of acetic anhydride alone on thieno-[3,4-d]triazinone did not afford the acetyl derivative, starting material being recovered.

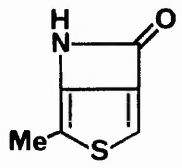
Data from the GC-MS spectra of the unknown compound, obtained from the low temperature deazoniation reaction, suggested the existence of the monoacetyl derivative. It is possible that under mass spectroscopy conditions some decomposition could have occurred to give the acetyl derivative. It was therefore thought possible that the original low temperature reaction initially forms the acetyl derivative which is then further acetylated to the product.

A repetition of this reaction, carried out at room temperature, gave the 'acetoacetyl' compound as the only product. Acetylation under the conditions of Gibson and Murray[76], *via* the sodium salt, also failed, liberation of the free base by hydrolysis of the salt giving the parent triazinone. Use of a more reactive acetylating agent, such as acetyl chloride in the presence of base, again failed to give the required acetyl compound. Finally, formation of the thienotriazinone anion, by reaction with sodium hydride followed by addition of acetyl chloride did not produce the acetyl derivative, starting material was regenerated.

It was decided at this juncture that, due to lack of time, the identity of the low temperature deazoniation product could not be investigated further. A more important requirement was to explore the possibility of bringing about the deazoniation of thieno[3,4-d]-1,2,3-triazin-4-one.

It was envisaged that much higher temperatures would be required since considerable extension of the reaction time at the lower temperature range afforded the undeazoniated product.

Use of the reaction conditions that successfully achieved deazoniation of thieno[3,2-d]triazinone, resulted in recovery of starting material in this case. There was no evidence for the self addition product. This clearly demonstrates that the energy barrier that would need to be overcome for the sulphur IV iminoketene to be formed (or some other, at present unrecognised, factor) makes deazoniation of thieno[3,4-d]-1,2,3-triazin-4-one very unfavourable. Evidence that the reaction may occur during mass spectral examination was obtained from the peak at 140 m/e corresponding to the thienoazetinone (160), (mass 139).

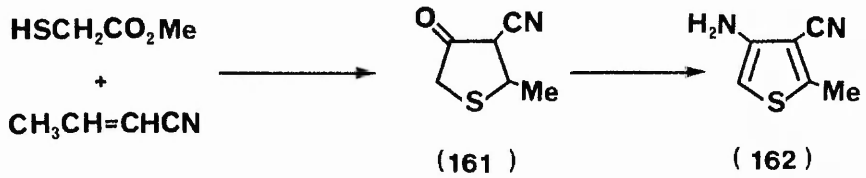


(160)

<u>An investigation into the versatility of the intermediate aminonitriles.</u>

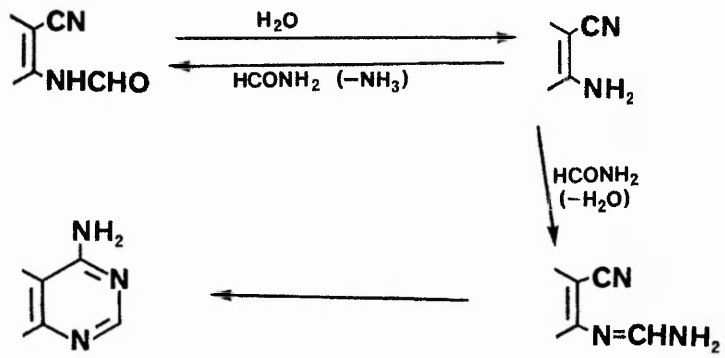
Aminonitriles are synthetically useful intermediates by virtue of the ease with which they can be converted to other condensed heterocyclic systems[84]. Formation of pyrimidines and the partially reduced dihydropyrimidines from o-aminonitriles are well documented[84].

A preliminary study into the accessibility of the above compounds from 4-amino-3-cyanothiophene and its methylated derivatives was undertaken. For the sake of completeness the 2-methyl congener of 4-amino-3-cyanothiophene was prepared. The Michael addition of methyl thioglycolate and crotononitrile afforded the tetrahydrothiophene (161). Aromatisation, followed by liberation of the free base furnished the 2-methyl-4-amino-3-cyanothiophene (162) in good yield.



(161) (162)

An old and sometimes inefficient method of preparing 4-aminopyrimidines is the action of formamide on o-aminonitriles. The yields vary from excellent to poor depending on the degree of decomposition that occurs during reaction. Also, large quantities of starting aminonitrile are often recovered due to formylation of the amino function by amide exchange, followed by hydrolysis back to the amine during workup. The o-cyanoformamidine intermediate (163) formed by addition of the aminonitrile to formamide followed by elimination of water, cyclises under the reaction conditions to a condensed 4-amino-pyrimidine (164).

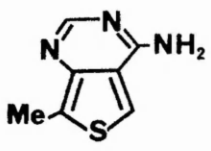


(164) (163)

Formation of the intermediate (163) can be facilitated by promoting dehydration[85] and acetic anhydride is often added for this purpose. Reaction of 4-amino-3-cyanothiophene with formamide resulted in decomposition of the thiophene ring. An attempt to aid the reaction by addition of acetic anhydride resulted in isolation of a small quantity of the N-acetyl aminonitrile, decomposition being the major reaction.

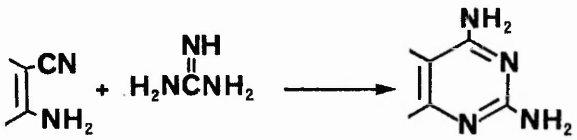
Direct interaction of an aminonitrile with an amidine[86] by loss of ammonia also leads to a 4-aminopyrimidine via the intermediate formamidine (163). Formamidine itself is used in the form of its acetate, since unlike the case of the deliquescent hydrochloride, it is not necesary to liberate free formamidine prior to condensation.

4-Amino-3-cyano-5-methylthiophene on reaction with formamidine acetate did not afford the pyrimidine (165); possibly hydrolysis of the nitrile occurred.

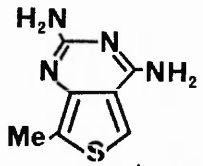


(165)

2,4-Diaminopyrimidines may be prepared by addition of guanidine hydrochloride to o-aminonitriles.



(166)

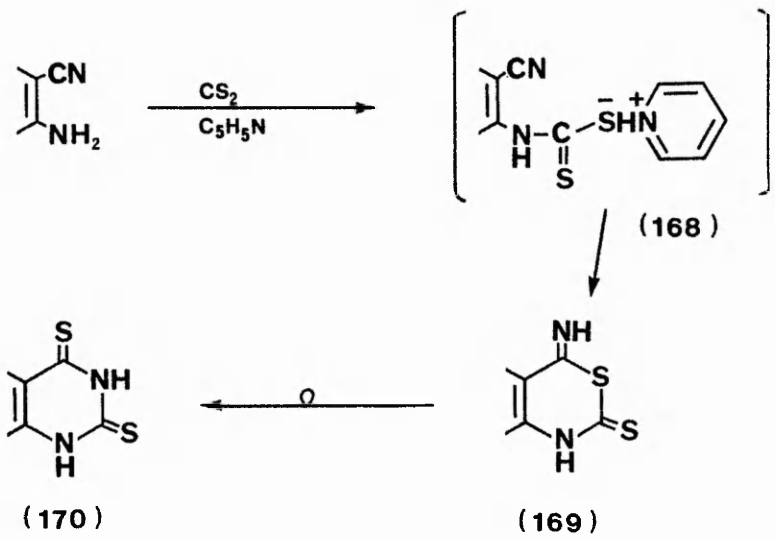


(167)

The reaction is normally carried out in the presence of base to liberate free guanidine. Under the conditions of Taylor *et al*[87], prolonged heating of (126) with sodium methoxide and guanidine hydrochloride, gave a multi-component mixture smelling of hydrogen sulphide. Starting material was one of the components of the product. An alternative method of preparation[88], involving ethanolic guanidine, yielded only unreacted (126). A procedure of intermediate strength between the two may be needed to prepare the 2,4-diaminopyrimidine (167).

Dihydropyrimidines, *via* the 1,3-thiazines, are obtained by reaction of o-aminonitriles with carbon disulphide. The dithiocarbamate salt (168) initially formed is not isolated, but cyclises to form the 1,3-thiazine (169). Success of this initial reaction is dependent upon both the basicity of the amino function and the ability of the nitrile to act as a site for nucleophilic addition.

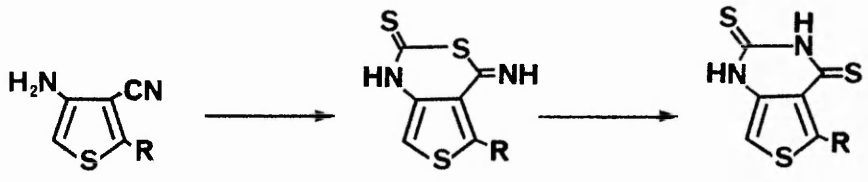
In some cases[89] a ring-opening followed by rotation and a ring closure, initiated by the base present, affords the dihydropyrimidine dithione (170).



In other instances[90] only the thiazine is obtained from the initial reaction, but a base induced, irreversible conversion to the dithione (170) can be achieved in almost quantitative yield.

4-Amino-3-cyanothiophene and its 2-methyl congener on reaction with carbon disulphide in pyridine both afforded the thiazine (171a & 171b), after treatment with acid of the pyridinium salt.

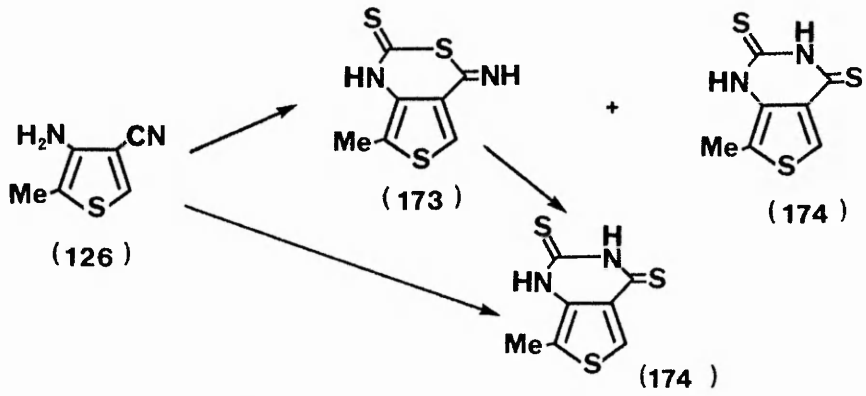
Conversion to the dihydropyrimidine (172a & 172b) was readily achieved in the unsubstituted case, but the 2-methyl compound required prolonged heating with base to cause rearrangement.



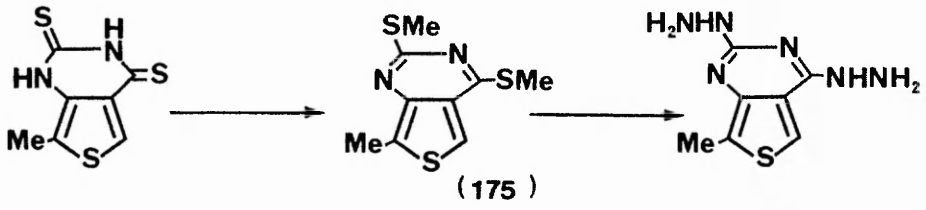
(171) a R=H b R=Me

(172) a R=H b R=Me

4-Amino-3-cyano-5-methylthiophene (126) on reaction with a 0.07Molar solution of carbon disulphide and pyridine gave a mixture of both the thiazine (173) and the dithione (174), though the latter was in poor yield.

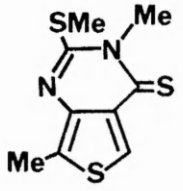


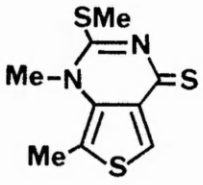
Since in the presence of a greater quantity of pyridine the thiazine alone was produced, it must be assumed that the low yield of the dithione in the previous reaction was an anomalous result. Rearrangement from the thiazine to the dithione occurred in almost quantitative yield. An acceptable analysis result could not be obtained for the dithione. The subsequent methylation of the dithione, however, did give a satisfactory analysis indicating that the starting dithione was genuine. It was envisaged that replacement of the thio (C=S) functionality of the dihydropyrimidine would give access to other substituted pyrimidines eg:

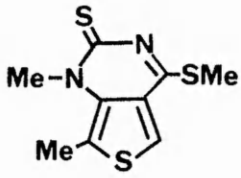


The dithione was alkylated with dimethyl sulphate to give the di-S-methyl compound (175).

Attempts to repeat this methylation resulted in a two component mixture being formed which was separated by column chromatography (silica, eluted with chloroform). The minor fraction was the desired di-S-methyl compound. The major component was also a dimethylated product but spectroscopic analysis suggested that N-methylation as well as S-methylation had occurred. Several plausible structures for the product can be envisaged:



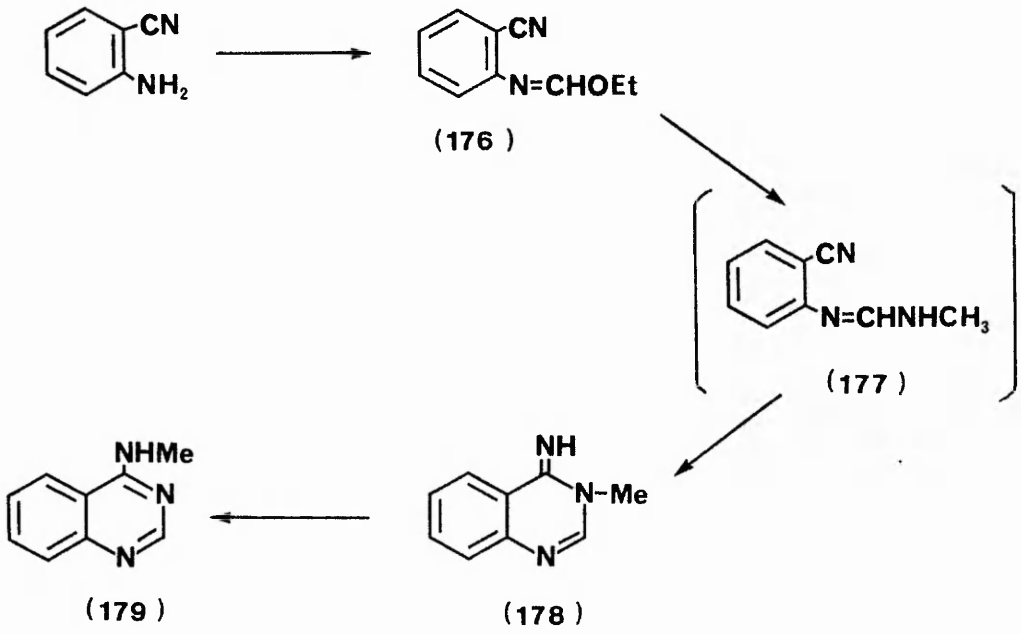




So far it has not been possible to differentiate between these isomers and assign a structure to the unknown dimethylated product. Since the di-S-methylated compound (175) could not be prepared in quantity, this part of the work had to be abandoned.

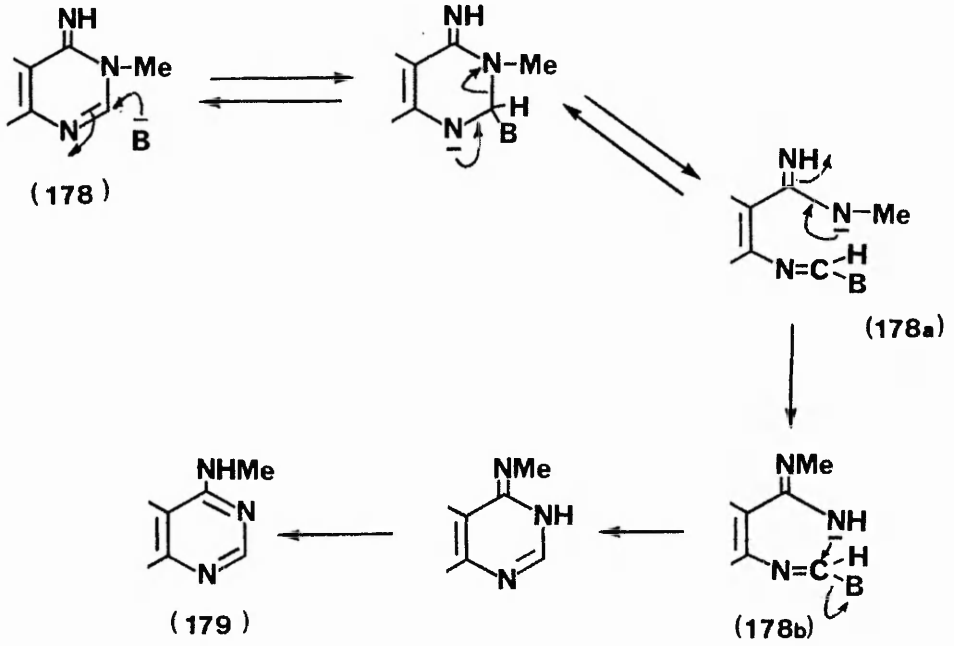
Pyrimidines may be prepared by an isomerisation reaction known as the Dimroth rearrangement. The initial iminopyrimidine is prepared by treatment of the aminonitrile with triethyl orthoformate to give the ethoxymethylene amino intermediate (176). Subsequent treatment with alcoholic methylamine gives the cyanoamidine (177) which often undergoes an immediate

intramolecular amine-nitrile addition to afford the pyrimidine (178).

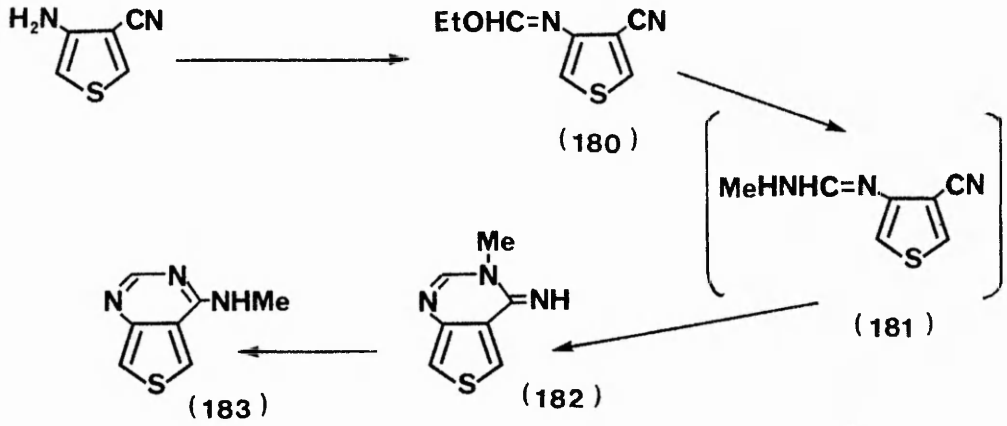


The rearrangement of (178) to (179) is readily affected in water or base. Under some reaction conditions the iminoquinazoline is not isolated as the rearrangement occurs spontaneously to give the aminopyrimidine as the sole reaction product.

The mechanism for the Dimroth rearrangement[91] (178-179) is thought to involve initial nucleophilic attack of the base on C-2 of the pyrimidine (178). Fission of the C2-N3 bond results in the amidine (178a) which suffers free rotation around the carbon-carbon bond joining the amidine and the aromatic ring. A subsequent recyclisation, involving the unsubstituted amidine nitrogen (178b), and concomitant expulsion of the original attacking nucleophile results in isomerisation to the 4-substituted aminopyrimidine (179).

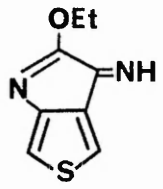


It was envisaged that 4-amino-3-cyanothiophene (119) would undergo this reaction to give either the iminopyrimidine (182) or the rearranged 4-aminopyrimidine (183).

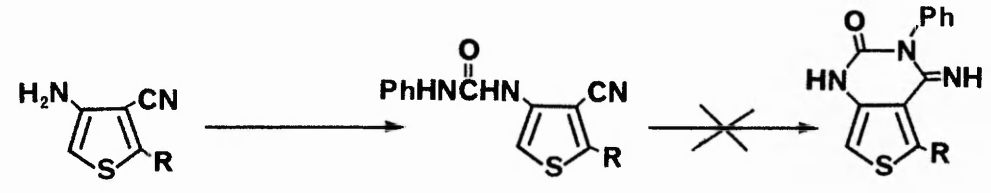


The reaction conditions of Taylor and Loeffler[92], which involved reflux of the aminonitrile with triethyl orthoformate and acetic anhydride, afforded N-acetylamino-nitrile (129) as product. Reducing the quantity of acetic anhydride resulted in a mixture of starting material and the acetyl derivative.

Heating the aminonitrile with triethyl orthoformate and a catalytic quantity of trifluoroacetic acid to facilitate N-aryl formimidate formation caused hydrolysis of the nitrile function whilst leaving the amino group intact. Reaction of the aminonitrile with the ester in the presence of a catalytic amount of the amine hydrochloride (118) gave a product whose spectroscopic data did not correspond to that expected for the ethoxymethylene compound. Both the amino function and the nitrile group had been altered. A plausible ring closed structure for this product could be:



Aminonitriles react with isocyanates and isothiocyanates to give pyrimidines. 4-Amino-3-cyanothiophene (119) and its 2-methyl congener (162) underwent an immediate, exothermic reaction on addition of phenyl isocyanate to afford the urea (184a,b).

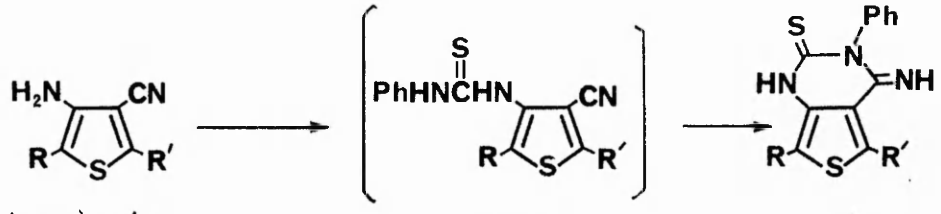


(119) R=H
(162) R=Me

(184) a R=H
b R=Me

(185) a R=H
b R=Me

Attempts to cyclise the urea by reaction with sodium ethoxide failed to give the desired pyrimidine (185). 4-Amino-3-cyano-5-methylthiophene (126) did not undergo an immediate exothermic reaction with phenyl isocyanate. Heating at 50°c for 24 hours gave a multi-component mixture, the main fraction being starting aminonitrile. The failure of this reaction is almost certainly due to steric hindrance of the methyl group on the incoming, bulky isocyanate fragment (see table five).
Reaction of all the aminonitriles with phenyl isothiocyanate gave their respective N-phenylpyrimidines (187a,b,c), without isolation of the urea (186).

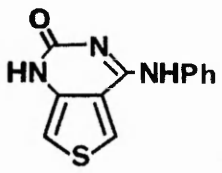


(119) R,R′=H
(162) R=H,R′=Me
(126) R=Me,R′=H

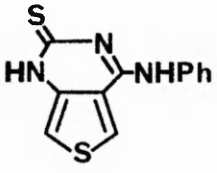
(186)

(187) a R,R′=H
b R=H,R′=Me
c R=Me,R′=H

Attempts to prepare the pyrimidine (188) and the pyrimidine thione (189) directly[93], by reaction of phenyl isocyanate and phenyl isothiocyanate respectively, at high temperatures resulted in decomposition of the amino-nitriles.



(188)



(189)

Spacefilled low energy representation of N-phenyl-N(o-cyano-thienyl-5-methyl)urea.

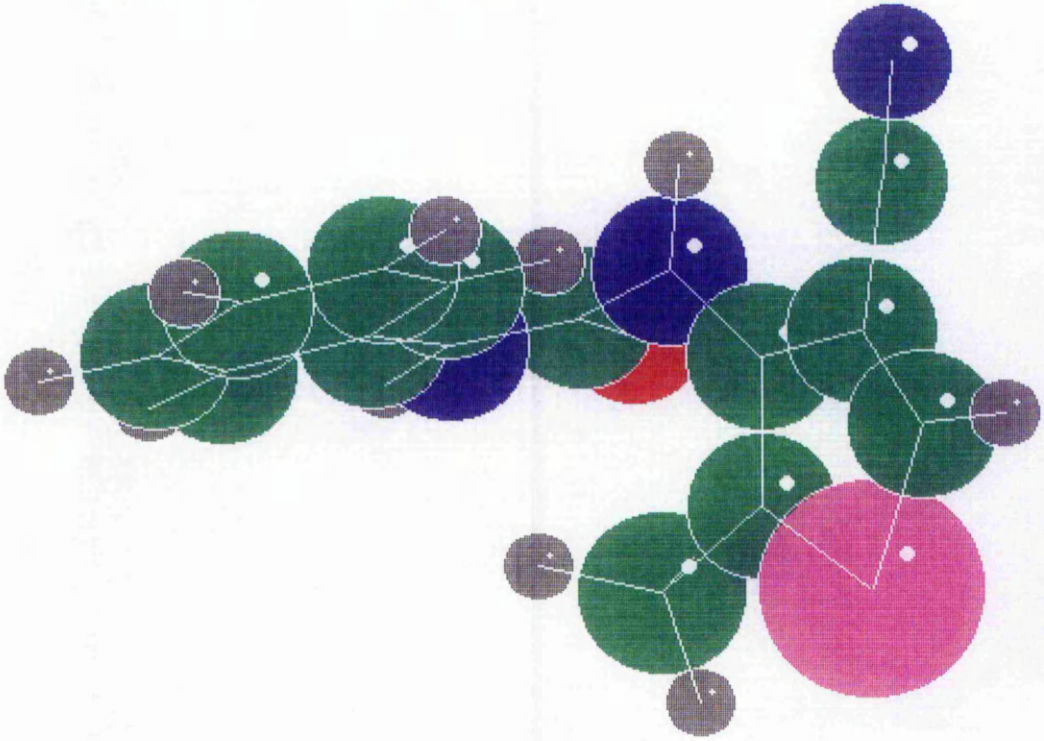


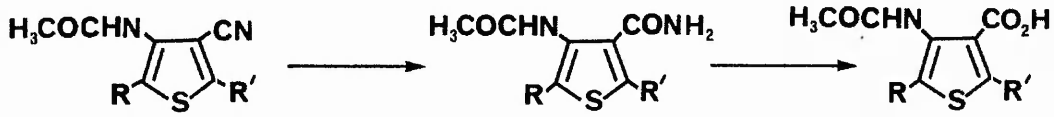
Table Five.

Compound	Potential Energy after Newton-Raphson minimization
N-Phenyl-N(o-cyano-thienyl-5-methyl)urea	197.61 Kcal per mole
N-Phenyl-N(o-cyano-thienyl)urea	82.66 Kcal per mole

In addition to the ability of aminonitriles to produce condensed heterocycles, the modification of the nitrile or amino function may also be synthetically useful. Hydrolysis of the cyano group of an o-aminonitrile leads first to the o-aminocarboxamide and then to the o-amino acid. Acetylaminonitriles on hydrolysis afford pyrimidines as seen in the case of 3-acetylamino-4-cyano-2-methylthiophene.

(148)

Under identical reaction conditions both 4-amino-3-cyano-thiophene and its 2-methyl congener decomposed. The mild hydrolysis method of Katritzky et al [80] gave the carboxamides (149 & 191) for both the methyl derivatives of (119), but the parent compound further reacted to give the acid (192).



(129) R,R′=H
(136) R=Me,R′=H
(190) R=H,R′=Me

(149) R=Me,R′=H
(191) R=H,R′=Me

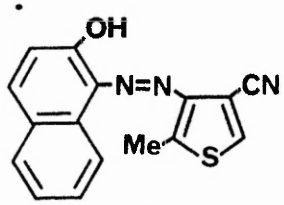
(192) R,R′=H

The amino function of aromatic aminonitriles can be diazotised normally and the resulting diazonium salts can undergo replacement reactions or be coupled to give azo-dyes.

Due to the activation exerted by the amino group on the vacant C-5 position neither 4-amino-3-cyanothiophene nor its 2-methyl derivative could be diazotised. The C-5 blocked thiophene (126) readily diazotised and reaction of the diazonium salt under Sandmeyer conditions afforded the 4-chloro compound (193).

(126) (193)

The azo-dye (194) was obtained by coupling the diazonium salt with β-naphthol [94].



(194)

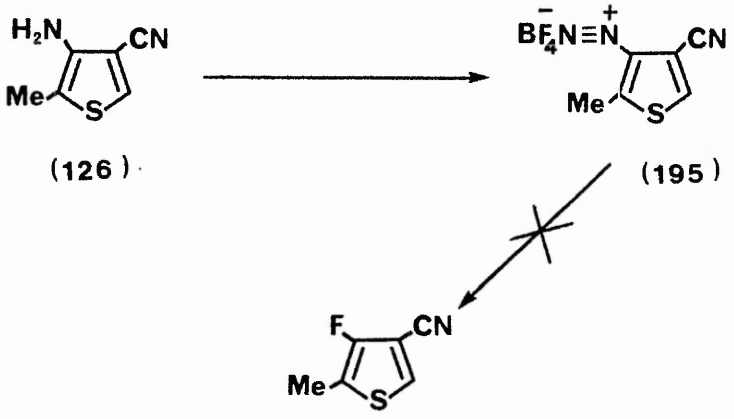
The introduction of fluorine into an aromatic compound can be achieved by the Balz-Schiemann reaction [95]. The method is a two-step process; first, the preparation and isolation of a dry diazonium fluoroborate; and second, a heat controlled decomposition giving the aromatic fluoride, nitrogen and boron trifluoride.

$$ArNH_2 + HNO_2 + BF_4^- \longrightarrow ArN_2BF_4 + H_2O + {}^-OH$$

$$ArN_2BF_4 \xrightarrow{\Delta} ArF + N_2 + BF_3$$

Most dry diazonium fluoroborates are remarkably stable and show definite decomposition temperatures[95].

4-Amino-3-cyano-5-methylthiophene (126) on diazotisation in the presence of fluoroboric acid, afforded a dark fluoroborate salt (195). Infra-red analysis showed a diazonium peak next to the nitrile stretch. A definite decomposition range was exhibited (146-148°c) when the dry salt was heated. Decomposition of the salt to the aromatic fluoride (196) was not achieved, however; in each attempt both nitrogen and boron trifluoride were driven off but the residue, smelling strongly of hydrogen sulphide, showed no aromatic peaks on proton nmr. It must therefore be concluded that the thiophene ring did not survive the reaction. Also a sodium fusion of the residue, followed by a test with zirconium-alizarin reagent failed to indicate the presence of fluorine.



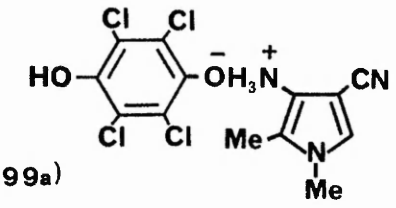
The attempted synthesis of pyrrolo- and furano[3,4-d]-1,2,3-triazin-4(3H)-ones.

Entry into the pyrrole series was achieved by the useful precursor, 4-amino-3-cyano-1,5-dimethylpyrroline (198), described by Cavalla[96]. This was readily prepared by a dehydrative coupling of β-methylaminopropionitrile and lactonitrile, giving the α,ω-dinitrile (197) which underwent a Thorpe-Ziegler cyclisation to afford the desired pyrroline (198). It was envisaged that dehydrogenation to the pyrrole (199), hydration of the nitrile function and subsequent diazotisation of the amino-amide (200) would lead to the pyrrolo[3,4-d]-1,2,3-triazin-4-one (201) (see scheme seventeen).
Access to the furanotriazinone was deemed possible by cyanoethylation of ethyl lactate to afford 3-cyano-5-methyl-4-oxotetrahydrofuran (216). Subsequent aromatisation with hydroxylamine hydrochloride was envisaged, giving an aminonitrile (217) analogous to that described in the thiophene work (see scheme twenty-one).

The attempted synthesis of pyrrolo[3,4-d]-1,2,3-triazin-4(3H)-one.

4-Amino-3-cyano-1,5-dimethylpyrroline (198) was readily prepared by the method of Cavalla.[96] The pyrroline obtained

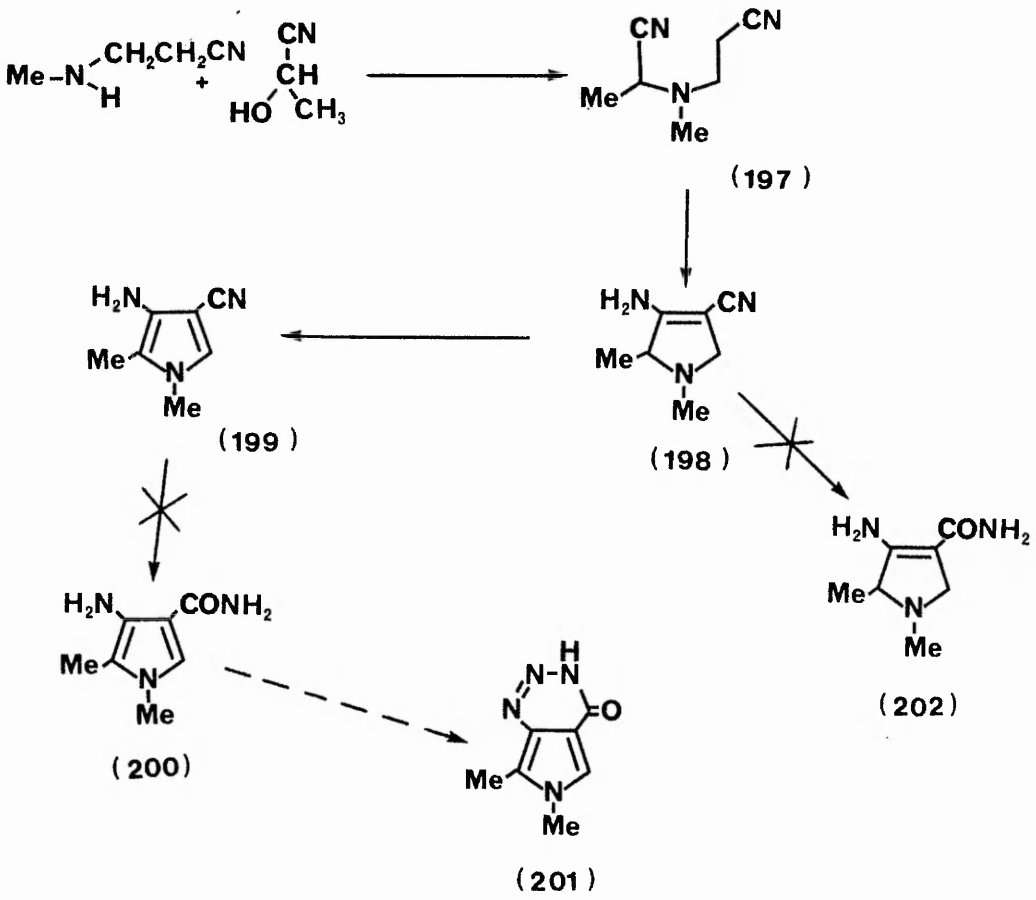
was dehydrogenated to the pyrrole (199) by use of the quinone, p-chloranil, the product being isolated as the salt (199a), whose probable structure is:

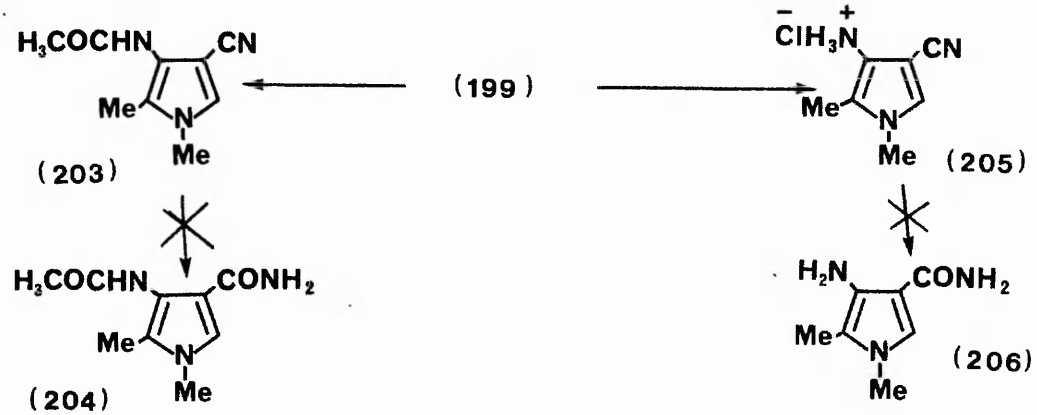


(199a)

Initial attempts to decompose the salt in ammonia, followed by extraction of the free base with chloroform, were greatly hampered by the presence of reduced chloranil. A more successful method of decomposition using dilute acid allowed removal of the insoluble reduced chloranil. Basification and subsequent extraction with ethyl acetate, using a continous liquid-liquid extractor, gave a moderate yield of the pyrrole. Purification of the pyrrole was achieved by either recrystallisation from cyclohexane, or by sublimation at 100°c, giving white needles. Although the pyrrole was relatively stable, decomposition did occur over a period of several days. This was seen by the discolouration of the pure sample. This lack of stability made the attainment of accurate analysis data difficult. The data presented in the experimental section indicate that the correct compound has been prepared, the discrepencies in the analysis being attributed to the partial decomposition of the sample.

Scheme seventeen:





The initial attempt to prepare the amide (200), by hydration of the nitrile with hydrogen peroxide[80], failed and the starting aminonitrile was recovered. Hydration, using finely powdered potassium hydroxide[79] resulted in a product that decomposed on exposure to the atmosphere. Tlc of the reaction mixture suggested that the desired reaction had occurred, since in addition to the absence of starting material, a blue fluorescing, base-line component was evident. Analogous tlc properties to these are exhibited by 4-amino-3-carboxamido-5-methylthiophene (127). The 'amide' appeared to be stable before evaporation of the solvent, thus a possible course of action was to use the amide in situ and diazotise straight to the triazinone. For this to be practical the bulk of the reaction mixture had to be greatly reduced. This allowed a small enough volume to be used in the diazotisation reaction without actually decomposing the amide. Addition of the solution to dilute hydrochloric acid should give the amine hydrochloride which reacts with nitrous acid to form the triazinone.

Under the conditions just stated, '4-amino-3-carboxamido-1,5-dimethylpyrrole' (200) was diazotised with saturated sodium nitrite solution.

Tlc of the reaction mixture showed an absence of the blue fluorescent spot, indicating that reaction had taken place. This was further substantiated by the fact that a positive test for excess nitrous acid was obtained with starch-potassium iodide paper. Unfortunately, the triazinone did not precipitate out of the reaction mixture. This suggested that either the triazinone was water soluble or that the anticipated reaction had not occurred. Ethyl acetate extraction of the mixture gave a residue that revealed that the pyrrole ring had been destroyed.

Other methods for the preparation of the amide *in situ* were investigated.

A standard mode of hydration of a nitrile is its reaction with concentrated sulphuric acid. 4-Amino-3-cyano-1,5-dimethylpyrrole (199) showed evidence of the blue fluorescent component under these conditions. Extraction of the 'amide' from the aqueous phase, partial evaporation and diazotisation with sodium nitrite did not afford a precipitate of the desired triazinone. Again, the residue obtained from the diazotisation mixture indicated that the pyrrole had decomposed.

Polyphosphoric acid[104] has been used in the hydration of nitriles. When heated in this medium, 4-amino-3-cyano-1,5-dimethylpyrrole (199) showed the previously described tlc properties.

After diazotisation none of the triazinone precipitated out, even though a positive test for nitrous acid was obtained. Extraction of the diazotisation liquor gave a residue that showed the pyrrole ring had been destroyed. Failure to isolate either the amide or the triazinone prompted an investigation into the preparation of a substituted amide which could be stabilized by a protecting group.

The initial attempt involved formation of the amide *via* the potassium hydroxide method, followed by treatment, *in situ*, with p-toluenesulphonic acid monohydrate. Diazotisation of this 'tosyl derivative' did not afford any triazinone. Extraction of the mother liquor resulted in a residue that showed decomposition of the heterocyclic ring had occurred.

Deactivation of the amino function by introduction of an acetyl group was envisaged as an adequate method of stabilizing the system. 3-Acetylamino-4-cyano-1,2-dimethylpyrrole (203) was readily prepared by action of acetic anhydride on the pyrrole aminonitrile (199). Using the potassium hydroxide hydrolysis method[79] the acetyl derivative (203) failed to react and starting material was recovered.

In the thiophene work the acetylaminonitriles (129,136) were adequately hydrated using hydrogen peroxide[80]. Under these conditions the pyrrolo-nitrile did not give an exothermic reaction and the starting material was recovered unchanged.

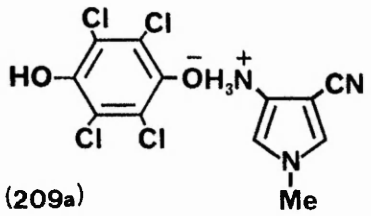
An alternative derivative was envisaged in the amine hydrochloride (205). Reaction of the pyrrole with hydrogen chloride gas in ether gave a precipitate of the hydrochloride, which was stable in air. 4-Amino-3-cyano-1,5-dimethylpyrrole hydrochloride (205) was treated with hydrogen peroxide. No exothermic reaction ensued and the hydrochloride was returned in good yield.

Finally, an attempt was made to prepare 4-amino-3-carboxamido-1,5-dimethylpyrroline (202) to see if it would possess greater stability on isolation. It was envisaged that preparation of this compound could present two possible pathways to the triazinone. Initial protection of the amino function could be followed by either diazotisation to the triazinone and then dehydrogenation to the full pyrrole, or by dehydrogenation and subsequent diazotisation, depending on the stabilities of the compounds obtained.

Unfortunately the pyrroline proved to be inert towards hydration and so this proposed pathway was abandoned.

Scheme Eighteen:

In conjunction with the 1,5-dimethyl compound (199), the monomethylated pyrrole (209) was prepared. The general method of Cavalla[96] was used, lactonitrile being replaced by glycolonitrile. The dinitrile (207) produced underwent the Thorpe-Ziegler cyclisation to afford 4-amino-3-cyano-1-methylpyrroline (208) in good yield. Aromatisation to the pyrrole with p-chloanil gave the salt (209a), whose probable structure is:

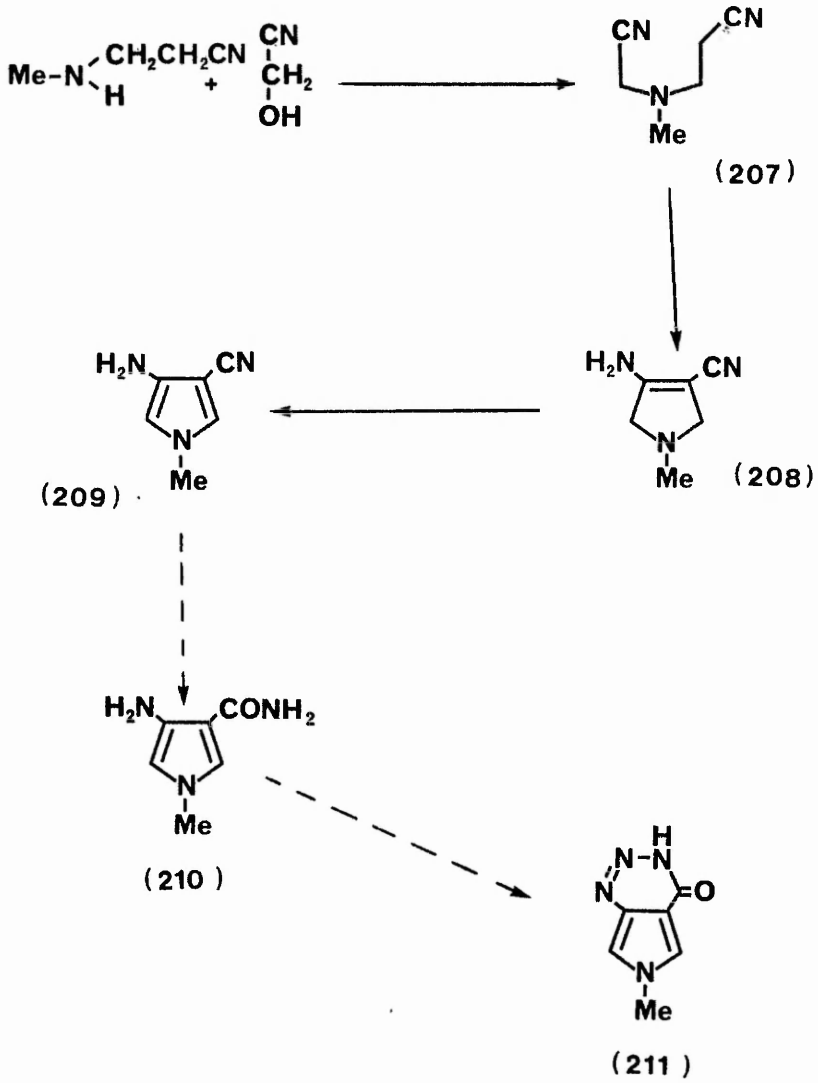


(209a)

Liberation of the free base followed by extraction, using a continous liquid-liquid extractor, gave a moderate yield of the aminonitrile (209). This compound proved to be less stable than the dimethylated pyrrole, discolouration of the sample occurring overnight.

Due to the inability to prepare the amide of 4-amino-3-cyano-1,5-dimethylpyrrole (199) further work on this monomethylated cyano-compound was discontinued.

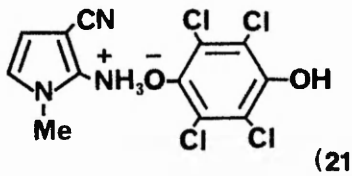
Scheme eighteen:



3-Amino-2-cyanothiophene appears to show greater stability towards oxidation than its 4-amino-3-cyano isomer. It was felt that this increase in stability may also exist in the pyrrole series, thus prompting a study into the preparation of 3-amino-2-cyano-1-methylpyrrole (213). A kinetically controlled approach was envisaged as being the best route to prepare this compound.

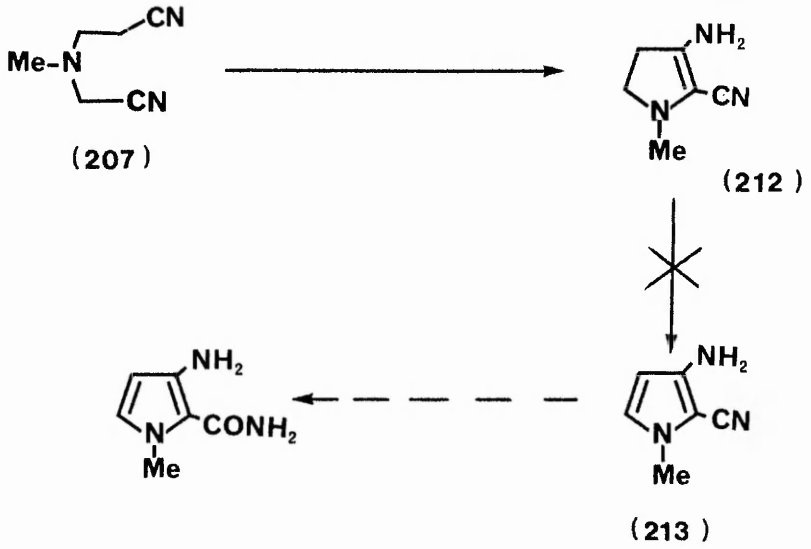
Scheme Nineteen:

A very reactive form of sodium methoxide was required to carry out this reaction. This was prepared by distilling off the excess methanol from a solution of sodium in methanol in a nitrogen atmosphere and maintaining the volume of the reagent by the addition of toluene. Cooling was used to direct the cyclisation of the dinitrile to give 3-amino-2-cyano-1-methylpyrroline (212) preferentially. None of the 4-amino-3-cyano isomer was isolated. Dehydrogenation of the pyrroline with p-chloranil in toluene gave a mixture of the desired pyrrole and unreacted starting material. Increasing the reaction temperature by using xylene as the solvent gave a quantity of the salt (213a).

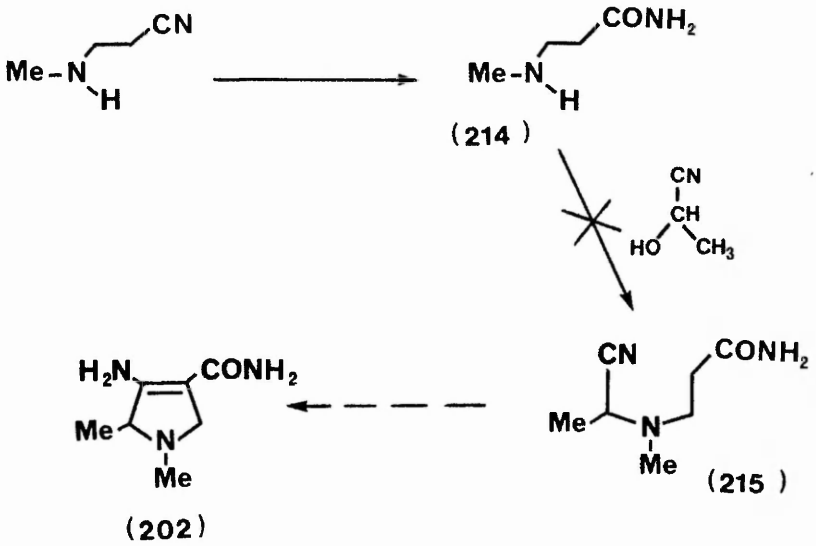


(213a)

Scheme nineteen:



Scheme twenty:



Decomposition of the salt in dilute acid, followed by removal of the insoluble reduced chloranil, basification of the filtrate and extraction using a continuous liquid-liquid extractor, gave a poor yield of the desired pyrrole. The product was very water soluble and use of the lengthy extraction procedure failed to increase the yield in this case. An attempt to decompose the salt by sublimation resulted in the separation of a small quantity of unreacted chloranil, the salt remaining unchanged. The possibility of using dicyanodichlorohydroquinone as an alternative dehydrogenating agent was investigated. It was hoped that separation of the salt by sublimation may be successful in this case. Unfortunately, the greater dehydrogenating strength of this quinone produced a multi-component mixture, probably indicating that oxidation, partial oxidation and decomposition of the pyrrole had taken place. Since the pyrrole could not be prepared in significant quantities, this route was of little practical use.

A brief study into the feasibility of introducing the amide function into the system before ring closure to the pyrroline was undertaken. β-Methylaminopropionitrile was hydrated with potassium hydroxide to afford β-methyl-aminopropionamide (214) (scheme twenty).

The previously successful dehydrative coupling reaction with lactonitrile failed to work in this case. Attempts to force the reaction in the direction of the product, by using Dean and Stark conditions, did not produce any free water and a mixture of the two starting materials was recovered.

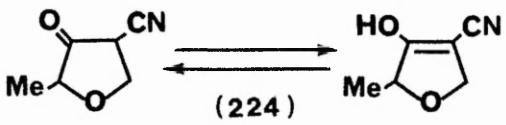
The preparation of pyrrolo[3,4-d]-1,2,3-triazin-4-one needs further study before it is a viable synthetic route. The major difficulties encountered in this work were the water solubility of the aminonitriles and the unstable nature of the amide. Both of these problems may be addressed by the use of a protecting group introduced onto the amine function. The critera for the group used would necessitate that while it reduced the water solubility of the nitrile, it increased the stability of the amide. The alternative to this would involve introduction of a hydrophobic functionality, its removal and replacement with a hydration stable group, followed by preparation of the amide and finally removal of this second protecting group to give the desired product. The introduction of the amido function into the system before cyclisation to the pyrroline would be synthetically useful if ideal reaction conditions could be found.

The attempted synthesis of furano[3,4-d]-1,2,3-triazin-4(3H)-one.

Entry into the furano[3,4-d]-1,2,3-triazin-4-one series was proposed *via* the ketonitrile (216). This structure was analogous to that of the tetrahydrothiophene (124) and a similar route of preparation was envisaged.

Scheme twenty-one.

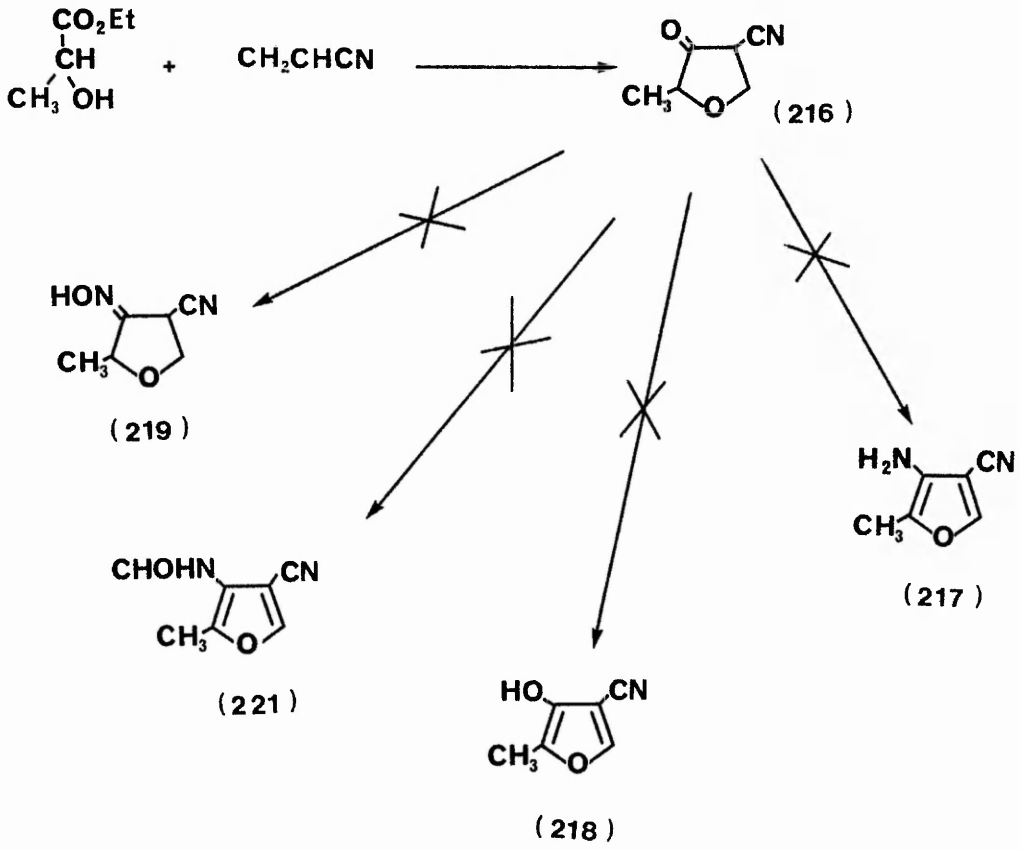
3-Cyano-4-oxo-5-methyltetrahydrofuran (216) was prepared by the cyanoethylation of ethyl lactate, the anion being generated in the presence of sodium hydride. Spectral evidence suggested that this structure existed in two tautomeric forms. The predominant tautomer appears to be the keto form but the infra-red spectrum shows an enolic OHst at $3500cm^{-1}$. Separation of these two isomers was not necessary since the subsequent dehydrogenation was expected to produce only one aromatic product.



(224)

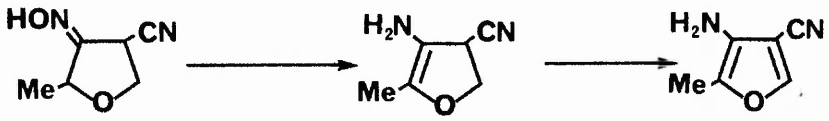
Treatment with hydroxylamine hydrochloride failed to give the hydrochloride salt of the aminonitrile (217), starting material was recovered. Increasing the temperature of the reaction by replacing acetonitrile with n-butanol did not produce the furan.

Scheme twenty-one:



Dehydrogenation using p-chloranil was anticipated to give the hydroxy compound (218), no salt being formed in this case. The oil obtained from this reaction showed an infra-red spectrum that closely resembled that of the ketonitrile, although a major discrepency was the size of the OHst at 3500cm^{-1}. This had been greatly enlarged possibly suggesting that the enolic form of the tetrahydrofuran had been trapped.

The reluctance of the ketonitrile to undergo dehydrogenation to give a fully aromatic compound may indicate that this is energetically unfavourable. An alternative route was considered using the oxime (219), since this could be dehydrated to give the partially oxidised amine (220). With one double bond already introduced into the system it was envisaged that further dehydrogenation to aquire full aromaticity would be a favourable process.



(219) (220) (217)

Reaction of the ketonitrile with free hydroxylamine[98], generated by the action of barium chloride on hydroxylamine hydrochloride, did not afford the oxime but appeared to give the enolic tautomer of (216).

An alternative procedure[99] involving dehydration of the oxime, *in situ*, using dicyclohexylcarbodiimide was investigated. 3-Cyano-4-oxo-5-methyltetrahydrofuran (216) did not react under these conditions and starting material was recovered.

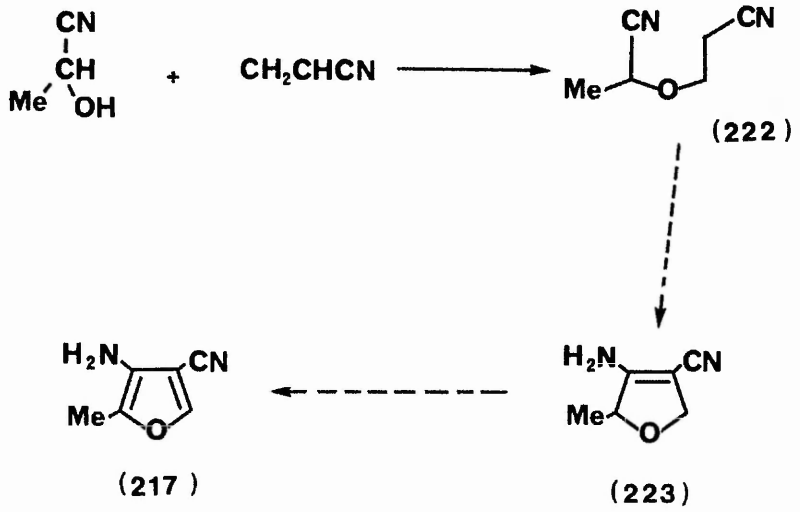
Finally, Van Es[100] described a procedure whereby the amine produced by aromatisation of a ketonitrile was trapped as its formyl derivative (221). It was hoped that if any amine could be prepared from (216), its removal as the formyl derivative would act as a driving force and promote aromatisation. Under these reaction conditions the ketonitrile (216) remained unaltered.

Since the tetrahydrofuran (216) resisted all attempts at dehydrogenation and the carbonyl function could not be modified to aid aromatisation, it appears that this compound is of little synthetic use in this case.

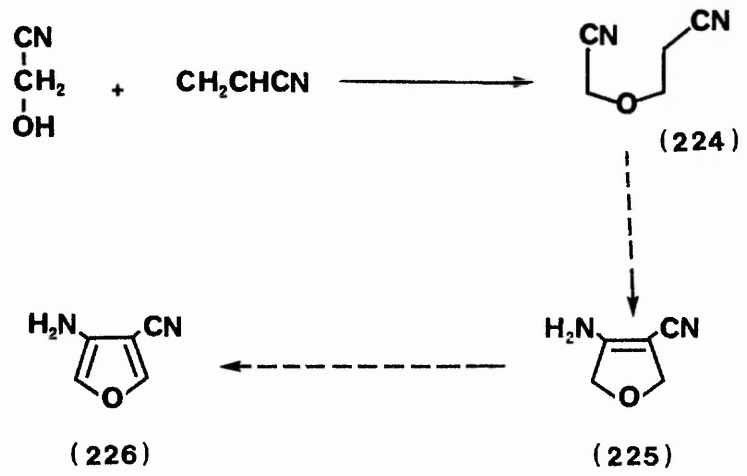
Scheme twenty-two:

An alternative approach to the preparation of 4-amino-3-cyano-5-methylfuran (217) involved the cyanoethylation of the cyanohydrin, lactonitrile. In general the hydroxyl group of cyanohydrins cyanoethylate normally with acrylonitrile[101]. The dinitrile (222) from this reaction was expected to undergo a Thorpe-Ziegler cyclisation to afford the dihydrofuran (223).

Scheme twenty-two:



Scheme twenty-three:



The advantage of this approach is that both an amino group and a double bond have been introduced into the ring system. Further oxidation to the furan is expected to be energetically favourable.

Hansley[102] cyanoethylated lactonitrile in the presence of tributylamine. Under the conditions specified in his patent no exothermic reaction ensued in our hands and lactonitrile was recovered. Warming the mixture after the addition of the acrylonitrile also had no effect on the reaction. Attempts to induce the reaction by altering the type of base used and increasing the concentration of the mixture by removing the solvent were unsuccessful.

Scheme Twenty-three:

An alternative cyanoethylation of glycolonitrile to afford β-cyanoethoxyacetonitrile (224) was also attempted but again no exothermic reaction occurred and altering the reaction conditions had no effect.

The proposed route via the dihydrofuran (223 or 225) may still be feasible if the ideal cyanoethylation conditions can be found. One possible problem that may be encountered if dehydrogenation of the dihydrofuran can be accomplished is the expected water solubility of the furan aminonitrile (217 or 226).

CHAPTER THREE

E X P E R I M E N T A L

Key to Experimental

All petroleum ether used was of the 60-80 fraction unless stated otherwise. Unless specified the drying agent used was magnesium sulphate. Thin layer chromatography was carried out on silica gel plates.

The infra-red spectra of liquid compounds were carried out neat, whereas all solid compounds were run as KBr discs.

All proton nmr spectra were obtained using a Perkin Elmer R24B spectrophotometer. Carbon 13 nmr spectra were obtained from a Jeol FX60Q spectrophotometer.

The following 1,2,3-benzotriazin-4(3H)-ones were prepared by literature methods.

6-Chloro-1,2,3-benzotriazin-4(3H)-one (92a)

6-Chloroisatoic anhydride prepared (7.9g, 90%) by reaction of 20% phosgene in toluene on 5-chloroanthranilic acid, was converted into 2-amino-5-chlorobenzamide (0.75g, 43%) [mpt.166-168°c, lit.mpt.[104] 172°c]. Diazotisation afforded 6-chlorobenzotriazinone (1.0g, 96%) as a cream solid [mpt.198-200°c, lit.mpt.[15] 205-206°c].

7-Chloro-1,2,3-benzotriazin-4(3H)-one (92b)

2-Amino-4-chlorobenzamide (1.0g, 61%) [mpt.180-182°c, lit.mpt.[105] 181-182°c] was prepared from 7-chloroisatoic anhydride (7.6g, 94%), obtained from 4-chloroanthranilic acid, as described above. Diazotisation gave a good yield of the desired 7-chlorobenzotriazinone (0.95g, 90%) [mpt.212-214°c, lit.mpt.[15] 215- 216°c].

6-Methyl-1,2,3-benzotriazin-4(3H)-one (92c)

2-Amino-5-methylbenzamide (1.8g, 75%) [mpt.175-178°c, lit.mpt.179°c]. was prepared from 6-methylisatoic anhydride (6.7g, 95%) obtained from 5-methylanthranilic acid. Diazotisation gave 6-methylbenzotriazinone (2.8g, 89%) [mpt.220-221°c, lit.mpt.[107] 228°c].

6-Nitro-1,2,3-benzotriazin-4(3H)-one (96)

5-Nitroisatin was oxidised to 5-nitroanthranilic acid (0.79g, 83%) [mpt.267-268°c, lit.mpt.268-270°c] and converted via the acid chloride to 2-amino-5-nitro-benzamide (2.8g, 49%) [mpt.225-227°c, lit.mpt.230°c]. Diazotisation gave 6-nitrobenzotriazinone (0.36g, 82%) [mpt.196-197°c, lit.mpt.[15] 194°c(dec)].

7-Methoxy-1,2,3-benzotriazin-4(3H)-one (102a)

3-Methoxyisonitrosoacetanilide[63] (6.07g, 84%) prepared from m-anisidine, was ring closed to 6-methoxyisatin (12.28g, 96%) with polyphosphoric acid[63]. Oxidation with alkaline hydrogen peroxide to 4-methoxyanthranilic acid (2.49g, 67%) [mpt.168-171°c, lit.mpt.172°c], was followed by reaction with phosgene to give the isatoic anhydride (3.0g, 87%). Basification with ammonia afforded

2-amino-4-methoxybenzamide (0.5g, 59%) [mpt.156-157°c, lit.mpt.[15]156°c]. The desired triazinone (1.9g, 90%) [mpt.216-218°c, lit.mpt.[15]218-221°c] was produced on diazotisation.

7-Methyl-1,2,3-benzotriazin-4(3H)-one (102b)

3-Methylisonitrosoacetanilide[63] (3.0g, 91%) prepared from m-toluidine, was converted to 6-methylisatin (4.4g, 90%) with polyphosphoric acid. ~~Liberation of~~ Conversion to the acid (1.07g, 57%) [mpt.166-168°c, lit.mpt.168°c], conversion to the isatoic anhydride (2.27g, 97%) and formation of the amide (0.92g, 53%) [mpt.142-145°c, lit.mpt.146-147°c] was followed by diazotisation to 7-methylbenzotriazinone (1.63g, 97%) [mpt.224-225°c, lit.mpt.[10]226°c].

7-Nitro-1,2,3-benzotriazin-4(3H)-one (107)

4-Nitroacetamidobenzoic acid (3.62g, 79%) [mpt.219-221°c, lit.mpt.220-222°c], prepared by potassium permanganate oxidation of N-acetyl-5-nitro-2-toluidine, was hydrolysed to 4-nitroanthranilic acid (4.08g, 83%) [mpt.267-270°c, lit.mpt.[65]263-264°c]. 2-Amino-4-nitrobenzamide (3.05g, 44%) obtained via the acid chloride was diazotised to give the title triazinone (2.58g, 81%) [mpt.189-190°c, lit.mpt.[65]192°c].

6-Methoxy-1,2,3-benzotriazin-4(3H)-one (112)

5-Methoxy-2-nitrobenzoic acid (5.5g, 47%) [mpt.129-131°c, lit.mpt.[15] 133°c] was prepared by oxidation of 3-methyl-4-nitroanisole, obtained from 3-methyl-4-nitrophenol, (40.79g, 49%) [mpt.53-56°c, lit.mpt.[67] 55°c] with alkaline potassium permanganate. 5-Methoxy-2-nitrobenzoic acid was converted *via* the acid chloride to 5-methoxy-2-nitro benzamide (1.2g, 61%) [mpt.156-158°c, lit.mpt.[15] 158°c]. 2-Amino-5-methoxybenzamide (2.0g, 75%) [mpt.129-132°c, lit.mpt.[15] 133°c] was prepared by reduction with nickel(II) chloride and sodium borohydride[71]. Diazotisation of the amide afforded the title triazinone (0.63g, 84%) [mpt.229-231°c, lit.mpt.[15] 232-233°c].

Carbon-13 n.m.r. spectra of substituted 1,2,3-benzotriazin-4(3H)-ones.

Subs	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	Other
None	156.0	120.5	127.9	131.9	134.9	124.4	144.5	-
6-NO_2	154.6	121.1	120.4	148.4	130.1	129.0	146.5	-
6-OMe	155.7	122.1	104.1	161.8	124.3	129.9	139.5	OMe 56.1
6-Me	155.8	120.3	127.7	142.8	136.1	123.6	142.8	Me 21.6
6-Cl	155.0	121.7	129.9	137.9	135.3	124.0	143.0	-
7-NO_2	154.5	124.5	127.1	125.5	151.3	123.4	146.5	-
7-OMe	155.4	113.9	126.0	121.6	164.5	108.4	146.6	OMe 56.0
7-Me	155.8	118.0	127.3	133.3	145.9	124.5	144.6	Me 21.7
7-Cl	154.9	119.0	127.0	132.4	140.2	126.4	145.0	-

General method for the deazoniation of benzotriazinones.

The benzotriazinone (0.0068mol) was suspended in dry pyridine (5ml) and acetic anhydride (2ml) and heated on a steam bath for one hour. The solution was poured into a mixture of ice/concentrated hydrochloric acid and the precipitated solid filtered off, washed with water and dried. The crude mixture was dissolved in ethyl acetate and washed with saturated potassium bicarbonate (2x20ml). The combined aqueous layers were acidified with 4M hydrochloric acid to liberate the acid. The precipitated acid was filtered off, washed with water and dried. The organic layer was washed with water and dried over sodium sulphate. Removal of the drying agent, followed by evaporation afforded the oxazinone.

General method used in the attempted trapping of the diradical intermediate (88).

Benzotriazinone (0.0068mol), the trapping agent (0.0068mol), pyridine (5ml) and acetic anhydride (2ml) were heated together on a steam bath for 30 minutes. The mixture was poured onto ice/concentrated hydrochloric acid and the precipitated solid filtered off, washed with water and dried.

4-Amino-3-cyanothiophene hydrochloride (118)

3-Cyano-4-oxotetrahydrothiophene (22.0g, 0.17mol) and hydroxylamine hydrochloride (12.0g, 0.17mol) were refluxed with acetonitrile (150ml) for 4 hours. Ether (100ml) was added to the cooled mixture, and the precipitated amine hydrochloride was collected, washed with ether and dried. (21.4g, 77%) mpt.164-166°c.

4-Amino-3-cyanothiophene (119)

The free base from the hydrochloride (118) (4.0g,0.03mol) was liberated by addition to ammonia (10ml,0.88d in water 20ml) and extracted with dichloromethane(3x20ml). The combined organic fractions were washed with water (1x20ml), dried over sodium sulphate, filtered and evaporated to give an oil which solidified on cooling to a cream solid (2.62g,84%) mpt.52-55°c (Found: C, 48.2; H, 3.3; N, 22.4. $C_5H_4N_2S$ requires C, 48.3; H, 3.22; N, 22.5) MS(CI) M+H 125. ν max 3400cm^{-1} (NH_2st), 3100cm^{-1} (CHst), 2200cm^{-1} (CNst) 1620cm^{-1} (NH_2def). δ H[$CDCl_3$] 4.3(2H, br, exchanges with D_2O, NH_2), 6.2 & 7.5 (2H, d, ArH). δ C[$CDCl_3$] 100.38 (C-2), 103.89 (C-3), 146.09 (C-4), 134.02 (C-5), 114.15 (CN).

4-Amino-3-carboxamidothiophene (120)

4-Amino-3-cyanothiophene (1.24g, 0.01mol) and potassium fluoride supported on alumina (4.0g) were refluxed in t-butanol (30ml), with stirring, for 2 hours. The mixture was cooled and filtered, the filtercake being washed with chloroform (50ml). The combined organic fractions were evaporated to give a cream solid (1.33g, 94%) mpt.108-110°c (Found: C, 42.2; H, 4.4; N, 19.8. $C_5H_6N_2OS$ requires C, 42.25; H, 4.22; N, 19.71) MS(CI) M+H 143. ν max 3400-3200cm^{-1} (NH_2st), 1660cm^{-1} (COst), 1600cm^{-1} (NH_2 def). δ H[$CDCl_3$] 3.4 & 5.5 (4H, br, 2x NH_2), 6.0 & 8.0 (2H, d, ArH). δ C[$CDCl_3$] 97.85 (C-2), 124.54 (C-3), 147.46 (C-4), 128.24 (C-5), 166.48 (CO).

Attempted preparation of Thieno[3,4-d]-1,2,3-triazin-4-one (121)

4-Amino-3-carboxamidothiophene (120) (1.42g, 0.01mol) in 4M hydrochloric acid (5ml) was stirred and cooled at 0°c. A solution of sodium nitrite (0.69g, 0.01mol) in water (2ml) was added dropwise keeping the temperature below 5°c. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. The precipitated solid was collected, washed with water and dried. Mpt.>350°c. Polymer.

Methyl thiolactate (123)

Thiolactic acid (35.6g, 0.33mol), methanol (40ml) and concentrated sulphuric acid (0.5ml) were heated under reflux for 6 hours. The homogeneous solution was cooled and anhydrous sodium acetate (8.0g) was added. The mixture was filtered, and the filtrate poured into water (100ml). The organic layer was separated and the aqueous layer extracted with dichloromethane (3x20ml). The combined organic layers were dried, filtered and evaporated to give a colourless liquid (39.42g, 98%) bpt.153-157°c, lit [106] bpt_{15}.44-46°c.

3-Cyano-5-methyl-4-oxotetrahydrothiophene (124)

A mixture of methyl thiolactate (12.0g, 0.1mol) and acrylonitrile (5.3g, 0.1mol) was added dropwise to a suspension of sodium methoxide (2.3g Na, 0.1mol) in dry toluene (50ml). The reaction mixture was refluxed for one hour, cooled and the sodium salt collected, washed with ether and dried. The salt was added to a two-phase mixture of 2M sulphuric acid/dichloromethane (2x100ml). The organic layer was separated, dried, filtered and evaporated to give an orange oil (10.67g, 76%). ν max 3300cm^{-1} (OHst), 2950cm^{-1} (CHst), 2200cm^{-1} (CNst), 1740cm^{-1} (COst). δ H[$CDCl_3$] 1.3 & 1.4 (3H,d, CH_3), 3.0-3.8 (4H,m,CH's). δ C[$CDCl_3$] 15.58 (CH_3), 45.97 (C-2), 40.25 (C-3), 202.97 (C-4), 27.79 (C-5), 115.31 (CN).

4-Amino-3-cyano-5-methylthiophene hydrochloride (125)

3-Cyano-5-methyl-4-oxotetrahydrothiophene (17.0g, 0.12mol) and hydroxylamine hydrochloride (8.4g, 0.12mol) were refluxed with acetonitrile (150ml) for 4 hours. Ether (100ml) was added to the cooled mixture and the precipitated amine hydrochloride was collected, washed with ether and dried (11.93g, 57%) mpt.145-148°c.

4-Amino-3-cyano-5-methylthiophene (126)

The free base from the hydrochloride (125) (4.0g, 0.02mol) was liberated by addition to ammonia (10ml, 0.880d, in water 20ml). The amine was extracted with dichloromethane (3x20ml) and the combined extracts were washed with water (1x20ml), dried over sodium sulphate, filtered and evaporated. The oil obtained solidified on cooling to give a cream solid (2.03g, 64%) mpt.56-57°c (Found: C, 51.8; H, 4.3; N, 20.3. $C_6H_6N_2S$ requires C, 52.17; H, 4.34; N, 20.28) MS(CI) M+H 139. ν max 3500-3200cm^{-1} (NH_2 st), 3100cm^{-1} (CHst), 2900cm^{-1} (CHst), 2200cm^{-1} (CNst), 1620cm^{-1} (NH_2def). δ H[$CDCl_3$] 2.4(3H, s, $ArCH_3$) 4.4(2H, br, exchanges with D_2O, NH_2), 7.7(1H, s, ArH). δ C[$CDCl_3$] 129.66 (C-2), 104.08 (C-3), 141.30 (C-4), 113.04 (C-5), 114.60 (CN), 11.36 (CH_3).

4-Amino-3-carboxamido-5-methylthiophene (127)

4-Amino-3-cyano-5-methylthiophene hydrochloride (4.0g, 0.02mol), finely powdered potassium hydroxide (5.6g, 0.1mol) and t-butanol (150ml) were refluxed with stirring for 1 hour. The mixture was cooled and poured into saturated sodium chloride solution (100ml). The amide was extracted with chloroform (3x25ml), dried over sodium sulphate, filtered and evaporated to give a cream solid (2.14g, 60%) mpt.158-160°c (Found: C, 46.1; H, 5.0; N, 17.5. $C_6H_8N_2OS$ requires, C, 46.14; H, 5.16; N, 17.93) MS(CI) M+H 157. ν max 3500-3200cm^{-1} (NH_2st), 1670cm^{-1} (COst), 1620cm^{-1} (NH_2def). δ H[$CDCl_3$/DMSO] 2.3 (3H, s, CH_3), 3.5 & 7.0 (2x2H, br, exchanges with D_2O, NH_2), 7.8 (1H, s, ArH). δ C[$CDCl_3$/DMSO] 123.95 (C-2), 125.25 (C-3), 142.39 (C-4), 110.77 (C-5), 166.67 (CO), 11.23 (CH_3).

7-Methylthieno[3,4-d]-1,2,3-triazin-4(3H)-one (128)

To a stirred and cooled solution (0-5°c) of 4-amino-3-carboxamido-5-methylthiophene (2.0g, 0.01mol) in 4M hydrochloric acid (8ml), was added dropwise a solution of sodium nitrite (0.83g, 0.01mol) in water (2ml), maintaining the temperature between 0-5°c. After the addition was complete any insoluble material was removed by filtration. The mixture was allowed to warm to room temperature and stirred for 2hrs. The product was

filtered off, washed with water and dried. A second crop was obtained from the mother liquor after standing overnight. The crude product was recrystallised from ethanol to give the title compound (1.48g, 69%) mpt.217-218°c (Found: C, 43.3; H, 3.1; N, 25.1. $C_6H_5N_3OS$ requires, C, 43.11; H, 2.99; N, 25.14) MS(CI) M+H 168. ν max 3100cm^{-1} (NHst), 1660cm^{-1} (COst). δ H[$CDCl_3$/DMSO] 2.9 (3H, s, $ArCH_3$), 3.5 (1H, exchanges with D_2O, NH), 8.3 (1H, s, ArH). δ C[$CDCl_3$/DMSO) 141.03 (C-7), 143.37 (C-7a), 122.98 (C-5a), 122.98 (C-5), 153.68 (CO), 11.95 (CH_3).

3-Acetylamino-4-cyanothiophene (129)

4-Amino-3-cyanothiophene (4.0g, 0.03mol) was added to acetic anhydride (10ml) and stirred at room temperature for 10 minutes. The crude mixture was poured into ice/water and the solid filtered off, washed with water and dried. The crude acetyl derivative was recrystallised from ethanol to give the pure product (4.58g, 86%) mpt.169-170°c (Found: C, 50.6; H, 3.6; N, 16.8. $C_7H_6N_2OS$ requires, C, 50.59; H, 3.64; N, 16.85) MS(CI) M+H 167. ν max 3300cm^{-1} (NHst), 2200cm^{-1} (CNst), 1680cm^{-1} (COst), 1560cm^{-1} (NHdef). δ H[$CDCl_3$/DMSO] 2.2 (3H, s, $COCH_3$), 3.4 (1H, s, exchanges with D_2O, NH), 7.7 & 8.2 (2H, d, ArH). δ C[$CDCl_3$/DMSO] 113.30 (C-2), 136.42 (C-3), 113.69 (C-4), 134.67 (C-5), 23.16 ($COCH_3$), 105.06 (CN), 168.88 (CO).

3-Acetylamino-2-bromo-4-cyanothiophene (130)

3-Acetylamino-4-cyanothiophene (1.6g, 0.01mol), glacial acetic acid (15ml) and sodium acetate (0.82g, 0.01mol) were stirred at room temperature while a solution of bromine (0.8g, 0.01mol) in glacial acetic acid (5ml) was added portionwise. The mixture was stirred at room temperature for a further hour, then the precipitated product was collected, washed with water and dried. The crude product was recrystallised from ethanol to give the title compound (1.2g, 51%) mpt.188-190°c (Found: C, 34.51; H, 2.10; N, 11.65. $C_7H_5BrN_2OS$ requires, C, 34.3; H, 2.04; N, 11.43) MS(CI) M+H 246. ν max 3250cm^{-1} (NHst), 2200cm^{-1} (CNst), 1660cm^{-1} (COst), 1560cm^{-1} (NHdef). δ H[$CDCl_3$/DMSO] 2.2 (3H, s, $ArCH_3$), 8.4 (1H, s, ArH), 9.8 (1H, br, exchanges with D_2O, NH). δ C[$CDCl_3$/DMSO] 108.25 (C-2), 133.04 (C-3), 113.93 (C-4), 130.30 (C-5), 162.94 (CO), 22.79 (CH_3), 109.47 (CN).

Attempted preparation of 4-Amino-5-bromo-3-cyanothiophene (131)

3-Acetylamino-2-bromo-4-cyanothiophene (0.5g, 0.002mol) was warmed on a steam bath with 4M hydrochloric acid (15ml) for 30 minutes. The reaction mixture was cooled and basified with 4M sodium hydroxide. The amine was extracted with chloroform (3x20ml), the combined extracts

being dried over sodium sulphate, filtered and evaporated. The resulting solid was shown, by spectroscopy, not to be the required product.

3-Acetylamino-2-bromo-4-carboxamidothiophene (132)

3-Acetylamino-2-bromo-4-cyanothiophene (2.0g, 0.008mol) and dimethyl sulphoxide (15ml) were stirred and cooled in ice, while 30% hydrogen peroxide (2ml) and a catalytic amount of potassium carbonate were added. An exothermic reaction took place. The cooling was then removed and the mixture was stirred at room temperature for 30 minutes. The precipitated amide was collected, washed with water and dried. The crude product was recrystallised from ethanol to give the desired amide (1.37g, 64%) mpt.229-231°c (Found: C, 32.4; H, 2.8; N, 10.5. $C_7H_7BrN_2O_2S$ requires, C, 31.95; H, 2.69; N, 10.64) MS(CI) M+H 263. ν max 3450cm^{-1} (NH_2st), 3300cm^{-1} (NHst), 1660cm^{-1} (COst). δ H[$CDCl_3$/DMSO] 2.0 (3H, s, $COCH_3$), 3.2 (1H, s, exchanges with D_2O, NH), 7.0-7.5 (2H, br, exchanges with D_2O, NH_2), 8.0 (1H, s, ArH). δ C[$CDCl_3$/DMSO] 108.05 (C-2), 133.17 (C-3), 134.60 (C-4), 128.30 (C-5), 168.62 ($CONH_2$), 163.63 (CO), 22.79 (CH_3).

Attempted preparation of 4-Amino-5-bromo-3-carboxamido-thiophene (133)

3-Acetylamino-2-bromo-4-carboxamidothiophene (0.5g, 0.002mol) was heated on a steam bath with 4M hydrochloric acid (20ml) for 30 minutes. The mixture became very dark in colour and smelled strongly of hydrogen sulphide. The solution was cooled and basified with 4M sodium hydroxide. The amine was extracted with chloroform (2x20ml) and the combined fractions were dried over sodium sulphate, filtered and evaporated. Spectroscopy showed that the desired product had not been obtained.

3-Trifluoroacetylamino-4-cyanothiophene (134)

4-Amino-3-cyanothiophene (1.0g, 0.008mol) was added to ice cold trifluoroacetic anhydride (5ml). A vigorous exothermic reaction occurred. The semi-solid was poured into ice/water and the precipitated solid was collected, washed with water and dried. The crude product was recrystallised from cyclohexane to give the title compound (0.85g, 48%) mpt.123-125°c (Found: C, 38.18; H, 1.42; N, 12.73. $C_7H_3N_2OSF_3$ requires, C, 37.97; H, 1.33; N, 12.7) MS(CI) M+H 221. ν max 3300cm^{-1} (NHst), 2250cm^{-1} (CNst), 1720cm^{-1} (COst), 1590cm^{-1} (NHdef). δ H[$CDCl_3$] 7.9 (1H, s, ArH), 8.0 (1H, s, ArH), 8.5-8.7 (1H, br, exchanges with

D_2O, NH). δ C[$CDCl_3$/DMSO] 135.58 (C-2), 133.43 (C-3), 125.38 (C-4), 118.30 (C-5), 113.24 (CN), 107.14 (CF_3), 157.13 (CO).

Attempted preparation of 3-Trifluoroacetylamino-2-bromo-4-cyanothiophene (135)

A. The trifluoroacetyl derivative (134) (0.5g, 0.002mol) and sodium acetate (0.4g) in glacial acetic acid (10ml) were stirred at room temperature while bromine (0.2g, 0.002mol) in glacial acetic acid (5ml) was added dropwise. The mixture was stirred for a further 30 minutes then poured into water (50ml). The solid was collected, washed with water and dried; it was then found to be recovered starting material.

B. The trifluoroacetyl derivative (0.5g, 0.002mol) was refluxed with N-bromosuccinimide (0.4g, 0.002mol) in glacial acetic acid (20ml) for 6 hours. The reaction mixture was poured into water (50ml) and the solid collected. Starting material was recovered.

C. The trifluoroacetyl derivative (0.5g, 0.002mol) in glacial acetic acid (10ml) was stirred at room temperature while pyridinium bromine perbromide (0.73g, 0.002mol) was added. The mixture was refluxed for 4 hours, then poured

into water (50ml). The precipitated solid was found to be recovered starting material.

3-Acetylamino-4-cyano-2-methylthiophene (136)

4-Amino-3-cyano-5-methylthiophene (1.38g, 0.01mol) and acetic anhydride (1.02g, 0.01mol) were mixed together at room temperature. The aminonitrile dissolved to give a clear solution, then the product precipitated out. The semi-solid was poured into ice-water and the product was collected, washed with water and dried. The crude product was recrystallised from ethanol to give the title compound (1.48g, 82%) mpt.199-200°c (Found: C, 53.3; H, 4.50; N, 15.40. $C_8H_8N_2OS$ requires, C, 53.31; H, 4.47; N, 15.54) MS(CI) M+H 181. ν max 3200cm^{-1} (NHst), 2200cm^{-1} (CNst), 1660cm^{-1} (COst), 1560cm^{-1} (NHdef). δ H[$CDCl_3$/DMSO] 2.1 (3H, s, $ArCH_3$), 2.3 (3H, s, $COCH_3$), 3.3 (1H, br, exchanges with D_2O, NH), 8.1 (1H, s, ArH). δ C[$CDCl_3$/DMSO] 133.76 (C-2), 132.52 (C-3), 114.28 (C-4), 131.09 (C-5), 12.99 (CH_3), 22.79 ($COCH_3$), 109.93 (CN), 169.34 (CO).

Attempted preparation of 3-acetylamino-4-cyano-2-thenoic acid (137)

3-Acetylamino-4-cyano-2-methylthiophene (1.8g, 0.01mol), water (40ml) and magnesium sulphate heptahydrate (1.34g)

were stirred and refluxed. Potassium permanganate (3.4g) was added portionwise over a period of one hour. After addition the mixture was refluxed for a further 30 minutes, then filtered hot and the filtercake washed with hot water. The filtrate and washings were left to stand overnight. The precipitated starting material was collected. The filtrate was then acidified with concentrated hydrochloric acid. No product was obtained.

Attempted preparation of diethyl mercaptomalonate (138)

A. Diethyl bromomalonate (1.0g, 0.004mol) in ethanol (10ml) was stirred at room temperature while a suspension of sodium hydrogen sulphide (0.31g, 0.004mol) in ethanol (5ml) was added portionwise. The reaction mixture was stirred for 1 hour, then the precipitated sodium bromide was filtered off and the filtrate evaporated to give a brown oil. The absence of ethyl peaks in the proton nmr indicated that the desired product had not been obtained.

B. Thiourea (0.84g, 0.01mol) in triethylene glycol (25ml) was heated, with stirring, to 75°c. Diethyl bromomalonate (2.4g, 0.01mol) was added dropwise. There was no evidence of an exothermic reaction. The mixture was heated for a further 10 minutes, cooled and 4M sodium hydroxide was added until the liquid was slightly basic. The thiol was extracted with ether (3x15ml). The combined extracts were dried, filtered and evaporated. The oil obtained showed no evidence for ethyl groups in the proton nmr.

Attempted preparation of diethyl S-acetylmercapto-malonate (139)

Potassium thiolacetate (5.0g, 0.04mol) was stirred in ethanol (50ml) and a solution of diethyl bromomalonate (10.4g, 0.04mol) in ethanol (10ml) was added dropwise. The solution was stirred at room temperature for 4 hours. The mixture was poured into water (200ml) and extracted with chloroform (2x30ml). The combined organic fractions were dried over magnesium sulphate, filtered and evaporated to give an oil. The crude oil was distilled under high vaccuum (Bpt..80°c/0.2mbar). Diethyl bromo-malonate was recovered.

2-Cyanoethylthiolacetate (140)

Thiolacetic acid (50g, 0.66mol) and Triton B (1ml) were preheated to 35°c and then acrylonitrile (34.8g, 0.66mol) was added dropwise. An exothermic reaction took place after several drops of acrylonitrile had been added. The solution was stirred at room temperature for 1 hour, then the product (63.3g, 75%) was isolated by vacuum distillation bpt.101-105°c / 3mm, lit[82] bpt.94°c/ 3mmHg.

ν max 2900cm^{-1} (CHst), 2200cm^{-1} (CNst), 1685cm^{-1} (COst).

δ H[$CDCl_3$] 2.4 (3H, s, $COCH_3$), 8.0-7.5 (4H, m, ArH).

Attempted preparation of diethyl 2-cyanoethylmercapto-malonate (141)

2-Cyanoethylthiolacetate (5g, 0.038mol) and diethyl bromomalonate (9.3g, 0.038mol) were added dropwise to an ice cooled solution of sodium (0.9g) in dry ethanol (40ml). After the addition was complete the reaction mixture was warmed to room temperature and stirred for 30 minutes. A small quantity of precipitated sodium bromide was filtered off, and the filtrate was added to water and extracted with dichloromethane (3x20ml). The combined organic layers were dried, filtered and evaporated. Spectral analysis of the crude oil showed it to be recovered 2-cyanoethylthiolacetate.

Attempted preparation of 4-acetylamino-5-methyl-3-thenoic acid (145)

3-Acetylamino-4-carboxamido-2-methylthiophene (0.5g, 0.003mol) in 4M hydrochloric acid (13ml) was stirred and cooled in ice. A solution of sodium nitrite (0.18g, 0.003mol) in water (2.5ml) was added dropwise, maintaining the temperature between 0-5°c. The mixture was stirred at room temperature for 1 hour. The precipitated solid was filtered, washed with water and dried. Starting material was recovered.

4-Acetylamino-5-methyl-3-thenoic acid (145)

4-Acetylamino-3-methoxycarbonyl-5-methylthiophene (0.88g, 0.004mol) was added to a mixture of potassium bicarbonate (0.8g), water (2ml) and methanol (10ml) and refluxed for 90 minutes. The reaction mixture was cooled, poured into water (50ml) and extracted with dichloromethane (3x20ml), the organic layers being discarded. The aqueous layer was cooled and acidified to Congo Red with concentrated sulphuric acid. The precipitated acid was collected, washed with water and dried. The crude product was recrystallised from ethanol/water to afford the acid (0.61g, 74%) mpt.209-211°c (Found: C,48.4; H, 4.60; N, 6.90. $C_8H_9NO_3S$ requires C, 48.24; H, 4.56; N, 7.04).

MS(CI) M+H 200. ν max 3300-2700cm^{-1} (OHst), 3250cm^{-1} (NHst), 1700cm^{-1} (COst), 1620cm^{-1} (COst). δ H[$CDCl_3$/DMSO] 2.2 (3H, s, $ArCH_3$), 2.4 (3H, s, $COCH_3$), 7.9 (1H, s, ArH), 9.2-9.0 (1H, br, exchanges with D_2O, OH). δ C[$CDCl_3$/DMSO] 129.04 (C-2), 128.70 (C-3), 132.76 (C-4), 125.69 (C-5), 14.23 (CH_3), 167.24 ($\underline{C}OCH_3$), 21.63 ($CO\underline{C}H_3$), 164.92 (COOH).

Attempted preparation of 3-acetylamino-4-carboxamido-2-methylthiophene (148)

A.

3-Acetylamino-4-cyano-2-methylthiophene (0.5g, 0.0027mol) and 4M sodium hydroxide (15ml) were refluxed for 1 hour. The mixture was cooled and neutralised with 4M hydrochloric acid. The solid was filtered off, washed with water and dried. The crude product was recrystallised from ethanol. Spectral analysis showed the product to be the pyrimidine (148) (0.28g, 56%) mpt.232-235°c (Found: C, 53.4; H, 4.5; N, 15.4. $C_8H_8N_2OS$ requires, C, 53.3; H, 4.4; N, 15.5) MS(CI) M+H 181. ν max 3150cm^{-1} (NHst), 1680cm^{-1} (COst), 1620cm^{-1} (NHdef). δ H[$CDCl_3$/DMSO] 2.3 (3H, s, $ArCH_3$), 2.5 (3H, s, CH_3), 7.9 (1H, s, ArH).
δ C[$CDCl_3$/DMSO] 129.47 (C-2), 159.21 (C-4), 121.48 (C-5), 150.96 (C-5a), 125.51 (C-7), 144.99 (C-7a), 11.49 (CH_3), 21.43 (CH_3).

B.

To a stirred solution of 3-acetylamino-4-cyano-2-methyl-thiophene (0.86g, 0.005mol) in t-butanol (25ml), was added finely powdered potassium hydroxide (1.34g, 0.023mol). The mixture was refluxed for 30 minutes, cooled and poured into saturated brine solution (100ml). The product was extracted with chloroform (3x50ml), dried, filtered and evaporated. The crude product was recrystallised from ethanol. Spectral analysis showed the product to be the pyrimidine (148) (0.4g, 47%) mpt.232-235°c.

3-Acetylamino-4-carboxamido-2-methylthiophene (149)

3-Acetylamino-4-cyano-2-methylthiophene (1.0g, 0.005mol) and dimethyl sulphoxide (7ml) were stirred and cooled in ice, while 30% hydrogen peroxide (1ml) and a catalytic amount of potassium carbonate (0.1g) were added. An exothermic reaction took place; when it had subsided the cooling was removed and the mixture was stirred at room temperature for ten minutes. The precipitated solid was collected, washed with water and dried. The crude product was recrystallised from ethanol to furnish the pure amide (0.8g, 73%) Mpt.208-210°c (Found: C, 48.9; H, 5.0; N, 14.13. $C_8H_{10}N_2O_2S$ requires, C, 48.47; H, 5.08; N, 14.13) MS(CI) M+H 199. ν max 3400cm^{-1} (NHst), 3200-3100cm^{-1}(NH_2st),

1650cm^{-1} (COst), 1645cm^{-1} (COst). δ H[$CDCl_3$/DMSO] 2.0 (3H, s, $COCH_3$), 2.2 (3H, s, $ArCH_3$), 3.3 (1H, s, exchanges with D_2O, NH), 7.0-7.5 (2H, br, exchanges with D_2O, NH_2), 7.7 (1H, s, ArH). δ C[$CDCl_3$/DMSO] 124.60 (C-2), 131.29 (C-3), 130.64 (C-4), 124.64 (C-5), 13.89 (CH_3), 23.24 ($CO\underline{C}H_3$), 165.38 ($CONH_2$), 168.04 (CO).

Methyl 2-(β -methylcarbonylethylthio)propanoate (150)

To a stirred solution of methyl thiolactate (16.28g, 0.14mol) and piperidine (0.1ml) was added methyl acrylate (12.89g, 0.15mol) dropwise at such a rate that the temperature did not rise above 55°c. The resulting mixture was then heated to 90°c , with stirring, for 5 minutes. The crude product was vacuum distilled (19.67g, 70%) Bpt..98-100°c / 0.25mbar, lit[108] bpt.110-120°c/ 0.3mbar. ν max 2950cm^{-1} (CHst), 1740cm^{-1} (COst). δ H[$CDCl_3$] 3.7 (6H, s, 2xOMe), 3.5 (1H, q, CH), 3.0-2.5 (4H, t, 2xCH_3), 1.6-1.4 (3H, d, CH_3).

3-Methoxycarbonyl-5-methyl-4-oxotetrahydrothiophene (151)

To a boiling solution of sodium (1.45g, 0.06mol) in methanol (25ml) was added the thioester (150) (8.7g, 0.04mol) over 40 minutes. The resulting solution was refluxed for 30 minutes, cooled and poured into 2M

sulphuric acid (50ml). The product was extracted with dichloromethane (3x50ml), washed with sodium bicarbonate (1x20ml), dried and evaporated to give an oil (7.35g, 82%). ν max 2995cm^{-1} (CHst), 1740cm^{-1} (COst), 1670cm^{-1} (COst). δ H[$CDCl_3$] 3.9-3.7 (6H, s, 2xOMe), 3.5-2.0 (4H, m, CH_2 & CH), 1.7-1.5 (6H, s, 2xCH_3).

4-Amino-3-methoxycarbonyl-5-methylthiophene hydrochloride (152)

The ketoester (151) (6.0g, 0.034mol) was refluxed with hydroxylamine hydrochloride (3.13g, 0.045mol) in acetonitrile (50ml) for 4 hours. The mixture was cooled and diluted with ether (100ml). The precipitated hydrochloride was filtered off, washed with ether and dried (4.74g, 66%) mpt.189-191°c, lit.[109] mpt.191-192°c.

4-Amino-3-methoxycarbonyl-5-methylthiophene (153)

The hydrochloride (152) (5.0g, 0.024mol) in 2M sodium hydroxide (20ml) was extracted with 1:1 ethyl acetate/ ether (3x20ml). The combined organic layers were washed with brine (1x20ml), water (1x20ml) and dried over sodium sulphate. The drying agent was removed and the solvent evaporated to give an oil which solidified on cooling (2.76g, 67%) mpt..63-65°c. ν max 3400-3300cm^{-1} (NH_2st), 1700cm^{-1} (COst), 1610cm^{-1} (NH_2def). δ H[$CDCl_3$] 2.3 (3H, s,

$ArCH_3$), 3.9 (3H, s, OMe), 4.7-4.3 (2H, br, exchanges with D_2O, NH_2), 7.8 (1H, s, ArH). δ C[$CDCl_3$] 110.83 (C-2), 142.07 (C-3), 122.13 (C-4), 128.24 (C-5), 11.23 (CH_3), 51.36 (CO_2Me), 164.07 (CO_2).

4-Acetylamino-3-methoxycarbonyl-5-methylthiophene (154)

4-Amino-3-methoxycarbonyl-5-methylthiophene (0.5g, 0.003mol), acetic anhydride (5ml) and concentrated sulphuric acid (0.1ml) were stirred together at room temperature until the ester dissolved. The reaction mixture was poured into ice-water (50ml) and stirred. The oil that formed was extracted with chloroform (3x20ml). The combined extracts were washed with water, dried over sodium sulphate, filtered and evaporated. The oil obtained solidified on cooling (0.38g, 61%) mpt..83-85°c (Found: C, 50.5; H, 5.2; N, 6.4. $C_9H_{11}NO_3S$ requires, C, 50.70; H, 5.21; N, 6.57) MS(CI) M+H 214. ν max 3300cm^{-1} (NHst), 1740cm^{-1} (COst), 1660cm^{-1} (COst), 1580cm^{-1}(NHdef). δ H[$CDCl_3$] 2.2 (3H, s, $ArCH_3$), 2.4 (3H, s, $COCH_3$), 3.9 (3H, s, OMe), 7.9 (1H, s, ArH), 8.2-8.6 (1H, br, exchanges with D_2O, NH). δ C[$CDCl_3$] 131.35 (C-2), 129.34 (C-3), 131.37 (C-4), 125.45 (C-5), 14.61 (CH_3), 23.63 ($CO_2\underline{C}H_3$), 51.68 ($CO\underline{C}H_3$), 167.91 (CO), 163.56 (CO_2).

2,7-Dimethylthieno[3,4-d]-1,3-oxazin-4-one (144)

4-Acetylamino-5-methyl-3-thenoic acid (145) (0.5g, 0.003mol) was refluxed in acetic anhydride (15ml) for one hour. The mixture was cooled and the excess anhydride removed by distillation. The solid obtained was triturated with petroleum ether, filtered off and dried. The crude product was recrystallised from ethanol to afford the oxazinone (0.23g, 51%) mpt.118-120°c (Found: C, 53.7; H, 4.2; N, 7.52. $C_8H_7NO_2S$ requires, C, 53.04; H, 3.90; N, 7.73) MS(CI) M+H 182. ν max 1750cm^{-1} (COst). δ H[$CDCl_3$/DMSO] 2.4 (3H, s, CH_3), 2.6 (3H, s, CH_3), 8.2 (1H, s, ArH). δ C[$CDCl_3$/DMSO] 156.74 (C-2), 164.79 (C-4), 119.92 (C-5a), 127.65 (C-5), 132.46 (C-7a), 129.27 (C-7), 11.49 (CH_3), 20.71 (CH_3).

The attempted deazoniation of 7-methylthieno[3,4-d]-1,2,3-triazin-4(3H)-one (128)

A. The 7-methylthieno[3,4-d]triazin-4-one (128) (1.0g, 0.006mol), pyridine (5ml) and acetic anhydride (2ml) were heated on a steam bath for 1 hour. The solution was poured onto ice/concentrated hydrochloric acid and the precipitated solid was collected, washed with water and dried. The crude substance was recrystallised from ethanol to give the product (0.51g, 34%) mpt..200-201°c

(Found: C, 47.9; H, 3.8; N, 16.6. $C_{10}H_9N_3OS$ requires, C, 47.8; H, 3.6 ; N, 16.7). ν max 3350cm^{-1}(NHst), 1750cm^{-1} (COst), 1700cm^{-1}(COst), 1580cm^{-1} (NHdef). δ H[$CDCl_3$] 2.7 (3H, s, $ArCH_3$or $COCH_3$), 2.9 (3H, s, $ArCH_3$or $COCH_3$), 7.3 (1H, s, ArH), 8.6 (2H, d, ArH). δ C[$CDCl_3$] 21.56, 25.39, 120.77, 121.87, 123.37, 149.53, 157.07, 158.23, 169.40, 171.54. MS(CI) 252 (M+H), 238, 210, 193, 168, 151, 141, 125. GCMS(EI) 251 (M), 210, 209, 168, 151, 141, 124, 94, 70, 43, 28.

B. The thienotriazinone (128) (0.5g, 0.003mol) was refluxed with pyridine (5ml) and acetic anhydride (2ml) for 5 hours. The solution was poured onto ice/ concentrated hydrochloric acid, the precipitate was collected, washed with water and dried. The crude product was recrystallised from ethanol. Spectral analysis showed the product to be identical to that above.

C. The thienotriazinone (128) (0.5g, 0.003mol), 3,5-lutidine (5ml) and acetic anhydride (2ml) were refluxed for 1 hour. The solution was poured onto ice/concentrated hydrochloric acid. The precipitate was collected, washed with water and dried. Spectral analysis showed the product to be identical to that obtained from method A.

D. The thienotriazinone (128) (1.0g, 0.006mol) and diphenyl ether (30ml) were heated to 180-200°c for 1 hour. The mixture was poured into petroleum ether (100ml) and the precipitated solid was filtered off, washed with petroleum ether and dried. Starting material was recovered.

Attempted preparation of 3-acetoacetyl-7-methylthieno-[3,4-d]-1,2,3-triazin-4-one (155c)

A. The thienotriazinone (128) (0.5g, 0.003mol) was dissolved in dry pyridine (2ml) with a ltte warming. Diketene (0.25g, 0.003mol) was added and the mixture was stirred at room temperature for 10 minutes. The mixture was poured into ice/concentrated hydrochloric acid. The precipitate was filtered off, washed with water and dried. Starting material was recovered.

B. The thienotriazinone (128) (0.5g, 0.003mol) and 2,2,6-trimethyl-1,3-dioxen-4-one (0.42g, 0.003mol) were heated to 170°c in diphenyl ether (10ml) for 1 hour. The mixture was cooled and poured into 60-80 petrol. The precipitate was filtered, washed with petrol and dried. Starting material was recovered.

C. The thienotriazinone (128) (0.5g, 0.003mol) and 2,2,6-trimethyl-1,3-dioxen-4-one (0.42g, 0.003mol) were

heated to 160°c in 3,5-lutidine (10ml) for 1 hour. The mixture was cooled, poured into petroleum ether and the precipitate filtered off, washed with pet.ether and dried. Starting material was recovered.

Attempted preparation of 3-acetyl-7-methylthieno[3,4-d]-1,2,3-triazin-4-one (159)

A. The thienotriazinone (128) (0.2g, 0.001mol) was added to acetic anhydride and stirred at room temperature for one hour. The solution was poured onto ice/concentrated hydrochloric acid. The precipitated solid was collected, washed with water and dried. Starting material was recovered.

B. The thienotriazinone (128) (0.2g, 0.001mol) was added to pyridine (5ml) and acetic anhydride (2ml) and stirred at room temperature overnight. The crude mixture was poured into ice/water and the solid collected, washed with water and dried (0.15g). Spectral analysis showed the product to be identical to that obtained under deazoniation conditions.

C. The thienotriazinone (128) (1.0g, 0.006mol) was dissolved in dry pyridine (10ml) and acetyl chloride (0.45g, 0.006mol) was added dropwise. The mixture was

stirred at room temperature for 30 minutes, then poured into petroleum ether. The precipitated solid was collected, washed with petroleum ether and dried. Starting material was recovered.

D. Sodium (0.5g, 0.02mol) was dissolved in ethanol (20ml). The thienotriazinone (128) (1.0g, 0.006mol) was dissolved in hot ethanol (100ml) and added to the sodium ethoxide solution. The solution was refluxed for 1 hour, then left to stand overnight. The solvent was removed to give the sodium salt of the thienotriazinone (mpt.250°c). The sodium salt was refluxed with acetic anhydride (0.6g, 0.006mol) in benzene (50ml) for 3 hours. The solvent was evaporated to give a cream solid. Starting material was recovered.

E. The thienotriazinone (128) (0.5g, 0.003mol) was dissolved in dry dimethyl sulphoxide (20ml) and stirred in a nitrogen atmosphere, while sodium hydride (0.07g, 0.003mol) was added. Acetyl chloride (0.25g, 0.003mol) was then added and the mixture was allowed to stir, under nitrogen, at room temperature for 30 minutes. The mixture was poured into water (50ml) and the precipitate was collected, washed with water and dried. Starting material was recovered.

3-Cyano-2-methyl-4-oxotetrahydrothiophene (161)

A mixture of crotononitrile (13.4g, 0.2mol) and methyl thiogylcolate (21.2g, 0.2mol) was added dropwise, with stirring, to a suspension of sodium methoxide (from sodium 5.4g, 0.2mol) in toluene (500ml). The mixture was refluxed for 1 hour, cooled in ice and ether (500ml) added. The precipitated sodium salt was collected, washed with ether and dried. The product was isolated by adding the salt, portionwise, to a two-phase mixture of 2M sulphuric acid-dichloromethane (300ml) with stirring. The organic layer was separated, washed with water, dried, filtered and evaporated to give an orange oil (16.85g, 60%). ν max 3500-3200cm^{-1} (OHst-enol), 2250cm^{-1} (CNst), 2200cm^{-1} (CNst), 1780-1700cm^{-1} (COst).

4-Amino-3-cyano-2-methylthiophene (162)

3-Cyano-2-methyl-4-oxotetrahydrothiophene (16.85g, 0.12mol), hydroxylamine hydrochloride (9.0g, 0.12mol) and acetonitrile (200ml) were refluxed, with stirring, for 4 hours. The mixture was cooled a nd diluted with ether (200ml). The precipitated hydrochloride was collected, washed with ether and dried (13.23g, 63%) mpt.>350°c. The hydrochloride was added to 1M ammonium hydroxide (20ml) and the free base was extracted with

50/50 ethyl acetate/ether (3x30ml). The combined organic layers were washed with brine (1x20ml), dried over sodium sulphate, filtered and evaporated to give an oil that solidified on cooling. The crude product was recrystallised from petroleum ether to give the free base (5.96g, 63%) mpt.75-77°c (Found: C, 51.73; H, 4.42; N, 20.32. $C_6H_6N_2S$ requires, C, 52.17; H, 4.34; N, 20.28) MS(CI) M+H 139. ν max 3500-3400cm^{-1} (NH_2st), 2200cm^{-1} (CNst), 1620cm^{-1}(NH_2def). δ H[$CDCl_3$] 2.6 (3H, s, $ArCH_3$), 4.0-3.8 (2H, br, exchanges with D_2O, NH_2), 6.0 (1H, s, ArH). δ C[$CDCl_3$] 96.81 (C-2), 144.9 (C-3), 103.11 (C-4), 150.2 (C-5), 15.26 (CH_3), 114.08 (CN).

Attempted preparation of 4-amino-7-methylthieno[3,4-d]-pyrimidine (165)

A. 4-Amino-3-cyano-5-methylthiophene (2.0g, 0.014mol), formamidine acetate (2.9g, 0.028mol) and 2-ethoxyethanol (25ml) were refluxed for 4 hours. The reaction mixture was cooled in ice and the solid collected, washed with petroleum ether and dried. The ir spectrum of the product showed that the nitrile was still intact.

B. 4-Amino-3-cyano-5-methylthiophene (1.24g, 0.01mol) was refluxed with formamide (5ml) for 30 minutes. The semi-solid was stirred in chloroform/charcoal at room

temperature for 30 minutes and the solution was filtered and evaporated to give a black oil. Spectroscopic analysis showed that the thiophene ring had decomposed.

Attempted preparation of 2,4-diamino-7-methylthieno-[3,4-d]-pyrimidine (167)

A. Sodium (0.46g, 0.02mol) was dissolved in ethanol (50ml) and guanidine hydrochloride (1.92g, 0.02mol) was added. 4-Amino-3-cyano-5-methylthiophene (1.38g, 0.01mol) was added to the ethanolic guanidine mixture and the whole was refluxed for 48 hours. Evaporation of the solvent led to recovery of the starting material.

B. To a solution of sodium methoxide (from sodium 0.8g, 0.03mol) in 2-ethoxyethanol (30ml) was added 4-amino-3-cyano-5-methylthiophene (2.0g, 0.015mol) and guanidine hydrochloride (2.84g, 0.03mol). The mixture was refluxed for 48 hours, cooled and poured into water. The product was extracted with dichloromethane (3x20ml), dried over sodium sulphate, filtered and evaporated. Starting material was recovered.

Thieno[3,4-d]thiazine-1,3-thione (171a)

4-Amino-3-cyanothiophene (2.1g, 0.017mol), pyridine (16.6g, 0.2mol) and carbon disulphide (21.5g, 0.2mol) were refluxed for 1 hour. The mixture was cooled in ice and ether (50ml) was added. The precipitated solid was collected, washed with ether and dried. The pyridine salt was ground in a mortar with 0.1M hydrochloric acid (20ml) and the resulting thiazine was filtered off, washed with water, ethanol and dried. The crude product was recrystallised from glacial acetic acid to give the thione (2.34g, 69%) mpt.357°c dec (Found: C, 36.8; H, 2.16; N, 14.3 . $C_6H_4N_2S_3$ requires, C, 36.01; H, 2.02; N, 14.7) MS(CI) M+H 201. ν max 3100cm^{-1} (NHst), 1600cm^{-1} (NHdef). δ H[$(CD_3)_2CO$/DMSO] 3.5 (1H, s, exchanges with D_2O, NH), 8.0-8.3 (2H, d, 2xArH). δ C[$(CD_3)_2CO$/DMSO] 105.12 (C-7), 133.76 (C-7a), 129.92 (C-5a), 132.00 (C-5), 170.24 (C=S), 183.17 (C=N).

5-Methylthieno[3,4-d]thiazine-1,3-thione (171b)

4-Amino-3-cyano-2-methylthiophene (2.3g, 0.017mol), pyridine (16.6g, 0.2mol) and carbon disulphide (21.5g, 0.2mol) were refluxed for 1 hour. The solution was cooled and diluted with ether (50ml), the precipitate being collected, washed with ether and dried. The crude

pyridine salt was ground in a mortar with 0.1M hydrochloric acid (20ml). The resulting thiazine was filtered off, washed with ether and dried. The crude product was purified with glacial acetic acid to give the thiazine thione (1.96g, 54%) mpt.>350°c (Found: C, 39.9; H, 3.00; N, 12.6. $C_7H_6N_2S_3$ requires, C, 39.23; H, 2.82; N, 13.07) MS(CI) M+H 215. ν max 3100cm^{-1} (NHst), 1600cm^{-1} (NHdef). δ H[$(CD_3)_2$CO/DMSO] 2.7 (3H, s, $ArCH_3$), 3.2 (1H, s, exchanges with D_2O, NH), 7.9 (1H, s, ArH).

δ C[$(CD_3)_2$CO/DMSO] 98.36 (C-7), 135.11 (C-7a), 135.06 (C-5a), 150.57 (C-5), 184.07 (C=S), 169.99 (C=N), 18.05 (CH_3).

Thieno[3,4-d]pyrimidine-1,3-dithione (172a)

The thienothiazine thione (171a) (1.0g, 0.005mol) and 1M sodium hydroxide (15ml) were heated on a steam bath for 30 minutes. The solution was cooled and acidified with glacial acetic acid. The precipitated solid was collected, washed with ether and dried. The crude product was recrystallised from glacial acetic acid to give the dithione (0.88g, 88%) mpt.329-332°c dec (Found: C, 36.9; H, 2.2; N, 14.7. $C_6H_4N_2S_3$ requires, C, 36.01; H, 2.02; N, 14.7) MS(CI) M+H 201. ν max 3100cm^{-1} (NHst), 1680cm^{-1} (C=Sst), 1600cm^{-1} (NHdef). δ H[$(CD_3)_2$CO/DMSO] 6.8 & 8.1 (2H, d, ArH). δ C[$(CD_3)_2$CO/DMSO] 104.99 (C-7), 138.17 (C-7a), 122.52 (C-5a), 129.86 (C-5), 174.14 (C=S), 155.96 (C=S).

5-Methylthieno[3,4-d]pyrimidine-1,3-dithione (172b)

The thiazine (171b) (1.0g, 0.005mol) was heated on a steam bath with 1M sodium hydroxide (20ml) for 3 hours. The resulting deep red solution was cooled in ice and acidified with glacial acetic acid. The solid was filtered off, washed with water, then ether and dried. The crude product was recrystallised from glacial acetic acid to yield the dithione (0.67g, 67%) mpt.299-301°c (Found: C, 39.81; H, 3.04; N, 12.93. $C_7H_6N_2S_3$ requires, C, 39.23; H, 2.82; N, 13.07) MS(CI) M+H 215. ν max 3100cm^{-1} (NHst), 1600cm^{-1} (NHdef). δ H[$(CD_3)_2$CO/DMSO] 2.2 (3H, s, $ArCH_3$), 2.5 (1H, s, exchanges with D_2O, NH), 7.6 (1H, s, ArH). δ C[$(CD_3)_2$CO/DMSO] 106.83 (C-7), 132.47 (C-7a), 128.96 (C-5a), 128.53 (C-5), 183.31 (C=S), 183.59 (C=S), 11.49 (CH_3).

7-Methylthieno[3,4-d]-1,3-thiazinethione (173)

4-Amino-3-cyano-5-methylthiophene (2.3g, 0.017mol), pyridine (16.6g, 0.2mol) and carbon disulphide (21.5g, 0.2mol) were refluxed for 1 hour. The solution was cooled and diluted with ether (50ml), the precipitate being filtered off, washed well with ether and dried. The pyridine salt was ground in a mortar with 0.1M hydrochloric acid (20ml). The resulting thiazine was

collected, washed with water then ethanol and dried. The crude product was recrystallised from glacial acetic acid to give the thiazine (2.24g, 63%) mpt.272-274°c dec (Found: C, 39.30; H, 3.06; N, 13.20. $C_7H_6N_2S_3$ requires, C, 39.25; H, 2.80; N, 13.08) MS(CI) M+H 215. ν max 3100cm^{-1} (NHst), 1600cm^{-1} (NHdef). δ H[$(CD_3)_2CO$/DMSO] 2.5 (3H, s, $ArCH_3$), 3.2 (1H, s, exchanges with D_2O, NH), 8.1 (1H, s, ArH). δ C[$(CD_3)_2CO$/DMSO] 118.30 (C-7), 130.12 (C-7a), 129.80 (C-5a), 128.43 (C-5), 170.38 (C=S), 183.23 (C=N), 11.56 (CH_3).

7-Methylthieno[3,4-d]pyrimidine-1,3-dithione (174)

4-Amino-3-cyano-5-methylthiophene (1.72g, 0.012mol) in a mixture of pyridine (4.9g, 0.06mol) and carbon disulphide (6.3g, 0.06mol) was refluxed for 2 hours and then allowed to stand overnight at room temperature. The precipitated pyridine salt of the thiazine was filtered off and ground in a mortar with 0.1M hydrochloric acid, washed with water, ethanol and dried. The filtrate was diluted with ethanol (60ml) and the precipitated dithione was collected, washed with ethanol and ether and dried. Both the thiazine and the dithione were recrystallised from glacial acetic acid.

Thiazine: (1.42g, 53%) mpt.272-275°c dec.

Dithione: (0.31g, 12%) mpt.269-271°c dec.

7-Methylthieno[3,4-d]pyrimidine-1,3-dithione (174)

The thieno[3,4-d]thiazinethione (173) (1.0g, 0.005mol) and 1M sodium hydroxide were heated on steam bath for 30 minutes. The solution was cooled and acidified with glacial acetic acid. The precipitated solid was collected, washed with water and ether and dried. The crude product was recrystallised from glacial acetic acid to give the dithione (0.97g, 97%) mpt.268-270°c dec (Found: C, 42.3; H, 3.2; N, 14.1. $C_7H_6N_2S_3$ requires, C, 39.23 H, 2.82; N, 13.07) MS(CI) M+H 215. ν max 3100cm^{-1} (NHst), 1680cm^{-1} (C=Sst), 1600cm^{-1} (NHdef).

δ H[$(CD_3)_2CO$/DMSO] 2.1 (3H, s, $ArCH_3$), 2.6 (1H, s, exchanges with D_2O, NH), 7.7 (1H, s, ArH).

δ C[$(CD_3)_2CO$/ DMSO] 128.30 (C-7), 130.25 (C-7a), 129.92 (C-5a), 118.23 (C-5), 183.23 (C=S),183.69 (C=S), 11.56 (CH_3).

Bis(methylthio)-7-methylthieno[3,4-d]pyrimidine (175)

The thienopyrimidine-1,3-dithione (174) (0.5g, 0.0023mol), dimethyl sulphate (0.57g, 0.0046mol), potassium carbonate (1.0g) and butan-2-one (25ml) were stirred and refluxed for 1 hour. The mixture was filtered hot and the solvent evaporated to give an orange-yellow solid. This crude

mixture was purified by column chromatography (silica gel,eluted with chloroform). The product was recrystallised from ethanol to give the bis-methylated thiopyrimidine (0.35g, 63%) mpt.86-88°c (Found: C, 44.6; H, 4.3; N, 11.7. $C_9H_{10}N_2S_3$ requires, C, 44.62; H, 4.13; N, 11.57) MS(CI) M+H 243. ν max 3100cm^{-1} (CHst), 2900cm^{-1} (CHst), 1560 & 1500cm^{-1} (C=Cst). δ H[$CDCl_3$] 2.7-2.8 (9H, t, 3xCH_3), 7.7 (1H, s, ArH). δ C[$CDCl_3$] 128.50 (C-7), 145.19 (C-7a), 126.23 (C-5a), 115.70 (C-5), 163.43 (C-2), 166.87 (C-4), 11.30 (CH_3), 11.82 (SCH_3), 14.15 (SCH_3).

Attempted preparation of 3-ethoxymethyleneamino-4-cyano-thiophene (180)

A. 4-Amino-3-cyanothiophene (2.0g, 0.016mol), triethyl orthoformate (7.0g, 0.05mol) and acetic anhydride (2ml) were refluxed for 2 hours. The excess solvent was removed and the semi-solid was triturated with ice-cold petroleum ether. The product was collected, washed with petroleum ether and dried. Spectral analysis showed the product to be 3-acetylamino-4-cyanothiophene (129) (1.96g, 73%) mpt.170-171°c.

B. 4-Amino-3-cyanothiophene (1.24g, 0.01mol), triethyl orthoformate (3.7g, 0.025mol) and trifluoroacetic acid (0.1ml) were refluxed for 2 hours. The excess triethyl orthoformate was evaporated to give a brown solid which was triturated with petroleum ether and collected. Spectral analysis showed that the nitrile function had been lost, but that the NH_2 group was still intact.

C. 4-Amino-3-cyanothiophene (2.0g, 0.016mol) with a catalytic amount of the amine hydrochloride, was added to triethyl orthoformate (10ml) and heated. The ethanol formed during the reaction was removed by fractional distillation. The excess triethyl orthoformate was removed and the crude solid was triturated with petroleum ether, filtered off and dried. Spectral analysis showed loss of the nitrile function.

N-phenyl-N-(o-cyanothienyl)urea (184a)

4-Amino-3-cyanothiophene (1.0g, 0.008mol) was added to phenyl isocyanate (0.95g, 0.008mol) at room temperature. There was an immediate exothermic reaction and the mixture solidified. The product was collected and recrystallised from ethanol to furnish the title product (1.56g, 80%)

Mpt.181-183°c (Found: C, 59.5; H, 3.7; N, 17.3. $C_{12}H_9N_3OS$ requires, C,59.24; H, 3.73; N, 17.27) MS(CI) M+H 244. ν max 3350cm^{-1} (NHst), 2200cm^{-1} (CNst), 1710cm^{-1} (COst), 1600cm^{-1} (NHdef). δ H[$CDCl_3$/DMSO] 3.3 (1H, s, exchanges with D_2O, NH), 7.0-9.2 (7H, m, ArH), 7.0 (1H, s, exchanges with D_2O, NH). δ C[$CDCl_3$/DMSO] 107.91 (C-2), 137.65 (C-3), 103.2 (C-4), 134.08 (C-5), 139.21 (C-6), 118.37 (C-7), 128.69 (C-8), 122.26 (C-9), 113.89 (CN), 152.26 (CO).

N-Phenyl-N-(o-cyanothienyl-5-methyl)urea (184b)

4-Amino-3-cyano-2-methylthiophene (1.0g, 0.007mol) was added to phenyl isocyanate (0.95g, 0.007mol) at room temperature. There was an immediate exothermic reaction and the mixture solidified. The product was collected and recrystallised from ethanol to afford the urea (0.92g, 49%) mpt.198-200°c (Found: C, 60.8; H, 4.3; N, 16.1. $C_{13}H_{11}N_3OS$ requires, C, 60.68; H, 4.31; N, 16.33) MS(CI) M+H 258. ν max 3350cm^{-1} (NHst), 2200cm^{-1} (CNst), 1700cm^{-1} (COst), 1580cm^{-1} (NHdef). δ H[$CDCl_3$/DMSO] 2.6 (3H, s, $ArCH_3$), 7.0-9.1 (7H, m, ArH). δ C[$CDCl_3$/DMSO] 104.80 (C-2), 136.42 (C-3), 102.59 (C-4), 149.14 (C-5), 139.27 (C-6), 118.17 (C-7), 128.63 (C-8), 122.07 (C-9), 14.80 (CH_3), 152.13 (CO), 113.56 (CN).

Attempted preparation of N-phenylthieno[3,4-d]-1,3-pyrimidine (185a)

A suspension of N-phenyl-N-(o-cyanothienyl)urea (184a) (0.3g, 0.001mol) in methanol (75ml) containing sodium (1.2g, 0.05mol) was heated under reflux, with stirring, for 16 hours. The solvent was evaporated to give a cream solid (0.1g). The desired pyrimidine was not obtained; hydrolysis of the nitrile function was suspected.

3-Phenyl-4(3H)-imino-2(1H)-thienopyrimidinethione (187a)

4-Amino-3-cyanothiophene (1.15g, 0.01mol) and phenyl isothiocyanate (1.5g, 0.01mol) were heated to 50°c for 20 hours with occasional shaking. The cooled semi-solid was triturated with ether, collected, washed with ether and dried. The crude product was recrystallised from ethanol to afford the pyrimidine (1.63g, 72%) mpt.233-234°c (Found: C, 55.7; H, 3.84; N, 16.30. $C_{12}H_9N_3S_2$ requires, C, 55.6 ; H, 3.51; N 16.20) MS(CI) M+H 260. ν max 3200cm^{-1} (NHst), 1590cm^{-1} (NHdef). δ H[$CDCl_3$/DMSO] 3.3 (1H, br, exchanges with D O, NH), 6.8-8.0 (7H, m, ArH).
δ C[$CDCl_3$/DMSO] 122.26 (C-7), 116.42 (C-7a), 104.08 (C-5a), 129.27 (C-5), 186.93 (C=S), 174.20 (C=N), 138.24 (C-8), 128.50 (C-9), 128.50 (C-10), 130.23 (C-11).

3-Phenyl-4(3H)-imino-2(1H)-5-methylthienopyrimidinethione

(187b)

4-Amino-3-cyano-2-methylthiophene (1.0g, 0.007mol) and phenyl isothiocyanate (0.95g, 0.007mol) were reacted as described for compound (187a). The crude product was recrystallised from ethanol to give the title pyrimidine (1.25g, 66%) mpt.350°c dec (Found: C, 56.9; H, 3.9; N, 15.42 . $C_{13}H_{11}N_3S_2$ requires, C, 57.14; H, 4.0; N, 15.38) MS(CI) M+H 274. ν max 3200cm^{-1} (NHst), 1600cm^{-1} (NHdef). δ H[$CDCl_3$/DMSO] 2.5 (3H, s, $ArCH_3$), 7.0-7.8 (6H, m, ArH), 3.6 (1H, br,exchanges with D_2O, NH). δ C[$CDCl_3$/DMSO] 99.08 (C-7), 116.68 (C-7a), 135.45 (C-5a), 145.64 (C-5), 172.66 (C=S), 146.16 (C=N), 139.66 (C-8), 120.77 (C-9), 130.18 (C-10), 124.41 (C-11), 16.30 (CH_3).

3-Phenyl-4(3H)-imino-2(1H)-7-methylthienopyrimidinethione

(187c)

4-Amino-3-cyano-5-methylthiophene (1.28g, 0.009mol) and phenyl isothiocyanate (1.5g, 0.01mol) were treated as described above. The crude product was recrystallised from ethanol to afford the pyrimidine (1.82g, 76%) mpt.245°c dec (Found: C, 57.3; H, 4.0; N, 15.3. $C_{13}H_{11}N_3S_2$ requires C, 57.12; H, 4.06; N, 15.37) MS(CI) M+H 274. ν max 3200cm^{-1} (NHst), 1600cm^{-1} (NHdef). δ H[$CDCl_3$/DMSO] 2.6 (3H, s, $ArCH_3$), 7.0-8.1 (6H, m, ArH), 3.4 (1H, br,

exchanges with D_2O, NH). δ C[$CDCl_3$/DMSO] 115.38 (C-7), 138.6 (C-7a), 117.98 (C-5a), 124.21 (C-5), 181.81 (C=S), 150.51 (C=N), 121.03 (C-8), 122.13 (C-9), 128.37 (C-10), 135.77 (C-11), 11.07 (CH_3).

Attempted preparation of 4-anilino-2(1H)thieno[3,4-d]-pyrimidine (188)

A mixture of 4-amino-3-cyanothiophene (1.24g, 0.01mol) and phenyl isocyanate (1.2g, 0.01mol) was immersed in an oil bath preheated to 130°c. A vigorous exothermic reaction occurred and the mixture became solid. Heating was continued for a further 2 hours. The solid was cooled, crushed and stirred with hot 1M sodium hydroxide. Undissolved material was discarded and the filtrate acidified with 4M hydrochloric acid. No product was obtained, most of the mass seemed to be the insoluble charred material.

Attempted preparation of 4-anilino-2(1H)thieno[3,4-d]-pyrimidinethione (189)

A mixture of 4-amino-3-cyanothiophene (1.24g, 0.01mol) and phenyl isothiocyanate (1.48g, 0.01mol) were heated together in a Woods metal bath at 160-180°c for 30 minutes. The solid was cooled, crushed and digested in

hot ethyl acetate (50ml). The undissolved material was filtered off and the filtrate evaporated to dryness to give a black solid. Spectroscopic analysis showed that the thiophene ring had been decomposed.

3-Acetylamino-4-cyano-5-methylthiophene (190)

4-Amino-3-cyano-2-methylthiophene (1.38g, 0.01mol) and acetic anhydride (1.02g, 0.01mol) were swirled together at room temperature. The semi-solid was poured into ice/water and the solid was collected, washed with water, and dried. The crude product was recrystallised from ethanol to give the amide (1.35g, 75%) mpt.176-178°c (Found: C, 53.3; H, 4.5; N, 15.4. $C_8H_8N_2OS$ requires, C, 53.31; H, 4.47; N, 15.54) MS(CI) M+H 181. ν max 3300cm^{-1} (NHst), 2200cm^{-1} (CNst), 1700cm^{-1} (COst), 1580cm^{-1} (NHdef). δ H[$CDCl_3$] 2.2 (3H, s, $ArCH_3$), 2.4 (3H, s, $ArCOCH_3$), 3.5 (1H, br, exchanges with D_2O, NH), 8.0 (1H, S, ArH). δ C[$CDCl_3$] 109.02 (C-2), 134.80 (C-3), 113.50 (C-4), 149.86 (C-5), 23.76 ($CO\underline{C}H_3$), 15.00 (CH_3), 102.65 (CN), 168.23 (CO).

3-Acetylamino-4-carboxamido-5-methylthiophene (191a)

3-Acetylamino-4-cyano-5-methylthiophene (1.0g, 0.005mol) and dimethyl sulphoxide (7ml) were stirred and cooled in

ice, while 30% hydrogen peroxide (1ml) and a catalytic amount of potassium carbonate (0.1g) were added. An exothermic reaction occurred. When this had subsided, the cooling was removed and the mixture was stirred at room temperature for 10 minutes. The precipitated solid was collected, washed with water and dried. The crude product was recrystallised from water to afford the title compound (0.74g, 67%) mpt.189-190°c (Found: C, 49.1; H, 5.0; N, 14.1. $C_8H_{10}N_2O_2S$ requires, C, 48.47; H, 5.08; N, 14.13) MS(CI) M+H 199. ν max 3400cm^{-1} (NHst), 3300cm^{-1} (NH_2st), 1670cm^{-1} (COst), 1650cm^{-1} (COst), 1600cm^{-1} (NH_2def), 1570cm^{-1} (NHdef). δ H[$CDCl_3$/DMSO] 2.1 (3H, s, $ArCH_3$), 2.7 (3H, s, $COCH_3$), 3.4 (1H, s, exchanges with D_2O, NH), 7.7-7.5 (2H, br, exchanges with D_2O, NH_2), 8.1 (1H, s, ArH). δ C[$CDCl_3$/DMSO] 106.03 (C-2), 135.77 (C-3), 123.82 (C-4), 140.05 (C-5), 23.96 ($CO\underline{C}H_3$), 15.45 (CH_3), 167.00 ($CONH_2$), 167.19 (CO).

4-Acetylamino-3-thenoic acid (192)

3-Acetylamino-4-cyanothiophene (129) (1.0g, 0.006mol) and dimethyl sulphoxide (7ml) were stirred and cooled in ice, while 30% hydrogen peroxide (1ml) and a catalytic amount of potassium carbonate (0.1g) were added. An exothermic reaction occurred. When this subsided the cooling was removed and the mixture was stirred at room temperature

for 10 minutes. The precipitated solid was collected, washed with water and dried. The crude product was recrystallised from water to afford the acid (0.7g, 63%) mpt.198-200°c (lit.[103]..207-208°c). ν max 3300-3100cm^{-1} (OHst), 1660cm^{-1} (COst), 1650cm^{-1} (COst), 1600cm^{-1} (NHdef).

δ H[$CDCl_3$/DMSO] 2.1 (3H, s, $COCH_3$), 3.4 (1H, s, exchanges with D_2O, NH), 7.8 & 8.3 (2H, d, ArH), 12.2 (1H, br, exchanges with D_2O, OH). δ C[$CDCl_3$/DMSO] 128.24 (C-2), 123.95 (C-3), 136.87 (C-4), 109.55 (C-5), 167.45 ($COCH_3$), 24.09 (CH_3), 166.45 (COOH).

4-Chloro-3-cyano-5-methylthiophene (193)

Copper sulphate (3.7g) and sodium chloride (3.4g) in water (7ml) were refluxed, then concentrated hydrochloric acid (1ml) and copper turnings (2.0g) were added. The mixture was refluxed until a colourless solution was obtained. The solution was cooled in ice.

4-Amino-3-cyano-5-methylthiophene (2.0g, 0.015mol) was added to a stirred solution of concentrated hydrochloric acid (3ml) and water (14ml) and cooled to 0°c. A solution of sodium nitrite (1.0g, 0.015mol) in water (3.5ml) was added dropwise, maintaining the temperature range between 0-5°c. This diazonium solution was added portionwise to the previously prepared solution of cuprous chloride, slowly with stirring. The mixture was allowed to stand at

room temperature for 1 hour, then filtered and the solid washed with water and dried. The crude product was sublimed using a water pump (2.0g, 54%) mpt.69-71°c (Found: C, 46.3; H, 2.7; N, 8.9. C_6H_4NSCl requires, C, 45.72; H, 2.56; N, 8.89) MS(CI) M+H 158. ν max 2225cm^{-1} (CNst). δ H[$CDCl_3$] 2.8 (3H, S, $ArCH_3$), 8.1 (1H, s, ArH). δ C[$CDCl_3$] 113.97 (C-2), 134.60 (C-3), 127.20 (C-4), 132.85 (C-5), 13.12 (CH_3), 111.03 (CN).

1-(4-Azo-3-cyano-5-methylthienyl)-2-naphthol (194)

4-Amino-3-cyano-5-methylthiophene hydrochloride (1.0g, 0.005mol) in water (25ml) and concentrated hydrochloric acid (2.5ml) was stirred and cooled in ice. A saturated solution of sodium nitrite was added dropwise, maintaining the temperature between 0-5°c, until starch-iodide paper showed a positive test for excess nitrous acid. The reaction mixture was neutralised to Congo Red paper with saturated sodium acetate solution. A solution of β-naphthol (0.87g, 0.006mol) in 10% sodium hydroxide (19ml) was added. The cooling was removed and the mixture was stirred at room temperature for 1 hour. Acidification with concentrated hydrochloric acid afforded a brown solid which was collected, washed with water and dried. The crude product was recrystallised from ethanol to yield the azo compound (0.87g, 52%) mpt.224-225°c (Found: C, 65.7;

H, 3.9; N, 13.8. $C_{16}H_{11}N_3OS$ requires, C, 65.51; H, 3.78; N, 14.32) MS(CI) M+H 294. ν max 3300cm^{-1} (OHst), 2200cm^{-1} (CNst). δ H[$CDCl_3$/DMSO] 2.8 (3H, s, $ArCH_3$), 7.1-8.0 (7H, m, ArH). δ C[$CDCl_3$/DMSO] 136.48 (C-2), 128.43 (C-3), 133.36 (C-4), 122.39 (C-5), 122.02 (C-6), 122.39 (C-7), 124.86 (C-8), 128.17 (C-9), 128.23 (C-10), 129.86 (C-11), 130.24 (C-12), 132.14 (C-13), 132.78 (C-14), 154.66 (C-15), 13.31 (CH_3).

4-Azo-3-cyano-5-methylthiophene tetrafluoroborate (195).

4-Amino-3-cyano-5-methylthiophene hydrochloride (1.74g, 0.01mol), fluoroboric acid (2.64g, 0.03mol) and water (3ml) were stirred and cooled to 0-5°c. A solution of sodium nitrite (0.69g, 0.01mol) in water (2ml) was added dropwise maintaining the temperature range. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The solid was filtered off, washed with water and dried affording the salt (0.78g, 33%) mpt.146-148°c (dec). ν max 2225cm^{-1} (N=Nst), 2200cm^{-1} (CNst).

Attempted preparation of 3-cyano-4-fluoro-5-methyl-thiophene (196)

The diazonium tetrafluoroborate (0.2g, 0.008mol) was

heated on a steam bath. After several seconds the solid began to bubble and a cloud of white fumes was given off. The dark brown residue, which smelled strongly of H_2S, was extracted with chloroform and stirred at room temperature with charcoal for 30 minutes. Filtration and evaporation gave a sticky, brown gum which would not solidify on trituration with ether. Spectral analysis showed the thiophene ring had decomposed.

N-1-Cyanoethyl-N-2-cyanoethylmethylamine (197)

A stirred solution of β-methylaminopropionitrile (16.8g, 0.2mol) in benzene (20ml) was treated at 50°c with lactonitrile (14.2g, 0.2mol). The heat was removed and an exothermic reaction ensued. The mixture was allowed to stand at room temperature overnight. The free water was removed and the organic fraction dried over sodium sulphate, filtered and evaporated. The crude yellow/orange oil was distilled to give the dinitrile (25.29g, 92%) bpt.125-130°c/1.5mm, lit.[96] bpt.117-121°c/1mm. ν max 2990cm^{-1} (CHst), 2250cm^{-1} (CNst). δ H[$CDCl_3$] 1.4-1.5 (3H, d, CH_3), 2.3 (1H, s, CH), 2.4-2.7 (4H, m, 2xCH_2), 3.5-4.0(1H, q, CH).

4-Amino-3-cyano-1,5-dimethyl-3-pyrroline (198)

The dinitrile (197) (25.0g, 0.18mol) was added dropwise over a period of one hour to a refluxing solution of sodium (0.2g, 0.008mol) in t-butanol (50ml). The mixture was refluxed for a further two hours after the addition was complete. The mixture was cooled, diluted with ether (100ml) and left to stand at room temperature overnight. The precipitated product was collected, washed with ether and dried to afford the pyrroline (15.5g, 62%). Mpt.150-152°c, lit.[96] mpt.148-151°c. ν max 3400-3200cm^{-1}

(NH_2 st), 2200cm^{-1} (CNst), 1680cm^{-1} (C=Cst), 1620cm^{-1} (NH_2def). δ H[$CDCl_3$/DMSO] 1.1-1.3 (3H, d, CH_3), 1.9 (2H, s, CH), 2.4 (3H, s, CH_3), 3.2-3.7 (1H, q, CH). δ C[$CDCl_3$/DMSO] 16.42 (CH_3), 39.93 (N-CH_3), 58.37 (C-5), 65.64 (C-2), 66.94 (=C-CN), 117.85 (CN), 163.17 (=C-NH_2).

4-Amino-3-cyano-1,5-dimethylpyrrole (199)

The pyrroline (2.0g, 0.015mol), p-chloranil (3.58g, 0.015mol) and dry toluene (20ml) were refluxed together for three hours. The mixture was allowed to cool and the solvent was removed to give a green-brown salt (3.0g). The salt was added to 4M hydrochloric acid and the insoluble reduced chloranil was removed by filtration. The filtrate was basified with concentrated ammonia solution and the product extracted with ethyl acetate, using a liquid-liquid extractor. The crude product was recrystallised from cyclohexane to give the pyrrole (1.76g, 89%) mpt.102-103°c (Found: C, 62.4; H, 6.5; N, 30.8. $C_7H_9N_3$ requires C, 62.20; H, 6.71; N, 31.09.) MS(CI) M+H 136. ν max 3400-3300cm^{-1} (NH_2st), 3100cm^{-1} (CHst), 2200cm^{-1} (CNst), 1620cm^{-1} (NH_2def). δ H[$CDCl_3$] 2.0 (3H, s, CH_3), 3.0-3.3 (2H, br, exchanges with D_2O, NH_2), 3.5 (3H, s, CH_3), 6.8 (1H, s, ArH). δ C[$CDCl_3$] 8.44 (C5-CH_3), 34.61 (N-CH_3), 85.00 (C-3), 115.00 (C-5), 116.16 (CN), 123.76 (C-2), 129.53 (C-4).

Attempted preparation of 4-Amino-3-carboxamido-1,5-dimethylpyrrole (200)

A.

The aminonitrile (199) (0.5g, 0.003mol) was refluxed with finely powdered potassium hydroxide (0.84g, 0.015mol) in t-butanol (25ml) for one hour. The mixture was cooled and the solvent removed. Saturated brine solution (50ml) was added to the residue and the product extracted with chloroform (3x20ml). The combined organic extracts were dried over sodium sulphate, filtered and the solvent evaporated to give an orange-brown solid which immediately decomposed on exposure to the atmosphere.

B.

The aminonitrile (199) (0.5g, 0.003mol) in dimethyl sulphoxide (7ml) was stirred and cooled in ice while 30% hydrogen peroxide (1ml) and a catalytic amount of potassium carbonate (0.1g) were added. The cooling was removed but the expected exothermic reaction did not ensue. The mixture was then warmed to 50°c for 30 mins. The reaction mixture was poured into water and the precipitated solid filtered off, washed with water and dried. The starting aminonitrile was recovered (0.42g, 84% recovery).

Attempted preparation of pyrrolo[3,4-d]-1,2,3-triazin-4-one (201)

A.

The aminonitrile (199) (0.5g, 0.003mol) was refluxed with finely powdered potassium hydroxide (1.0g, 0.02mol) in t-butanol (25ml) for one hour. The mixture was cooled and the solvent evaporated off. Saturated brine solution (20ml) was poured onto the residue and the product extracted with chloroform (3x20ml). The combined organic fractions were dried over sodium sulphate, filtered and the filtrate evaporated to approximately 2ml of solution. This residue was added to 2M hydrochloric acid. The separated aqueous layer was stirred and cooled in ice. Saturated sodium nitrite was added dropwise, keeping the temperature between 0-5°c, until a positive test for excess nitrous acid was obtained with starch-iodide paper. The mixture was stirred at room temperature for four hours. No product had precipitated out during this time. Extraction with ethyl acetate (1x10ml) did not yield the desired triazinone upon evaporation. Decomposition of the product seemed to have occurred.

B.

The aminonitrile (0.2g. 0.0015mol) was added to concentrated sulphuric acid (5ml) and left to stand at room temperature overnight. The solution was poured onto ice, basified with concentrated ammonia and then extracted with ethyl acetate (2x10ml). The organic fractions were dried over sodium sulphate, filtered and evaporated to appoximately 2ml in volume. This residue was added to 4M hydrochloric acid (5ml) and the resultant mixture was stirred and cooled to 0°c. A saturated solution of sodium nitrite was added , maintaining the temperature range between 0-5°c, until a positive test with starch-potassium iodide paper was obtained. The reaction mixture was left to stand at room temperature for several hours, but no precipitated solid was obtained. The mixture was extracted with ethyl acetate (2x10ml), dried and evaporated. The title product was not obtained since decomposition of the pyrrole had occurred.

C.

The aminonitrile (0.5g, 0.003mol) was refluxed with finely powdered potassium hydroxide (1.0g, 0.02mol) in t-butanol (25ml) for one hour. The mixture was cooled and the butanol removed. Saturated brine solution (5ml) was added to the residue and the mixture was extracted with

ethyl acetate (2x20ml). The combined extracts were dried and evaporated to approximately 15ml in volume. p-Toluene sulphonic acid monohydrate (0.68g, 0.004mol) was added and the mixture was evaporated down to about 2ml in volume then added to 4M hydrochloric acid (10ml). The aqueous layer was separated off and cooled in ice to 0°c. A saturated sodium nitrite solution was added dropwise, maintaining the temperature range, until starch-potassium iodide paper gave a positive test for excess nitrous acid. The mixture was stirred at room temperature overnight. No solid precipitated out. The mixture was extracted with ethyl acetate (2x20ml), dried, filtered and evaporated. The spectral data of the residue indicated that decomposition of the pyrrole had occurred.

D.

The aminonitrile (0.5g, 0.003mol) was heated at 100°c with polyphosphoric acid (approx.1.0g) for two hours. The mixture was poured into ice-water (20ml) and basified with 4M potassium hydroxide and extracted with ether (3x10ml). The combined ether extracts were evaporated to approximately 2ml in volume and then 4M hydrochloric acid (10ml) was added. The mixture was cooled in ice and diazotised with saturated sodium nitrite, maintaining the temperature between 0-5°c. The mixture was allowed to

stir at room temperature overnight. No solid precipitated out. The mixture was extracted with ethyl acetate (2x20ml) and the combined extracts were dried, filtered and evaporated. The residue was malodorous indicating that decomposition had taken place.

Attempted preparation of 4-Amino-3-carboxamido-1,5-dimethyl-3-pyrroline (202)

The pyrroline (1.0g, 0.007mol) was refluxed with finely powdered potassium hydroxide (2.0g, 0.036g) in t-butanol (50ml) for two hours. Tlc of the reaction mixture was inconclusive. The mixture was cooled and the butanol removed. Saturated brine (10ml) was poured onto the residue and the product was extracted with chloroform (3x50ml). The combined organic fractions were dried, filtered and evaporated to give a cream solid. Identification of this solid showed it to be recovered pyrroline (0.88g, 88% recovery).

3-Acetylamino-4-cyano-1,2-dimethylpyrrole (203)

4-Amino-3-cyano-1,5-dimethylpyrrole (199) (1.0g, 0.007mol) was added to acetic anhydride (2ml) with cooling. The mixture was left to stand at room temperature for ten minutes and then poured into ice-water (20ml); no solid

formed. The product was extracted with chloroform (3x20ml). The combined extracts were washed with sodium bicarbonate (2x20ml) and water (1x20ml). The organic layer was dried, filtered and evaporated to give an oil which solidified on standing. The crude product was recrystallised from ethanol to give the pure acetyl derivative (0.84g, 64%) mpt.120-122°c (Found C, 60.96; H, 6.25; N, 23.48. $C_9H_{11}N_3O$ requires C, 61.02; H, 6.21; N, 23.73) MS(CI) M+H 178. ν max 3300cm^{-1} (NHst), 2200cm^{-1} (CNst), 1660cm^{-1} (COst), 1620cm^{-1} (NHdef). δ H[$CDCl_3$/DMSO] 2.1 (3H,s,CH_3), 2.6 (3H, s, $COCH_3$), 3.5 (3H, s, NCH_3), 6.9 (1H, s, ArH). δ C[$CDCl_3$/DMSO] 10.26 (CH_3), 27.04 ($CO\underline{C}H_3$), 35.79 (NCH_3), 85.21 (C4), 115.72 (C2), 122.96 (C5), 129.16 (C3), 153.27 ($\underline{C}OCH_3$).

Attempted preparation of 3-acetylamino-4-carboxamido-1,2-dimethylpyrrole (204)

A.

3-Acetylamino-4-cyanopyrrole (203) (0.2g, 0.001mol) was refluxed with finely powdered potassium hydroxide (0.33g, 0.006mol) in t-butanol (25ml). The mixture was cooled and the solvent removed. Saturated brine solution (10ml) was added to the residue and the product was extracted with chloroform (2x20ml). The combined layers were dried,

filtered and evaporated to give a solid which was shown to be recovered starting material (0.14g, 70% recovery).

B.

The acetylaminonitrile (203) (0.25g, 0.004mol) was stirred in dimethyl sulphoxide (7ml) and cooled in ice while 30% hydrogen peroxide (1ml) and a catalytic amount of potassium carbonate (0.1g) were added. The cooling was removed; no exothermic reaction occurred. The mixture was heated at 50°c for 30 minutes, then poured into water. The precipitated solid was filtered off, washed with water and dried; it was found to be starting material. (0.2g, 80% recovery).

4-Amino-3-cyano-1,5-dimethylpyrrole hydrochloride (205)

Hydrogen chloride gas was bubbled through dry ether (20ml) for five minutes. The aminonitrile (199) (0.5g, 0.003mol) was dissolved in dry ethanol (20ml) and added to the ether/hydrogen chloride solution. An exothermic reaction took place and a white precipitate formed. The suspension was cooled in ice and the solid was filtered off, washed with ether and dried to give the hydrochloride (0.55g, 87%) mpt.>250°c.

Attempted preparation of 4-amino-3-carboxamido-1,5-dimethylpyrrole hydrochloride (206)

The amine hydrochloride (205) (0.25g, 0.0015mol) was dissolved in dimethyl sulphoxide (5ml) and stirred in ice while 30% hydrogen peroxide (1ml) and a catalytic amount of potassium carbonate (0.1g) were added. No exothermic reaction took place. The mixture was warmed to 50°c for 30 minutes, then poured into water. The precipitated solid was filtered off, washed with water and dried. The solid was identified as recovered starting material (0.15g, 60%).

N-1-Cyanoethyl-N-2-cyanomethylamine (207)

β-Methylaminopropionitrile (16.8g, 0.2mol) in benzene (20ml) was stirred and heated to 50°c. Glycolonitrile (11.4g, 0.2mol) was added portionwise whereupon an exothermic reaction occurred. The mixture was left to stand at room temperature overnight. The free water was removed and the organic fraction was evaporated to give an oil (20.37, 83%) bpt.82-85°c/1mm. ν max 2900cm^{-1} (CHst), 2250cm^{-1} (CNst). δ H[$CDCl_3$] 2.3 (3H, s, NCH_3), 2.5-2.8 (4H, m, 2xCH_2), 3.6 (2H, s, CH_3).

4-Amino-3-cyano-1-methylpyrroline (208)

The dinitrile (207) (20.0g, 0.16mol) was added dropwise to a refluxing solution of sodium (0.2g) in t-butanol (50ml) over a period of one hour. After the addition was complete, the mixture was refluxed for a further two hours. The solution was cooled and the solvent evaporated off. The semi-solid was triturated with ether, filtered off and dried. The crude product was recrystallised from chloroform to give the title pyrroline (18.42g, 92%) mpt.127-128°c (Found: C, 58.2; H, 7.5; N, 34.3. $C_6H_9N_3$ requires: C, 58.52; H, 7.37; N, 34.12) MS(CI) M+H 124. ν max 3400-3300cm^{-1} (NH_2st), 2000cm^{-1} (CNst), 1680cm^{-1} (C=Cst), 1620cm^{-1} (NH_2def). δ H[$CDCl_3$/DMSO] 2.3 (3H, s, NCH_3), 3.4-3.2 (4H, s, 2xCH_2), 6.4-6.2 (2H, br, exchanges with D_2O, NH_2). δ C[$CDCl_3$/DMSO] 38.74 (N-Me), 66.17 (C-2), 69.04 (C-3), 118.23 (C=N), 162.91 (C-4), 60.32 (C-5).

Attempted preparation of 4-amino-3-cyano-1-methylpyrrole (209)

The pyrroline (208) (1.0g, 0.008mol) was refluxed with p-chloranil (2.0g, 0.008mol) in dry toluene (20ml) for four hours. The solvent was removed to give a brown-green salt. The salt was decomposed in 4M hydrochloric acid and

the reduced chloranil was filtered off. The solution was basified with concentrated ammonia solution and the product extracted with ethyl acetate, using a liquid-liquid extractor. Evaporation of the organic fraction failed to furnish the pyrrole. Reduction of the volume of the aqueous layer by evaporation and subsequent extraction with ethyl acetate also failed to give the product. The aqueous fraction was evaporated to dryness. The residue, which had an unpleasant odour, indicated that the pyrrole had decomposed under these conditions.

3-Amino-2-cyano-1-methylpyrroline (212)

Sodium (4.6g, 0.2mol) was dissolved in dry methanol (50ml). Dry toluene (150ml) was added to the refluxing solution while the methanol was distilled off under a nitrogen atmosphere until the temperature of the distillate reached 106°c. The suspension of methoxide was then cooled in ice and the dinitrile (12.3g, 0.1mol) was added dropwise. The mixture was stirred at room temperature for twenty-four hours, then cooled in ice while glacial acetic acid (12.6g, 0.2mol) in ether (150ml) was added. The mixture was stirred at room temperature for thirty minutes. The precipitated sodium acetate was removed by filtration and washed with ether. The filtrate

and ether washings were dried, filtered and evaporated to give an oil which solidified on trituration with petroleum ether. The crude product was recrystallised from ethanol to give the title pyrroline (5.14g, 42%) mpt.86-88°c (Found: C, 57.5; H, 7.4; N, 33.3. $C_6H_9N_3$ requires, C, 58.52; H, 7.37; N, 34.12) MS(CI) M+H 124. ν max 3300cm^{-1} (NH_2st), 2000cm^{-1} (CNst), 1680cm^{-1} (C=Cst), 1620cm^{-1} (NH_2 def). δ H[$CDCl_3$/DMSO] 2.4 (3H, s, NCH_3), 2.7 (2H, t, CH_2), 3.4 (2H, t, CH_2), 6.4-6.5 (2H, br, exchanges with D_2O, NH_2). δ C[$CDCl_3$/DMSO] 38.51 (N-Me), 67.00 (C-2), 118.39 (C=N), 163.84 (C-3), 66.44 (C-4), 62.95 (C-5).

Attempted preparation of 3-Amino-2-cyano-1-methylpyrrole (213)

A.

3-Amino-2-cyano-1-methylpyrroline (0.5g, 0.004mol) was refluxed with p-chloranil (1.0g, 0.008mol) in dry toluene (20ml) for three hours. TLC showed evidence of both reduced chloranil and the pyrrole although some starting material was still present. Further refluxing did not remove the pyrroline. The mixture was cooled and the solvent evaporated to give a brown solid; this was

decomposed with 4M hydrochloric acid and any insoluble material was removed by filtration. The filtrate was basified with concentrated ammonia solution and the product extracted with ethyl acetate, using a liquid-liquid extractor. The organic layer was separated, dried, filtered and evaporated to give a cream solid which was found to be recovered pyrroline (0.35g, 70%).

B.

The pyrroline (0.5g, 0.004mol) was refluxed with dicyano-dichlorohydroquinone (1.0g, 0.004mol) in dry toluene (20ml) for one hour. TLC of the reaction mixture showed a multitude of reaction components. This reaction was abandoned.

C.

The pyrroline (0.5g, 0.004mol) and p-chloranil (1.0g, 0.004mol) were refluxed in dry xylene (20ml) for four hours. The mixture was cooled and the solvent removed to give a green salt. The salt was decomposed in 4M hydrochloric acid and the insoluble reduced chloranil was removed by filtration. The filtrate was basified with concentrated ammonia solution. The product was extracted with ethyl acetate using a liquid-liquid extractor.

The organic layer was separated, dried, filtered and evaporated. No product was obtained ~~for~~ From this fraction. The volume of the aqueous layer was reduced and the solution was again extracted with ethyl acetate. Evaporation failed to yield any product.

D.

The method above was repeated to obtain a quantity of the salt. The salt was sublimed up to a temperature of 200°c. A slight coating of p-chloranil was seen on the sublimator but the residue was unchanged salt.

β-Methylaminopropionamide (214)

β-Methylaminopropionitrile (1.0g, 0.012mol) was refluxed with powdered potassium hydroxide (3.36g, 0.06mol) in t-butanol (50ml) for three hours. The mixture was cooled, poured into saturated brine (100ml) and the product was extracted with chloroform (3x20ml). The combined organic fractions were dried, filtered and evaporated to give an oil (0.99g, 82%). ν max 3500-3300cm^{-1} (NH_2st & NHst), 1640cm^{-1} (C=Ost). δ H[$CDCl_3$] 2.5 (3H, s, N-CH_3), 3.2-2.6 (4H, m, 2xCH_2), 4.0-3.5 (2H, br, exchanges with D_2O, NH_2).

Attempted preparation of N-1-amidoethyl-N-2-cyanoethyl-methylamine (215)

A.

β-Methylaminopropionamide (214) (0.9g, 0.009mol) in benzene (20ml) was stirred and preheated to 50°c while lactonitrile (0.6g, 0.009mol) was added. No exothermic reaction took place. The mixture was warmed to 50°c for one hour, then allowed to stand at room temperature overnight. No free water had formed. The solvent was evaporated to give a mixture of the two starting materials.

B.

The amide (214) (2.0g, 0.02mol), lactonitrile (1.42g, 0.02mol) and benzene (20ml) were refluxed in a Dean and Stark apparatus for four hours. No water formed. Evaporation of the solvent returned a mixture of the two starting materials.

3-Cyano-5-methyl-4-oxotetrahydrofuran (216)

To a stirred suspension of sodium hydride (80% dispersion in oil, 3.0g, 0.1mol) in toluene (100ml) was added dropwise a mixture of ethyl lactate (11.8g, 0.1mol) and acrylonitrile (5.0g, 0.1mol). An exothermic reaction

occurred. After the addition was complete the mixture was stirred for one hour. The mixture was diluted with ether (100ml) to aid precipitation of the sodium salt. The salt was collected, washed with ether and dried. Liberation of the product was achieved by portionwise addition of the salt to a two-phase mixture of 2M sulphuric acid/ dichloromethane (50ml/50ml). The organic layer was separated, dried over magnesium sulphate, filtered and evaporated. The crude oil obtained was purified by vacuum distillation to give the title ketonitrile (7.32g, 59%) bpt.120°c/1.5mm (Found C,57.4; H, 5.7; N, 11.35. $C_6H_7NO_2$ requires C, 57.6; H, 5.6; N, 11.2) MS(CI) M+H 126. ν max 3500cm^{-1} (OHst-enolic), 2250cm^{-1} (CNst), 1780cm^{-1} (COst). δ H[$CDCl_3$] 1.4-1.5 (3H, d, CH_3), 3.5-4.8 (4H, m, CH_2). δ C[$CDCl_3$] 15.45 (CH_3), 37.27 (C3), 37.59 (C5), 66.42 (C4), 66.68 (C2), 113.69 (CN), 204.40 (CO).

Attempted preparation of 4-Amino-3-cyano-5-methylfuran hydrochloride (217a)

3-Cyano-5-methyl-4-oxotetrahydrofuran (1.0g, 0.008mol) was refluxed with hydroxylamine hydrochloride (0.56g, 0.008mol) in n-butanol (20ml) for one hour. The mixture was cooled and diluted with ether (50ml). No precipitated hydrochloride was obtained. Evaporation of the solvent afforded an oil that resembled the starting material although the enolic OHst seemed to have increased.

Attempted preparation of 4-amino-3-cyano-5-methylfuran (217)

The ketonitrile (1.0g, 0.008mol) in pyridine (4ml) was added to a stirred solution of hydroxylamine hydrochloride (0.6g, 0.0084mol) in water (1ml). After one hour copper sulphate (0.4g, 0.0016mol) was added followed by triethylamine (1.7g, 0.0168mol) in dichloromethane (4ml). Additional copper sulphate was introduced to the reaction mixture until an olive-green colouration was obtained. A solution of N,N'-dicyclohexylcarbodiimide (1.98g, 0.0096mol) in dichloromethane (16ml) was added dropwise maintaining the temperature at 30°c. The reaction mixture was stirred at room temperature for two hours and then 98% formic acid (1ml) was added to decompose the excess dicyclohexylcarbodiimide. The precipitated urea was removed and the filtrate was added to dichloromethane (20ml) and washed with water (2x20ml). The separated organic layer was dried, filtered and evaporated to a small volume. The crude product was passed down a small silica gel column and eluted with dichloromethane. The solvent was evaporated to give an oil that was found to be recovered starting material.

Attempted preparation of 3-cyano-4-hydroxy-5-methylfuran (218)

3-Cyano-5-methyl-4-oxotetrahydrofuran (2.0g, 0.016mol) was refluxed with p-chloranil (3.93g, 0.016mol) in dry toluene (50ml) for six hours. The unreacted/reduced chloranil was filtered off and the filtrate was evaporated. The oil obtained did not solidify on trituration with ether. Spectral analysis indicated that the reaction product obtained was starting ketonitrile, although the enolic OHst had intensified

Attempted preparation of 3-cyano-5-methyltetrahydrofuran-4-oxime (219)

3-Cyano-5-methyl-4-oxotetrahydrofuran (5.0g, 0.04mol) was stirred and refluxed with hydroxylamine hydrochloride (6.48g, 0.093mol), barium carbonate (18.32g, 0.093mol) and methanol (75ml) for four hours. The mixture was filtered hot and the filtrate was evaporated keeping the temperature below 35°c. The semi-solid was triturated with ether and filtered. The filtrate was evaporated to give a pale green oil. Spectral evidence indicated that the oxime had not been obtained, the starting ketonitrile was recovered.

Attempted preparation of 4-cyano-3-formylamine-2-methyl furan (221)

The ketonitrile (1.25g, 0.01mol), hydroxylamine hydrochloride (1.0g, 0.01mol + 15% excess), sodium formate (1.25g) and 98% formic acid (15ml) were refluxed together for one hour. The reaction was cooled slightly and the excess formic acid was removed. The residue was triturated with ethyl acetate. The combined organic washings were dried, filtered and evaporated to give an oil which was shown to be recovered starting material.

Attempted preparation of 2-β-cyanoethoxypropionitrile (222)

A.

Lactonitrile (5.0g, 0.07mol), p-dioxane (25ml) and Triton B (0.5ml) were heated to 60°c and then acrylonitrile (3.71g, 0.07mol) was added. No exothermic reaction occurred. The mixture was heated to 60°c for thirty minutes, then allowed to stand at room temperature overnight. Evaporation of the solvent gave recovered lactonitrile as the product.

B.

Lactonitrile (5.0g, 0.07mol) in p-dioxane (20ml) and tributylamine (0.5ml) were heated to 50°c. Acrylonitrile (3.71g, 0.07mol) was added but no exothermic reaction occurred. The mixture was kept at 50°c for one hour then allowed to stand at room temperature overnight. The mixture was washed with 4M hydrochloric acid, dried and evaporated. Lactonitrile was recovered.

C.

Acrylonitrile (3.71g, 0.07mol) was heated to 60°c with stirring. A solution of lactonitrile containing Triton B (0.5ml) was added; no exothermic reaction took place. The mixture was warmed to 60°c for one hour and then allowed to stand at room temperature overnight. The mixture was washed with 4M hydrochloric acid, dried, filtered and evaporated to yield lactonitrile as the sole product.

D.

A mixture of lactonitrile (5.0g, 0.07mol) and acrylonitrile (3.71g, 0.07mol) were added to a mixture of acrylonitrile (5ml) and a catalytic amount of sodium hydroxide (one pellet crushed) preheated to 60°c. The heat was maintained for one hour, then the mixture was cooled and acidified to pH 4. The mixture was filtered,

diluted with benzene (20ml) and washed with water until neutral. Evaporation of the solvent afforded lactonitrile as the product.

Attempted preparation of β-cyanoethoxyacetonitrile (224)

A.

Glycolonitrile (4.0g, 0.07mol) and acrylonitrile (3.71g, 0.07mol) were added dropwise to a previously warmed (60°c) mixture of acrylonitrile (5ml) and tributylamine (0.5ml). No exothermic reaction took place. The mixture was warmed at 60°c for one hour and then allowed to stand at room temperature overnight. The mixture was washed with 4M hydrochloric acid, dried, filtered and the solvent evaporated to return glycolonitrile as the product.

B.

Glycolonitrile (2.0g, 0.035mol), acrylonitrile (1.85g, 0.035mol) and tributylamine (0.5ml) were refluxed for six hours. The mixture was cooled, washed with 4M hydrochloric acid, dried, filtered and evaporated. Starting material was recovered.

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1,2,3-Benzotriazinone

t	t′	θ	θ′	θ′-θ	-Ln (θ′-θ)
50	150	0.145	0.332	0.187	1.677
52	152	0.150	0.334	0.184	1.693
54	154	0.155	0.335	0.180	1.715
56	156	0.160	0.338	0.178	1.726
58	158	0.165	0.340	0.175	1.743
60	160	0.170	0.343	0.173	1.754
62	162	0.175	0.345	0.170	1.772
64	164	0.180	0.348	0.168	1.784
66	166	0.185	0.350	0.165	1.802
68	168	0.190	0.353	0.163	1.814
70	170	0.195	0.355	0.160	1.833
72	172	0.199	0.357	0.158	1.845
74	174	0.203	0.358	0.155	1.864
76	176	0.208	0.359	0.151	1.890
78	178	0.213	0.362	0.149	1.904
80	180	0.218	0.364	0.146	1.924
82	182	0.223	0.365	0.142	1.952
84	184	0.225	0.368	0.143	1.945
86	186	0.230	0.370	0.140	1.966
88	188	0.234	0.370	0.136	1.995
90	190	0.239	0.373	0.134	2.010
92	192	0.242	0.375	0.133	2.017
94	194	0.245	0.377	0.132	2.025
96	196	0.250	0.378	0.128	2.056
98	198	0.254	0.379	0.125	2.079
100	200	0.258	0.380	0.122	2.104

Chart speed...30mm/Min

Regression equation:

$$\text{Ln}(\theta'-\theta) = -1.26 - 0.0083t$$

Predictor	Coef	Stdev	t-ratio	p
Constant	-1.2556	0.0075	-167.68	0.000
t	-0.0008	0.0001	-85.07	0.000

s=0.0075 R-sq=99.7% R-sq(adj)=99.7%

6-Methylbenzotriazinone

t	t′	θ	θ'	$(\theta'-\theta)$	$-Ln(\theta'-\theta)$
30	90	0.120	0.245	0.125	2.079
31	91	0.123	0.247	0.124	2.087
32	92	0.125	0.249	0.124	2.087
33	93	0.128	0.250	0.122	2.104
34	94	0.130	0.252	0.122	2.104
35	95	0.134	0.254	0.120	2.120
36	96	0.136	0.255	0.119	2.129
37	97	0.140	0.256	0.116	2.154
38	98	0.143	0.258	0.115	2.163
39	99	0.145	0.259	0.114	2.171
40	100	0.148	0.260	0.112	2.189
41	101	0.150	0.260	0.110	2.207
42	102	0.152	0.262	0.110	2.207
43	103	0.155	0.264	0.109	2.216
44	104	0.157	0.265	0.108	2.226
45	105	0.160	0.266	0.106	2.244
46	106	0.163	0.268	0.105	2.254
47	107	0.165	0.270	0.105	2.254
48	108	0.167	0.270	0.103	2.273
49	109	0.170	0.272	0.102	2.283
50	110	0.172	0.273	0.101	2.293
51	111	0.175	0.274	0.099	2.313
52	112	0.177	0.275	0.098	2.323
53	113	0.180	0.275	0.095	2.354
54	114	0.182	0.276	0.094	2.364
55	115	0.185	0.278	0.093	2.375
56	116	0.186	0.279	0.093	2.375
57	117	0.188	0.280	0.092	2.386
58	118	0.190	0.280	0.090	2.408
59	119	0.193	0.282	0.089	2.419
60	120	0.195	0.282	0.087	2.442

chart speed...600mm/Hr

Regression equation:

$$Ln(\theta'-\theta) = -1.70 - 0.0121t$$

Predictor	Coef	Stdev	t-ratio	p
Constant	-1.7015	0.0079	-215.87	0.000
t	-0.0121	0.0002	-70.35	0.000

s=0.0086 R-sq=99.4% R-sq(adj)=99.4%

7-Methylbenzotriazinone

t	t′	θ	θ'	$\theta'-\theta$	$-\mathrm{Ln}(\theta'-\theta)$
30	70	0.127	0.240	0.113	2.180
31	71	0.130	0.243	0.113	2.180
32	72	0.135	0.244	0.109	2.216
33	73	0.137	0.245	0.108	2.226
34	74	0.140	0.249	0.109	2.216
35	75	0.145	0.250	0.105	2.254
36	76	0.149	0.253	0.104	2.263
37	77	0.152	0.254	0.102	2.283
38	78	0.155	0.256	0.101	2.293
39	79	0.158	0.258	0.100	2.303
40	80	0.162	0.260	0.098	2.323
41	81	0.165	0.262	0.097	2.333
42	82	0.168	0.265	0.097	2.333
43	83	0.170	0.265	0.095	2.354
44	84	0.174	0.268	0.094	2.364
45	85	0.178	0.270	0.092	2.386
46	86	0.180	0.272	0.092	2.386
47	87	0.183	0.274	0.091	2.400
48	88	0.185	0.275	0.090	2.408
49	89	0.188	0.277	0.089	2.419
50	90	0.190	0.279	0.089	2.419

Chart speed...600mm/Hr

Regression equation:

$$\mathrm{Ln}(\theta'-\theta) = -1.81 - 0.0126t$$

Predictor	Coef	Stdev	t-ratio	p
Constant	-1.8087	0.0138	-130.94	0.000
t	-0.0126	0.0003	-36.80	0.000

s=0.0010 R-sq=98.6% R-sq(adj)=98.5%

6-Chlorobenzotriazinone

t	t′	θ	θ′	θ′-θ	-Ln(θ′-θ)
30	55	0.190	0.294	0.104	2.263
31	56	0.194	0.298	0.104	2.263
32	57	0.200	0.300	0.100	2.302
33	58	0.205	0.303	0.098	2.323
34	59	0.209	0.305	0.096	2.343
35	60	0.214	0.308	0.094	2.364
36	61	0.219	0.310	0.091	2.397
37	62	0.224	0.313	0.089	2.419
38	63	0.229	0.315	0.086	2.453
39	64	0.234	0.318	0.084	2.477
40	65	0.238	0.320	0.082	2.501
41	66	0.243	0.322	0.080	2.526
42	67	0.245	0.325	0.080	2.526
43	68	0.250	0.327	0.077	2.564
44	69	0.255	0.329	0.074	2.604
45	70	0.260	0.331	0.071	2.645

Chart speed...30mm/Min

Regression equation:

$$\overline{Ln(\theta'-\theta)} = -1.49 - 0.0252t$$

Predictor	Coef	Stdev	t-ratio	p
Constant	-1.4920	0.0219	-68.14	0.000
t	-0.0252	0.0006	-43.42	0.000

s=0.0107 R-sq=99.3% R-sq(adj)=99.2%

7-Chlorobenzotriazinone

t	t′	θ	θ'	$\theta'-\theta$	$-\mathrm{Ln}(\theta'-\theta)$
30	60	0.213	0.336	0.123	2.096
31	61	0.218	0.338	0.120	2.120
32	62	0.227	0.340	0.113	2.180
33	63	0.233	0.344	0.111	2.198
34	64	0.238	0.345	0.107	2.234
35	65	0.244	0.347	0.103	2.273
36	66	0.250	0.349	0.099	2.313
37	67	0.255	0.352	0.097	2.333
38	68	0.260	0.353	0.093	2.375
39	69	0.265	0.354	0.089	2.419
40	70	0.270	0.355	0.085	2.465
41	71	0.275	0.356	0.082	2.501
42	72	0.278	0.358	0.080	2.526
43	73	0.283	0.360	0.077	2.564
44	74	0.286	0.362	0.076	2.577
45	75	0.290	0.363	0.073	2.617
46	76	0.293	0.364	0.071	2.645
47	77	0.297	0.365	0.068	2.688
48	78	0.301	0.368	0.067	2.703
49	79	0.304	0.369	0.065	2.733
50	80	0.308	0.370	0.062	2.780

Chart speed...30mm/Min

Regression equation:

$$\mathrm{Ln}(\theta'-\theta) = -1.08 - 0.0341t$$

Predictor	Coef	Stdev	t-ratio	p
Constant	-1.0790	0.0175	-61.63	0.000
t	-0.0341	0.0004	-78.89	0.000

s=0.0120 R-sq=99.7% R-sq(adj)=99.7%

6-Methoxybenzotriazinone

t	t′	θ	θ′	θ′-θ	-Ln(θ′-θ)
30	90	0.116	0.280	0.164	1.807
32	92	0.122	0.285	0.163	1.814
34	94	0.128	0.288	0.160	1.832
36	96	0.135	0.293	0.158	1.845
38	98	0.140	0.298	0.158	1.845
40	100	0.149	0.302	0.153	1.877
42	102	0.155	0.305	0.150	1.897
44	104	0.160	0.310	0.150	1.897
46	106	0.165	0.314	0.149	1.903
48	108	0.172	0.318	0.146	1.924
50	110	0.178	0.320	0.142	1.951
52	112	0.185	0.325	0.140	1.966
54	114	0.190	0.330	0.140	1.966
56	116	0.195	0.333	0.138	1.980
58	118	0.200	0.335	0.135	2.002
60	120	0.206	0.340	0.134	2.009
62	122	0.212	0.343	0.131	2.032
64	124	0.218	0.345	0.127	2.063
66	126	0.223	0.350	0.127	2.063
68	128	0.228	0.352	0.124	2.087
70	130	0.234	0.355	0.121	2.112

Chart speed...600mm/Hr

Regression equation:

$$\text{Ln}(\theta'-\theta) = -1.57 - 0.00747t$$

Predictor	Coef	Stdev	t-ratio	p
Constant	-1.5732	0.0085	-185.78	0.000
t	-0.0074	0.0002	-45.37	0.000

s=0.0091 R-sq=99.1% R-sq(adj)=99.0%

7-Methoxybenzotriazinone

t	t′	θ	θ'	$\theta'-\theta$	$-\mathrm{Ln}(\theta'-\theta)$
30	70	0.190	0.335	0.145	1.931
31	71	0.197	0.338	0.141	1.959
32	72	0.203	0.340	0.137	1.987
33	73	0.209	0.342	0.133	2.017
34	74	0.215	0.345	0.130	2.040
35	75	0.219	0.346	0.127	2.063
36	76	0.224	0.348	0.124	2.087
37	77	0.230	0.350	0.120	2.120
38	78	0.235	0.353	0.118	2.137
39	79	0.238	0.355	0.117	2.145
40	80	0.242	0.356	0.114	2.171
41	81	0.245	0.358	0.113	2.180
42	82	0.250	0.360	0.110	2.207
43	83	0.253	0.363	0.110	2.207
44	84	0.257	0.365	0.108	2.225
45	85	0.260	0.367	0.107	2.234
46	86	0.265	0.368	0.103	2.273
47	87	0.268	0.370	0.102	2.282
48	88	0.272	0.370	0.098	2.322
49	89	0.275	0.372	0.097	2.333
50	90	0.279	0.374	0.095	2.353

Chart speed...600mm/Hr

Regression equation:

$$\mathrm{Ln}(\theta'-\theta) = -1.36 - 0.020t$$

Predictor	Coef	Stdev	t-ratio	p
Constant	-1.3576	0.0199	-67.93	0.000
t	-0.0200	0.0005	-40.42	0.000

s=0.0137 R-sq=98.9% R-sq(adj)=98.8%

6-Nitrobenzotriazinone

t	t′	θ	θ′	θ′-θ	-Ln(θ′-θ)
120	200	0.125	0.270	0.145	1.931
122	202	0.130	0.273	0.143	1.945
124	204	0.134	0.275	0.141	1.959
126	206	0.138	0.278	0.140	1.966
128	208	0.142	0.280	0.138	1.980
130	210	0.146	0.284	0.138	1.980
132	212	0.150	0.285	0.135	2.002
134	214	0.155	0.288	0.133	2.017
136	216	0.160	0.292	0.132	2.025
138	218	0.162	0.293	0.131	2.032
140	220	0.166	0.295	0.129	2.048
142	222	0.170	0.298	0.128	2.056
144	224	0.174	0.300	0.126	2.071
146	226	0.178	0.302	0.124	2.087
148	228	0.183	0.304	0.121	2.112
150	230	0.186	0.305	0.119	2.129
152	232	0.190	0.307	0.117	2.146
154	234	0.193	0.309	0.116	2.154
156	236	0.197	0.310	0.113	2.180
158	238	0.200	0.312	0.112	2.189
160	240	0.204	0.313	0.109	2.216
162	242	0.207	0.315	0.108	2.226
164	244	0.210	0.316	0.106	2.244
166	246	0.215	0.317	0.102	2.283
168	248	0.218	0.318	0.100	2.303
170	250	0.222	0.320	0.098	2.323

Chart speed...600mm/Min

Regression equation:

$$Ln(\theta'-\theta) = -0.995 - 0.0076t$$

Predictor	Coef	Stdev	t-ratio	p
Constant	-0.9954	0.0305	-32.68	0.000
t	-0.0076	0.0002	-36.47	0.000

s=0.0160 R-sq=98.2% R-sq(adj)=98.2%

7-Nitrobenzotriazinone

t	t′	θ	θ'	$\theta'-\theta$	$-\mathrm{Ln}(\theta'-\theta)$
42	108	0.177	0.313	0.136	1.995
44	110	0.188	0.315	0.127	2.064
46	112	0.200	0.315	0.155	2.163
48	114	0.208	0.316	0.108	2.226
50	116	0.214	0.318	0.104	2.263
52	118	0.223	0.318	0.095	2.354
54	120	0.228	0.318	0.090	2.408
56	122	0.230	0.320	0.090	2.408
58	124	0.235	0.322	0.087	2.442
60	126	0.243	0.325	0.082	2.501
62	128	0.252	0.325	0.073	2.617
64	130	0.258	0.327	0.069	2.674
66	132	0.260	0.329	0.069	2.674
68	134	0.265	0.331	0.066	2.718
70	136	0.269	0.333	0.064	2.749

Chart speed... 120mm/Min

Regression equation:

$$\mathrm{Ln}(\theta'-\theta) = -0.923 - 0.324t$$

Predictor	Coef	Stdev	t-ratio	p
Constant	-0.92317	0.0577	-16.00	0.000
t	-0.02667	0.0010	-26.20	0.000

s=0.0341 R-sq=98.1% R-sq(adj)=98.0%

Infinity plot.

7-Nitrobenzotriazinone

∞ = 0.3V			
t	Θ	$(\infty - \Theta)$	$-Ln(\infty - \Theta)$
100	0.125	0.175	1.743
110	0.130	0.170	1.772
120	0.138	0.162	1.820
130	0.145	0.155	1.864
140	0.150	0.150	1.897
150	0.155	0.145	1.931
160	0.163	0.137	1.988
170	0.168	0.132	2.025
180	0.175	0.125	2.079
190	0.180	0.120	2.120
200	0.187	0.113	2.180
210	0.194	0.106	2.244
220	0.200	0.100	2.303
230	0.205	0.095	2.354
240	0.210	0.090	2.408
250	0.215	0.085	2.465
260	0.218	0.082	2.501
270	0.223	0.077	2.564
280	0.228	0.072	2.631
290	0.233	0.067	2.703
300	0.238	0.062	2.781

Chart speed... 600mm/Min

Regression equation:

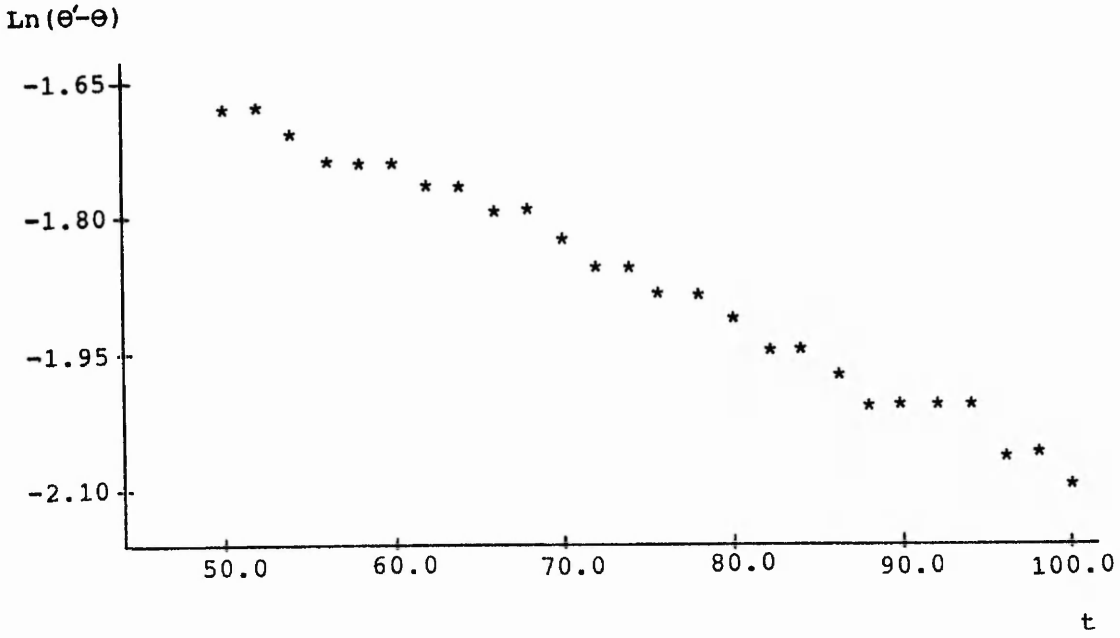
$$Ln(\infty - \Theta) = -1.18 - 0.313t$$

Predictor	Coef	Stdev	t-ratio	p
Constant	-1.178	0.020	-58.95	0.00
t	-0.005	0.0001	-53.89	0.00

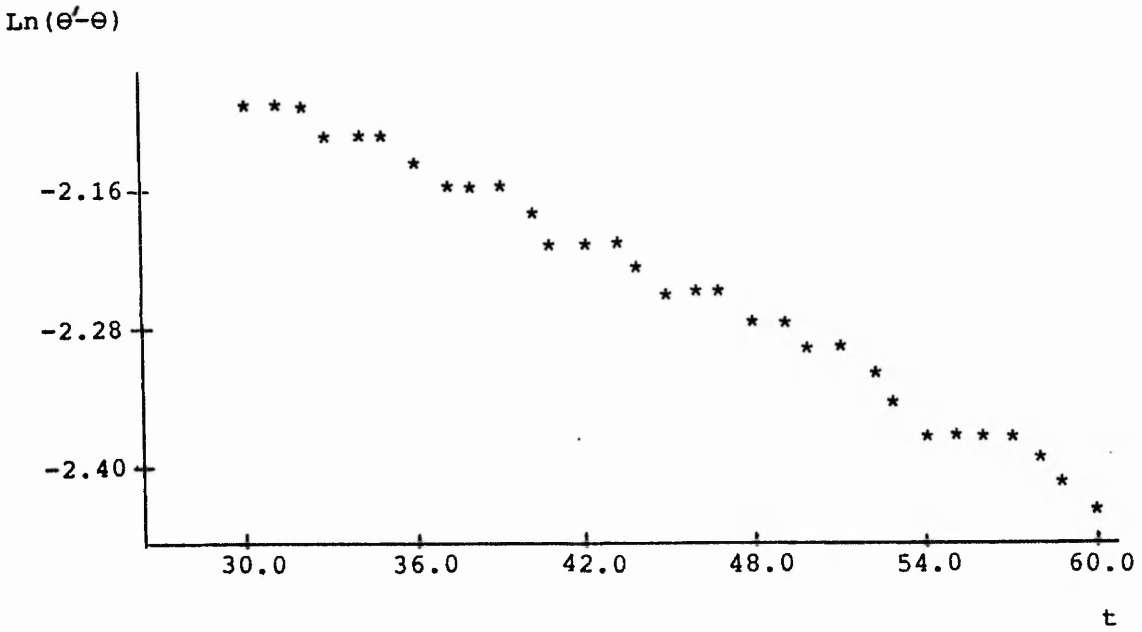
s= 0.026 R-sq=99.4% R-sq(adj)=99.3%

Graphs of Ln(θ′-θ) against t for substituted benzotriazinones.

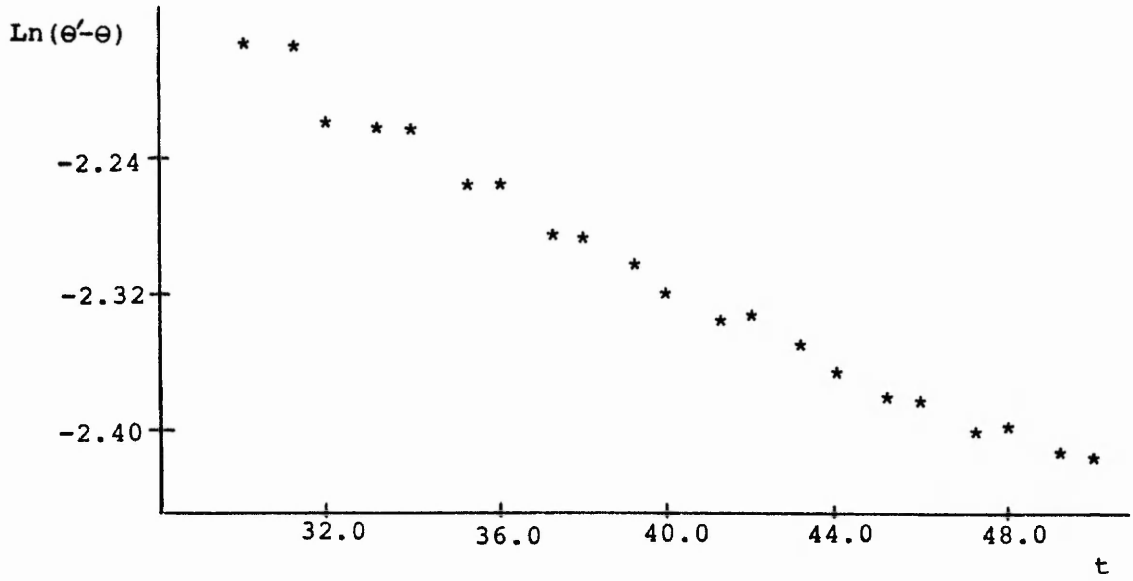
1,2,3-Benzotriazinone



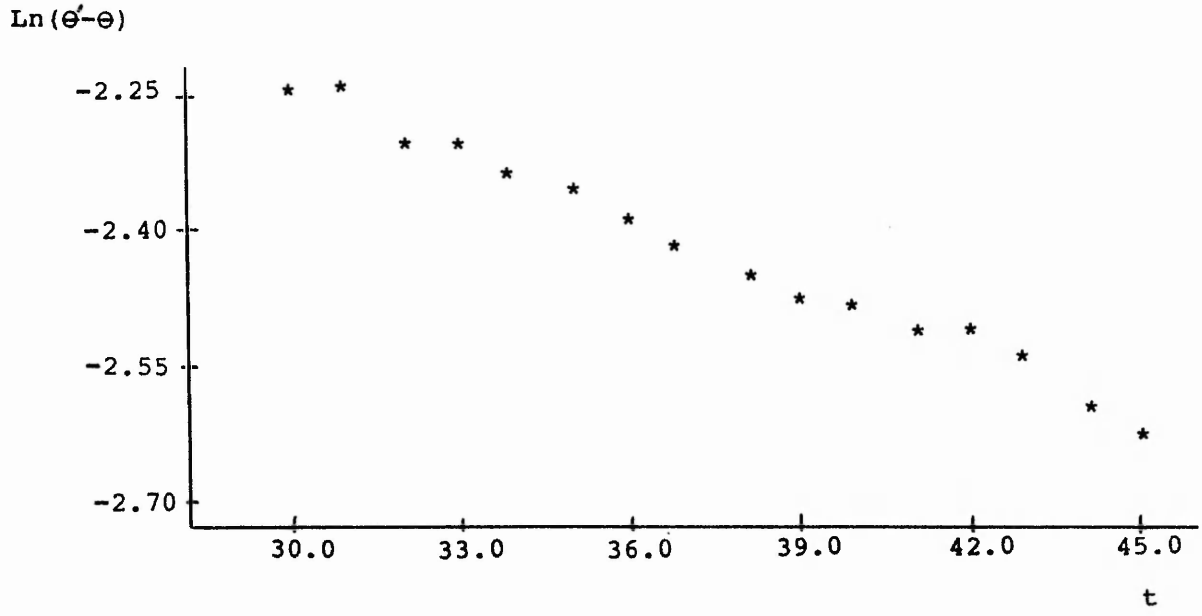
6-Methylbenzotriazinone



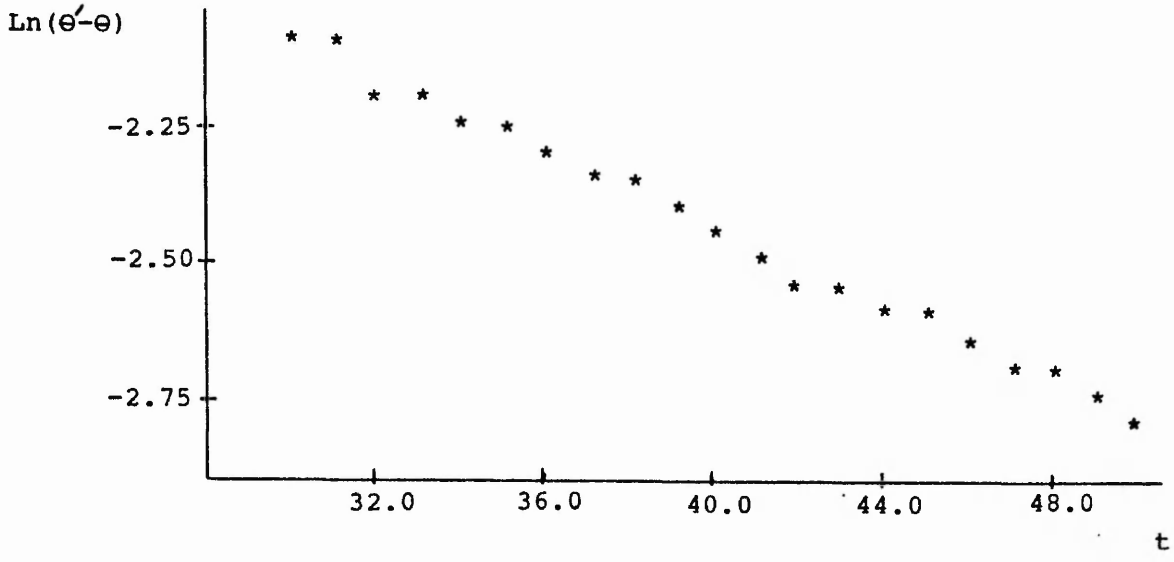
7-Methylbenzotriazinone



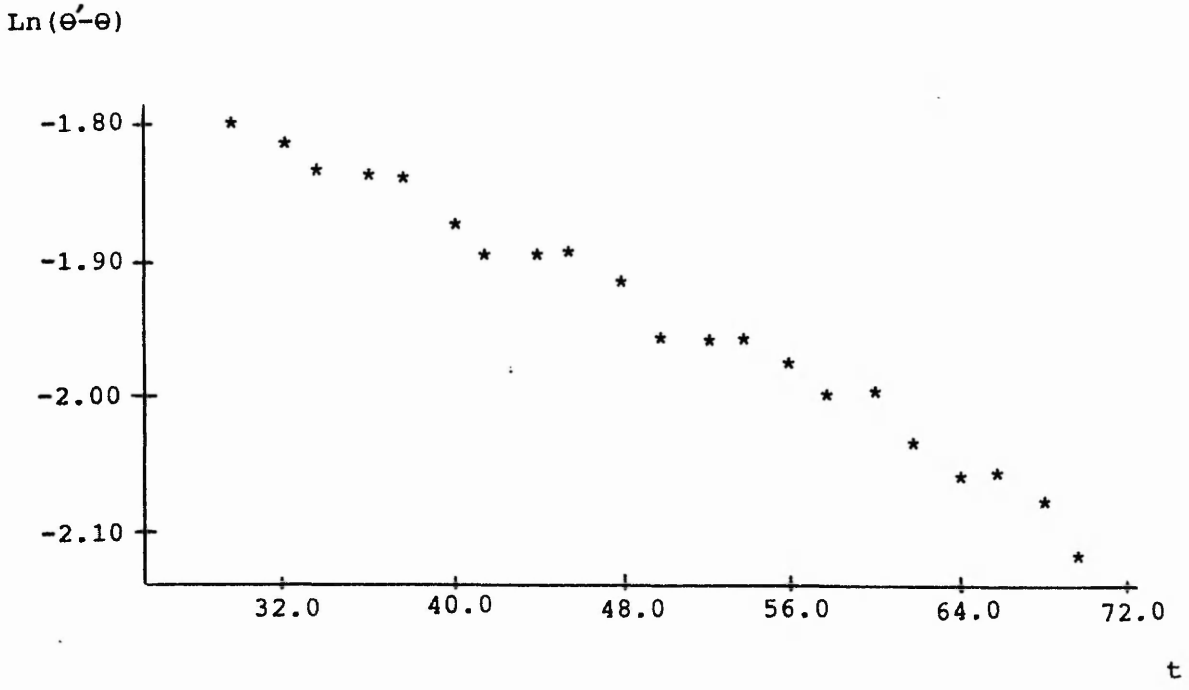
6-Chlorobenzotriazinone



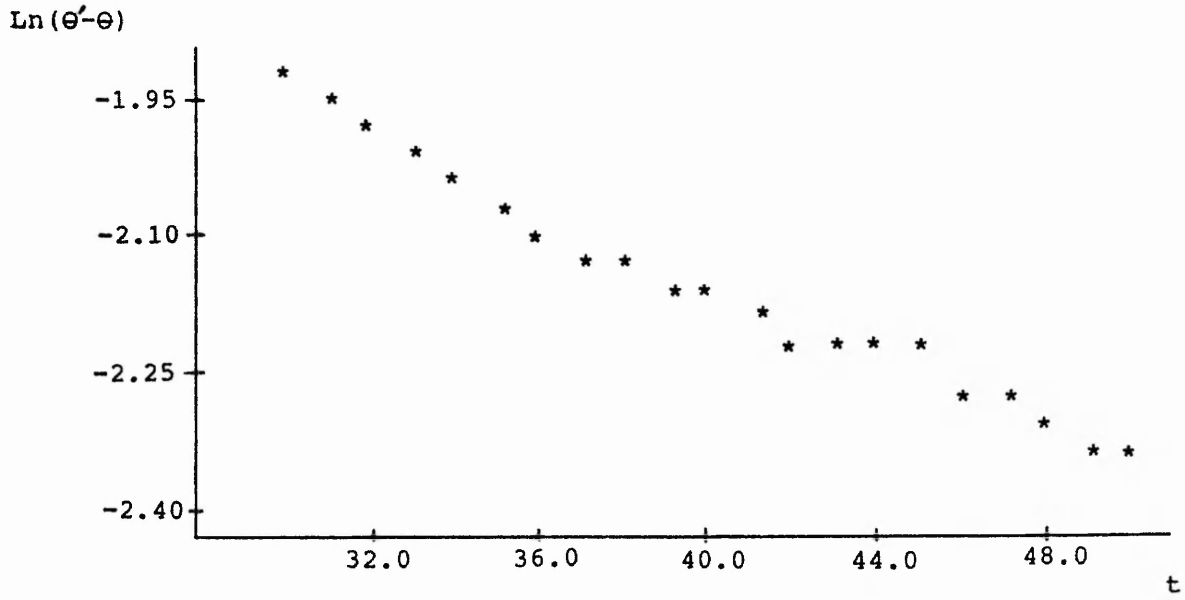
7-Chlorobenzotriazinone



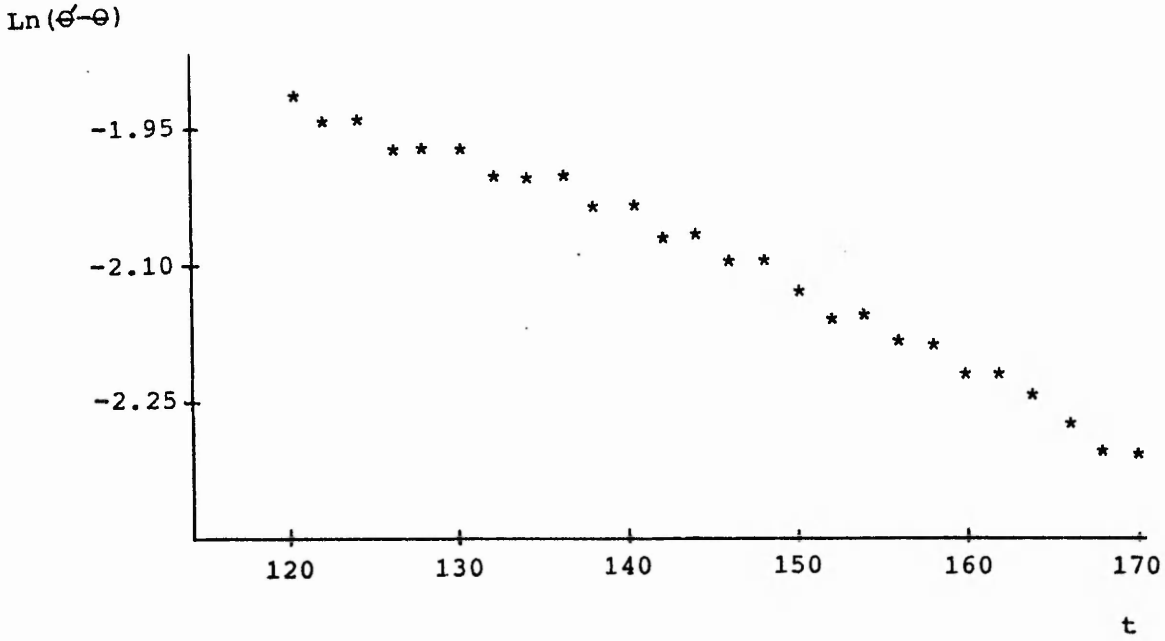
6-Methoxybenzotriazinone



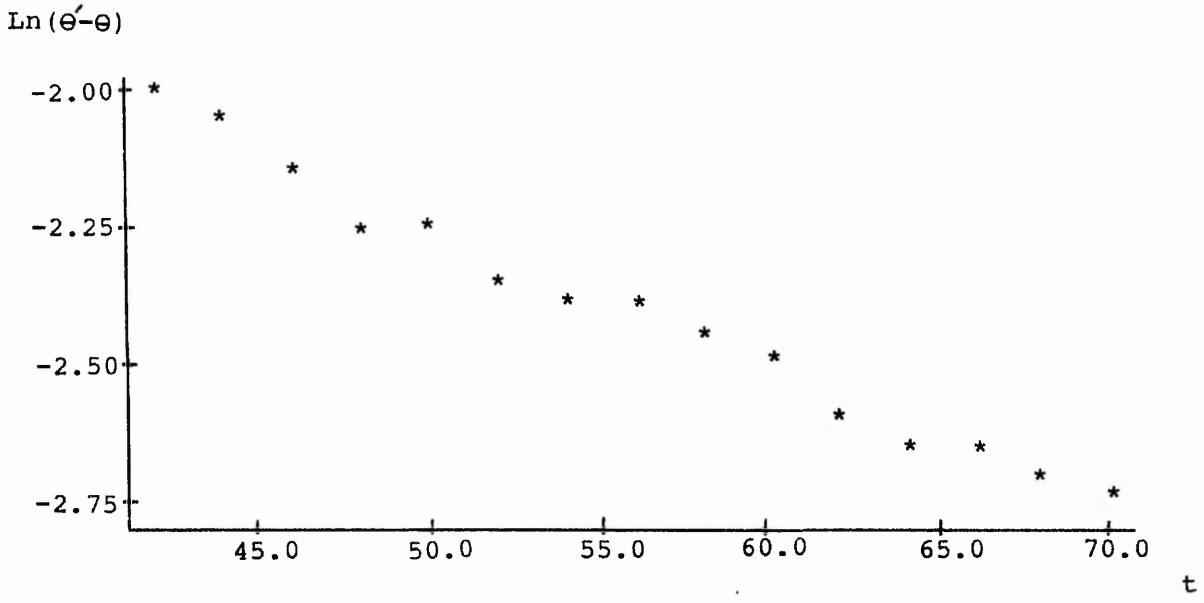
7-Methoxybenzotriazinone



6-Nitrobenzotriazinone



7-Nitrobenzotriazinone.



Graph of Ln(∞ -θ) against t for 7-nitrobenzotriazinone.

7-Nitrobenzotriazinone.